PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING
Hilton Washington, DC North/Silver Spring
8727 Colesville Road
Silver Spring, MD
April 7, 2010
NDA 22-522: Daxas (roflumilast 500 mcg tablets)
For the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought roflumilast (Daxas) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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DIVISION MEMORANDUM

Date: March 15, 2010

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To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for NDA 22-522, Daxas (roflumilast) Tablets, 500 mcg, for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on April 7, 2010. As members of the PADAC you provide important expert scientific advice and recommendation to the US Food and Drug Administration (the Agency) on the regulatory decision making process related to the approval of a drug product for marketing in the United States. The upcoming meeting is to discuss the New Drug Application (NDA) from Forest Research Institute [ownership transferred from Nycomed on December 4, 2009], seeking an approval for roflumilast 500 mcg to be administered once daily for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor, which is a new molecular entity and a new drug class for the treatment of COPD. Roflumilast is pharmacologically related to theophylline, which is a non-specific phosphodiesterase (PDE) inhibitor that is approved in the United States for the treatment of patients with COPD and asthma. No PDE-4 inhibitor is approved for use in the United States. The proposed commercial name of roflumilast is Daxas. The drug product is an immediate release tablet. The proposed dose is 500 mcg once daily. It is purported to act as an anti-inflammatory agent in patients with COPD.

One issue that is important to note is a proposed change in indication late into the review period. Nycomed submitted the NDA on July 15, 2009, and the NDA was transferred to Forest on December 4, 2009. The new Applicant, Forest, submitted new labeling for roflumilast on January 29, 2010, which included substantial labeling changes including a new indication for roflumilast and a new warning regarding neuropsychiatric events. The new proposed indication for roflumilast is the "maintenance treatment to reduce exacerbations of

chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations". The change in indication is notably narrower from a broad maintenance treatment of COPD indication to an indication focused only on reduction in COPD exacerbations. This change of indication 6 months into the review period and 2 months prior to the advisory committee meeting is problematic because it shifts the focus of the efficacy analysis, which was based upon the original indication. Therefore, the Agency briefing package and questions focus on the originally proposed indication.

The materials to be discussed in this meeting and the opinions we are seeking are primarily related to the clinical issues related to the efficacy and safety of roflumilast. Keep in mind that in the regulatory decision making process to determine approvability of a product, the Agency takes into consideration various factors in addition to clinical issues, including manufacturing and controls of a product and preclinical considerations. These will not be the focus of this Advisory Committee meeting.

Attached are the background materials for the meeting. The background materials include several documents prepared by the Agency: a clinical briefing document, a statistical briefing document, and brief summaries of the nonclinical program and clinical pharmacology program. In addition, the background package contains both the Applicant's originally proposed product label for roflumilast and the newly submitted product label received on January 29, 2010.

This memorandum summarizes the contents of the Agency background materials and the key issues and questions for discussion at the meeting. The materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Nycomed/Forest. These background materials represent preliminary findings, and do not represent the final position of the Agency. An important piece in our decision on this application will be the opinions and input that we receive from you at this meeting.

Background

Drug Development for Chronic Obstructive Pulmonary Disease

COPD is a chronic progressive disease caused by chronic inflammation and destruction of the airways and lung parenchyma that is characterized by progressive airflow obstruction that is not fully reversible with the administration of a bronchodilator. COPD is the cause of major morbidity and mortality and is a leading cause of death in the world. The term COPD encompasses a spectrum of pulmonary processes, ranging from symptoms primarily associated with chronic bronchitis (cough and excess sputum production) to purely emphysema-related pulmonary disease, although the specific terms chronic bronchitis and emphysema are not used in some treatment guidelines (e.g. Global Initiative for Chronic Obstructive Lung Disease).[1] Because of the heterogeneity of COPD, the nature of symptomatic impairment experienced by patients (cough, excess sputum production, dyspnea, etc.) will differ. In general, it is desirable to include patients broadly representative

[1] Global Initiative for Chronic Obstructive Lung Disease – Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2009). Available at http://www.goldcopd.com/

of the spectrum of the COPD population in clinical trials intended to support product registration.

Although most medications to treat COPD are bronchodilators, in recent years several products are now indicated for the reduction in COPD exacerbations. Tiotropium bromide (marketed as Spiriva HandiHaler), is a once-daily anticholinergic that is a bronchodilator, but clinical trials have shown that tiotropium reduces COPD exacerbations. Additionally, although inflammation plays a critical role in the pathogenesis of COPD, there are no single-ingredient corticosteroid products approved for the treatment of this disease. However, a combination product containing both a long-acting beta agonist (salmeterol) and an inhaled corticosteroid (fluticasone propionate), marketed as Advair Diskus 250/50, is approved for the maintenance treatment of airflow obstruction and for reduction in exacerbations of COPD in patients with a history of exacerbations. A second combination product containing both a long-acting beta agonist (formoterol) and an inhaled corticosteroid (budesonide), marketed as Symbicort Inhalation Aerosol 160/4.5, is approved for the maintenance treatment of airflow obstruction in patients with COPD.

Also of interest is theophylline, a non-specific member of the phosphodiesterase inhibitor class, which is available in immediate and sustained released formulations and is approved for the treatment of the symptoms and reversible airflow obstruction associated with chronic lung diseases, e.g. emphysema and chronic bronchitis.[2] According to the product label, in patients with COPD, theophylline may decrease dyspnea and air trapping and improve diaphragmatic contractility but is not viewed as a potent bronchodilator as it provides little improvement in pulmonary function measurements.[2] However, results of a 2002 Cochrane meta-analysis showed that theophylline had a statistically significant effect on FEV1 in COPD patients.[3] The meta-analysis addressed the efficacy of theophylline for the treatment of COPD and included 20 randomized, double-blind, placebo controlled trials in patients with COPD. Baseline FEV1 in these studies ranged from 0.96 L to 1.15 L. Thirteen studies with a total of 244 patients contributed data to an FEV1 outcome that showed a statistically significant mean improvement of 100 mL (95% confidence interval from 40 L to 160 mL) or about 10%.

Study endpoints for medications developed for COPD will differ based on whether the purported benefit of the drug is expected to improve airflow obstruction, provide symptom relief, prevent/reduce exacerbations, or provide some other clinically relevant benefit such as decrease the rate of decline in lung function, or increased survival. Improvement in airflow obstruction has been a main therapeutic strategy in COPD drug development. Bronchodilator drugs such as short and long-acting beta agonists and anticholinergic drugs provide benefit through relief of reversible airflow obstruction that is an important feature in some patients with COPD. Spirometry, specifically forced expiratory volume in one second (FEV1), is a commonly used objective physiological efficacy endpoint for bronchodilator drugs because it is a reflection of the extent of airway obstruction. To provide a sense of the bronchodilator effect of approved medications, tiotropium demonstrated 87 to 103 mL improvement in end

[2] Theolair prescription labeling accessed at http://dailymed.nlm.nih.gov/dailymed/about.cfm
[3] Ram FS, Jones PW, Castro AA, et. al. Oral theophylline for chronic obstructive pulmonary disease. Cochrane Database System Reviews 2002. Issue 4. Article No: CD003902

of dosing interval FEV_1 over placebo throughout a 4 year trial[4]. Similarly, salmeterol, a long-acting beta agonist, demonstrated an approximately 170 mL improvement in 2 hour post-dose FEV_1 relative to placebo at the end of a 24 week dosing period in COPD patients[5]. The resultant indication for bronchodilator drugs for COPD which demonstrate clinically relevant improvements in FEV1 would be reflective of their beneficial effect in relieving airflow obstruction, for example, "for the maintenance treatment of bronchoconstriction in patients with COPD".

The reduction or prevention of COPD exacerbations is a clinically relevant endpoint for patients with COPD that would provide a meaningful benefit to patients. Clinical studies have often used an intervention driven definition of a COPD exacerbation in which the determination of an exacerbation rests on a decision by a clinician to intervene in the care of the patient, typically by prescribing additional therapy such as antibiotics or corticosteroids and/or hospitalizing the patient. This intervention driven type of definition raises concerns because the decision to intervene may be a subjective decision by a health care provider that can vary depending on geography, the availability of healthcare, and local practices. Thus, in order to help standardize the definition of a COPD exacerbation, it is important to link a decision to intervene in the care of the patient with specific sign or symptom criteria which must be met in order to declare an intervention a COPD exacerbation.

Additional efficacy variables for clinical studies in COPD include multidimensional health-related quality-of-life instruments such as the St. George's Respiratory Questionnaire (SGRQ) which is designed to assess different aspects of the effect of COPD on a patient's life or the provision of symptom relief such as reduction in cough, sputum production, or dyspnea. To date these types of instruments are best used as co-primary or key secondary endpoints in COPD studies in order to further support efficacy.

Regulatory History

Roflumilast is currently not marketed in the United States or anywhere else in the world. The regulatory history for roflumilast is quite extensive as the overall clinical development program has been conducted over approximately a fifteen year period and includes a database of more than 15,000 patients with COPD. The Application has changed ownership multiple times. The large clinical program and many phase 3 trials are a reflection that the design, endpoints, and patient populations of the COPD clinical program evolved substantially over time.

For example, earlier Phase 2/3 dose-ranging and Phase 3 studies (FK1-101 and M2-107 conducted from 1999-2003) focused on quality of life [St. George Respiratory Questionnaire (SGRQ)] as a co-primary endpoint with spirometry measurements (FEV1). In 2003, however, exacerbation rate became the primary endpoint and quality of life and spirometric measurements were secondary endpoints in study M2-111. M2-111 was later amended to include FEV1 as a co-primary endpoint along with exacerbations. Concern was raised regarding the definition and determination of exacerbations and criteria used for assessing

[4] Spiriva HandiHaler (tiotropium bromide inhalation powder) prescription labeling
[5] Serevent Diskus (salmeterol xinafoate inhalation powder) prescription labeling

severity of exacerbations. In 2006, protocols for M2-124 and M2-125 with co-primary endpoints of pre-bronchodilator FEV1 and rate of exacerbations were submitted. In a correspondence dated February 7, 2007, regarding M2-124 and M2-125, the Agency had the following comments:

- *Based on evaluation of the data from studies M2-111 and M2-112 the patient population for studies M2-124 and M2-125 was modified to include only patients with a defined history of exacerbations, require signs of chronic bronchitis at inclusion, and meet a defined cough/sputum symptom score at randomization. In addition, concomitant inhaled corticosteroids (ICS), which were allowed in studies M2-111 and M2-112, were prohibited. Patients were only allowed concomitant medication consisting of long-acting beta agonists plus rescue medication or short acting anticholinergics plus rescue medication. Despite these restrictions based on the roflumilast clinical development program, the Division was asked if it agreed that a general claim for maintenance treatment of COPD could be obtained. The Division responded that the indication that could be claimed would be a review decision.*
- *Regarding whether efficacy and safety outcomes from US and non-US patients would allow adequate assessment for approvability, the Division reiterated that this would be a review issue. It added that (the endpoint of) COPD exacerbations is a clinical diagnosis and the decision to initiate treatment (with corticosteroids) or hospitalization is investigator-driven leaving room for variations in the definition of what constitutes an exacerbation and the severity of the exacerbations. "As much as it is feasible you are encouraged to standardize your definitions for a COPD exacerbation as well as the criteria that would prompt the Investigator to initiate corticosteroid therapy or hospitalize the patient."*

In a Pre-NDA meeting on April 16, 2008, studies M2-124 and M2-125 were identified as the pivotal studies. However, few results were provided, which limited Agency feedback regarding the adequacy of the program to support the proposed indication. The Agency noted it would look at the totality of the data and not only a statistical significance for the primary endpoint(s). The Agency acknowledged the definition of exacerbations based solely on the requirement of oral or parental glucocorticoids and/or hospitalization and stated that the acceptability of the definition of exacerbation would be a review issue. The Agency explained that there is no consensus definition of a "COPD exacerbation". It acknowledged that the start of the roflumilast program almost 10 years previously pre-dates much of the more recent discussion regarding how to define COPD exacerbations. The Agency suggested that it would be in the Applicant's best interest to address these issues prospectively, as they would be likely to come up during an advisory committee discussion regarding their application. In addition the NDA submission should discuss and provide justification for the minimal clinically important difference in trough FEV1 between active treatment with roflumilast and placebo.

PDE-4 Inhibitor Development

Another PDE-4 inhibitor, cilomilast, was developed by a different company for patients with COPD. Cilomilast, like roflumilast, is a selective type 4 PDE inhibitor which has been studied extensively in patients with COPD. Thus, a brief discussion of the cilomilast experience is relevant for the current application. The following is a brief summary of the notable efficacy and safety findings in the cilomilast program.

In the cilomilast phase 3 program, co-primary efficacy endpoints were change in FEV1 and SGRQ from baseline. As mentioned above, PDE inhibitors are relatively weak bronchodilators and the SGRQ endpoint was utilized to corroborate and add additional efficacy support to the improvement in the pulmonary function endpoint, FEV1. In four, 24 week Phase 3 clinical trials, the difference between the cilomilast and the placebo groups in FEV1 change from baseline was 30-40 mL and was statistically significant in 2 of the 4 studies. As for the co-primary endpoint, SGRQ, the difference between the cilomilast and placebo groups in change from baseline SGRQ ranged between -4.1 and +0.7 (-4 is accepted as the minimum important difference) in the 4 studies. Again, the difference between the cilomilast and placebo group reached statistical significance in 2 of the 4 studies but crossed the threshold of minimal clinical significance in only one study.

The major safety concerns with cilomilast were gastrointestinal safety, and the possibility of mesenteric arteritis based on finding seen in rats. In the clinical program, frequency of gastrointestinal adverse reaction was high with cilomilast compared to placebo (12% for cilomilast vs 4.2% for placebo, for gastrointestinal symptoms that concerned patients or interfered with daily activities). Limited fecal occult blood testing did not show concerning findings for cilomilast, and colonoscopy in a small number of patients with blood in stool were unremarkable.

The cilomilast data were presented to the Pulmonary-Allergy Advisory Committee on September 5, 2003.[6] The committee members discussed the efficacy and safety of cilomilast for the maintenance of lung function (FEV1) in patients with COPD. At the meeting, the members were not convinced of the efficacy of cilomilast. The committee was asked "Has cilomilast at a dose of 15 mg twice daily shown a magnitude and consistency of efficacy that is sufficient to support approval of cilomilast for the maintenance of lung function (FEV1) in patients with COPD?" and the members voted Yes-3 and No-7. The committee members were asked two safety questions, one related to overall safety (aside from the concern of vasculitis), and the other specific to the concern of mesenteric vasculitis. The members were satisfied with the safety data presented. On the question whether the overall safety data support approval, 9 voted Yes and 1 voted No. On the question whether the concern of mesenteric vasculitis has been adequately studies, 10 members voted Yes while none voted No. When asked "Do the efficacy and safety data provide substantial and convincing evidence that support the approval of cilomilast at a dose of 15 mg twice daily for the maintenance of lung function (FEV1) in patients with COPD?" the committee voted Yes-3 and No-7. Thus, the AC feedback was that cilomilast failed to demonstrate substantial evidence for the maintenance of lung function (FEV1) in patients with COPD. Despite being satisfied with the safety data, the committee voted against approval of cilomilast.

Specific PDE4 inhibitors have also demonstrated prominent dose-dependent toxicities related to the gastrointestinal system in clinical studies, including nausea, vomiting, diarrhea, anorexia, and weight loss. Vasculitis, which was noted in animal toxicology studies of PDE4 inhibitors, has also been a concern, but was not apparent in nonclinical animal studies with roflumilast. The adverse event profile of PDE 4 inhibitors has resulted in marginal

[6] September 5, 2003 Pulmonary-Allergy Drugs Advisory Committee
http://www fda.gov/ohrms/dockets/ac/cder03.html#PulmonaryAllergyDrugs

tolerability at doses felt to be effective and which must be taken into consideration when making a risk-benefit determination.

Chemistry and Manufacturing

Roflumilast is a small, synthetic, non-peptide molecule and is a new molecular entity. The proposed commercial drug product for roflumilast is a 500 mcg immediate release film coated tablet. The active pharmaceutical ingredient is a white to off-white powder and is incorporated with the inactive ingredients into the tablet. The product is proposed to be packaged in bottles as well as in blister trays.

Pharmacology/Toxicology

A separate document summarizing the pharmacology/toxicology program is provided in the briefing package. A brief summary is provided here. Nonclinical toxicities of roflumilast and/or its metabolites included carcinogenicity, reproductive toxicity, and cardiovascular and GI toxicities. GI toxicities included inflammation and erosion of the mucosa. Cardiac toxicities included cardiac lesions, periarteritis, and myocarditis. Roflumilast showed adverse fertility effects in male rats but these effects where not replicated in clinical trials. Structural damage to male reproductive organs was observed in rats, mice and dogs, but not in hamsters and monkeys. Reproductive effects of roflumilast included stillbirths and pup deaths in mice attributed to a tocolytic effect of the drug. Roflumilast metabolite (ADCP N-oxide) induced nasal tumor formation in hamsters. This metabolite has been observed in human plasma and urine; therefore, the metabolite related nasal tumors observed in hamsters may be relevant to humans.

Clinical Pharmacology

A separate document summarizing the clinical pharmacology program is provided in the briefing package. A brief summary of the pharmacokinetic profile is provided here.

Roflumilast is metabolized via cytochrome P450 and conjugation reactions. Roflumilast N-oxide is the major metabolite observed in human plasma. *In vitro* studies and clinical drug-drug interaction studies suggested that the metabolism of roflumilast to roflumilast N-oxide was mediated by CYP1A2 and CYP3A4. In healthy subjects, the absolute bioavailability of roflumilast following a 500 mcg oral dose is 79%. The median time to reach maximum plasma concentrations of roflumilast (t_{max}) is approximately one hour, while t_{max} of roflumilast N-oxide is about eight hours in the fasted state. Food intake delays t_{max} of roflumilast by one hour and reduces C_{max} by approximately 40%, but the C_{max} and t_{max} of roflumilast N-oxide are not affected. The plasma AUC of roflumilast N-oxide is about 10-fold greater than the plasma AUC of roflumilast. Following an oral dose of roflumilast, the median plasma effective half-lives of roflumilast and roflumilast N-oxide were approximately 17 and 30 hours, respectively. Steady state plasma concentrations were reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing of roflumilast. Based on a population PK analysis, COPD

patients have a 65% higher AUC for roflumilast and about 8% higher AUC for roflumilast N-oxide compared to healthy subjects.

Clinical program

The overall COPD clinical development program for roflumilast conducted over approximately a fifteen year period is rather large and includes eighteen Phase 2/3 clinical studies. Our review will focus primarily on eight studies conducted over the span of the roflumilast COPD development program, 4 one-year studies (Studies M2-111, M2-112, M2-124, and M2-125) which evaluated COPD exacerbations and 4 six-month studies (FK1-101, M2-107, M2-127, and M2-128) (see Table 1).

Table 1 Relevant Clinical Studies for Roflumilast for COPD

Study/ Years conducted	Study Type	Study Duration	Pt age, (yr)	Disease severity*	Treatment groups	N (ITT)	Countries
Dose-ranging and Initial Phase 3 Studies							
FK1-101/ 1999-2001	Dose-ranging, efficacy and safety	26 weeks	≥ 40	35-75%	Rof 250 mcg Rof 500 mcg Placebo	175 169 172	Europe, South Africa
M2-107/ 2002-03	Efficacy and safety	24 weeks	≥ 40	30-80%	Rof 250 mcg Rof 500 mcg Placebo	576 555 280	Europe, Australia, North America (Canada)
Later Phase 3 and Supportive Studies							
M2-111/ 2003-05	Efficacy and safety	52 weeks	≥ 40	≤ 50%	Rof 500 mcg Placebo	567 606	Europe, South Africa, North America
M2-112/ 2003-04	Efficacy and safety	52 weeks	≥ 40	≤ 50%	Rof 500 mcg Placebo	760 753	Europe, Australia, South Africa, North America (Canada)
M2-124/ 2006-08 Pivotal	Efficacy and safety	52 weeks	≥ 40	≤ 50%a	Rof 500 mcg Placebo	765 758	Europe, Australia, North America
M2-125/ 2006/08 Pivotal	Efficacy and safety	52 weeks	≥ 40	≤ 50%a	Rof 500 mcg Placebo	772 796	Europe, India, South Africa, North America
M2-127/ 2006-07 Supportive	Efficacy and safety	24 weeks	≥ 40	40-70%b	Rof 500 mcg + salmeterol Placebo + salmeterol	466 467	Europe, South Africa, North America (Canada)
M2-128/ 2007-08 Supportive	Efficacy and safety	24 weeks	≥ 40	40-70%b	Rof 500 mcg + tiotropium Placebo + tiotropium	371 372	Europe

Early clinical studies had demonstrated only modest improvements in lung function, and because a broad COPD indication such as was proposed by the Applicant (maintenance treatment of the disease entity, COPD, as a whole) would require demonstrating a clinically meaningful improvement in more than one aspect of the disease, co-primary endpoints were designated for most Phase 3 studies. The design, endpoints, and patient populations of these Phase 3 studies evolved over time but can be separated into 2 general periods; an initial dose-ranging and Phase 3 development period during which the Applicant focused on quality of life [St. George Respiratory Questionnaire (SGRQ)] as a co-primary endpoint (studies FK1-

101 and M2-107) followed later by a Phase 3 program that utilized the rate of COPD exacerbations as a co-primary endpoint (FEV1 served as the other co-primary endpoint in all studies). During this later period, the first 2 studies of one year duration (M2-111 and M2-112) failed to demonstrate a statistically significant reduction in the rate of moderate or severe exacerbations. Post hoc analyses were then used to define a more responsive patient population (those with chronic bronchitis and a history of cough, sputum production, and recent exacerbations) which was carried forth in the year long studies designated as pivotal (M2-124 and M2-125). Supportive studies of 6 month duration (M2-127 and M2-128) were also conducted to assess the effects of concomitant use of standard COPD bronchodilator treatments, the LABA, salmeterol and the long-acting anti-muscarinic drug (LAMA), tiotropium, on lung function (FEV1).

Dose-ranging studies

The dose ranging data for the roflumilast clinical program primarily comes from two studies (studies FK1-101 and M2-107) in which two doses of roflumilast (250 and 500 mcg once daily) were compared against placebo. Both trials were double-blind, placebo-controlled, parallel-group, non-US, multinational studies in patients ≥ 40 years of age with non-reversible airway obstruction across the full range of COPD severity (FEV1 30 to75-80% predicted). Study FK1-101 was a phase II/III trial with 2 week run-in followed by 26 week treatment while study M2-107 was a phase III trial with 4 week run-in and 24 week treatment. Patients were randomized 1:1:1 (516 in study FK1-101 and 1411 in study M2-107) to receive either roflumilast 250 or 500 mcg or placebo once daily. It is notable that the 500 mcg once daily dose of roflumilast is regarded as the maximally tolerated dose. Concomitant uses of systemic or inhaled corticosteroids and long acting beta agonists were not permitted. Stable daily dose of short-acting anticholinergics were permitted. Uses of other COPD medications were also restricted except rescue salbutamol, which was provided to all eligible subjects. Co-primary endpoints were pre-bronchodilator FEV1 and the SGRQ in trial FK1-101 and post-bronchodilator FEV1 and SGRQ in trial M2-107. Note that although SGRQ as a primary or key secondary endpoint was the hallmark of earlier COPD trials, it was not evaluated in trials designated as pivotal.

For study FK1-101, pre-bronchodilator FEV1 increased by 20 and 24 mL from baseline for the roflumilast 250 and 500 mcg dose groups, respectively while a decrease of 17 mL was noted in the placebo group. With regard to study M2-107, post-bronchodilator FEV1 increased 29 and 51 mL from baseline for the roflumilast 250 and 500 mcg doses respectively while a decrease of 45 mL was noted in the placebo group.

Regarding the other co-primary endpoint, SGRQ, in both studies there was no significant difference in SGRQ between either the 250 or 500 mcg roflumilast dose group and placebo or between each other. Based on the general lack of separation in efficacy parameters between the 250 and 500 mcg doses, dose selection for the roflumilast program appears to have been arrived at by selection of the maximally tolerated dose.

Establishment of a once daily dosing regimen was based on the results of a pharmacokinetic study in healthy volunteers which demonstrated that roflumilast and its active metabolite

(roflumilast-N-oxide) had respective half lives of 17 and 30 hours. Dosing intervals less than or greater than 24 hours were not evaluated in COPD clinical trials.

Pivotal and additional supportive studies

In addition to the two Phase 2b and 3 studies which evaluated 2 dose levels of roflumilast that are described above, 4 studies of one year duration and 2 studies of 6-months duration were conducted and identified by the Applicant as pivotal (studies M2-124 and M2-125) or supportive (M2-111, M2-112, M2-127 and M2-128). All studies were multicenter, multi-national, randomized, double-blind, placebo controlled parallel group trials which included a 2-4 week run-in period followed by a double blind treatment period of 52 weeks (M2-111, M2-112, M2-124, and M2-125,) or 24-26 weeks (M2-127 and M2-128). The 4 one year studies all had lung function as assessed by FEV1 and the rate of COPD exacerbations as co-primary endpoints in patients ≥ 40 years of age with severe COPD (FEV1 ≤ 50%) and nonreversible airway obstruction. After a 4-week run-in period in which patients were taken off prohibited concomitant medications, patients were randomized 1:1 to receive either roflumilast 500 mcg or placebo once daily (see table above for number of patients/group). While generally similar in design, there were some notable differences between the studies. Studies M2-111 and M2-112 evaluated a broad population of patients with severe COPD while M2-124 and M2-125 required patients to have recent histories of chronic bronchitis (cough and sputum production) and COPD exacerbations. Additionally, studies M2-124 and M2-125 allowed concomitant treatment with LABAs (50% of the patients in each study took LABAs) but prohibited the use of inhaled corticosteroids and LAMAs during the treatment period. Conversely, studies M2-111 and M2-112 allowed the use of inhaled corticosteroids however prohibited use of LABAs and LAMAs altogether. The differences in study design and use of concomitant medications used to treat COPD make inter-study comparisons difficult. It should be noted that in no study was the efficacy of roflumilast evaluated compared to what has become standard of care treatment for patients with COPD, concomitant use of a LAMA and an inhaled corticosteroid in combination with a LABA.

Studies M2-127 and M2-128 were 24-week supportive studies that investigated the benefit of roflumilast treatment in patients with moderate to severe COPD who were receiving maintenance therapy with either salmeterol, administered as Serevent® Diskus 50 mcg twice daily (Study M2-127) or tiotropium administered as Spiriva HandiHaler 18 mcg once daily (Study M2-128). The focus of these studies was to evaluate if roflumilast adds additional benefit on lung function (FEV1 as primary endpoint) beyond the effects of long-acting bronchodilators. These studies included patients with moderate as well as severe COPD (FEV1 of 40-70% predicted) and were not required to have a history of chronic bronchitis with sputum production bronchitis and/or COPD exacerbations. Following is a discussion of the various primary endpoints utilized throughout the extensive Phase 3 program for roflumilast with emphasis on the 4 one year clinical studies.

Primary Efficacy Variables

Pre-bronchodilator FEV1

Change in pre-bronchodilator FEV1 was a primary or co-primary endpoint in most of the Phase 3 studies conducted for the roflumilast clinical program. In the one-year pivotal (M2-124 and M2-125) and supportive (M2-111 and M2-112) studies, patients treated with roflumilast had a statistically significant, albeit quite modest, increase in pre-bronchodilator FEV1 compared to placebo (see table below). In these studies, the effect size ranged from 39 to 58 mL. This increase in FEV1 (about 3-5%), although significant statistically, would not constitute a clinically meaningful benefit. Improvements of this magnitude of FEV1 were observed in most other clinical studies in the roflumilast COPD program.

Table 2 Change (in mL) from baseline in pre-bronchodilator FEV1 to end of treatment in the one year studies (ITT populations)

Study	Weeks	Pre-Bronchodilator FEV1 (ml)				
		R500	Placebo	Diff	P-Value	Pooled Diff
M2-124	52	46 (745)	8 (745)	39	<0.001	48
M2-125	52	33 (730)	-25 (766)	58	<0.001	
M2-111	52	30 (545)	-12 (596)	42	<0.001	51
M2-112	52	49 (737)	-8 (741)	57	<0.001	

* pre-bronchodilator FEV1 is one of many secondary endpoints (p-value unadjusted)
Diff: difference between roflumilast and placebo.
P-Value: p-value for difference
Number of individuals randomized is provided in parentheses.

The two 6-month supportive studies, M2-127 and M2-128, in which a LABA (salmeterol) and LAMA (tiotropium) were required concomitant medications, respectively, designated pre-bronchodilator FEV1 as the sole primary endpoint. Similar to the results of the one year studies described above, modest increases (3-5%) in pre-bronchodilator FEV1 were observed compared to placebo in both studies, 49 and 80 mL for studies M2-127 and M2-128, respectively (Table 3). These results are consistent with a mild bronchodilatory effect for roflumilast.

Table 3 Change (in mL) from baseline in pre-bronchodilator FEV1 to end of treatment for studies M2-127 and M2-128 (ITT populations)

Study	Weeks	Pre-Bronchodilator FEV1 (ml)			
		R500	Placebo	Diff	P-Value
M2-127[1]	24	39 (456)	-10 (463)	49	<0.001
M2-128[2]	24	65 (365)	-16 (364)	80	<0.001

1. All patients received salmeterol in addition to roflumilast or placebo
2. All patients received tiotropium in addition to roflumilast or placebo
Diff: difference between roflumilast and placebo.
P-Value: p-value for difference
Number of individuals randomized is provided in parentheses.

Rate of COPD exacerbations

The year-long studies (M2-124, M2-125, M2-111, and M2-112) were specifically designed to assess the effect of roflumilast on the rate of COPD exacerbations. The definition of an exacerbation in Study M2-112 differed slightly from the other 3 studies as it included exacerbations requiring antibiotics treatment (moderate) and exacerbations leading to death were added post-protocol (severe).

The annual rates of moderate or severe COPD exacerbations in Studies M2-124, M2-125, M2-111, and M2-112 are presented in the following table. In these studies, roflumilast numerically reduced the annual rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate (studies M2-124 and M2-125) reaching statistical significance while reduction in exacerbation rates from studies M2-111, and M2-112, were not statistically significant. It is notable that studies M2-111 and M2-112 included a general population of patients with severe COPD while studies M2-124 and M2-125 studied a narrow, more restricted patient population of severe COPD patients who had to have a history of both chronic bronchitis with cough and sputum production and have recent exacerbations of COPD.

To facilitate direct comparison of studies M2-111 and M2-112 with studies M2-124 and M2-125, the definitions of moderate and severe exacerbations for studies M2-111 and M2-112 were modified post-hoc by the sponsor to match those of M2-124 and M2-125. However, without these post hoc changes, the rate ratio comparing roflumilast and placebo was also not significant in either study. The p-value in Study M2-111 would be 0.218 rather than 0.129 and the p-value in Study M2-112 would be 0.451 rather than 0.085.

Table 4 Rates of moderate or severe exacerbations* (ITT Population)

Study	Weeks	Poisson Exacerbation Rate				
		R500	Placebo	Rate Ratio	P-Value	Pooled Rate Ratio
124	52	1.1 (765)	1.3 (758)	0.85	0.028	0.83
125	52	1.2 (772)	1.5 (796)	0.82	0.004	
111**	52	0.6 (567)	0.7 (606)	0.86	0.129	0.85
112**	52	0.5 (760)	0.5 (753)	0.85	0.085	

M2-111, M2-112 from report 22/2009_Table 2.7.3-39
* Poisson analysis
** Based on exacerbation definition and analysis method used in Studies 124 and 125

Quality of life (SGRQ)

The SGRQ is one of the most commonly used measures of the quality of life in patients with pulmonary disease, including COPD. It is comprised of 16 questions that assess disease symptoms, disturbances to patients' daily physical activity, and the impact of the disease on the patient. It is frequently used as a quality of life assessment in clinical trials conducted in

drug development programs. Results of the SGRQ are reported because it was used as a co-primary endpoint in several of the earlier dose-ranging and Phase 3 studies (FK1-101 and M2-107) and as an important secondary endpoint in others. In reviewing the SGRQ data note that a lower number is viewed as an improvement and that the defined difference between measurements that is a minimally clinically meaningful effect is -4.0 units while differences of -8 and -12 denote meaningful and very meaningful clinical effects, respectively.

Change from baseline in total SGRQ score failed to achieve the clinically significant difference of ≥ -4.0 units in any study. Note that SGRQ was not included as an endpoint in the designated pivotal studies (M2-124, M2-125).

Table 5 Change from Baseline in SGRQ total score

Study	Roflumilast	Placebo	Diff	P-Value
FK1101*	-4.7	-4.5	-0.3	0.425
M2-107 **	-3.5	-1.8	-1.7	0.053
M2-111**	-1.8	-0.3	-1.5	0.016
M2-112**	-3.7	-3.2	-0.5	0.268

Source: individual clinical study reports
* co-primary endpoint
** secondary endpoint

Other endpoints

Other secondary endpoints evaluated in the studies designated as pivotal by the Applicant (M2-124 and M2-125) included assessments for dyspnea (BDI/TDI), quality of life measured by the EuroQol, time to mortality, the use of rescue medication, COPD symptom scores, the inflammatory mediator, C-reactive protein, and time to study withdrawal. For both studies M2-124 and M2-125 there were no meaningful differences between roflumilast and placebo for any of these secondary endpoints.

Specifically, in study M2-124, the change from baseline TDI was 0.233 (< the clinically meaningful difference of ≥ 1 unit), the change in use of rescue medication was -0.20 puffs/day driven by increased use in the placebo group, and the time to mortality was similar (214 and 208 days in the roflumilast and placebo groups, respectively). Time to study withdrawal was decreased in the roflumilast treated patients (121 and 141 days in the roflumilast and placebo groups, respectively). This difference was driven by a 60% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.

For study M2-125, the change from baseline TDI was 0.286, the change in use of rescue medication was -0.43 puffs/day and was again driven by increased use in the placebo group, and the time to mortality was again similar (201 and 215 days in the roflumilast and placebo groups, respectively). Time to study withdrawal was again decreased in the roflumilast treated patients (109 and 146 days in the roflumilast and placebo groups, respectively). This difference was driven by a 40% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.

Safety

Safety assessments conducted throughout the Phase 3 program included assessment of adverse events, clinical laboratory studies (including hematology, blood chemistry, and stool for occult blood), vital signs, physical examinations (including body weight), 12-lead electrocardiograms, and 24 Holter monitoring (in a subset of patients).

More patients receiving roflumilast discontinued from clinical studies early. The overall dropout rate for COPD patients receiving roflumilast was approximately 28% compared to about 23% for patients who received placebo. For nearly all phase II and III trials included in the COPD development program, the roflumilast 500 mcg groups had a higher early termination rate than the placebo groups, largely driven by the higher number of adverse events that ultimately led to early withdrawal. Adverse events as a cause of early withdrawal occurred in 807 (14%) of patients who received roflumilast 500 mcg once daily compared to 465 (9%) of patients who received placebo.

Following are brief discussions regarding significant safety signals observed in patients treated with roflumilast; gastrointestinal adverse reactions, weight loss, psychiatric events including suicide, and the potential for cancer.

Gastrointestinal adverse reactions

Gastrointestinal adverse events such as diarrhea and nausea, known class effects of PDE4 inhibitors, were the most common adverse events reported from all roflumilast clinical trials and were the leading cause for early study termination. The percentage of patients in the COPD program safety pool who experienced at least one GI adverse event in the 500 mcg roflumilast treatment groups was 22% compared to 11% for placebo treated patients. Among those 22%, approximately half experienced diarrhea (10%) and a quarter experienced nausea (5%). Both the frequency and severity of GI AEs appeared to be dose dependent. In the COPD safety pool, which contained 4 studies that included a 250 mcg roflumilast treatment arm, the frequency of GI AEs in the 250 mcg groups was about half of what was seen in the 500 mcg group but still greater than placebo.

The more severe GI side effects were intractable diarrhea and pancreatitis. Though small in number, both occurred almost exclusively in roflumilast treatment groups. Among the 13 cases of intractable diarrhea and 7 cases of acute pancreatitis reported in the COPD safety pool, all but one case of each occurred in the roflumilast treated groups. Of the two patients who had acute pancreatitis and died, both were receiving roflumilast 500 mcg at the time of occurrence.

Weight Loss

Weight loss was a common adverse event reported in roflumilast clinical trials. Patient populations for all indications studied with roflumilast (COPD, asthma, diabetes, arthritis, and allergic rhinitis) were affected, which suggests that roflumilast related weight loss is a drug specific effect.

As weight was regularly assessed in the pivotal studies, M2-124 and M2-125, and because they were long (one year) in duration, the results from the pivotal COPD weight pool are most applicable. The results from analysis of other study pools were similar. Overall, in the pooled safety data from studies M2-124 and M2-125, 62% patients in the roflumilast group and 38% patients in the placebo group lost weight. The reported rates of weight loss as an adverse event were 10.3% and 2.8% respectively for the roflumilast and the placebo treated groups. The mean weight change for patients in the roflumilast group was - 2.09 kg, which compares to a small increase in mean body weight (+0.08 kg) for patients in the placebo group.

Severity of weight loss was categorized as mild, moderate and severe, which were defined respectively as weight loss of ≤ 5%, more than > 5% but ≤ 10%, and > 10% of the baseline weight, respectively. For the pooled data from studies M2-124 and M2-125, 35% of the patients in the roflumilast group had mild weight loss, 20% had moderate weight loss and 7% had severe weight loss. In comparison, 28%, 8%, and 2% of the patients in the placebo group had mild, moderate and severe weight loss, respectively. Severe weight loss disproportionally affected more patients with very severe COPD (FEV1 < 30% predicted) compared to other subgroups.

Psychiatric AEs including Suicide

Adverse events related to the psychiatric system organ class were more common in patients who received roflumilast 500 mcg compared to those who received the 250 mcg dose or placebo. There were a total of 403 (6%) psychiatric adverse events reported in patients who received roflumilast 500 mcg once daily compared to 190 (3%) total events in the placebo group. There were 2-3 times greater insomnia, anxiety, and depression related adverse events in the 500 mcg roflumilast group compared to placebo.

Of significant concern are the occurrence of three completed suicides and two suicide attempts in COPD patients compared to no suicides/suicide attempts in patients receiving placebo. Of the three completed suicides, 2 were in patients receiving roflumilast 500 mcg and the third was in a patient receiving 250 mcg. In none of the three completed suicide cases (all males) did the patient have a prior history of depression. In two of the cases the patient had reportedly discontinued roflumilast approximately 20-21 days prior to the suicide event. With regard to the suicide attempts, both females had prior psychiatric histories (depression in one patient and previous suicide attempt in the other). Both patients were receiving roflumilast at the time of the suicide attempt.

In order to assess whether the incidence of psychiatric AEs was consistent across other disease clinical development programs, psychiatric system organ class AEs were reviewed for COPD studies conducted by a different sponsor in Japan and in asthma and “other” disease indications that roflumilast has been studied (diabetes, allergic rhinitis, rheumatoid arthritis, and osteoarthritis). Review of these data show that an approximately 2-fold increase in psychiatric AEs in patients receiving 500 mcg of roflumilast once daily is persistent across studies in different patient populations and appears to be dose-related. The types of AEs

reported in these studies are consistent with those reported in the COPD population (insomnia, anxiety, depression).

Cancer

Roflumilast has been demonstrated to be carcinogenic in animal species. Thus, cancer and tumor-related adverse events were identified as a topic of special interest.

In the overall roflumilast clinical development program, a total of 218 cancer/tumor events were reported in 208 patients. One hundred thirty one (60%) were in patients in the roflumilast group and 86 (40%) were in patients in the placebo group. These data are consistent with what was observed in COPD patients where 105 of 185 (57%) and 80 of 185 (43%) of cancer/tumors were in the roflumilast and placebo treated groups, respectively. There was more lung and prostate cancer reported for patients treated with roflumilast than those who received placebo (33 and 14 compared to 17 and 7, for lung and prostate cancers in the roflumilast and placebo groups, respectively. These differences could not be due to preferential drop-out in the placebo group since more patients receiving roflumilast withdrew from clinical studies prematurely than patients receiving placebo.

Key issues and questions

From the efficacy standpoint, the magnitude of the effects seen on the efficacy variables as well as the generalizability of the efficacy findings for exacerbations and lack of support for any additional independent secondary endpoint are key points for discussion at the PADAC meeting. While the difference in FEV1 between roflumilast and placebo was statistically significant in the clinical studies, the differences between the groups in mean change from baseline were quite modest at approximately 50 mL. Also, the separation between the two groups was driven in part by a decrease of FEV1 in the placebo group. With regard to the COPD exacerbation endpoint, it is notable that 2 of the one year duration studies in patients with severe COPD (M2-111 and M2-112) failed to demonstrate a significant difference in exacerbation rate between roflumilast and placebo while in the other 2 one year studies (M2-124 and M2-125), in which a more restricted patient population was studied (severe COPD with chronic bronchitis and a recent history of exacerbations), a statistically significant reduction of exacerbation rate was achieved. With regard to other non-spirometric or exacerbation-related endpoints, there were no meaningful differences between roflumilast and placebo for quality of life (SGRQ and EuroQol), dyspnea, rescue medication use, COPD symptom scores, mortality, time to mortality, etc.

The overall safety of roflumilast is another key point of discussion at the PADAC meeting. In addition to the PDE4 class effect of frequent and potentially severe gastrointestinal toxicities, the clinical development program of roflumilast has allowed an assessment of relatively rare but profound adverse occurrences such as psychiatric adverse events including suicide. Other safety issues of concern are potential carcinogenicity, pancreatits, and weight loss. Weight loss is specifically relevant to COPD patients because one of the manifestations of the disease is weight loss..

Summary

The purpose of the PADAC meeting is to discuss the efficacy and safety data that have been provided to support the approval of roflumilast for the treatment of COPD in the United States. The main issues for the PADAC to consider are the overall risk-benefit assessment of roflumilast for the treatment of COPD. We are asking for detailed deliberation on the clinical relevance and generalizability of the magnitude of the effect seen on the efficacy variables, particularly for the reduction in exacerbations, and on the adequacy of overall safety data base to assure patient safety.

At the PADAC meeting, the Applicant will present an overview of the efficacy and safety data on roflumilast, followed by the Agency's presentation.

Please keep in mind the following discussion points and questions, some of which are voting questions, that you will be asked to deliberate on following the presentations and discussion.

Draft Questions

1. Discuss the evidence to support the efficacy of roflumilast at a dose of 500 mcg once daily for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.

2. Discuss the overall safety profile of roflumilast.

3. Considering the totality of the data, has roflumilast at a dose of 500 mcg once daily demonstrated substantial evidence of efficacy for the indication of maintenance treatment of COPD? **(Voting Question)**

a) If not, what further efficacy data should be obtained?

4. Is the safety profile for roflumilast for the maintenance treatment of COPD sufficient to support approval? **(Voting Question)**

a) If not, what further safety data should be obtained?

5. Do the efficacy and safety data provide substantial evidence to support the approval of roflumilast at a dose of 500 mcg once daily for the indication of maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations? **(Voting Question)**

We look forward to a very interesting meeting and again thank you for your time and commitment in this important public health service.

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING

April 7, 2010

CLINICAL BRIEFING DOCUMENT

NDA 22-522

Daxas (roflumilast) 500 mcg tablets: for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

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1. Executive Summary

1.1 Brief Overview of Clinical Program

Nycomed submitted a New Drug Application (NDA) on July 15, 2009, for roflumilast 500 mcg tablets for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. COPD is a chronic progressive disease caused by chronic inflammation and destruction of the airways and lung parenchyma that is characterized by progressive airflow obstruction that is sometimes partially reversible with the administration of a bronchodilator. Current therapies for the treatment of various disease aspects of COPD include bronchodilators (short and long-acting beta agonists such as albuterol, salmeterol, formoterol and anti-muscarinic agents such as ipratropium, tiotropium) that are used to treat reversible bronchoconstriction associated with COPD. Advair® 250/50, a salmeterol (50 mcg) and fluticasone propionate (250 mcg) combination product contains both a long-acting beta agonist (LABA) and inhaled corticosteroid and is approved to treat both reversible bronchoconstriction and to reduce exacerbations of COPD in patients with a history of exacerbations. Theophylline, a non-specific member of the phosphodiesterase inhibitor class is available in immediate and sustained released formulations and has been used for many years for the treatment of both COPD and asthma.

Roflumilast is a new molecular entity and a selective phosphodiesterase type 4 (PDE4) inhibitor. It is purported to act as an anti-inflammatory agent in patients with COPD. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and it has a molecular weight is 403.22. The proposed tradename is Daxas® which is to be supplied as a yellow, film-coated 500 mcg tablet. The proposed dosing regimen is 500 mcg once daily.

The FDA was notified on December 4, 2009, of a change in ownership of the NDA from Nycomed to Forest Research Institute. Subsequently the new Applicant submitted new product labeling in submission dated January 29, 2010 which included extensive revisions to the original label submitted with the NDA. At this time a change in the product indication was made from a broad “maintenance treatment of COPD” indication to the more limited indication of “reduction of exacerbations of COPD”. Because the regulatory review of an NDA by the FDA is based on the proposed product indication, it should be final at the time of the NDA submission. A change in the indication is therefore not acceptable late in the review cycle regardless of a change in ownership. Thus, this application will be evaluated based on the originally proposed indication “for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations. Additional changes to the label included revisions to the clinical pharmacology and clinical studies sections and the inclusion of “Neuropsychiatric” adverse events, including suicide, to the Warnings and Precautions section.

The overall COPD clinical development program for roflumilast conducted over approximately a fifteen year period is rather large as evidenced by the COPD safety data base encompassing more than 15,000 COPD patients and includes eighteen Phase 2/3 clinical studies. This review will

focus primarily on 4 one-year studies (Studies M2-111, M2-112, M2-124, and M2-125) which evaluated COPD exacerbations and 4 six-month other supportive studies (FK1-101, M2-107, M2-127, and M2-128) (see table 1 below). Because early clinical studies had demonstrated only modest improvements in lung function, and because a broad COPD indication such as was proposed by the Applicant (maintenance treatment of the disease entity, COPD, as a whole) would require demonstrating a clinically meaningful improvement in more than one aspect of the disease, co-primary endpoints were designated for most Phase 3 studies. The design, endpoints, and patient populations of these Phase 3 studies evolved over time but can be separated into 2 general periods; an initial dose-ranging and Phase 3 development period during which the Applicant focused on quality of life [St. George Respiratory Questionnaire (SGRQ)] as a co-primary endpoint (studies FK1-101 and M2-107) followed later by a Phase 3 program that utilized the rate of COPD exacerbations as a co-primary endpoint (FEV1 served as the other co-primary endpoint in all studies). During this later period, the first 2 studies of one year duration (M2-111 and M2-112) failed to demonstrate a statistically significant reduction in the rate of moderate or severe exacerbations. Post hoc analyses were then used to define a more responsive patient population (those with a history of chronic bronchitis and a history of cough, sputum production, and recent exacerbations) which was carried forth in the year long studies designated as pivotal (M2-124 and M2-125). Supportive studies of 6 month duration (M2-127 and M2-128) were also conducted to assess the effects of concomitant use of standard COPD bronchodilator treatments, the LABA, salmeterol and the long-acting anti-muscarinic drug (LAMA), tiotropium, on lung function (FEV1).

All studies were multicenter, multi-national, randomized, double-blind, placebo controlled parallel group trials which included a 2-4 week run-in period followed by a double blind treatment period of 52 (M2-111, M2-112, M2-124, and M2-125,) or 24-26 weeks (FLK1-101, M2-107, M2-127 and M2-128). Studies M2-107 and FK1-101 included both 250 and 500 mcg roflumilast once daily treatment groups in addition to placebo while the treatment regimens for all other studies was roflumilast 500 mcg once daily compared to placebo.

Table 1 Relevant Roflumilast Clinical Studies for COPD

Trial Number & Years Conducted	Study Types and Design	Study Duration (weeks)	Population COPD Disease Severity (FEV1% predicted)	Treatment Groups	N (ITT)	Study Center Country Origins
Dose ranging and initial phase III studies						
FK1-101 1999-2001	Dose-ranging, efficacy & safety DB, RM, PC, PG	26 weeks	35-75%	Rof250 mcg Rof500 mcg Placebo	175 169 172	Europe, South Africa
M2-107 2002-2003	Dose-ranging, efficacy & safety DB, RM, PC, PG	24 weeks	30-80%	Rof250 mcg Rof500 mcg Placebo	576 555 280	Europe, Australia and Canada
Later phase III studies						

M2-111 2003-2005	Efficacy and safety DB, RM, PC, PG	52 weeks	≤ 50%	Rof500 mcg Placebo	567 606	Europe, South Africa, US and Canada
M2-112 2003-2004	Efficacy and safety DB, RM, PC, PG	52 weeks	≤ 50%	Rof500 mcg Placebo	760 753	Europe, Australia, South Africa and Canada
M2-124 (Pivotal) 2006-2008	Efficacy and safety DB, RM, PC, PG	52 weeks	≤ 50%a	Rof500 mcg Placebo	765 758	Europe, Australia, US and Canada
M2-125 (Pivotal) 2006-2008	Efficacy and safety DB, RM, PC, PG	52 weeks	≤ 50%a	Rof500 mcg Placebo	772 796	Europe, India, South Africa, US and Canada
M2-127 (supportive) 2006-2007	Efficacy and safety DB, RM, PC, PG	24 weeks	40-70%b	Rof500 mcg + salmeterol Placebo + salmeterol	466 467	Europe, South Africa and Canada
M2-128 (supportive) 2007-2008	Efficacy and safety DB, RM, PC, PG	24 weeks	40-70%b	Rof500 mcg + tiotropium Placebo + tiotropium	371 372	Europe

Note: All trial participants were ages 40 and above.
a: requires FEV1 criteria plus history of chronic bronchitis and COPD exacerbation.
b. evaluated effect of roflumilast to concurrent LABA (M2-127) or LAMA (M2-128)

The 4 one year studies all had lung function as assessed by FEV1 and the rate of COPD exacerbations as co-primary endpoints in patients ≥ 40 years of age with severe COPD (FEV1 ≤ 50%) and nonreversible airway obstruction. After a 4-week run-in period in which patients were taken off prohibited concomitant medications, patients were randomized 1:1 to receive either roflumilast 500 mcg or placebo once daily (see table above for number of patients/group). While generally similar in design, there were some notable differences between the studies. Studies M2-111 and M2-112 evaluated a broad population of patients with severe COPD while M2-124 and M2-125 required patients to have recent histories of chronic bronchitis (cough and sputum production) and COPD exacerbations. Additionally, studies M2-124 and M2-125 allowed concomitant treatment with LABAs (50% of the patients in each study took LABAs) but prohibited the use of inhaled corticosteroids and LAMAs during the treatment period. Conversely, studies M2-111 and M2-112 allowed the use of inhaled corticosteroids however prohibited use of LABAs and LAMAs altogether. The difference in study designs and use of concomitant medications used to treat COPD make inter-study comparisons difficult. It should be noted that in no study was the efficacy of roflumilast evaluated compared to what has become standard of care treatment for patients with COPD, concomitant use of a LAMA, and a LABA and inhaled corticosteroid in combination.

Studies M2-127 and M2-128 were 24-week supportive studies that investigated the benefit of roflumilast treatment in patients with moderate to severe COPD who were receiving maintenance therapy with either salmeterol, administered as Serevent® Diskus 50 mcg twice daily (Study M2-127) or tiotropium18 mcg via the HandiHaler device (Study M2-128). The focus of these studies was to evaluate if roflumilast adds additional benefit on lung function (FEV1 as primary

endpoint) beyond the effects of long-acting bronchodilators. These studies included patients with moderate as well as severe COPD (FEV1 of 40-70% predicted) and were not required to have a history of chronic bronchitis with sputum production bronchitis and/or COPD exacerbations.

The dose ranging data for the roflumilast clinical program primarily comes from two studies mentioned above (studies FK1-101 and M2-107) in which two doses of roflumilast (250 and 500 mcg once daily) were compared against placebo. Both trials were double-blind, placebo-controlled, parallel-group, non-US, multinational studies in patients ≥ 40 years of age with non-reversible airway obstruction across the full range of COPD severity (FEV1 30-75-80% predicted). Study FK1-101 was a phase II/III trial with 2 week run-in followed by 26 week treatment while study M2-107 was a phase III trial with 4 week run-in and 24 week treatment. Patients were randomized 1:1:1 (516 for study FK1-101 and 1411 in study M2-107) to receive either roflumilast 250 or 500 mcg or placebo once daily. Concomitant uses of systemic or inhaled steroids and long acting beta agonists were not permitted. Stable daily dose of short-acting anticholinergics were permitted. Uses of other COPD medications were also restricted except rescue salbutamol, which was provided to all eligible subjects. Co-primary endpoints were pre-bronchodilator FEV1 and the SGRQ in trial FK1-101 and post-bronchodilator FEV1 and SGRQ in trial M2-107. Note that although SGRQ as a primary or key secondary endpoint was the hallmark of earlier COPD trials, it was not evaluated in trials designated as pivotal.

Establishment of a once daily dosing regimen was based on the results of a pharmacokinetic study in healthy volunteers which demonstrated that roflumilast and its active metabolite (roflumilast-N-oxide) had respective half lives of 17 and 30 hours. Dosing intervals less than or greater than 24 hours were not evaluated.

A more detailed description of the design, conduct, and results of these studies are presented in Section 5.3 of this briefing document.

Safety assessments conducted included assessment of adverse events, clinical laboratory studies (including hematology, blood chemistry, and stool for occult blood), vital signs, physical examinations (including body weight), 12-lead electrocardiograms, and 24 Holter monitoring (in a subset of patients).

1.2 Efficacy

Dose-ranging

Co-primary endpoints were pre-bronchodilator FEV1 and the SGRQ in trial FK1-101 and post-bronchodilator FEV1 and SGRQ in trial M2-107. For study FK1-101, pre-bronchodilator FEV1 increased by 20 and 24 mL from baseline for the roflumilast 250 and 500 mcg dose groups, respectively while a decrease of 17 mL was noted in the placebo group.

With regard to study M2-107, post-bronchodilator FEV1 increased 29 and 51 mL from baseline for the roflumilast 250 and 500 mcg doses respectively while a decrease of 45 mL was noted in the placebo group.

Regarding the other co-primary endpoint, SGRQ, in both studies there was no significant difference in SGRQ between either the 250 or 500 mcg roflumilast dose group and placebo or between each other.

Primary Efficacy Variables

Pre-bronchodilator FEV1

Change in pre-bronchodilator FEV1 was a primary or co-primary endpoint in most of the Phase 3 studies conducted for the roflumilast clinical program. In the one-year pivotal (M2-124 and M2-125) and supportive (M2-111 and M2-112) studies, patients treated with roflumilast had a statistically significant, albeit quite modest, increase pre-bronchodilator FEV1 compared to placebo (see table below). In these studies, the size of the effect ranged from 39 to 58 mL. This increase in FEV1 (about 3-5%), although significant statistically, would not constitute a clinically meaningful benefit. Improvements of this magnitude of FEV1 were observed in most other clinical studies in the roflumilast COPD program.

Table 2 Change (in mL) from baseline in pre-bronchodilator FEV1 to end of treatment in the one year studies (ITT populations)

Trial Number	Duration (Weeks)	Pre-Bronchodilator FEV1 (ml)				
		Rof500 mcg	Placebo	Difference	P-Value	Pooled Diff
M2-124	52	46 (745)	8 (745)	39	<0.001	48
M2-125	52	33 (730)	-25 (766)	58	<0.001	
M2-111	52	30 (545)	-12 (596)	42	<0.001	51
M2-112	52	49 (737)	-8 (741)	57	<0.001	

* pre-bronchodilator FEV1 is one of many secondary endpoints (p-value unadjusted)
Diff: difference between roflumilast and placebo.
P-Value: p-value for difference
Number of individuals randomized is provided in parentheses.

The two 6-month supportive studies, M2-127 and M2-128, in which a LABA (salmeterol) and LAMA (tiotropium) were required concomitant medications, respectively, designated pre-bronchodilator FEV1 as the sole primary endpoint. Similar to the results of the one year studies described above, modest increases (3-5%) in pre-bronchodilator FEV1 were observed compared to placebo in both studies, 49 and 80 mL for studies M2-127 and M2-128, respectively (Table 3). These results are consistent with a mild bronchodilatory effect for roflumilast.

Table 3 Change (in mL) from baseline in pre-bronchodilator FEV1 to end of treatment for studies M2-127 and M2-128 (ITT populations)

Trial Number	Duration (Weeks)	Pre-Bronchodilator FEV1 (ml)			
		Rof500 mcg	Placebo	Difference	P-Value
M2-127[1]	24	39 (456)	-10 (463)	49	<0.001
M2-128[2]	24	65 (365)	-16 (364)	80	<0.001

1. All patients received salmeterol in addition to roflumilast or placebo
2. All patients received tiotropium in addition to roflumilast or placebo
Diff: difference between roflumilast and placebo.
P-Value: p-value for difference
Number of individuals randomized is provided in parentheses.

Rate of COPD exacerbations

The year-long studies M2-124, M2-125, M2-111, and M2-112 were specifically designed to assess the effect of roflumilast on the rate of COPD exacerbations. The definition of an exacerbation in Study M2-112 differed slightly from the other 3 studies as it included exacerbations requiring antibiotics treatment (moderate) and exacerbations leading to death were added post-protocol (severe).

The annual rates of moderate or severe COPD exacerbations in Studies M2-124, M2-125, M2-111, and M2-112 are presented in the following table. In these studies, roflumilast numerically reduced the annual rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate (studies M2-124 and M2-125) reaching statistical significance while reduction in exacerbation rates from studies M2-111, and M2-112, were not statistically significant. It is notable that studies M2-111 and M2-112 included a general population of patients with severe COPD while studies M2-124 and M2-125 studied a narrow, more restricted patient population of severe COPD patients who had to have a history of both chronic bronchitis with cough and sputum production and have recent exacerbations of COPD.

To facilitate direct comparison of studies M2-111 and M2-112 with studies M2-124 and M2-125, the definitions of moderate and severe exacerbations for studies M2-111 and M2-112 were modified post-hoc by the sponsor to match those of M2-124 and M2-125. However, without these post hoc changes, the rate ratio comparing roflumilast and placebo was also not significant in either study. The p-value in Study M2-111 would be 0.218 rather than 0.129 and the p-value in Study M2-112 would be 0.4514 rather than 0.085.

Table 4 Rates of moderate or severe exacerbations* (ITT Population)

Trial Number	Duration (Weeks)	Poisson Exacerbation Rate				
		Rof500 mcg	Placebo	Rate Ratio	P-Value	Pooled Rate Ratio
M2-124	52	1.1 (765)	1.3 (758)	0.85	0.028	0.83
M2-125	52	1.2 (772)	1.5 (796)	0.82	0.004	
M2-111**	52	0.6 (567)	0.7 (606)	0.86	0.129	0.85
M2-112**	52	0.5 (760)	0.5 (753)	0.85	0.085	

M2-111, M2-112 from report 22/2009_Table 2.7.3-39
* Poisson analysis
** Based on exacerbation definition and analysis method used in Studies 124 and 125.

Quality of life (SGRQ)

The SGRQ is one of the most commonly used measures of the quality of life in patients with pulmonary disease, including COPD. It is comprised of 16 questions that assess disease symptoms, disturbances to patients' daily physical activity, and the impact of the disease on the patient. It is frequently used as a quality of life assessment in clinical trials conducted in drug development programs. Results of the SGRQ are reported because it was used as a co-primary endpoint in several of the earlier dose-ranging and Phase 3 studies (FK1-101 and M2-107) and as an important secondary endpoint in others. In reviewing the SGRQ data note that a lower number is viewed as an improvement and that the defined difference between measurements that is felt to denote a clinically meaningful effect is -4.0 units.

Change from baseline in total SGRQ score failed to achieve the clinically significant difference of ≥ -4.0 units in any study. Note that SGRQ was not included as an endpoint in the designated pivotal studies (M2-124, M2-125).

Table 5 Change from Baseline in SGRQ total score

Trial Number	Duration (weeks)	Rof500 mcg	Placebo	Difference	P-Value
FK1101*	26	-4.7	-4.5	-0.3	0.425
M2-107 **	24	-3.5	-1.8	-1.7	0.053
M2-111**	52	-1.8	-0.3	-1.5	0.016
M2-112**	52	-3.7	-3.2	-0.5	0.268

Source: individual clinical study reports
* co-primary endpoint
** secondary endpoint

Other endpoints

Other secondary endpoints evaluated in the studies designated as pivotal by the Applicant (M2-124 and M2-125) included assessments for dyspnea (BDI/TDI), quality of life measured by the

EuroQol, time to mortality, the use of rescue medication, COPD symptom scores, the inflammatory mediator, C-reactive protein, and time to study withdrawal. For both studies M2-124 and M2-125 there were no meaningful differences between roflumilast and placebo for any of these secondary endpoints.

Specifically, in study M2-124, the change from baseline TDI was 0.233 (< the clinically meaningful difference of ≥ 1 unit), the change in use of rescue medication was -0.20 puffs/day driven by increased use in the placebo group, and the time to mortality was similar (214 and 208 days in the roflumilast and placebo groups, respectively). Time to study withdrawal was decreased in the roflumilast treated patients (121 and 141 days in the roflumilast and placebo groups, respectively). This difference was driven by a 60% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.

For study M2-125, the change from baseline TDI was 0.286, the change in use of rescue medication was -0.43 puffs/day and was again driven by increased use in the placebo group, and the time to mortality was again similar (201 and 215 days in the roflumilast and placebo groups, respectively). Time to study withdrawal was again decreased in the roflumilast treated patients (109 and 146 days in the roflumilast and placebo groups, respectively). This difference was driven by a 40% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.

1.3 Safety

Early withdrawal

The overall dropout rate for COPD patients receiving roflumilast was approximately 28% compared to about 23% for patients who received placebo. For nearly all phase II and III trials included in the COPD development program, the roflumilast 500 mcg groups had higher early termination rate than the placebo groups, largely driven by the higher number of adverse events that ultimately led to early withdrawal. Adverse events as a cause of early withdrawal occurred in 807 (14%) of patients who received roflumilast 500 mcg once daily compared to 465 (9%) of patients who received placebo.

Following are brief discussions regarding significant safety signals observed in patients treated with roflumilast; gastrointestinal adverse reactions, weight loss, psychiatric events including suicide, and the potential for cancer. For more complete discussions on these safety signals see the clinical briefing document, section 7.3.4, Significant Adverse Events.

Gastrointestinal adverse reactions

Gastrointestinal adverse events such as diarrhea, nausea, a class effect of PDE4 inhibitors, were the most common adverse events reported from all roflumilast clinical trials and the leading cause for early study termination. The percentage of patients in the COPD program safety pool who experienced at least one GI adverse event in the 500 mcg roflumilast treatment groups was 22% compared to 11% for placebo treated patients. Among those 22%, approximately half experienced diarrhea (10.1%) and a quarter experienced nausea (5%). Both the frequency and

severity of GI AEs appeared to be dose dependent. In the COPD safety pool, which contained 4 independent trials that had a 250 mcg roflumilast treatment arm, the frequency of GI AEs in the 250 mcg groups was about half of what was seen in the 500 mcg group but still greater than placebo.

The more severe GI side effects were intractable diarrhea and pancreatitis. Though small in number, both occurred almost exclusively in roflumilast treatment groups. Among the 13 cases of intractable diarrhea and 7 cases of acute pancreatitis reported in the COPD safety pool, all but one case of each occurred in the roflumilast treated groups. Of the two patients who had acute pancreatitis and died, both were receiving roflumilast 500 mcg at the time of occurrence.

Weight Loss

Weight loss was a common adverse event reported in roflumilast clinical trials. Patient populations for all indications studied with roflumilast (COPD, asthma, diabetes, arthritis, and allergic rhinitis) were affected, which suggests that roflumilast related weight loss is a drug specific effect.

As weight was regularly assessed in the pivotal studies, M2-124 and M2-125, and because they were long (one year) in duration, the results from the pivotal COPD weight pool are most applicable. The results from analysis of other study pools were similar. Overall, in the pooled safety data from studies M2-124 and M2-125, 62% patients in the roflumilast group and 38% patients in the placebo group lost weight. The reported rates of weight loss as an adverse event were 10.3 and 2.8% respectively for the roflumilast and the placebo treated groups. The mean weight change for patients in the roflumilast group was - 2.09 kg, which compares to a small increase in mean body weight (+0.08 kg) for patients in the placebo group.

Severity of weight loss was categorized as mild, moderate and severe, which were defined respectively as weight loss of 5% or less, more than 5% but equal or less than10%, and more than 10% of the baseline weight, respectively. In the pivotal studies pool, 35% of the patients in the roflumilast group had mild weight loss, 20% had moderate weight loss and 7% had severe weight loss. In comparison, 28, 8, and 2% of the patients in the placebo group had mild, moderate and severe weight loss, respectively. Severe weight loss disproportionally affected more patients with very severe COPD (FEV1 < 30% predicted) than other subgroups.

Psychiatric AEs including Suicide

Adverse events related to the psychiatric system organ class were more common in patients who received roflumilast 500 mcg compared to those who received the 250 mcg dose or placebo. There were a total of 403 (6%) psychiatric adverse events reported in patients who received roflumilast 500 mcg once daily compared to 190 (3%) total events in the placebo group. There were 2-3 times greater insomnia, anxiety, and depression related adverse events in the 500 mcg roflumilast group compared to placebo.

Of significant concern are the occurrence of three completed suicides and two suicide attempts in COPD patients compared to no suicides/suicide attempts in patients receiving placebo Of the

three completed suicides, 2 were in patients receiving roflumilast 500 mcg and the third was in patient receiving 250 mcg. In none of the three completed suicide cases (all males) did the patient have a prior history of depression. In two of the cases the patient had reportedly discontinued roflumilast approximately 20-21 days prior to the suicide event. With regard to the suicide attempts, both females had prior psychiatric histories (depression in one patient and previous suicide attempt in the other). Both patients were receiving roflumilast at the time of the suicide attempt.

In order to assess whether the incidence of psychiatric AEs was consistent across other disease clinical development programs, psychiatric system organ class AEs were reviewed for COPD studies conducted by a different sponsor in Japan and in asthma and "other" disease indications that roflumilast has been studied (diabetes, allergic rhinitis, rheumatoid arthritis, and osteoarthritis). Review of these data show that an approximately 2-fold increase in psychiatric AEs in patients receiving 500 mcg of roflumilast once daily is persistent across studies in different patient populations and appears to be dose-related. The types of AEs reported in these studies is consistent with those reported in the COPD population (insomnia, anxiety, depression).

Cancer

Roflumilast has been demonstrated to be carcinogenic in animal species (see the Summary of Nonclinical Pharmacology and Toxicology in the briefing package). Although no human carcinogenicity studies have been performed for roflumilast tumor adverse events were identified as a topic of special interest.

In the overall roflumilast clinical development program, a total of 218 cancer/tumor events were reported in 208 patients. One hundred thirty one (60%) were in patients in the roflumilast group and 86 (40%) were in patients in the placebo group. These data are consistent with what was observed in COPD patients where 105 of 185 (57%) and 80 of 185 (43%) were in the roflumilast and placebo treated groups, respectively. There was more lung and prostate cancer reported for patients treated with roflumilast than those who received placebo (33 and 14 compared to 17 and 7, for lung and prostate cancers in the roflumilast and placebo groups, respectively.

2 Introduction and Regulatory Background

2.1 Background: Considerations on COPD Drug Development Endpoints

COPD is a chronic progressive disease caused by chronic inflammation and destruction of the airways and lung parenchyma that is characterized by progressive airflow obstruction that is not fully reversible with the administration of a bronchodilator. COPD is the cause of major morbidity and mortality and is a leading cause of death in the world. The term COPD encompasses a spectrum of pulmonary processes, ranging from symptoms primarily associated with chronic bronchitis (cough and excess sputum production) to purely emphysema-related pulmonary disease, although the specific terms chronic bronchitis and emphysema are not used

in some treatment guidelines (e.g. Global Initiative for Chronic Obstructive Lung Disease).1 Because of the heterogeneity of COPD, the nature of symptomatic impairment experienced by patients (cough, excess sputum production, dyspnea, etc.) will differ. In general, it is desirable to include patients broadly representative of the spectrum of the COPD population in clinical trials intended to support product registration.

Although most medications to treat COPD are bronchodilators, in recent years several products are now indicated for the reduction in COPD exacerbations. Tiotropium bromide (marketed as Spiriva HandiHaler), is a once-daily anticholinergic that is a bronchodilator, but clinical trials have shown that tiotropium reduces COPD exacerbations. Additionally, although inflammation plays a critical role in the pathogenesis of COPD, there are no single-ingredient corticosteroid products approved for the treatment of this disease. However, a combination product containing both a long-acting beta agonist (salmeterol) and an inhaled corticosteroid (fluticasone propionate), marketed as Advair Diskus 250/50, is approved for the maintenance treatment of airflow obstruction and for reduction in exacerbations of COPD in patients with a history of exacerbations. A second combination product containing both a long-acting beta agonist (formoterol) and an inhaled corticosteroid (budesonide), marketed as Symbicort Inhalation Aerosol 160/4.5, is approved for the maintenance treatment of airflow obstruction in patients with COPD.

Also of interest is theophylline, a non-specific member of the phosphodiesterase inhibitor class, which is available in immediate and sustained released formulations and is approved for the treatment of the symptoms and reversible airflow obstruction associated with chronic lung diseases, e.g. emphysema and chronic bronchitis.[2] According to the product label, in patients with COPD, theophylline may decrease dyspnea and air trapping and improve diaphragmatic contractility but is not viewed as a potent bronchodilator as it provides little improvement in pulmonary function measurements.[2] However, results of a 2002 Cochrane meta-analysis showed that theophylline had a statistically significant effect on FEV1 in COPD patients.[3] The meta-analysis addressed the efficacy of theophylline for the treatment of COPD and included 20 randomized, double-blind, placebo controlled trials in patients with COPD. Baseline FEV1 in these studies ranged from 0.96 L to 1.15 L. Thirteen studies with a total of 244 patients contributed data to an FEV1 outcome that showed a statistically significant mean improvement of 100 mL (95% confidence interval from 40 L to 160 mL) or about 10%.

Study endpoints for medications developed for COPD will differ based on whether the purported benefit of the drug is expected to improve airflow obstruction, provide symptom relief, prevent/reduce exacerbations, or provide some other clinically relevant benefit such as decrease the rate of decline in lung function, or increased survival. Improvement in airflow obstruction has been a main therapeutic strategy in COPD drug development. Bronchodilator drugs such as short and long-acting beta agonists and anticholinergic drugs provide benefit through relief of reversible airflow obstruction that is an important feature in some patients with COPD.

1 Global Initiative for Chronic Obstructive Lung Disease – Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2009). Available at http://www.goldcopd.com/
2 Theolair prescription labeling accessed at http://dailymed.nlm.nih.gov/dailymed/about.cfm
3 Ram FS, Jones PW, Castro AA, et. al. Oral theophylline for chronic obstructive pulmonary disease. Cochrane Database System Reviews 2002. Issue 4. Article No: CD003902

Spirometry, specifically forced expiratory volume in one second (FEV1), is a commonly used objective physiological efficacy endpoint for bronchodilator drugs because it is a reflection of the extent of airway obstruction. To provide a sense of the bronchodilator effect of approved medications, tiotropium demonstrated 87 to 103 mL improvement in end of dosing interval FEV_1 over placebo throughout a 4 year trial[4]. Similarly, salmeterol, a long-acting beta agonist, demonstrated an approximately 170 mL improvement in 2 hour post-dose FEV_1 relative to placebo at the end of a 24 week dosing period in COPD patients[5]. The resultant indication for bronchodilator drugs for COPD which demonstrate clinically relevant improvements in FEV1 would be reflective of their beneficial effect in relieving airflow obstruction, for example, "for the maintenance treatment of bronchoconstriction in patients with COPD".

The reduction or prevention of COPD exacerbations is a clinically relevant endpoint for patients with COPD that would provide a meaningful benefit to patients. Clinical studies have often used an action driven definition of a COPD exacerbation in which the determination of an exacerbation rests on a decision by a clinician to intervene in the care of the patient, typically by prescribing additional therapy such as antibiotics or corticosteroids and/or hospitalizing the patient. This intervention driven type of definition is problematic in that the decision to intervene may be a subjective decision by a health care provider that can vary depending on geography, the availability of healthcare, and local practices. Thus, in order to help standardize the definition of a COPD exacerbation, it is important to link a decision to intervene in the care of the patient with specific symptom criteria which must be met in order to declare an intervention a COPD exacerbation. This type of operational definition was used in the Advair Diskus (salmeterol xinafoate/fluticasone propionate combination product) clinical program that resulted in an indication for Advair Diskus 250/50 "to reduce exacerbations of COPD in patients with a history of exacerbations". In that program exacerbations were defined as a worsening of two or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any one major symptom together with any one minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. The exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotics was required and considered severe if hospitalization was required. Using this definition, Advair Diskus demonstrated 30 and 31 % reductions in moderate/severe exacerbations compared to COPD patients treated with the LABA, salmeterol, in two studies of one year duration each (Advair prescribing information).

Additional relevant endpoints for clinical studies in COPD include multidimensional health-related quality-of-life instruments such as the St. George's Respiratory Questionnaire (SGRQ) which is designed to assess different aspects of the effect of COPD on a patient's life or the provision of symptom relief such as reduction in cough, sputum production, or dyspnea. To date the usefulness of these types of endpoints would be to be used as co-primary or key secondary endpoints in clinical COPD studies in order to further support efficacy.

The dose or doses of drugs for definitive phase 3 efficacy and safety studies should be selected based on pharmacokinetic considerations and from earlier phase dose-ranging studies using a

4 Spiriva HandiHaler (tiotropium bromide inhalation powder) prescription labeling
5 Serevent Diskus (salmeterol xinafoate inhalation powder) prescription labeling

pharmacodynamic (PD) or clinical efficacy endpoint that is consistent with the expected benefit to be derived from the drug. The dose or doses selected for phase 3 studies should be based on benefit to risk assessment. In circumstances where PD measures are used in phase 2 for dose identification, there is merit in considering including more than one dose level in at least one phase 3 study, even if the goal is to market a single dose. This is because even a well-validated PD endpoint may not fully predict efficacy as assessed by a clinical outcome endpoint in larger, longer term phase 3 studies, and usually will not be predictive of safety.

Theophylline is a PDE inhibitor that has been used for many years for the treatment of COPD and is the only PDE inhibitor approved for use in the United States. While regarded as a non-specific PDE inhibitor its mechanism of action appears to be mediated by the inhibition of PDE types 3 and 4 (Theolair product label, Clinical Pharmacology Section). In patients with COPD theophylline may decrease dyspnea and air trapping and improve diaphragmatic contractility but is not viewed as a potent bronchodilator as it provides little improvement in pulmonary function measurements (Theolair product label, Clinical Studies Section). In a 2002 Cochrane meta-analysis that addressed the efficacy of theophylline for the treatment of COPD, 20 randomized studies met the selection criteria for including patients with COPD and included a randomized, double-blind comparison of theophylline to placebo. Baseline FEV1 in these studies ranged from 0.96 L to 1.15 L. Thirteen studies with a total of 244 patients contributed data to an FEV1 outcome that showed a statistically significant mean improvement of 100 mL (95% confidence interval from 40 L to 160 mL) or about 10%.

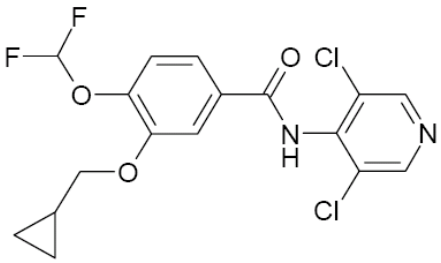
Cilomilast, like roflumilast, is a selective type 4 PDE inhibitor which has been studied extensively in patients with COPD. In Phase 3 clinical trials, co-primary endpoints were change in FEV1 and SGRQ from baseline. As mentioned above, because PDE inhibitors are relatively weak bronchodilators that may demonstrate small but statistically significant differences in FEV1 in large clinical trials that may have questionable clinical relevance, the SGRQ endpoint was utilized to corroborate and add additional efficacy support to the improvement in the pulmonary function endpoint, FEV1. In four, 24 week Phase 3 clinical trials, the differences in FEV1 change between the cilomilast and the placebo groups was 30-40 mL and was statistically significant in 2 of the 4 studies. As for the co-primary endpoint, SGRQ, the difference in SGRQ change between the cilomilast and placebo groups ranged between -4.1 and +0.7 (a decrease is better) in the 4 studies. Again, the difference between the cilomilast and placebo group reached statistical significance in 2 of the 4 studies but crossed the threshold (-4 is accepted as the minimum important difference) of clinical significance in only one study. The cilomilast data were presented to the Pulmonary-Allergy Advisory Committee on September 5, 2003. At that time the committee members discussed the efficacy and safety of cilomilast in the maintenance of lung function (FEV1) in patients with COPD. At the committee meeting, the members were not convinced of the efficacy of cilomilast. When asked “Has cilomilast at a dose of 15 mg twice daily shown a magnitude and consistency of efficacy that is sufficient to support approval of cilomilast for the maintenance of lung function (FEV1) in patients with COPD?” the committee members voted 3 for Yes and 7 for No. When asked “Do the efficacy and safety data provide substantial and convincing evidence that support the approval of cilomilast at a dose of 15 mg twice daily for the maintenance of lung function (FEV1) in patients with COPD?” again the committee voted 3 for Yes and 7 for No.

In addition to clinical study design endpoints discussed above that are relevant to the demonstration of efficacy for PDE inhibitors, is that PDE inhibitors, as a drug class, have demonstrated a significant adverse event profile which has resulted in marginal tolerability at doses felt to be effective and which must be taken into consideration when making a risk-benefit determination. Adverse events are most commonly associated with the gastrointestinal system and include nausea, vomiting, diarrhea, and weight loss.

2.2 Product Information

The established name for the proposed product is roflumilast and the proposed tradename is Daxas®. The established name will be used in this review to refer to the product. Roflumilast is supplied as a yellow, film-coated 500 mcg tablet. The active ingredient, roflumilast, is a new molecular entity and a selective phosphodiesterase type 4 (PDE4) inhibitor which is proposed to act as an anti-inflammatory agent in patients with COPD. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and it has a molecular weight is 403.22 (see chemical structure below).

Roflumilast Chemical Structure



Roflumilast N-oxide is an active metabolite of roflumilast which also has PDE4 inhibitory activity.

The proposed indication for roflumilast is for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. It is notable that this is a general indication for the treatment of the disease as a whole rather than that the more specific indications of other drugs used to treat COPD (e.g., treatment of bronchoconstriction).

2.3 Currently Available Treatments for Proposed Indications

Current therapies available for the treatment of various disease aspects of COPD include short and long-acting beta agonists (albuterol, salmeterol, and formoterol) and anti-muscarinic agents (ipratropium, tiotropium). These drugs are bronchodilators used to treat reversible bronchoconstriction which can be associated with COPD. Advair® 250/50, a salmeterol (50 mcg) and fluticasone propionate (250 mcg) combination product is used to treat both reversible bronchoconstriction and to reduce exacerbations of COPD in patients with a history of exacerbations. Theophylline, a non-specific PDE inhibitor available in immediate and sustained released formulations, has been used for many years for the treatment of both COPD and asthma.

2.4 Availability of Proposed Active Ingredient in the United States

Roflumilast is currently not marketed in the United States.

2.5 Important Safety Issues With Consideration to Related Drugs

Theophylline, a nonspecific member of the phosphodiesterase inhibitor class of drugs has an adverse event profile that includes significant toxicities especially in the gastrointestinal and neurologic systems (nausea, vomiting, headache, insomnia). At high levels it can produce cardiac arrhythmias and seizure activity. Its metabolism is affected by many drugs (H-2 blockers, macrolide and other antibiotics, benzodiazepines, etc.). Its use generally requires monitoring of blood levels.

Specific PDE4 inhibitors such as roflumilast and cilomilast have also demonstrated prominent dose-dependent toxicities related to the gastrointestinal system in clinical studies (nausea, vomiting, diarrhea, anorexia, weight loss).

2.6 Summary of Regulatory Activity Related to Submission

IND# 57883 for roflumilast for both asthma and COPD indications was opened with the Division of Pulmonary and Allergy Products on February 12, 1999. During the ensuing 10-year development period to date, the Division has had extensive communication with each of the then relevant Sponsors/Applicants (BYK-Gulden, Altana and Altana with Pharmacia & Upjohn as US agent, Nycomed, and Forest Research Institute) via face-to face meetings, teleconferences, or written communications. Following is a summary of significant interactions with the Sponsor that are pertinent to this program.

Discussion based on early Phase 3 studies

- December 6, 2001: End of Phase 2 Meeting (Byk-Gulden/Altana).
    - Discussion of design of originally proposed 6 month Phase 3 studies with FEV1 only as the primary endpoint studies (M2-107, M2-110).
        - In response to the proposal of FEV1 as a primary endpoint, the Division indicated that although the change in FEV1 was a reasonable endpoint, because the change seen with roflumilast was very small, supportive evidence would be needed with the secondary endpoints.

- June 23, 2003: Follow-up teleconference with Altana/Pharmacia & Upjohn to discuss adequacy of study design for study PDEACO-9287-001 submitted for a Special Protocol Assessment (SPA) on February 21, 2003.
    - The Division referred to the meeting minutes of a March 4, 2003, meeting in which the clinical development programs for asthma and COPD were discussed and reiterated that while FEV1 is an acceptable measure of lung function, a statistically significant improvement in FEV1 alone would not be sufficient for approval for an indication in COPD, given that roflumilast is not a bronchodilator.

In determining approvability, the Agency would take into account not only the improvement in lung function but in addition, the associated clinical benefit (e.g., effect on exacerbations, improvement in patient-reported outcome, etc.).

- Regarding the agreement for a SPA, the Division stated that it is difficult to get into a binding agreement under a SPA when the decision for approval will depend on the totality of the data submitted and that we may also seek the advice of an advisory committee.

Discussion based on Phase 3 studies with exacerbation rate as primary endpoint

- October 21, 2003 (Altana): Study M2-111 submitted to IND# 57,883 with exacerbation rate the primary efficacy endpoint and quality of life and spirometric measurements as secondary endpoints.

- October 26, 2005 (Altana): Comments regarding study M2-111 amendments.
  - FEV1 added as a co-primary endpoint (exacerbations is the other). FEV1 should be pre-bronchodilator not post-bronchodilator as proposed. Post-bronchodilator FEV1 even if done at the trough of the study medication, is not a meaningful measure of the FEV1 improvement with the study drug because this is not the way in which the drug is proposed to be used in the clinical setting (Sponsor had already been told (February 2005) that post-bronchodilator FEV1 would not allow demonstration of end-of-dosing-interval efficacy which would need to be established for a once daily dosing regimen.
  - Sponsor told that their proposal to define moderate or severe exacerbations based on corticosteroid use alone is not viewed as acceptable because severe COPD exacerbations are defined as exacerbations requiring hospitalizations (as had been defined in the initial protocol submission). The criterion of hospitalizations for severe COPD exacerbations should be maintained. Treatment with corticosteroids is an acceptable criterion to define moderate COPD exacerbations.

- March 13, 2006 (Altana): Communication regarding the statistical analyses of the proposed pivotal studies, M2-111 and M2-112.
  - The Division does not generally accept pooled results as substantial evidence of efficacy.
  - The Division noted that the definition of a moderate exacerbation is not consistent throughout the statistical analysis plan. In certain instances, it appears to have been managed by initiating oral glucocorticosteroids and/or antibiotics. In other sections a moderate COPD exacerbation is required to have been managed by oral or parenteral glucocortiosteroids).
  - The Division noted that exacerbations could be both determined by the decisions of investigators or by physicians from non-research facilities.

Discussions based on final proposed Phase 3 pivotal studies (M2-124 and M2-125)

- February 22, 2006 (Altana): Identical studies M2-124 and M2-125 with co-primary endpoints of pre-bronchodilator FEV1 and rate of exacerbations were submitted to IND# 57883.
- November 30, 2006 (Altana): Meeting request to discuss studies M2-124 and M2-125 submitted. Request denied and responses to submitted questions dated February 7, 2007 communicated.
    - Based on evaluation of the data from studies M2-111 and M2-112 the patient population for studies M2-124 and M2-125 was modified to include only patients with a defined history of exacerbations, require signs of chronic bronchitis at inclusion, and meet a defined cough/sputum symptom score at randomization. In addition, concomitant inhaled corticosteroids (ICS), which were allowed in studies M2-111 and M2-112, were prohibited. Patients were only allowed concomitant medication consisting of long-acting beta agonists plus rescue medication or short acting anticholinergics plus rescue medication. Despite these restrictions based on the roflumilast clinical development program, the Division was asked if it agreed that a general claim for maintenance treatment of COPD could be obtained. The Division responded that the indication that could be claimed would be a review decision.
    - Regarding whether efficacy and safety outcomes from US and non-US patients would allow adequate assessment for approvability, the Division reiterated that this would be a review issue. It added that (the endpoint of) COPD exacerbations is a clinical diagnosis and the decision to initiate treatment (with corticosteroids) or hospitalization is investigator-driven leaving room for variations in the definition of what constitutes an exacerbation and the severity of the exacerbations. "As much as it is feasible you are encouraged to standardize your definitions for a COPD exacerbation as well as the criteria that would prompt the Investigator to initiate corticosteroid therapy or hospitalize the patient."

- April 16, 2008: Pre-NDA Meeting (Nycomed).
    - Studies M2-124 and M2-125 conducted to investigate reduction in exacerbation frequency and lung function in severe COPD patients with chronic bronchitis were identified as the pivotal studies.
    - The Division noted that there were few results reported from the clinical development program in the pre-NDA meeting package and that without results from the Phase 3 program, we are unable to provide general comments on the adequacy of your program to support the proposed indication(s) or labeling claims.
    - Supportive data efficacy variables were outlined by the Applicant. The Division responded by stating that it would look at the totality of the data, and not just a statistically significant difference in the primary endpoint.
    - The Division acknowledged the Nycomed's definition of exacerbations based solely on the requirement of oral or parental glucocorticoids and/or hospitalization and stated that the acceptability of the definition of exacerbation would be a review issue. The Division explained that there is no consensus definition of a "COPD exacerbation". It acknowledged that the start of the roflumilast program

almost 10 years previously pre-dates much of the more recent discussion regarding how to define COPD exacerbations. The Division suggested that it would be in Nycomed's best interest to address these issues prospectively, as they would be likely to come up during an advisory committee discussion regarding their application.

- The NDA submission should discuss and provide justification for the minimal clinically important difference in trough FEV1 between active treatment with roflumilast and placebo.

- NDA 22-522 submitted on July 15, 2009 by Nycomed.

- December 4, 2010: The Division was notified of the transfer of ownership of IND# 57883 and NDA 22-522 from Nycomed to Forest Research Institute.

- February 1, 2010: The Division received newly proposed labeling for roflumilast from Forest Research Institute in which the product indication was changed, Neuropsychiatric Adverse Events were added to the Warnings and Precautions section of the label, and other significant changes made to other sections.

3 Ethics and Good Clinical Practices

The Applicant states that no debarred investigators participated in the study, and all studies were conducted in accordance with the Declaration of Helsinki and local, ethical and Good Clinical Practice (GCP) requirements that were in force at the time of study conduct.

The Division requested audits by the Division of Scientific Investigations (DSI) for this NDA since roflumilast is a new molecular entity and most of the sites were located outside the United States where differing standards of relating to study conduct may exist.

Reviewer's comment: At the time of this review, results of the DSI audit are pending.

4 Issues Related to Other Review Disciplines

4.1 Preclinical Pharmacology/Toxicology

The Applicant submitted a complete pharmacology/toxicology package for this NDA. See the accompanying Summary of Nonclinical Pharmacology and Toxicology for a discussion of findings relevant to the clinical program.

4.2 Clinical Pharmacology

The Applicant submitted a complete clinical pharmacology package for this NDA. See the accompanying Summary of Clinical Pharmacology and Biopharmaceutics for a discussion of the clinical pharmacology program.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The primary sources of data for this review are the clinical trials contained within the original NDA submission (NDA 22522), dated July 15, 2009. Additional safety data submitted on Nov 17, 2009 (sequence 0004) were also reviewed.

The overall roflumilast clinical development program is large. This submission contains results from 18 Phase 2 and 3 COPD trials and information from 29 asthma trials and more than 60 clinical pharmacology studies. Among the 18 Phase 2 and 3 COPD clinical trials submitted with the application, this review focus on 8 trials which span the course of the roflumilast clinical development program. Table 5 displays the characteristics of the 8 trails reviewed. Two of the trials (M2-124 and M2-125) have been designated as pivotal trials and the other 6 trials are considered supportive.

Table 6 Representative Late Phase Clinical Studies Spanning the Roflumilast for COPD Program

Study/ Years conducted	Study Type	Study Duration	Pt age, (yr)	Disease severity*	Treatment groups	N (ITT)	Countries
Dose-ranging and Initial Phase 3 Studies							
FK1-101/ 1999-2001	Dose-ranging, efficacy and safety	26 weeks	≥ 40	35-75%	Rof 250 mcg Rof 500 mcg Placebo	175 169 172	Europe, South Africa
M2-107/ 2002-03	Efficacy and safety	24 weeks	≥ 40	30-80%	Rof 250 mcg Rof 500 mcg Placebo	576 555 280	Europe, Australia, North America (Canada)
Later Phase 3 and Supportive Studies							
M2-111/ 2003-05	Efficacy and safety	52 weeks	≥ 40	≤ 50%	Rof 500 mcg Placebo	567 606	Europe, South Africa, North America
M2-112/ 2003-04	Efficacy and safety	52 weeks	≥ 40	≤ 50%	Rof 500 mcg Placebo	760 753	Europe, Australia, South Africa, North America (Canada)
M2-124/ 2006-08 Pivotal	Efficacy and safety	52 weeks	≥ 40	≤ 50%a	Rof 500 mcg Placebo	765 758	Europe, Australia, North America
M2-125/ 2006/08 Pivotal	Efficacy and safety	52 weeks	≥ 40	≤ 50%a	Rof 500 mcg Placebo	772 796	Europe, India, South Africa, North America
M2-127/ 2006-07 Supportive	Efficacy and safety	24 weeks	≥ 40	40-70%b	Rof 500 mcg + salmeterol Placebo + salmeterol	466 467	Europe, South Africa, North America (Canada)
M2-128/ 2007-08 Supportive	Efficacy and safety	24 weeks	≥ 40	40-70%b	Rof 500 mcg + tiotropium Placebo + tiotropium	371 372	Europe

Other phase 2/3 clinical trials conducted as part of the roflumilast COPD development program also included:

- Trials M2-107, M2-110, M2-121, FK1-101 and FK1-103
    - Treatment regimen:
        - Roflumilast 250 (M2-107 and FK1-101 only) and 500 mcg once daily (total 1596 treated)
        - Placebo, once daily
    - Duration:
        - 24 wk (26 wk, FK1-101)
    - Design:
        - all randomized, double blind, placebo controlled, parallel grouping
    - Population:
        - FEV1: 30-80 % (M2-107, M2-110)
        - FEV1: $\leq$ 65% (M2-121)
    - Co-Primary EPs:
        - post FEV1 (all except FK1-101, preFEV1)
        - post FRC (M2-121)
        - SGRQ (M2-110, FK1-101 and FK1-103)

Seven additional trials not listed above were conducted during early stage of roflumilast COPD development program. These trials had shorter duration, open cross over design and different end points and are not reviewed.

5.2 Review Strategy

The Applicant has designated two of the roflumilast Phase 3 trials, M2-124 and M2-125, as the pivotal trials for the program. However, to obtain a more balanced view of the entire drug development program, this review will focus on 8 trials that span the course of the roflumilast clinical development program that are relevant to the original proposed indication for "maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations". Four of the trials (M2-124, M2-125, M2-111, and M2-112) were one year (52 weeks) studies designed to evaluate the effects of roflumilast treatment on lung function and the rate of COPD exacerbations. The other trials (FK1-101, M2-107, M2-127, and M2-128) were 24-26 weeks in duration that included either a lower 250 mcg dose of roflumilast or were designed to evaluate the impact of concomitant treatment with LABA or LAMA on lung function.

Reviews of the studies are based primarily on the final clinical study reports, original protocols, and statistical analysis plans. The Applicant's summary data tables were reviewed in detail. Appendix tables were also reviewed in varying amounts of detail, depending upon the endpoint and review issue.

5.3 Discussion of Individual Studies

This section presents an overview of efficacy data from relevant Phase 3 studies in the roflumilast clinical development program. An integrated discussion of these studies can be found in Section 6. A detailed discussion of safety data is presented separately in Section 7.

Eight COPD clinical trials were reviewed in detail. Studies M2-124 and M2-125 were nearly identical to each other in design, as were studies M2-111 and M2-112, M2-127 and M2-128, and FK1-101 and M2-107. Therefore, these clinical trials will be discussed in their respective pairs. Similarities and differences between the trials will be highlighted where applicable.

All studies were multicenter, multi-national, randomized, double-blind, placebo controlled parallel group trials and had a 2-4-week single blind run-in period followed by a double blind treatment period of 52 (M2-124, M2-125, M2-111 and M2-112) or 24-26 weeks (FK1-101, M2-107, M2-127, and M2-128). The regimens were once daily placebo for the run-in period and once daily roflumilast 500 mcg or placebo for the treatment period.

The main differences among the six trials were subject COPD severity, study endpoints, definition of COPD exacerbation and restrictions on concomitant use of bronchodilators and inhaled steroids. Some of those differences reflected the progression of the roflumilast development program over time.

Trials M2-111 and M2-112 had less restrictive entry criteria and limitations on concomitant medications. Both trials were conducted in severe COPD patients (FEV1 < 50% predicted), similar to those in the pivotal trials, however, presence of chronic bronchitis were not required for enrollment as in the pivotal trials. ICS and anticholinergics were permitted in both trials as stable regimen during the treatment period. Study endpoints, definitions for COPD exacerbation and statistical analysis plan (SAP) underwent several revisions throughout the study periods. Both trials M2-111 and M2-112 win on the laboratory lung function endpoints (pre and post bronchodilator FEV1 as primary endpoints for M2-111 and M2-112 respectively) but failed on the clinically related outcome measures (rate of COPD exacerbation and SGRQ score for M2-111 and M2-112 respectively). Post-hoc analysis of M2-111 suggested that COPD patients with chronic bronchitis and productive cough responded better to roflumilast than those without.

Trials M2-124 and M2-125 were identically designed studies that incorporated the findings of earlier phase 3 trials in their design. They were intended for registration and were powered to demonstrate the benefit of roflumilast in reducing COPD exacerbation in addition to improving lung function. M2-124 and M2-125 were restricted to severe COPD patients with chronic bronchitis and recent COPD exacerbation, a subpopulation of severe COPD patients who shown to be most likely benefit from roflumilast treatment on pos-hoc analysis of trial M2-111. In addition, concomitant inhaled corticosteroids (ICS), which were allowed in trials M2-111 and M2-112 were prohibited and the trials only permitted long acting beta agonist (LABA) plus rescue short acting beta agonist (SABA) or short acting anticholinergic (SAMA) plus rescue SABA. The applicant designates trials M2-124 and M2-125 as pivotal trials for this NDA application.

Trials M2-127 and M2-128 were sister studies intended to demonstrate the benefit of roflumilast in COPD patients already on maintenance bronchodilator (LABA or LAMA) therapy. To support registration of the proposed indication: "for maintenance treatment of COPD", the trials expended the study population to patients with moderate to severe COPD (40% < FEV1 < 70% predicted). The trials were similar in design with the exceptions that M2-127 was for patients on maintenance treatment with salmeterol, while M2-128 was for patient already on tiotropium; and that M2-128 also required patients with chronic productive cough to be eligible, a conduct similar to those practiced in the pivotal trials.

5.3.1 Studies M2-124 and M2-125

Trail Number	Trial Period (Total N*)	Countries (# of Centers, N*)
M2-124	Feb 27, 2006 - July 7, 2008 (Total N=1525)	US (137, N=334) Austria/Germany (12, N=189), France (26, N=243), Hungary/Romania (18, N=358), Russia (17, N=241); Australia/New Zealand/UK (36, N=160)
M2-125	March 2, 2006 – April 29, 2008 (Total N=1571)	US (105, N= 298) Canada (34, N=230), Germany (18, N=230), India (16, N=338), Italy/Spain (24, N=280), Poland (11, N=156), South Africa (13, N=114)

* N: number randomized

These replicate trials were submitted as the pivotal studies to support the registration of roflumilast 500 mcg oral tablets and demonstrate the superiority of roflumilast over placebo in "maintenance treatment of COPD patients with chronic bronchitis at risk of COPD exacerbation".

Study regimen and restrictions on concomitant COPD medications

In both trials, eligible patients were randomized to receive either roflumilast 500 mcg or placebo once daily for 52 weeks.

Uses of other COPD medications were restricted. Depending on COPD regimen at screening visit (V0), inhaled corticosteroids (ICS) alone or in combination with long acting beta agonists (LABA) were allowed in the 4 week, single blind run-in period. However, only LABA or short acting anticholinergics (SAMA) plus rescue medication were allowed during the 52 week double blind treatment period. Long acting anticholinergics were allowed during run in if a patient had been on it for 12 month or longer at V0 but had to switch to short acting ones (SAMA) during the study. Otherwise, LAMA was changed to SAMA at beginning of the run in period and continued through out the treatment. Rescue salbutamol MDI with spacer were provided to all eligible subjects. Figure 1 and Table 7 illustrate the study design and medication restrictions for both trials.

Figure 1 Study Design for Trials M2-124 and M2-125

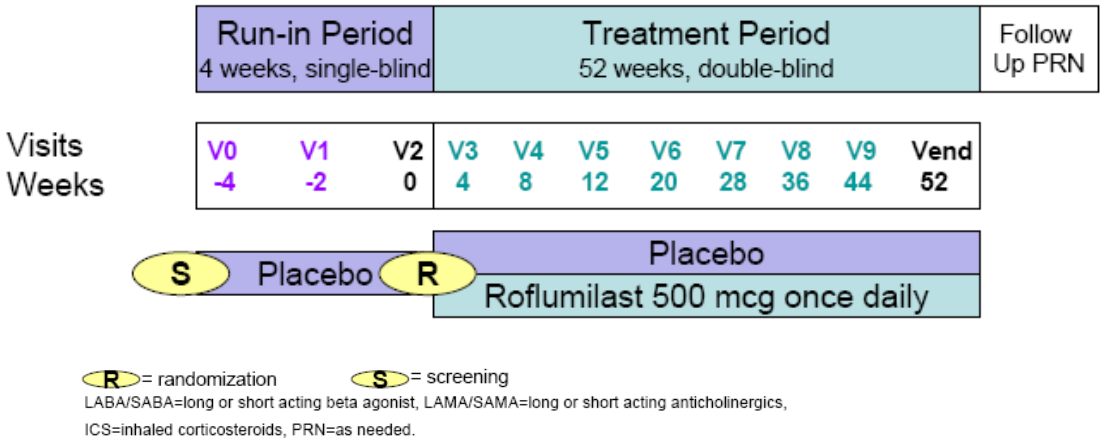


Table 7 Allowed and Disallowed Medications in Trials M2-124 and M2-125

Pretrial Mediations (at Enrollment, V0)	Disallowed Throughout (Stop at V0)	Allowed During Run-in	Disallowed During Treatment (must stop at V2)	Allowed During Treatment	Allowed Throughout
LABA ≥12m	No	LABA	No	LABA	SABA as needed
Fixed combo LABA+ICS ≥ 12 m	No	LABA+ICS	stop combo, may switch to LABA	LABA	
LAMA ≥ 12 m	stop LAMA	LABA or fixed dose SAMA	Already stopped or switched at V0	LABA or fixed dose SAMA	
Other *	stop LABA, LABA+ICS, LAMA	Fixed dose SAMA	Already stopped or switched at V0	Fixed dose SAMA	

Summary:

- PRN SABA allowed for all groups throughout.
- LABA allowed throughout for long term (≥ 12 months) baseline LABA or fixed combination LABA+ICS users.
- Fixed dose SAMA allowed throughout for long term (≥ 12 months) baseline LAMA users; baseline LABA, LABA+ICS, LAMA users of less than 12 month.; or non-users of baseline long acting bronchodilators.
- ICS disallowed during treatment.
- LAMA disallowed throughout the study.

*Other:
- no pretreatment or pretreatment with LABA, fixed combination LABA+ICS, or LAMA <12 month
- Patents pretreated with LAMA and LABA during the 12 month proceeded V0, may continue LABA
- (Applicable for trial M2#125 only) In Spain, patients who were well controlled on LAMA at V0 were excluded.

Eligibilities

These pivotal trials had the most selective patient population in the phase 3 roflumilast development program. Although the proposed indication is for COPD associated chronic bronchitis and did not specify disease severity, these trials required patients to have severe to very severe disease with characteristics of chronic bronchitis and recent history of COPD

exacerbation to be eligible for enrollment. These trials further restrict the patient population by excluding those enrolled patients who had COPD exacerbation during the run in period or had a cough and sputum score lower than 14.

The main pertinent criteria for inclusion were:

- male or female ages ≥ 40 years
- ≥12 month h/o COPD per ATS/ERS criteria
- h/o chronic productive cough for 3 months in EACH of the 2 years prior to baseline visit (V0)
- post bronchodilator FEV1 ≤ 50%, FEV1/FVC ≤ 70% predicted
- at least one documented COPD exacerbation (need for systemic CS or hospitalization) within 1 year prior to baseline visit (V0)
- current or former smoker, with ≥ 20 pack-years history
- has recent (≤ 6 months) chest X-ray or CT, or able to have one

To receive the double blind treatment, eligible patients must enter a 4 week single blind run in period and met the randomization criteria, which included:

- no COPD exacerbation between V0 (baseline) and V2 (randomization)
- total cough and sputum score ≥14 during the week before V2
- negative hemoccult test at V0
- medication compliance between 80% and 125% between V0 and V2

The main pertinent criteria for exclusion were**:**

- unstable patients
- not meet randomization criteria
- known history of alpha-1 antitrypsin deficiency or carrying diagnosis of other pulmonary diseases
- recent history (within 12 months of V0) of recurrent GI bleeding secondary to chronic GI disorders
- presence of other concurrent disease(s) or condition(s) that might interfere with study procedure, evaluation or jeopardize patient safety
- unable to give consent or compliant with protocol requirements

Reviewer's comment: According to the applicant, the estimated average rate of COPD exacerbation in the study population was 1 per patient year. By limiting the enrollment to patients who had exacerbation in the year proceed the trial and excluding patients who had exacerbation during the run-in period, the trials have selected a special patient population (those at the highest risk of exacerbation) during a specific time frame (a period when highest risk patients most likely to have exacerbation.

Study scheme and conduct

The scheme and conduct of both trials were identical and similar to those of other phase 3 trials reviewed here. Both consisted of 3 study periods: baseline or run-in, treatment and follow up. (Figure 1) The 4 week run-in period extends from the initial screening visit (V0) to randomization at visit 2 (V2), during which all eligible subjects received single blind (to patients

only) placebo treatment and adjustments of their pre trial COPD medications – withdraw of disallowed medications, mainly corticosteroids and long acting anticholinergics.

Upon completion of the run-in period, patients were reevaluated. Those who met the randomization criteria (cough/sputum score $\geq$ 14 and no COPD exacerbation during run-in, negative screening hemoccult and compliant with trial drugs) were randomized and went on to the 52 week double blind treatment period (V2 through Vend = V10). The randomization process was stratified according to pre trial LABA use (with or without) and smoking status (current or former smoker).

During treatment, randomized patients received once daily oral formulation of either roflumilast 500 mcg or matching placebo and rescue salbutamol/albuterol MDI, with or without a concomitant long acting beta agonist (LABA) or short acting anticholinergic (SAMA). Restrictions on concomitant COPD medications varied during the trials according to pre trial COPD regimen. (Refer to Table 7 for further details.)

Post treatment follow up was independent of AEs and may contain 1 or more visits per investigator judgment, but usually limited to 30 days.

Subject visits occurred at Weeks -4, -2, 0, 4, 8, 12, 20, 28, 36 44 and 52, during which assessments (including AEs, labs, PFTs, ECGs, COPD symptoms and heath status) were made. Additionally, regular safety checks through phone contacts between scheduled visits occurred around 2 weeks after visits 2 to 4 (V2-V4) and 4 weeks after visits 5 to 9 (V5-V9), respectively.

PFTs were conducted according to ATS/ERS guidelines in centralized labs using sponsor provided spirometers. Pre and post bronchodilator measurements were taken at each visit prior to the morning dose of randomized trial drug. Post bronchodilator measurements were taken 30 min after inhalation of 4 puffs of albuterol/salbutamol from a MDI with spacer. Any LABA treatment was to be discontinued at least 12 hours prior to any PFT readings. Short-acting beta-agonists and anticholinergics were prohibited 4 and 6 hours, respectively, prior to PFTs.

As part of the quality control process, a central over reader conducted “best test review” to checked the quality of all spirometry data and their compliance with ATS/ERS standards, then determine if to accept the selected best FEV1 reading or to select a different reading for analysis.

Detection and documentation of COPD exacerbation were based on patient symptoms and medical management required. All patients were required to record daily, in a paper diary, COPD symptoms (cough, sputum scores) and quantity of rescue inhaler used. If an exacerbation required additional treatment according to the investigator, the protocol recommended up to 40 mg daily prednisone for 7 to 14 days with or without antibiotics, and follow up visit within 10 days after the initial exacerbation visit.

Patients experienced exacerbations during the treatment period were allowed to remain in the study. However, if a patient experienced a moderate or severe exacerbation during the run-in period, the patient could not be randomized but was allowed to reenroll, only once, in the trial

after the exacerbation resolved. Patients who had exacerbation twice during the run-in period were excluded from participating in the trials.

All COPD exacerbations were recorded on CRF and must specify: duration (start and stop date) of the exacerbation, whether additional treatment or hospitalization were needed and if the exacerbation met the criteria for serious adverse event (SAE). The stop date for exacerbation was defined as the time point when patient's COPD symptoms or lung function returned to baseline or when the additional COPD treatment was stopped. COPD exacerbations that met the SAE criteria were recorded as adverse events (AE). Those that did not meet the criteria were counted as variation of the disease and were not recorded as AE. (Refer to efficacy section below for definitions of exacerbation).

Demographics

Both trials were multi national studies. While near 50% study sites were domestic, only 20% population came from US. The number of subjects randomized in trials M2-124 and M2-125 were 1525 and 1571, respectively. Majority of the subjects in both trials were white (>96% in M2-124 and 72 % in M2-125) and significantly more males (70-80%) than females (20-30%). The Asians in trial M2-125 were almost exclusively Indians. There were less than 2% each of blacks and other ethnic minorities in both trials. All demographic characteristics were generally matched between treatment groups within each trial and some were also similar across both trials. There were more current smokers in trial M2-124 than M2-125. Slightly more patients with very severe disease (FEV1< 30% predicted) were in trial M2-125. Table 5-3 (Source: Tables 9 through 11, M2-124 CSR, pp.109-111 and 113 of 52156 and M2-125 CSR, pp.106-108 and 110 of 50952, respectively)

Table 8 Demographics and Baseline Characteristics in Studies M2-124 and M2-125

Baseline Characteristics	M2-124 (ITT)		M2-125 (ITT)	
	Rof500 mcg (N=765)	Placebo (N=758)	Rof500 mcg (N=772)	Placebo (N=796)
Age				
median (range) in year	63 (40-89)	63 (40-92)	64 (40-90)	64 (40-90)
Gender				
Male, n (%)	540 (70.6)	538 (71)	610 (79)	648 (81.4)
Female, n (%)	225 (29.4)	220 (29)	162 (21)	148 (18.6)
Race (% randomized)				
White	737 (96.3)	732 (96.6)	559 (72.4)	568 (71.4)
Black	11 (1.4)	15 (2.0)	8 (1)	14 (1.8)
Asian	1 (0.1)	1 (0.1)	174 (22.5)	179 (22.5)
American Indian	0	1 (0.1)	2 (0.3)	1 (0.1)
Other	16 (2.1)	9 (1.2)	29 (3.8)	34 (4.3)
Weight				
mean+/- SD (kg)	76 +/- 17	75 +/- 18	71 +/- 20	71 +/- 19
BMI				
mean+/- SD (kg/m^2)	26.36 +/- 5.5	26.00 +/- 5.5	25.25 +/- 6.2	25.35 +/- 5.9
Smoking Status				
% Current/former	47.7/52.3	47.6/52.4	35/65	35.4/64.6

mean Cigarette pack year +/- SD	48 +/- 24	46 +/- 23	49 +/- 29	64.6
COPD Characteristics*				
Mild, n (%)	0	3 (0.4)	1 (0.1)	2 (0.3)
Moderate, n (%)	80 (10.5)	61 (8)	50 (6.5)	59 (7.4)
Severe, n (%)	486 (63.5)	510 (67.3)	457 (59.2)	479 (60.2)
Very severe, n (%)	199 (26)	184 (24.3)	264 (34.2)	256 (32.2)
PreFEV1				
mean+/- SD (L)	1.07+/-0.4	1.06+/-0.4	0.95+/-0.3	0.98+/-0.4
(mean % predicted+/-SD)	(34.6+/-10.2)	(34.6+/-10.3)	(31.4+/-10.1)	(32.2+/-10.8)
FEV1 reversibility				
mean+/- SD (mL)	88.9+/-150.7	89.9+/-141.7	95.9+/-134.1	94.8+/-131.7

*COPD severity was classified according to the value of post FEV1 as % predicted: mild (%), moderate (%), severe (FEV1 < 50 % and ≥ 30%), very severe (FEV1 < 30%)

Source: Tables 9-11, M2-124 CSR, pp 109-111 and 113 of 52156 and M2-125 CSR, pp106-108 and 110 of 50952, respectively.

These trials permitted concomitant LABA and SAMA use. Tables 9 and 10 displayed COPD treatments used by at least 10% of the patients in either treatment groups in at lease one study time period in trials M2-124 and M2-125, respectively. In both trials, nearly all patients (96-100%) used at least one concomitant COPD treatment through out the entire trial period. During the treatment period of both trials, nearly half (42-45%) of the patients used LABA, a third or more (31.4-40.7%) of the patients used SAMA and half or more (49.3-57%) of the patients used corticosteroids. Uses of prohibited concomitant COPD drugs or treatment that could affect outcome, such as supplemental oxygen, were common during the treatment period of both trials. The prevalence of using prohibited COPD treatments were: 9.1-24.2% for ICS, 4.9-6.3% for LAMA, 4.6-7.7% for LABA/SAMA combinations, 10.8-14.2% for LABA/ICS combinations and 5.1-8.7% for Xanthenes. The prevalence of supplemental oxygen use during treatment period was 10%-13.9%.

Table 9 Concomitant COPD drugs used in trial M2-124

	Number (%)[a] of patients					
	Before study[b]		Baseline[c]		Treatment	
Extended ATC code	Rof500 (N = 765)	Pbo (N = 758)	Rof500 (N = 765)	Pbo (N = 758)	Rof500 (N = 765)	Pbo (N = 758)
Corticosteroids						
Corticosteroids (excluding inhaled and nasal applications)	145 (19.0)	167 (22.0)	30 (3.9)	31 (4.1)	377 (49.3)	409 (54.0)
ICS	175 (22.9)	169 (22.3)	142 (18.6)	127 (16.8)	76 (9.9)	69 (9.1)
β_2 agonists and anticholinergics						
Inhaled short-acting β_2 agonists[d]	501 (65.5)	464 (61.2)	762 (99.6)	750 (98.9)	761 (99.5)	753 (99.3)
Inhaled short-acting anticholinergics	140 (18.3)	143 (18.9)	218 (28.5)	207 (27.3)	240 (31.4)	245 (32.3)
Inhaled combination of β_2 agonists + short-acting anticholinergics	223 (29.2)	220 (29.0)	63 (8.2)	41 (5.4)	48 (6.3)	35 (4.6)
Inhaled long-acting β_2 agonists	143 (18.7)	150 (19.8)	183 (23.9)	183 (24.1)	339 (44.3)	342 (45.1)
Inhaled combination of corticosteroids and LABAs	336 (43.9)	331 (43.7)	235 (30.7)	237 (31.3)	83 (10.8)	85 (11.2)
Inhaled long-acting anticholinergics	238 (31.1)	234 (30.9)	57 (7.5)	48 (6.3)	49 (6.4)	48 (6.3)
Other						
Xanthines	165 (21.6)	153 (20.2)	28 (3.7)	28 (3.7)	42 (5.5)	39 (5.1)
Oxygen	59 (7.7)	52 (6.9)	59 (7.7)	52 (6.9)	83 (10.8)	81 (10.7)
Number of patients with at least one COPD medication	753 (98.4)	741 (97.8)	765 (100.0)	757 (99.9)	765 (100.0)	757 (99.9)

Source: Table 8, M2-124 CSR, pp113

Table 10 Concomitant COPD drugs used in trial M2-125

	Number (%)[a] of patients					
	Before study[b]		Baseline[c]		Treatment	
Extended ATC code	Rof500 (N = 772)	Pbo (N = 796)	Rof500 (N = 772)	Pbo (N = 796)	Rof500 (N = 772)	Pbo (N = 796)
Corticosteroids						
Corticosteroids (excluding inhaled and nasal applications)	149 (19.3)	163 (20.5)	29 (3.8)	34 (4.3)	404 (52.3)	456 (57.3)
ICS	192 (24.9)	201 (25.3)	176 (22.8)	180 (22.6)	99 (12.8)	113 (14.2)
β_2 agonists and anticholinergics						
Inhaled short-acting β_2 agonists[d]	462 (59.8)	475 (59.7)	767 (99.4)	790 (99.2)	769 (99.6)	791 (99.4)
Inhaled short-acting anticholinergics	205 (26.6)	232 (29.1)	262 (33.9)	287 (36.1)	297 (38.5)	324 (40.7)
Inhaled combination of β_2 agonists + short-acting anticholinergics	149 (19.3)	145 (18.2)	49 (6.3)	52 (6.5)	56 (7.3)	61 (7.7)
Inhaled long-acting β_2 agonists	206 (26.7)	215 (27.0)	229 (29.7)	253 (31.8)	329 (42.6)	351 (44.1)
Inhaled combination of corticosteroids and LABAs	285 (36.9)	267 (33.5)	187 (24.2)	180 (22.6)	87 (11.3)	113 (14.2)
Inhaled long-acting anticholinergics	168 (21.8)	168 (21.1)	32 (4.1)	30 (3.8)	38 (4.9)	44 (5.5)
Other						
Xanthines	220 (28.5)	227 (28.5)	58 (7.5)	61 (7.7)	67 (8.7)	77 (9.7)
Oxygen	80 (10.4)	76 (9.5)	75 (9.7)	69 (8.7)	107 (13.9)	105 (13.2)
Number of patients with at least one COPD medication	756 (97.9)	770 (96.7)	772 (100)	796 (100)	772 (100)	796 (100)

Source: Table 8, M2-125 CSR, pp110.

<u>Reviewer's Comments:</u> The prevalent use of prohibited COPD drugs suggested that patients in the trials were under treated.

Dispositions

In both trials, approximately two-third (70%) of the recruited patients randomized and approximately two-third (30% to 35%) of the randomized patients completed the study. There were more premature discontinuations in the roflumilast treated groups, comparing to placebo, due to adverse events. In contrast, more patients withdrew from the placebo group because of COPD exacerbation. Similar % patients withdrew their consent in both study groups.

Table 11 Patient Dispositions for studies M2-124 and M2-125

Disposition, N (% recruited)	M2-124		M2-125	
Recruited	2238		2277	
Randomized (% recruited)	1525 (68.2)		1571 (69)	
Not randomized (% recruited)	713 (31.8)		706 (31)	
Disposition, N (% randomized)	Rof500 mcg	Placebo	Rof500 mcg	Placebo
Randomized	766	759	773	798
Completed	502 (65.5)	525 (69.2)	527 (68.2)	550 (68.9)
Premature Discontinued	264 (34.5)	234 (30.8)	246 (31.8)	248 (31.1)
Adverse events	119 (15.5)	78 (10.3)	101 (13.1)	83 (10.4)
Withdrew consent	120 (15.7)	100 (13.2)	108 (14)	107 (13.4)
COPD exacerbation	43 (5.6)	69 (9.1)	49 (6.3)	66 (8.3)
Lost to follow up	17 (2.2)	16 (2.1)	22 (2.8)	24 (3)
Met discontinuation criteria	7 (0.9)	4 (0.5)	9 (1.2)	4 (0.5)
Other reasons	29 (3.8)	28 (3.7)	29 (3.8)	30 (3.8)

Source: Figures 2 and Tables 3 in sections 10.1 of CSR M2-124 and CSR M2-125.

Compliance

Compliance was an issue. Approximately 30% of the patients had at least one major protocol violation in both trials. The top reasons for violations in the roflumilast treated groups were non compliance with study drug (9.8-10%) and use of systemic corticosteroids (6.8-7.2%) outside what was permitted during the trial (after screening visit V0) and/or use of ICS (6.9-8.2%) after randomization visit V2. Use of both systemic and inhaled cortical steroids was restricted during the trial according to the protocol. CS were prohibited throughout the study except for exacerbations during the treatment period, ICS was allowed during run in but prohibited during the treatment period. Similarly, use of the not allowed CS and/or ICS were also the top reasons for protocol violations in the placebo groups (CS: 5.1-6%, ICS: 9.3-9.6%). Non compliance with study drug was an issue with the placebo group but was not as pronounced as in the roflumilast groups (PBO: 6.2-6.9% versus roflumilast: 9.8-10%)

Table 12 Top Causes of Major Protocol Violations in studies M2-124 and M2-125

Major Violations N (% randomized)	**M2-124 (ITT)**		**M2-125 (ITT)**	
	Roflumilast (N=765)	**Placebo (N=758)**	**Roflumilast (N=772)**	**Placebo (N=796)**
Patients had major violations	213 (27.8)	210 (27.7)	245 (31.7%)	233 (29.2)
CS use during study (after V0)	52 (6.8)	39 (5.1)	56 (7.2)	48 (6)
ICS use during treatment (after V2)	53 (6.9)	73 (9.6)	63 (8.2)	74 (9.3)
Noncompliance with study drug	75 (9.8)	47 (6.2)	77 (10)	55 (6.9)

Source: Tables 4 in Sections 10.2 of CSR M2-124 and CSR M2-125.

Reviewer's comments: Both use of the prohibited CS and/or ICS and non compliance with the study drug can affect the study results and could favor the roflumilast groups – more efficacy from steroid use and less side effects from noncompliance with study drug. However, it is difficult to determine the precise impact of those violations on efficacy results. Therefore, comparing the efficacy results of ITT with PP might be important.

Efficacy Results

The proposed claims for registration are "for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations".

The co primary endpoints were:
- changes in mean pre bronchodilator FEV1 (pre-FEV1)
- rate of moderate or severe COPD exacerbation

The key secondary endpoints were:
- changes in mean post bronchodilator FEV1 (post-FEV1)
- time to mortality due to any reason
- changes in mean TDI (transition dyspnea index) focal score
- changes in mean natural log transformed CRP

The mean changes in pre- or post bronchodilator FEV1, TDI and CRP were stipulated as measurements from baseline (V2) to each post randomization visit during the treatment period using a repeat measurement ANCOVA analysis.

To reduce overall type I error, the statistical analysis plan (SAP) specified that the primary and key secondary endpoints were to be analysis according a predetermined order as listed above. If one endpoint failed to reach statistical significance, analysis on all lower ranking endpoints were considered exploratory. As neither trial win the second ranking key secondary endpoint, time to all mortality, only pre and post FEV1 and COPD exacerbation results will be reviewed.

The efficacy analysis was performed on both the intent-to-treat (ITT) and the per protocol (PP) population (referred to as the full analysis set or FAS and the valid case analysis set or VAS, respectively). As the results for ITT and PP do not always support each other, this review includes both analyses.

A. Pre and Post Bronchodilator FEV1

Pre bronchodilator FEV1 (co-primary endpoint)

Because roflumilast is considered primarily as an anti inflammatory agent, changes in pre bronchodilator FEV1 were considered to be the most appropriate measurement of its effects on lung function. As shown in Table 13, patients treated with roflumilast had slight improvements in pre-FEV1 (33-46 mL). In contrast, pre-FEV1 remained same (M2-124) or deteriorated (M2-125) slightly (25 mL) in patients received placebo. The overall between treatment differences were similar in both trials (39-58 mL for ITT).

Table 13 Change in pre bronchodilator FEV1 during Treatment from Baseline (studies M2-124 and M2-125

M2-124 (Repeated Measurement Analysis)

Δ in preFEV1 LS Mean in Lt (SD)	Rof500 mcg	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.046 (0.008) n = 745 obs = 4766	0.008 (0.008) n = 745 obs = 4961	0.039 (0.011) 95% CI (0.018, 0.060) P = 0.003
PP	0.043 (0.010) n = 478 Obs = 2989	- 0.004 (0.010) n = 491 obs =3132	0.047 (0.013) 95% CI (0.021, 0.073) P = 0.0005

M2-125 (Repeated Measurement Analysis)

Δ in preFEV1 LS Mean in Lt (SD)	Roflumilast	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.033 (0.007) n = 730 obs = 4841	- 0.025 (0.007) n = 766 obs = 5218	0.058 (0.009) 95% CI (0.041, 0.075) P < 0.0001
PP	0.038 (0.010) n = 450 Obs = 2920	- 0.029 (0.009) n = 483 obs =3130	0.067 (0.011) 95% CI (0.046, 0.089) P < 0.0001

n: number of patients with preFEV1 data available.
obs: number of observations.
Sources: Tables 9 of sections 11.4.1.1 in CSR M2-124 and CSR M2-125.

Subgroup analyses according to patient's characteristics were performed using the same repeated measurement ANCOVA. The parameters tested included: age (≤ 65 years or > 65 yrs), gender, race (white or Asian only), geographic origin (North America, or Europe or Rest of the world), smoking status (current or former – stopped for ≥ 12 months), COPD severity (very severe or severe), concomitant COPD medications during the treatment period (with or without LAMA or SAMA), presence or absence of pretrial treatment with ICS and trial completion (completed or premature withdrawal). In general, the between treatment differences were consistent with those of the entire study population.

Post bronchodilator FEV1 (first rank key secondary endpoint)

Similarly, the post bronchodilator FEV1 also improved in roflumilast treated groups and remained the same or deteriorated in the placebo groups. Again, the treatment differences between roflumilast and placebo were small but consistent (49-61 mL, ITT). (Table 14)

Table 14 Change in post Bronchodilator FEV1 during Treatment from Baseline in studies M2-124 and M2-125

M2-124 (Repeated Measurement Analysis)

Δ in post-FEV1 LS Mean in Lt (SD)	Roflumilast	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.057 (0.009) n = 729 obs = 4703	0.008 (0.008) n = 736 obs = 4896	0.049 (0.011) 95% CI (0.026, 0.071) P < 0.0001
PP	0.055 (0.011) n = 470 Obs = 2989	0.000 (0.011) n = 474 obs =3014	0.055 (0.014) 95% CI (0.027, 0.083) P = 0.0005

M2-125 (Repeated Measurement Analysis)

Δ in post-FEV1 LS Mean in Lt (SD)	Roflumilast	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.044 (0.007) n = 724 obs = 4804	- 0.017 (0.007) n = 764 obs = 5185	0.061 (0.009) 95% CI (0.044, 0.079) P < 0.0001
PP	0.046 (0.010) n = 444 Obs = 2865	- 0.018 (0.009) n = 494 obs =3159	0.065 (0.012) 95% CI (0.042, 0.087) P < 0.0001

n: number of patients with preFEV1 data available
obs: number of observations
Sources: Tables 14 of sections 11.4.1.2.1 in CSR M2-124 and CSR M2-125

B. COPD Exacerbations

Rate of moderate or severe COPD exacerbation per patient per year was the co primary endpoints for these studies. COPD exacerbations were classified according to the following definitions:

- Mild exacerbation: increase in rescue inhaler $\geq$ 3 puffs/day on at least 2 consecutive days
- Moderate exacerbation: requiring oral or parenteral corticosteroid therapy
- Severe exacerbation: requiring hospitalization and/or leading to death

Data on COPD exacerbation were analyzed with multiple statistical models by the applicant. This review will summarized results of the following analysis:

- Mean rate of moderate or severe COPD exacerbations per patient per year – the co primary endpoint (Poisson regression)
    - ITT and PP
    - subgroup analysis on exacerbation severity as function of patient characteristics
- Risk of COPD exacerbation per patient per year (log binomial regression)

- Number need to treat (NNT) to avoid one moderate or severe COPD exacerbation and NNT to avoid any COPD exacerbation (post-hoc)

- Time to onset of first moderate or severe COPD exacerbation (Cox proportional hazards and Kaplan-Meier)

- Number of COPD exacerbation days and duration of COPD exacerbation (Descriptive statistics)

Mean rates of moderate or severe COPD exacerbations (co-primary endpoint)

The co primary endpoint, mean rates of moderate or severe COPD exacerbations per patient per year were analyzed using Poisson regression and the results are shown in Table 15. Mean exacerbation rates in roflumilast treated groups were lower comparing to placebo and the difference were significant for the ITT population in both trials. However, those results were only partially confirmed by analysis in the PP population. In trial M2-124, the PP treatment difference between roflumilast and placebo were only approximately one half of that in ITT and did not reach statistical significance (PP: -7.8 % reduction, p = 0.3384 versus ITT: 14.9% reduction, p = 0.0278).

Table 15 Mean Rates of Moderate or Severe COPD Exacerbations per Patient per Year

Mean Rates of Moderate or Severe COPD Exacerbations, M2-124 (Poisson regression)

	Roflumilast	Placebo	Rate Difference % change Rate Ratio (SE)
ITT Mean Rate of Exacerbation Per patient per year	1.077 N = 765	1.266 N = 758	- 14.9% RR = 0.851 (0.062) 95% CI (0.737, 0.982) P = 0.0278
PP Mean Rate of Exacerbation Per patient per year	1.007 N = 553	1.093 N = 549	- 7.8% RR = 0.922 (0.079) 95% CI (0.780, 1.089) P = 0.3385

Mean Rates of Moderate or Severe COPD Exacerbations, M2-125 (Poisson regression)

	Roflumilast	Placebo	Rate Difference % change Rate Ratio (SE)
ITT Mean Rate of Exacerbation Per patient per year	1.210 N = 772	1.485 N = 796	- 18.5% RR = 0.815 (0.057) 95% CI (0.710, 0.935) P = 0.0035
PP Mean Rate of Exacerbation Per patient per year	1.085 N = 528	1.406 N = 565	- 22.8% RR = 0.772 (0.065) 95% CI (0.655, 0.910) P = 0.0021

Rate difference; roflumilast – placebo. RR = Rate ratio: roflumilast/placebo. SE: standard error
N: number of patients randomized in the respective treatment group.
Sources: Tables 12 of sections 11.4.1.1.2 in CSR M2-124 and CSR M2-125

Reviewer's comments: ITT is usually a more conservative estimate. However, in trial M2-124, the mean exacerbation rate was about ½ of that in ITT and did not reach statistical significance.

Analysis according to exacerbation severity in the ITT population indicated that COPD exacerbations of all severity (mild, moderate and severe) decreased in roflumilast treated groups in both trials. However, there were no statistically significant differences between treatments for severe exacerbations in either trial and for mild exacerbations in trial M2-124. The differences in moderate or severe exacerbation rate (co primary endpoint) between roflumilast and placebo were driven by the rate of moderate exacerbations, which was based on use of systemic steroid prescribed by the investigators according to their clinical judgments. There was no subgroup analysis on PP submitted with the application.

Table 16 COPD Exacerbations by Severity in studies M2-124 and M2-125

M2-124 (Poisson regression)

Exacerbation Rate Per patient per year	Mean Exacerbation Rate per Patient per Year		Rate Difference (% change) Rate Ratio (SE)
	Roflumilast	Placebo	
Mild Exacerbations ITT (N = 765)	2.797	3.083	- 9.3% RR = 0.907 (0.092) 95% CI (0.743, 1.108) P = 0.3384
Moderate Exacerbations ITT (N = 765)	0.938	1.113	- 15.7% RR = 0.843 (0.067) 95% CI (0.721, 0.986) P = 0.0325
Severe Exacerbations ITT (N = 765)	0.105	0.119	-11.4% RR = 0.886 (0.169) 95% CI (0.610, 1.288) P = 0.5273
All Exacerbations ITT (N = 765)	3.931	4.414	-10.9% RR = 0.891 (0.069) 95% CI (0.765, 1.037) P = 0.1363

M2-125 (Poisson regression)

Exacerbation Rate Per patient per year	Mean Exacerbation Rate per Patient per Year		Rate Difference (% change) Rate Ratio (SE)
	Roflumilast	Placebo	
Mild Exacerbations ITT (N = 765)	3.023	3.762	- 19.6% RR = 0.804 (0.077) 95% CI (0.666, 0.970) P = 0.0226
Moderate Exacerbations	1.038	1.265	- 18% RR = 0.820 (0.061)

ITT (N = 765)			95% CI (0.709, 0.948) P = 0.0075
Severe Exacerbations ITT (N = 765)	0.139	0.180	-22.9% RR = 0.771 (0.145) 95% CI (0.533, 1.114) P = 0.1656
All Exacerbations ITT (N = 765)	4.344	5.396	-19.5% RR = 0.805 (0.059) 95% CI (0.697, 0.930) P = 0.0033

Rate difference; roflumilast – placebo. RR = Rate ratio: roflumilast/placebo. SE: standard error
N: number of patients randomized in the respective treatment group.
Sources: Tables 12 of sections 11.4.1.1.2 in CSR M2-124 and CSR M2-125

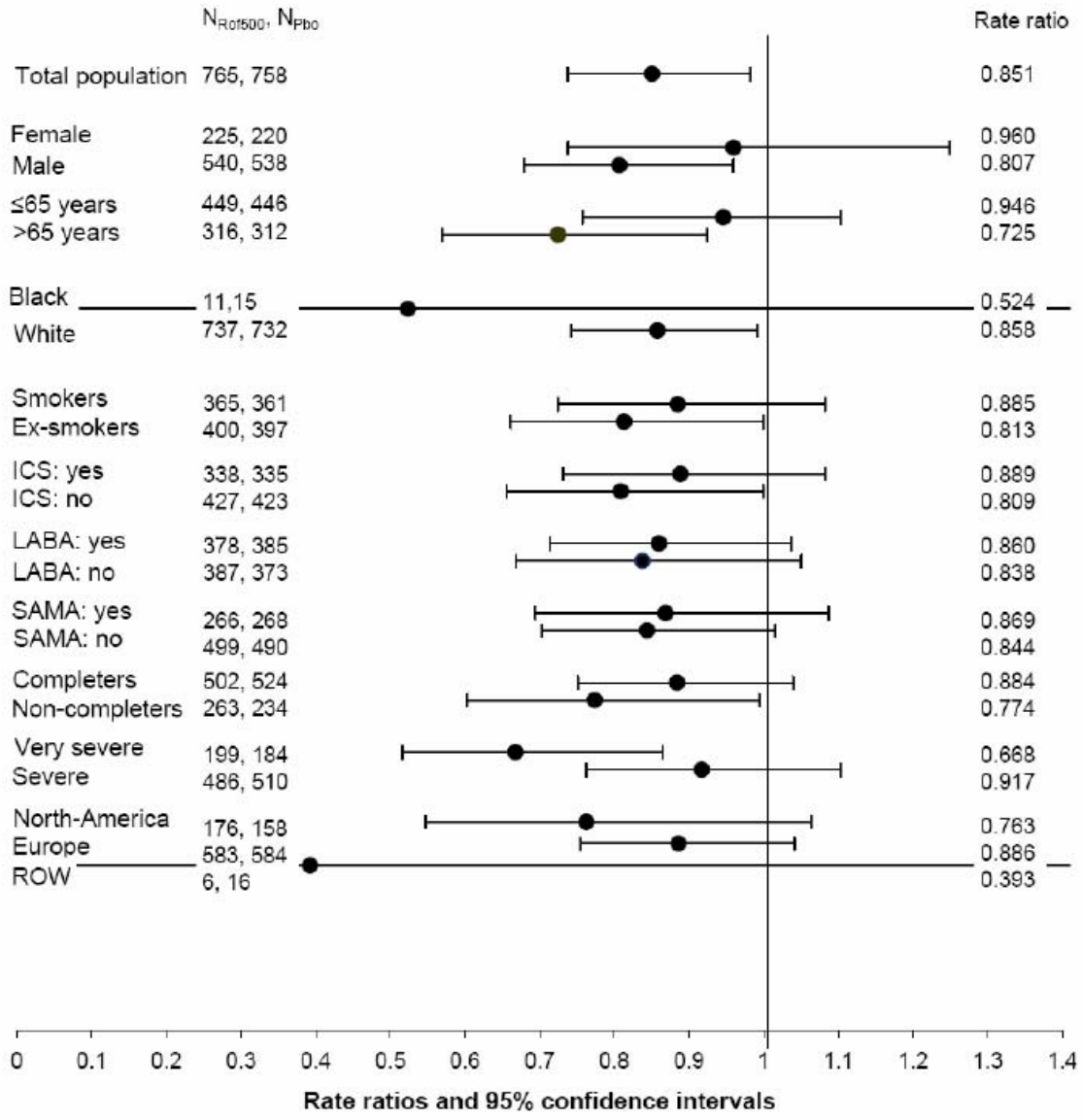
Subgroup analyses on the co primary endpoint (mean rates of moderate or severe COPD exacerbations) according to patient's characteristics were performed using Poisson regression in the ITT population (not in PP) and the results are shown in Figures 2 a and b. The parameters tested included: age ($\leq$ 65 years or > 65 yrs), gender, race (white or Asian only), geographic origin (North America, or Europe or Rest of the world), smoking status (current or former – stopped for $\geq$ 12 months), COPD severity (very severe or severe), concomitant COPD medications during the treatment period (with or without LAMA or SAMA), presence or absence of pretrial treatment with ICS and trial completion (completed or premature withdrawal).

The between treatment differences were statistically significant in trial M2-124 in the following subgroups: males, patients older than 65, whites, ex-smokers, patients without pretreatment with ICS, non-completers and patients with very severe COPD.

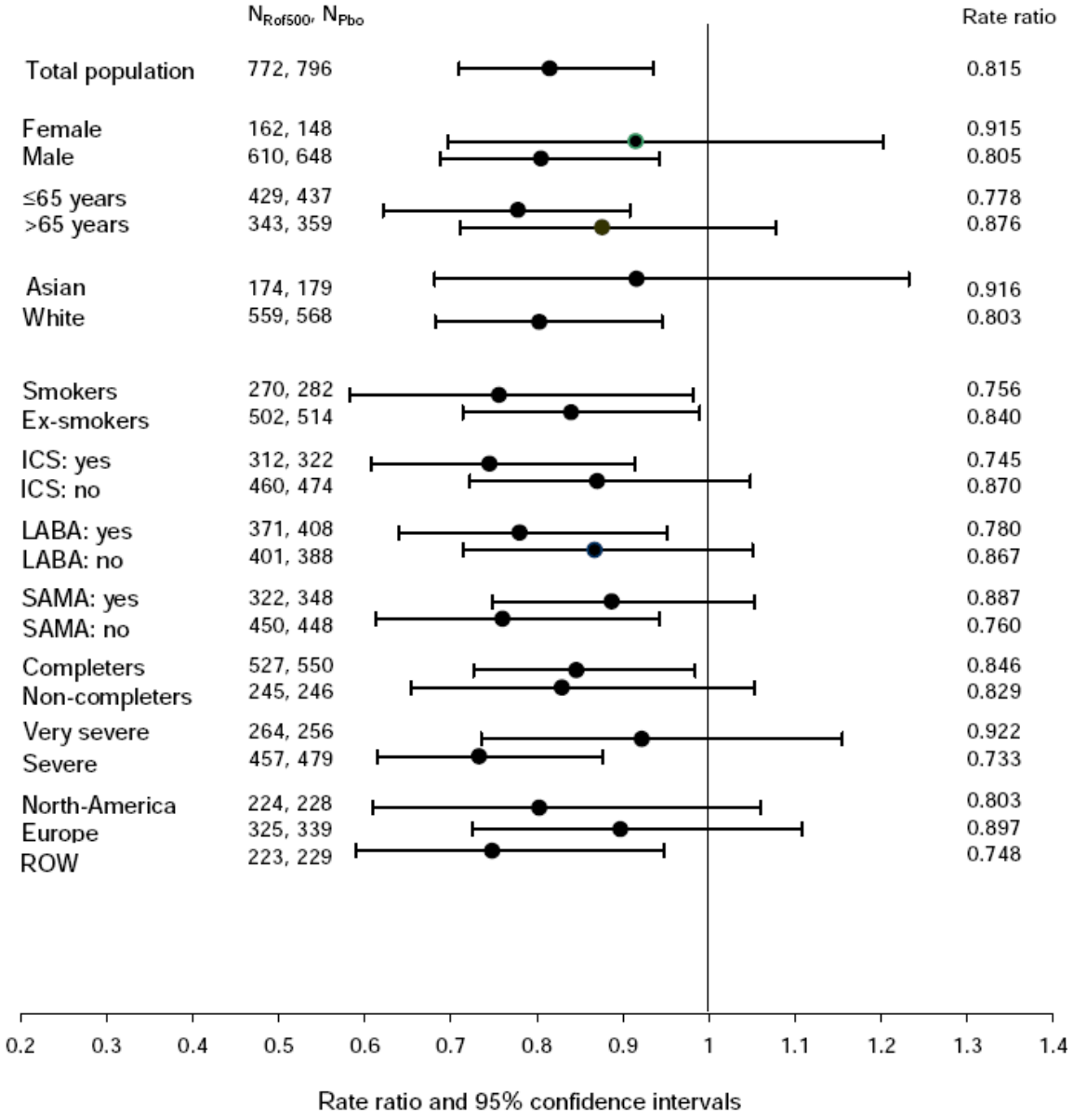
The between treatment differences were statistically significant in trial M2-125 in the following subgroups: males, patients 65 or younger (different from M2-124) and patients older than 65, whites, current (different from M2-124) and ex-smokers, patients with concurrent LABA (different from M2-124), patients without concurrent SAMA (different from M2-124), patients with pretreatment with ICS (different from M2-124), completers (different from M2-124) and non-completers and patients with severe COPD (different from M2-124).

Figure 2 Subgroup analyses: Mean rates of moderate or severe COPD exacerbations in studies M2-124 (a) and M2-125 (b) per patient per year (Poisson regression, ITT)

a) Trial M2-124



b) Trial M2-125



ICS = inhaled corticosteroids, ITT = intention-to-treat analysis , LABA = long-acting β_2-agonists, LSMeans = least squares mean adjusted for covariates, N = number of patients with data available, Pbo = placebo, Rof500 = roflumilast 500 mcg, ROW = rest of world, SAMA =short-acting anticholinergics

Note: A rate ratio <1 represents a favorable outcome for the Rof500 treatment.

Data source: Table 15.10.1.7, Table 15.10.1.17, Table 15.10.1.18, Table 15.10.1.19, Table 15.10.1.20, Table 15.10.1.21, Table 15.10.1.22, Table 15.10.1.23, Table 15.10.1.24, Table 15.10.1.25, Table 15.10.1.26.

Reviewer's Comments: Subgroup analysis confirmed the findings in ITT described above. The reduction in rate of COPD exacerbation was driven, primarily, by reduction in moderate exacerbations.

Risk of COPD exacerbation (secondary endpoint)

Risks of COPD exacerbation per patient per year were analyzed using the log binomial regression and the results are shown in Table 17 In both trials, the overall risk of COPD exacerbations (all category = mild, moderate or severe) were lower in roflumilast treated group comparing to placebo in ITT population of both trials. These differences were mostly driven by reduction in risk of moderate exacerbations in M2-124, mild and moderate exacerbations in M2-125. There were no statistically significant differences in the risk of severe exacerbations between the treatment groups in either trial. Furthermore, with the exception of moderate exacerbation, there were no significant differences in mild, severe, moderate or severe and overall exacerbations in the PP population of M2-125. (Unclear about the PP population of M2-124 as no results submitted.)

Table 17 Risk of COPD Exacerbations in studies M2-125 and M2-125

M2-124 (log binomial regression)

Population	Exacerbation Category	Number of Patients with Exacerbations (Risk of having COPD Exacerbations)		Risk Ratio (SE)/ P value (2 sided)
		Roflumilast	Placebo	
ITT		N = 765	N=758	
	Mild	276 (0.357)	290 (0.378)	0.945 (0.3893)-ns
	Moderate	299 (0.412)	343 (0.430)	0.884 (0.0343)
	Severe	69 (0.074)	81 (0.087)	0.852 (0.2978)-ns
	Moderate or severe	344 (0.465)	389 (0.524)	0.887 (0.196)-ns
	All category	455 (0.612)	508 (0.685)	0.894 (0.0034)
PP		N = 553	N = 549	
	Mild Moderate Severe Moderate or severe All category	Data not available	Data not available	Data missing, no respective table

M2-125 (log binomial regression)

Population	Exacerbation Category	Number of Patients with Exacerbations (Risk of having COPD Exacerbations)		Risk Ratio (SE)/ P value (2 sided)
		Roflumilast	Placebo	
ITT		N = 772	N = 796	
	Mild	293 (0.383)	357 (0.455)	0.842 (0.0037)
	Moderate	325 (0.441)	380 (0.500)	0.881 (0.0188)
	Severe	88 (0.099)	117 (0.119)	0.830 (0.1479)-ns
	Moderate or severe	373 (0.501)	432 (0.560)	0.894 (0.0183)
	All category	495 (0.666)	563 (0.727)	0.916 (0.0106)
PP		N = 528	N = 565	
	Mild	223 (0.415)	263 (0.467)	0.889 (0.0773)-ns
	Moderate	231 (0.448)	280 (0.507)	0.883 (0.0481)
	Severe	50 (0.090)	67 (0.106)	0.846 (0.3339)-ns
	Moderate or severe	257 (0.504)	306 (0.560)	0.900 (0.0618)-ns
	All category	355 (0.695)	400 (0.725)	0.959 (0.2995)-ns

Risk ratio: risk of exacerbation: roflumilast/placebo. SE: standard error
N: number of patients randomized in the respective treatment group.

Risk ratio: roflumilast/placebo
ns: not significant statistically ($p \geq 0.05$)
Sources: CSR M2-124 and CSR M2-125, ITT data from Tables 20 of sections 11.4.2.1 (equivalent of Tables 15.10.1.47), PP data from Table 15.10.1.48 of M2-125 (respective table missing in M2-124) in section 15.10.

Number needed to treat (NNT) (secondary endpoint)

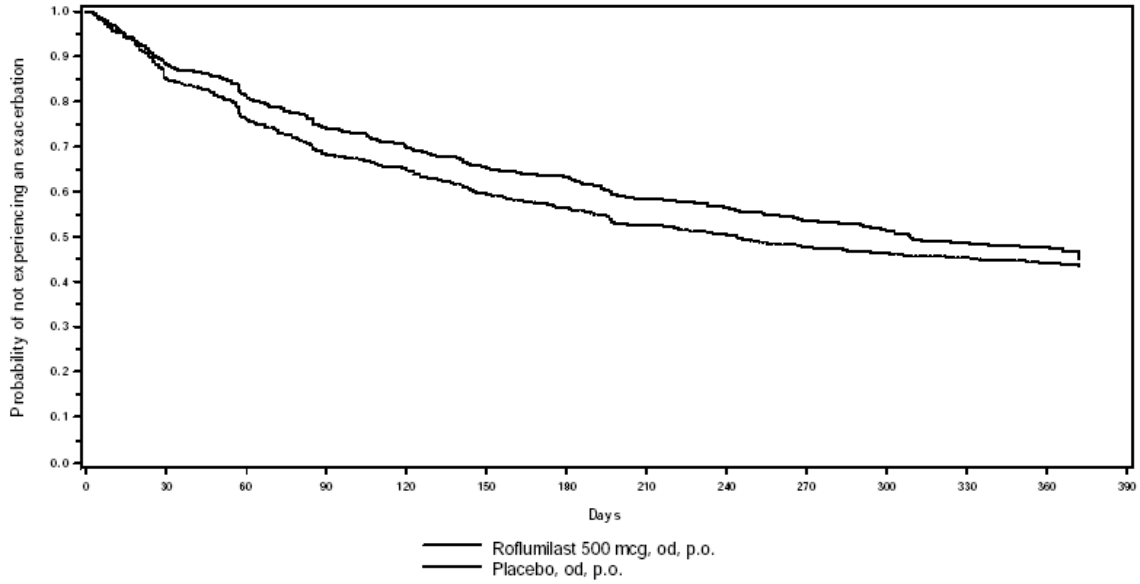
NNT to avoid one moderate or severe COPD exacerbation per patient per year in trials M2-124 and M2-125 were 5.29 and 3.64, respectively for ITT; 11.63 and 3.12, respectively for PP.

Time to onset of first moderate or severe COPD exacerbation (secondary endpoint)

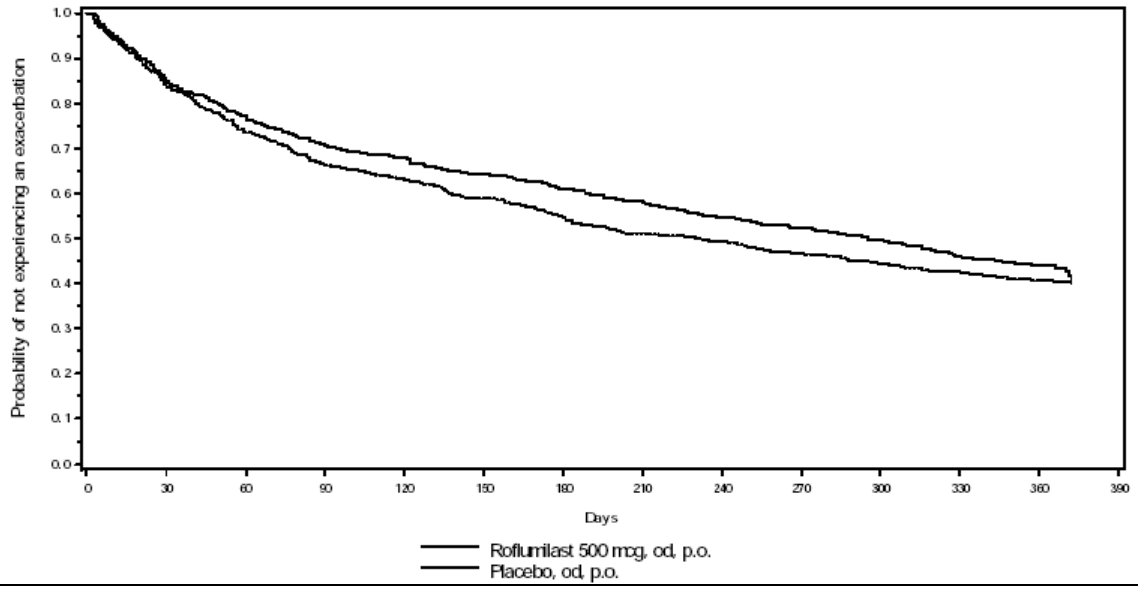
Time to onset of first COPD exacerbation was analyzed with Cox proportional hazards and the results can be found in Tables 21 of CSR in both trials. Results of time to onset of first moderate or severe COPD exacerbation are graphed as survival curve (Kaplan-Meier, ITT) in Table 18 a and b. There were no statistically significant differences between treatment groups ($p = 0.0859$ for trial M2-124, $p= 0.1132$ for trial M2-125).

Table 18 Time to onset of first moderate or severe COPD exacerbation (Kaplan-Meier, ITT)

a) Trial M2-124



b) Trial M2-125



Source: Figures 3, pp 129 of M2-124 CSR and pp 126 of M2-125 CSR.

Number of COPD exacerbation days and duration of COPD

In either trial, descriptive statistics did not display consistent trends in favor of the roflumilast treated groups in either number of COPD exacerbation days or duration of COPD exacerbation. The treatment differences in number of COPD exacerbation days were 1.7-4.4 days for ITT and 1.4-4.6 days for PP in trial M2-124; 3.2-6.6 days for ITT and 3.3 -9.1 days for PP in trial M2-125. The treatment differences in duration of COPD exacerbation were between 0.1 and 2.5 days in all group tested (both trials, ITT and PP).

Other analyses on COPD exacerbation

The trials also collected and analyzed data on patients with changes of COPD symptoms that did not meet the above classification of COPD exacerbation, but were captured on CRF by the investigators. These exacerbations were analyzed under the terms of CRF exacerbations, exacerbations treated with antibiotics only and exacerbation treated with systemic steroid or antibiotics. Rates of CRF exacerbations were statistically different between treatment groups in both trials (M2-124: - 14.5% reduction, p=0.0151; M2-125: -17.8% reduction, p = 0.0021). Also reached statistical significance were the rate of exacerbation treated with systemic steroids or antibiotics, which was the definition for moderate COPD exacerbation in earlier trials. The rates of moderate exacerbation were nearly identical regardless if the definition taking into account of antibiotic use in both trials. However, there was no between treatment difference in COPD exacerbations defined by antibiotics use alone.

C. Time to All Cause Mortality (second rank key secondary endpoint)

A total of 72 patients died during the double blind treatment period (32 in M2-124 and 50 in M2-125). Two additional deaths from the placebo group in trial M2-124 occurred 2 and 7 months

after the trial ended. Results of Cox proportional hazards modeling of time to all cause mortality were equivocal. Comparing to placebo, the mean time to mortality in roflumilast treated group was longer in trial M2-124 (roflumilast: 213.8+/- 118.9 days versus placebo: 207.5+/-108.5 days), but shorter in trial M2-125 (roflumilast: 201+/- 116.9 days versus placebo: 214.6+/-137.3 days). The hazard ratio for trials M2-124 and M2-125 were 1.035 (SE=0.357, p=0.92) and 1.213 (SE=0.35, p=0.5028), respectively.

Results for lower ranking key secondary endpoints, TDI (ranked third) and CRP (ranked fourth) demonstrated no meaningful differences between groups.

Safety Results

The adverse events profile reported in these trials were consistent with findings from other clinical trials. Refer to section 7 for the integrated safety review.

5.3.2 Studies M2-111 and M2-112

Trail Number	Trial Period (Total N*)	Countries (# of Centers)
M2-111	Dec 9, 2003 - Dec 2, 2005 (Total N=1176)	US (124, N=611) Canada (13), France (12), Germany (14), Poland (10) and South Africa (15)
M2-112	Jan 24, 2003 – Oct 27, 2004 (Total N=1514)	NON US Australia (11), Canada (21), Europe (101)-Austria, France, Hungary, Italy, Netherland, Poland, Portugal, Spain, Switzerland and UK; Russia (9) and South Africa (13)

Studies M2-111 and M20112 had similar conduct but different endpoints -- unlike those trial pairs discussed above. Because the complex history of the roflumilast development program, it is difficult to determine precisely what led to those differences. It appeared that these trials were designed by the original sponsor Altana and were intended serve as the potential phase 3 trials for registration for the US market. The trials stared with identical study protocol and the SAP (statistical analysis plan) was to pool their results. Trial M2-112 started to enroll patients in January 2003. Trial M2-111 did not start to enroll patients until December of the same year. During the same period, there were multiple protocol amendments for both trials. Because these trials were run on different time line, not all amendments were applicable to both trials. Trial 112 ended in Oct, 2004, the last 2 amendments (amendment 5 and 6) of trial M2-111 were dated in November 2005 and Februarys 2006. Amendments 5 and 6 of M2-111 added many changes that were later used in later trials, including addition of pre bronchodilator FEV1 as co primary variable and using Poisson regression instead of Wilcoxon rank sum test for exacerbation rate analysis. It's likely that both the preliminary results from trial 112 and FDA (DPAP) inputs contributed to those later amendments to trial M2-111 and the differences in endpoints between these trials.

Treatment groups and dose regimen

The treatment group and dose regimen in trails M2-111 and M2-112 were identical to those described for the pivotal trials. Eligible patients were randomized into 2 treatment groups: roflumilast 500 mcg once daily and placebo once daily.

However, concomitant use of ICS up to 2000 mcg/day ex valve (1680 ex actuator) of beclomethasone dipropionate or equivalent and short acting anticholinergics were permitted in trials M2-111 and M2-112, if patients were on a constant dose for 3 month or more prior to study enrollment. Uses of other COPD medications were restricted except rescue salbutamol, which was provided to all eligible subjects as MDI with spacer.

Eligibilities

The entry criteria for these trials were similar to those of the pivotal trials but with less restriction. Like the pivotal trials, patients were required to have severe disease (FEV1 $\leq$ 50% predicted) but were not required to have documented history of COPD exacerbation nor signs of chronic bronchitis. The COPD diagnosis was based on Gold rather than the revised ARS/ERS criteria and the requirement for smoking history was 10 rather than 20 pack-years. The main pertinent criteria for inclusion were:

- male or female ages $\geq$ 40 years
- $\geq$12 month history of COPD per GOLD criteria
- moderate or severe COPD with post bronchodilator FEV1/FVC $\leq$ 70%, FEV1 $\leq$ 50% predicted
- fixed airflow obstruction (FEV1 increase $\leq$ 12% or $\leq$ 200 mL after receiving 400 mcg salbutamol)
- current or former smoker, with $\geq$ 10 pack-years history
- absence of concurrent disease that might interfere with study procedure or evaluation

To be eligible for randomization, the patients needed to meet all of the following criteria:

- clinically stable, no moderate or severe COPD exacerbation between V0 (baseline) and V2 (randomization)
- medication compliance of 80% to 125% between V0 and V2
- Trial M2-111 also required negative hemoccult at screening

Patients who were not eligible for randomization were excluded from further study participation. Unlike in pivotal trials which permitted patients to reenroll once, if they did not meet the randomization criteria because of COPD exacerbation during run in period.

The main pertinent exclusions were similar to those described for the pivotal trials, except need for long term oxygen therapy (defined as $\geq$ 16 hours per day) was excluded in trials M2-111 and M2-112 but not in the pivotal trials. As Holter monitoring was Trials M2-111 also excluded patients who had baseline EKG or Holter findings that might interfere with interpretation of the Holter results.

Study Scheme and Conduct

The scheme and conduct of both trials were similar to those of the pivotal trials, which also consisted of 3 periods: a 4 week single blind run-in, a 52 week treatment and a 30 day follow up. Subject visits occurred at Weeks -4, -2, 0, 4, 8, 12, 20, 28, 36 44 and 52, during which assessments (including vital status, physical exams, body weight, AEs, labs, PFTs, ECGs/Holter, COPD symptoms and heath status) were made. PFTs were conducted according to ATS/ERS guidelines in centralized labs using sponsor provided spirometers. Twenty-four hour Holter monitoring was performed at selected sites in M2-111 only. SGRQ (St. George's respiratory questionnaire) was also evaluated in both trials.

Demographics

Both trials were multinational studies. While M2-111 included US sites, M2-112 was an international study. The number of subjects randomized in trials M2-111 and M2-112 were 1176 and 1514, respectively. The demographics and baseline characteristics of patients from trials M2-111 and M2-112 are shown in Table 19. Similar to the other trials discussed above, the study population in both trials was almost exclusively white and predominantly male. All other baseline characteristics were well matched between treatment groups within each trial and generally similar to other trials discussed above. The only exception was the FEV1 reversibility in patients from M2-111, which was higher than the other 5 Phase III trials reviewed.

Table 19 Demographics and Baseline Characteristics (M2-111 and M2-112)

Baseline Characteristics	M2-111 (ITT)		M2-112 (ITT)	
	Rof500 mcg (N=567)	Placebo (N=606)	Rof500 mcg (N=760)	Placebo (N=753)
Age				
median (range) in year	65 (40-87)	64 (41-86)	66 (40-88)	65 (40-89)
Gender				
Male, n (%)	387 (68.3)	400 (66)	571 (75.1)	574 (76.2)
Female, n (%)	180 (31.7)	206 (34)	189 (24.9)	179 (23.8)
Race (% randomized)				
White	532 (93.8)	564 (93.1)	753 (99.1)	746 (99.1)
Black	20 (3.5)	21 (3.5)	0	0
Asian	3 (0.5)	1 (0.2)	6 (0.8)	7 (0.9)
American Indian	0	1 (0.2)	0	0
Other	12 (2.1)	19 (3.1)	1 (0.1)	0
Weight				
mean+/- SD (kg) –M2-111	75 +/- 18.3	75 +/- 19.1		
or median (range)-M2-112			72 (33-138)	72 (35-150)
BMI				
mean+/- SD (kg/m^2)	26 +/- 5.7	26 +/- 5.7	25 +/- 5	26 +/- 5.1
Smoking Status				
% Current/former	42.3/57.7	43.7/56.3	38/62	34/66
mean Cigarette pack year +/- SD	50 +/- 28.2	51 +/- 26.7	42+/- 22.9	45+/-26.2
COPD Characteristics*				
Mild, n (%)	0	0		
Moderate, n (%)	64 (11.3)	45 (7.3)	N/A	N/A

Severe, n (%)	366 (64.6)	396 (65.3)		
Very severe, n (%)	137 (24.4)	165 (27.2)		
Chronic bronchitis, n, (%)			113 (24.7)	111 (22.4)
Emphysema, n, (%)			124 (27.1)	137 (27.6)
Both, n (%)			221 (48.3)	248 (50)
PreFEV1				
mean+/- SD (L)	0.96+/-0.4	0.93+/-0.3	1.029+/-0.345	1.047+/-0.344
(mean % predicted+/-SD)	(31.3+/-9.9)	(30.8+/-9.1)	(37.2+/-10.4)	(37.4+/-10.4)
FEV1 reversibility				
mean+/- SD (mL)	162.6+/-143.9	157.4+/-155.3	97.7+/-124.1	100.4+/-137.4

- *COPD severity was classified according to the value of post FEV1 as % predicted: mild (%), moderate (%), severe (FEV1 < 50 % and ≥ 30%), very severe (FEV1 < 30%)
- N/A, not tabulated in CSR.
- Source: Table 7, M2-111 CSR, pp 140. Table 5, M2-112 CSR, pp109.

Reviewer's comments: These earlier trials used GOLD rather than ATS/ERS definition for COPD and included COPD patients with both chronic bronchitis and emphysema. It should be noted that the study population in M2-111 had more reversibility than M2-112 and other trials discussed above (approximately 160 mL in M2-111 versus ≤100 mL in others).

Disposition

These trials had randomization and completion rates comparable to other trials discussed above. Between 65% (M2-111) and 82% (M2-112) patients enrolled were randomized and similar percentage of randomized patients completed the trial (M2-111: 62-69%, M2-112: 71-79%). In both trials, approximately 7% more subjects discontinued from the trial in the roflumilast treated group comparing to placebo, which was consistent with similar findings from other trials. The higher discontinuation rates in the roflumilast treated groups were driven by more adverse events. In trial M2-111 but not M2-112, slightly more patient withdrawal from the placebo group because of COPD exacerbation. However, the differences were small and not likely to be significant.

Table 20 Patient Disposition (Trials M2-111 and M2-112)

Disposition, N (%)	M2-111		M2-112	
Enrolled	1801		1829	
Randomized (% recruited)	1176 (65.3)		1514 (82.8)	
Not randomized (% recruited)	625 (34.7)		315 (17.2)	
Disposition, N (% randomized)	Rof500 mcg	Placebo	Rof500 mcg	Placebo
Randomized	568	608	761	753
Completed	352 (62)	421 (69.2)	544 (71.5)	590 (78.3)
Premature Discontinued	216 (38)	187 (30.8)	217(28.5)	163 (21.7)
Adverse events	113 (19.9)	67(11)	103 (13.5)	56 (7.4)
*Withdrew consent (M2-111)	93 (16.4)	77 (12.7)		
COPD exacerbation	32 (5.6)	26 (4.3)	27 (3.3)	24 (3.2)
*Lost to follow up (M2-111)	11 (1.9)	7 (1.2)		

*Met discontinuation criteria (M2-111)/ Other medical reasons (M2-112)	12 (2.1)	19 (3.1)	13 (1.7)	18 (2.4)
*Other reasons (M2-111)/ Non medical reasons (M2-112)	31 (5.5)	42 (6.9)	74 (9.7)	65 (8.6)

Source: M2-111 CSR, Table 4 and M2-112 CSR, Table 2. % Numbers in Table 2 M2-112 CSR were converted to % of randomized from % of discontinued to be consistent with results from M2-111 and other trials reviewed.
*Disposition data were classified differently in M2-111 and M2-112 and thus were labeled separately wherever applicable.

Compliance and protocol violations

The overall percentage of patients who had major protocol violations were similar between treatment groups and consistent with those reported from the other two 52 week trials (M2-124 and M2-125). Use of not allowed COPD medications and noncompliance were again the main causes of major protocol violations. In both trials, the rates of noncompliance were significantly higher in the roflumilast treated groups than that of the placebo groups. (Table 21)

Table 21 Top Causes of Major Protocol Violations in Trials M2-111 and M2-112

	M2-111 (ITT)		M2-112 (ITT)	
Major Violations N (% randomized)	Rof500 mcg (N=568)	Placebo (N=608)	Rof500 mcg (N=761)	Placebo (N=753)
Patients had major violations	151 (26.6)	140 (23)	247 (32.5)	217 (28.8)
Use of disallowed medications				
- Use CS or other disallowed medication during run in or treatment*	43 (7.6)	39 (6.4)	44 (5.8)	60 (8.8)
- Use disallowed ICS before trial or during treatment**	27 (4.8)	41 (6.7)	51 (6.7)	58 (7.7)
- Use disallowed anticholinergics before or during study	18 (3.2)	22 (3.6)	21 (2.8)	17 (2.3)
Noncompliance	53 (9.3)	18 (3)	122 (16)	66 (8.8)

*CS (systemic corticosteroids) or other not allowed medication not stopped at screening or started during treatment.
ICS (inhaled corticosteroids) use beyond what was permitted according to the protocol.
Source: Tables 5, CSR M2-111, pp 137. Table 3, CSR M2-112, pp 106.

Efficacy Results

As discussed earlier, due to amendments made to M2-111 protocol post completion of trial M2-112, these trials had different endpoints. The results will therefore be presented separately.

<u>M2-111:</u>

Although the actual phrases were different, the primary endpoints of trial M2-111 were nearly identical to those of the pivotal trials:

- The mean change from baseline during the treatment period in pre bronchodilator FEV1 based on repeat measurements ANCOVA analysis.

- The number of moderate COPD exacerbations treated with oral or parenteral glucocorticoids or severe COPD exacerbations per patient per year (abbreviated as rate of exacerbations below) based on Poisson regression model.

The key secondary endpoints for trial M2-111 were (in hierarchical order):

- The mean change from baseline during the treatment period in post bronchodilator FEV1 based on repeat measurements ANCOVA analysis.

- The number of moderate COPD exacerbations treated with oral or parenteral glucocorticoids or severe COPD exacerbations per patient per year in patients with different disease characters:

    - Baseline post bronchodilator FEV1 < 30% predicted (very severe) measured at the randomization visit V0. (V0 is used here for consistency with other trials. T0 was used in CSR)

    - History of chronic bronchitis and with or without history of emphysema

    - Cough score $\geq$ 2 in the week precede V0

    - Cough score $\geq$ 1 in the week precede V0

    - History of at least one moderate or severe COPD exacerbations in the year prior to screening (B0 is equivalent of V0)

- The number of moderate COPD exacerbations treated with oral or parenteral glucocorticoids and/or antibiotics (here a different definition for moderate exacerbation was used) or severe COPD exacerbations per patient per year

- The number of mild or moderate or severe COPD exacerbations per patient per year

Other secondary endpoints for trial M2-111 were:
- Additional analysis on PFT parameters not listed above
- Additional analysis on COPD exacerbations not listed above
- Change in BDI
- Change in patient diary
- Change in SGRQ
- Mortality
- Time to study withdrawal

Pre and post bronchodilator FEV1

Similar to those described for other studies reviewed, mean change during treatment in pre and post bronchodilator FEV1 from baseline were analyzed with repeat measurements ANOVA and the results are shown in Table 22. Consistent with findings from other roflumilast trials, patients treated with roflumilast had slight improves in pre-FEV1 (29 mL, ITT). In contrast, pre-FEV1 was largely unchanged (-7 mL, ITT) in patients received placebo. The difference between treatments was modest (36 mL, ITT) and confirmed in PP. Similar changes also occurred in post bronchodilator FEV1.

Table 22 Change in Pre and Post Bronchodilator FEV1 during Treatment from Baseline

M2-111, pre FEV1 (Repeated Measurement Analysis)

Δ in preFEV1 LS Mean in Lt (SD)	Rof500 mcg	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.029 (0.008) n = 488 obs = 2957	- 0.007 (0.007) n = 541 obs = 3526	0.036 (0.010) 95% CI (0.016, 0.055) P = 0.0003
PP	0.026 (0.009) n = 352 Obs = 2220	- 0.011 (0.008) n = 405 obs = 2574	0.037 (0.011) 95% CI (0.015, 0.059) P = 0.0011

M2-111, post FEV1 (Repeated Measurement Analysis)

Δ in post FEV1 LS Mean in Lt (SD)	Rof500 mcg	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.021 (0.008) n = 500 obs = 3020	- 0.017 (0.007) n = 534 obs = 3479	0.038 (0.010) 95% CI (0.018, 0.058) P = 0.0002
PP	0.026 (0.009) n = 361 Obs = 2262	- 0.022 (0.008) n = 410 obs =2617	0.048 (0.011) 95% CI (0.026, 0.71) P < 0.0001

n: number of patients with preFEV1 data available
obs: number of observations
Sources: Tables 10 (pre FEV1) and 15 (post FEV1) of CSR M2-111.

COPD Exacerbations

COPD exacerbations were the main focus of trial M2-111. Mean rate of COPD moderate or severe exacerbations were analyzed with Poisson regression and the results are shown in Table 23. Similar with findings from other trials, there was a 13.5% reduction in the rate of moderate or severe COPD exacerbation in the roflumilast treated group, comparing to placebo. However, the difference was not statistically significant in either ITT or PP population.

Table 23 Frequency of Moderate or Severe COPD Exacerbations per Patient per Year in Study M2-111

Mean Rate of Moderate or Severe COPD Exacerbations, M2-111 (Poisson regression)

	Rof500 mcg	Placebo	Rate Difference in % Change Rate Ratio (SE) 95% CI & P value
ITT Mean Rate of Exacerbation Per patient per year	0.623 N = 567	0.720 N = 606	- 13.5% RR = 0.865 (0.086) 95% CI (0.713, 1.051) P = 0.1440
PP Mean Rate of Exacerbation Per patient per year	0.552 N = 417	0.660 N = 468	- 16.4% RR = 0.836 (0.097) 95% CI (0.666, 1.050) P = 0.1237

Moderate exacerbations here refer to those treated with systemic steroids only.
Rate difference = 1-RR. RR = Rate ratio: roflumilast/placebo. SE: standard error
N: number of patients randomized in the respective treatment group.
Sources: Tables 13 in section 11.4.2.2 of CSR M2-111, pp148.

Non parametric analysis with Wilcoxon rank sum test reached statistical significance (results not shown here, refer to Table 14 of CSR). However, because the method did not correct for subject heterogeneity, the results is considered not as realizable as that of Poisson regression.

The secondary endpoints were to compare the rate of moderate or severe COPD exacerbation in patients with different disease characteristics. Subgroup analyses were stratified on COPD severity, presence of chronic bronchitis, productive cough, h/o COPD exacerbation, concomitant COPD treatments, smoking and study completion status. The results are shown in Table 25. Roflumilast treated patients from certain subgroups did better than their respective subgroup comparator. However, the between treatment differences for these better responder subgroups were still not statistically significant comparing to their respective placebo group. The subgroups of COPD patients had greater reduction in moderate or severe COPD exacerbation induced:

- patients had severe disease with FEV1 between 30 and 50% predicted
- patients had chronic bronchitis
- patients had cough or sputum score of 2 or greater
- patients had concomitant long acting anticholinergic treatment

The only subgroups that reached statistical significance in between treatment difference were patients with cough and/or sputum score of 2 or greater.

In contrast, among those with very severe COPD disease (FEV1 < 30% predicted) or emphysema (without chronic bronchitis), roflumilast treated patients did worse than the placebo group. Additionally, previous history of moderate or severe COPD exacerbation and concomitant ICS use during the treatment made little difference in COPD exacerbation rate.

Table 24 Subgroup analysis according to COPD characteristics (M2-111, Poisson regression, ITT)

Subgroups		Rof500 mcg		Placebo		Treatment Differences			
		N	Rate	N	Rate	% Rate Δ	Rate Ratio	95% CI	P value
FEV1 % predicted	< 30%	137	1.054	165	0.971	8.6	1.086	0.764, 1.542	0.6466
	30-50%	366	0.546	396	0.695	-21.5	0.785	0.608, 1.014	0.0640
Chronic bronchitis	No *	193	0.715	234	0.689	3.8	1.038	0.747, 1.442	0.8255
	Yes	374	0.614	372	0.758	-19.0	0.810	0.629, 1.044	0.1036
Mean cough score	< 2	420	0.656	468	0.661	-0.7	0.993	0.790, 1.247	0.9498
	≥ 2	124	0.631	117	1.026	-38.5	0.615	0.401, 0.944	0.0261
Mean sputum score	< 2	431	0.651	469	0.657	-0.9	0.991	0.790, 1.243	0.9369
	≥ 2	112	0.643	117	1.046	-38.5	0.615	0.394, 0.960	0.0323
h/o COPD** Exacerbations	No	220	0.452	235	0.521	-13.3	0.867	0.601, 1.253	0.4485
	Yes	217	0.910	229	1.081	-10.6	0.894	0.680, 1.175	0.4214
Concomitant LAMA	No	233	0.411	256	0.413	-0.5	0.995	0.676, 1.464	0.9788
	Yes	334	0.832	350	0.995	-16.4	0.836	0.665, 1.051	0.1247
Concomitant ICS	No	239	0.441	270	0.506	-12.9	0.871	0.622, 1.220	0.4212
	Yes	328	0.807	332	0.933	-13.5	0.865	0.680, 1.100	0.2366

Source: Table 17 M2-111 CSR, pp 153.
N: number of randomized patients in each respective treatment groups.
% Rate Δ: percent rate change = 1-RR. Rate ratio: rof500 mcg/placebo
* No chronic bronchitis refers to COPD patients with emphysema only.
** History of moderate (require systemic steroids) or severe (hospitalization) COPD exacerbations in the year prior to screening.

Study M2-112:

The primary endpoints for trial M2-112 were:

- Frequency of moderate or severe exacerbations per patient per year
- Change (endpoint minus baseline value) in post bronchodilator FEV1

Key secondary endpoint for trial M2-112 was:

- change in total score of SGRQ

Other secondary endpoints for trial M2-112 were:

- pre and post bronchodilator PFT parameters
- all exacerbations (mild, moderate and severe)
- SGRQ total and component score
- Morning PEF (diary)
- COPD symptom score and use of rescue medications

Pre and post bronchodilator FEV1

The statistic analysis plan in trial M2-112 was slightly different from other later trials reviewed here. Last value analysis, instead of repeat measurement analysis, was used as primary statistical method to compare within and between treatments differences in lung function parameters. Nevertheless, the results were consistent with findings from other roflumilast trials, patients treated with roflumilast had slight improves in pre-FEV1 (9 mL, ITT). In contrast, pre-FEV1 decreased (-27 mL, ITT) in patients received placebo. The difference between treatments was modest (36 mL, ITT) and confirmed. Similar changes also occurred in post bronchodilator FEV1. (Table 25)

Table 25 Change in Pre and Post Bronchodilator FEV1 during Treatment from Baseline (M2-112)

M2-112, pre FEV1, (Last Value Analysis)*

Δ in preFEV1 LS Mean in Lt (SD)	Rof500 mcg	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.009 (0.011) n = 705	- 0.027 (0.011) n = 710	0.036 (0.012) 95% CI (0.014, 0.059) P = 0.0009

M2-112, post FEV1, (Repeated Measurement Analysis)*

Δ in post FEV1 LS Mean in Lt (SD)	Rof500 mcg	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.035 (0.008) n = 701 obs = 4576	- 0.013 (0.008) n = 720 obs = 5060	0.0438 (0.009) 95% CI (0.030, 0.065) P < 0.0001

Pre FEV1 was secondary endpoint, post FEV1 was primary endpoint. Repeat measurement analysis was not the primary method of analysis specified by SAP in trial M2-112.
n: number of patients with preFEV1 data available.
obs: number of observations
Sources: Tables 25 (pre FEV1), pp128 and Table 13 (post FEV1), pp117 of CSR M2-112.

COPD Exacerbations:

Mean rate of COPD exacerbations were analyzed primarily with non parametric testing (Wilcox-rank sum). Poisson regression was performed as secondary analysis. To be consistent with other trials reviewed, only results from Poisson regression are presented below in Table 26. Similar with findings from other trials, there was a 13.6% reduction in the rate of moderate or severe COPD exacerbation in the roflumilast treated group, comparing to placebo when the definition for moderate exacerbation was use of systemic corticosteroids. When antibiotics use alone was included as moderate exacerbation in addition to systemic steroids, the rate difference drop to 6.6%. Nevertheless, the differences were not statistically significant regardless the definition used for moderate COPD exacerbation.

Table 26 Frequency of Moderate or Severe COPD Exacerbations per Patient per Year in Study M2-112

Mean Rate of Moderate or Severe COPD Exacerbations, M2-112 (ITT, Poisson regression)

	Rof500 mcg N = 760	Placebo N = 753	Rate Difference in % Change Rate Ratio (SE), 95% CI & P value
Mean Rate of Moderate or Severe* Exacerbation Per patient per year	0.857	0.918	- 6.6 % RR = 0.934 (0.075) 95% CI (0.798, 1.092) P = 0.3901
Mean Rate of Moderate or Severe Exacerbation** Per patient per year	0.474	0.549	- 13.6% RR = 0.864 (0.090) P = 0.1599

* Moderate exacerbations here refer to those treated with systemic steroids and/or antibiotics.
* *Moderate exacerbations here refer to those treated with systemic steroids only.
Rate difference: 1- RR. RR = Rate ratio: roflumilast/placebo. SE: standard error.
N: number of patients randomized in the respective treatment group.
Sources: Table16, pp119 and Table 18, pp121 of CSR M2-112.

Furthermore, there were no statistically significant between treatment differences in percentage of patients experiencing any COPD exacerbation (Fisher's exact test), in numbers of observed COPD exacerbations and in time to onset of first exacerbation (log rank sum test).

SGRQ

St. George's respiratory questionnaire (SGRQ) was the primary clinical endpoint chosen to demonstrate roflumilast superiority over placebo in early roflumilast trails. Change in total score of SGRQ (was the sole key secondary endpoint in trial M2-112. The within and between treatment differences are shown in Table 27. There was no meaningful difference between the roflumilast treated and the placebo treated groups (a clinically meaningful change in SGRQ is a difference of 4 or more units).

Table 27 Change in SGRQ Total Score during Treatment from baseline

	Δ LS Mean SGRQ Total Score (SEM) p value		Treatment Difference LS Mean (SEM) 95% CI & P value
	Rof500 mcg	Placebo	
ITT	N = 691 -1.7 (0.6) P = 0.0048	N = 712 -2.0 (0.6) P = 0.0010	0.3 (0.7) 95% CI (-1.0, 1.6) P = 0.6745
PP	N = 418 -3.7 (0.8) P <0.001	N = 447 -3.2 (0.8) P <0.001	- 0.5 (0.8) 95% CI (-2.1, 1.1) P = 0.2684

Δ LS Mean = LS mean SGRQ total score at end of study visit Vend – LS mean SGRQ total score at randomization visit V2. (In trial M2-112, V2=T0, Vend =T last)
SEM: standard error of the mean.
N: number of patients randomized in the respective treatment group.
Sources: Tables 20 and 21, pp123 CSR M2-112.

5.3.3 Studies M2-127 and M2-128

Trail Number	Trial Period (Total N*)	Countries (# of Centers)
M2-127	April 28, 2006 - July 3, 2007 (Total N=935)	NON US Canada (25), Europe (98)-Austria, Belgium, Germany, France, Italy, Netherland, Spain, UK and South Africa (12)
M2-128	Jan 5, 2007 - Jan 31, 2008 (Total N=744)	NON US Europe (85)-Austria, France, Germany, Hungary, Italy, Spain and UK

These 24 week replicate trials were submitted as additional evidence to support roflumilast registration and demonstrate the superiority of roflumilast over placebo at improving lung function (FEV1) in patients with moderate to severe COPD in a "real-world like" setting -- on maintenance long acting bronchodilator therapy.

Treatment groups and dose regimen

In trail M2-127, eligible patients were randomized into 2 treatment groups:
- roflumilast 500 mcg once daily (in the morning after breakfast) plus salmeterol (Serevent Diskus) 50 mcg twice daily (in the morning and in the evening)
- placebo once daily plus salmeterol (Serevent Diskus) 50 mcg twice daily

Similarly, in trail M2-128, eligible patients were randomized into 2 treatment groups:
- roflumilast 500 mcg once daily (in the morning after breakfast) plus tiotropium (Spiriva HandiHaler) 18 mcg once daily (in the morning)
- placebo once daily plus tiotropium (Spiriva HandiHaler) 18 mcg once daily

Uses of other COPD medications were restricted. Rescue salbutamol MDI with spacer was provided to eligible subjects.

Eligibilities

The population in both trials consisted of patients with moderate to severe COPD. Trial M2-128 also required history of chronic productive cough prior to trial participation and frequent rescue medication use during the run-in period. The main pertinent criteria for inclusion were:

- male or female ages $\geq$ 40 years
- $\geq$12 month history of COPD per ATS/ERS criteria
- moderate or severe COPD with post bronchodilator FEV1/FVC $\leq$ 70%, 40% $\leq$ FEV1 $\leq$ 70% predicted
- fixed airflow obstruction (FEV1 increase $\leq$ 12% or $\leq$ 200 mL after receiving 400 mcg salbutamol)
- current or former smoker, with $\geq$ 10 pack-years history
- absence of concurrent disease that might interfere with study procedure or evaluation

Additional requirements for trial M2-128 for enrollment: pretreatment with tiotropium for 3 month before baseline visit (V0) and history of chronic productive cough for 3 months in EACH of the 2 years prior to V0, excluding causes other than COPD.

To be eligible for randomization, the patients needed to meet all of the following criteria:

- clinically stable, no moderate or severe COPD exacerbation between V0 (baseline) and V2 (randomization)
- medication compliance of 80% to 125% between V0 and V2

Trial M2-128 also required $\geq$ 28 puffs of rescue medication use during the last week directly preceding the randomization visit (V2).

Patients who were not eligible for randomization were excluded from further study participation.

The main pertinent exclusions were:

- unstable patients
- recent COPD exacerbation required treatment with systemic corticosteroids and/or antibiotics that were not discontinued at least 4 weeks before V0
- recent lower respiratory tract infections not resolved at least 4 weeks before V0
- known history of alpha-1 antitrypsin deficiency or carrying diagnosis of other pulmonary diseases
- presence of other concurrent disease(s) or condition(s) that might interfere with study procedure, evaluation or jeopardize patient safety
- unable to give consent or compliant with protocol requirements

Study Scheme and Conduct

The scheme and conduct of both trials were similar to those of the pivotal trials, which consisted of a screening visit and 3 study periods: a 4 week single blind run-in, a 24 week treatment and a 30 day follow up. Subject visits occurred at Weeks 2, 4, 8, 12, 18 and 24 during which assessments (including AEs, labs, PFTs, ECGs, COPD symptoms and heath status) were made. PFTs were conducted according to ATS/ERS guidelines in centralized labs using sponsor provided spirometers. Spirometry results were reviewed by a central reviewer. Patients unable to generate reproducible acceptable spirometry results were excluded from enrollment or randomization.

Demographics

Both trials were international studies and did not have any US centers. While M2-127 included sites from Canada and South Africa, M2-128 was a pure European study. The number of subjects randomized in trials M2-127 and M2-128 were 935 and 744, respectively. Nearly all subjects in both trials were white (>95% in M2-127 and 100% in M2-128) and significantly more males (65-70%) than female (30-35%). All demographic characteristics were generally similar across treatment groups in both trials (Table 28).

Table 28 Demographics and Baseline Characteristics in Trials M2-127 and M2-128

	M2-127 (ITT)		M2-128 (ITT)	
Baseline Characteristics	Rof500 mcg & salmeterol (N=466)	Placebo & salmeterol (N=467)	Rof500 mcg & tiotropium (N=371)	Placebo & tiotropium (N=372)
Age				
median (range) in year	65 (42-87)	65 (40-89)	65 (40-91)	65 (41-87)
Gender				
Male, n (%)	319 (68.5)	299 (64)	262 (70.6)	267 (71.8)
Female, n (%)	147 (31.5)	168 (36)	109 (29.4)	105 (28.2)
Race (% randomized)				
White	445 (95.5)	444 (95.1)	371 (100)	371 (99.7)
Black	1 (0.2)	2 (0.4)	0	0
Asian	2 (0.4)	2 (0.4)	0	1 (0.3)
Other	18 (3.9)	19 (4.1)	0	0
Weight				
mean +/- SD (kg)	76.9 +/-15.3	76.4+/-17.5	78.4+/-17.7	80.0+/-17.3
Smoking Status				
% Current/former	60.5/39.3	60.6/39.4	60.4/39.6	60.8/39.2
Cigarette pack years	42.5+/-21.9	42.5+/-21.9	42.8+/-22.3	42.1+/-22.0
COPD Characteristics*				
Mild n, (%)	1 (0.2)	2 (0.4)	8 (2.2)	11 (3.0)
Moderate n, (%)	303 (65)	324 (69.4)	235 (63.3)	240 (64.5)
Severe n, (%)	162 (34.8)	141 (30.2)	125 (33.7)	119 (32)
Very severe n, (%)	0	0	3 (0.8)	2 (0.5)
PreFEV1				
mean+/- SD (L)	1.434+/-0.395	1.412+/-0.409	1.5+/-0.5	1.5+/-0.5
(mean % predicted+/-SD)	(51.89+/-9.55)	(52.4+/-9.84)	(53.3+/-11.7)	(53.4+/-11.6)
FEV1 reversibility				
mean+/- SD (mL)	75.24+/-122.32	80.73+/-119.57	75.1+/-128.1	74.0+/-125.3

*COPD severity was defined base on FEV1/FVC ratio as % predicted: mild (%), moderate (%), severe (%), very severe (%)
Source: Tables 9-11, M2-127 CSR, p.77, 78 and 80 of 40808 and M2-128 CSR, p.84, 85 and 87 of 36704, respectively.

Disposition

These trials had the highest randomization and completion rates among the 6 trials reviewed. Nearly 80% patients enrolled (77-82%) were randomized and similar percentage of patients randomized (77-89%) completed the trial. In both trials, approximately 5% more subjects discontinued from the trial in the roflumilast treated group comparing to placebo. The higher discontinuation rates in the roflumilast treated groups were driven by more adverse events and patient's consent withdrawals. In both trials, slightly more patient withdrawal from the placebo group because of COPD exacerbation or lack of efficacy. Nevertheless, the differences were small and not likely to be significant. Approximately 5% more subjects completed the study in trial M2-128 (83.2% roflumilast plus tiotropium, 89.5% placebo plus tiotropium) than trial M2-127 (77.1% roflumilast plus salmeterol, 82.5% placebo plus salmeterol). Trial M2-128 also had lowest rate of withdraw due to COPD exacerbation for both the roflumilast and the placebo

group, 1.1% and 2.2% respectively, comparing to 3.4-5.8% in M2-127, and 5.6-9.1% in the pivotal trials. Refer to Table 29 for disposition data from trials M2-127 and M2-128.

Table 29 Patient Dispositions (Trials M2-127 and M2-128)

Disposition, N (%)	M2-127		M2-128	
Enrolled	1221		910	
Not randomized (% recruited)	286 (23.4)		166 (18.2)	
N (% randomized)	Rof500 mcg	Placebo	Rof500 mcg	Placebo
Randomized	467	468	372	372
Completed	360 (77.1)	386 (82.5)	310 (83.3)	333 (89.5)
Premature Discontinued	107 (22.9)	82 (17.5)	62(16.7)	39 (10.5)
Adverse events	77 (16.5)	45 (9.6)	33 (8.9)	20 (5.4)
Withdrew consent	52 (11.1)	39 (8.3)	27 (7.3)	11 (3.0)
COPD exacerbation	16 (3.4)	27 (5.8)	4 (1.1)	8 (2.2)
Lost to follow up	2 (0.4)	2 (0.4)	3 (0.8)	5 (1.3)
Met discontinuation criteria	3 (0.6)	12 (2.6)	1 (0.3)	2 (0.5)
Other reasons	8 (1.7)	7 (1.5)	3 (0.8)	4 (1.1)

Source: M2-127 CSR, Tables 6, CSR of M2-127 and M2-128.

Compliance

Although the overall percentage of patients who had major protocol violations were similar to those in the pivotal trials, significantly less percentage of patients use the disallowed medications in these trials possibly because they were treated concomitantly with LABAs or LAMAs (approximately 5% in M2-127 and 2-3% in M2-128 versus 14-18% in the pivotal trials). There was also less non compliance with the trial drug in these trials (approximately 1% or less in M2-127 and M2-128 versus 6-10% in the pivotal trials).

Table 30 Top Causes of Major Protocol Violations (Trials M2-127 and M2-128)

Major Violations N (% randomized)	M2-127 (ITT)		M2-128 (ITT)	
	Rof500 mcg (N=467)	Placebo (N=468)	Rof500 mcg (N=772)	Placebo (N=796)
Patients had major violations	107 (22.9)	99 (21.2)	68 (18.3%)	70 (18.8)
Use of disallowed medications	25 (5.4)	25 (5.3)	8 (2.2)	1 (3.0)
Noncompliance with study drug	3 (0.6)	1 (0.2)	5 (1.3)	5 (1.3)

Source: Tables 7 in Sections 10.2 of CSR M2-127 and CSR M2-128

Reviewer's comments: The non compliance rate related to intake of COPD medications in trials M2-127 (add on to LABA) and M2-128 (add on to LAMA) was significantly lower than that of the pivotal trials is consistent with the known benefits of LABA or LAMA.

Efficacy results

The primary endpoint for both trials was the mean change in pre bronchodilator FEV1 from baseline to each post randomization visit during the treatment period.

The key secondary endpoints differed for trials M2-127 and M2-128.

M2-127:

- the rate of COPD exacerbations (mild, moderate or severe)
- TDI focal score during the treatment period
- mean change in SGRQ from baseline to each post randomization visit during the treatment period

M2-128:

- mean change in pre bronchodilator FEV1 from baseline to each post randomization visit (same as the first rank key secondary endpoint of pivotal trials M2-124 and M2-125)

- mean rate of COPD exacerbations (moderate or severe) per patient per year (same as the co primary endpoint in pivotal trials M2-124 and M2-125)

Similarly, to reduce overall type I error, the statistical analysis plan (SAP) specified that the primary and key secondary endpoints were to be analysis according a predetermined order as listed above. If one endpoint failed to reach statistical significance, analysis on all lower ranking endpoints were considered exploratory.

As trials M2-127 and M2-128 were to provide additional supports to the pivotal trials, this review will limit its discussion on efficacy endpoints to pre and post bronchodilator FEV1 and COPD exacerbation, which were the co primary and first rank key secondary endpoints discussed in the pivotal trials.

A. Pre and Post Bronchodilator FEV1

Pre bronchodilator FEV1

Mean change in pre and post bronchodilator FEV1 from baseline to each post randomization visit during the treatment period were analyzed with repeat measurements ANOVA and the results are shown in Tables 31 and 32. Similar to the findings of other roflumilast trials, patients treated with roflumilast and LABA (M2-127) or LAMA (M2-128) had improvements in pre-FEV1 (49-80 mL, ITT). In contrast, pre-FEV1 deteriorated slightly (10-18 mL) in patients who received placebo and LABA or LAMA. The between treatment differences in M2-127 (45 and 49 mL for PP and ITT respectively) were similar to those in the pivotal trials (47-67 mL and 39-58 mL for PP and ITT respectively), but were slightly smaller than that observed in M2-128 (76 and 80 mL for PP and ITT respectively).

Table 31 Mean Change in pre FEV1 during Treatment from Baseline in studies M2-127 and M2-128

M2-127 (Repeated Measurement Analysis)

Δ in preFEV1 LS Mean in Lt (SD)	Rof500 mcg plus salmeterol	Placebo plus salmeterol	Treatment Difference Roflumilast - Placebo
ITT	0.039 (0.009) n = 456 obs = 1987	- 0.010 (0.009) n = 463 obs = 2106	0.049 (0.011) 95% CI (0.027, 0.071) P < 0.0001
PP	0.027 (0.010) n = 355 Obs = 1583	- 0.018 (0.009) n = 365 obs = 1668	0.045 (0.012) 95% CI (0.021, 0.068) P = 0.0002

M2-128 (Repeated Measurement Analysis)

Δ in preFEV1 LS Mean in Lt (SD)	Rof500 mcg plus tiotropium	Placebo plus tiotropium	Treatment Difference Roflumilast - Placebo
ITT	0.065 (0.012) n = 365 obs = 1660	- 0.016 (0.012) n = 364 obs = 1744	0.080 (0.015) 95% CI (0.051, 0.110) P < 0.0001
PP	0.063 (0.013) n = 300 Obs = 1331	- 0.013 (0.013) n = 297 obs =1357	0.076 (0.016) 95% CI (0.045, 0.108) P < 0.0001

n: number of patients with preFEV1 data available
obs: number of observations
Sources: Tables 12 of sections 11.4.1.1 in CSR M2-127 and CSR M2-128.

Post bronchodilator FEV1

Similarly, the post bronchodilator FEV1 also improved in roflumilast treated groups and deteriorated in the placebo groups. Again, the treatment differences between roflumilast and placebo were small (60-81 mL, ITT) but statistically significant and consistent with results from other trials (Table 32).

Table 32 Mean Change in post FEV1 during Treatment from Baseline in studies M2-127 and M2-128

M2-127 (Repeated Measurement Analysis)

Δ in post-FEV1 LS Mean in Lt (SD)	Roflumilast plus salmeterol	Placebo plus salmeterol	Treatment Difference Roflumilast - Placebo
ITT	0.068 (0.009) n = 452 obs = 1978	0.008 (0.009) n = 460 obs = 2096	0.060 (0.011) 95% CI (0.038, 0.082) P < 0.0001

M2-128 (Repeated Measurement Analysis)

Δ in post-FEV1 LS Mean in Lt (SD)	Roflumilast plus tiotropium	Placebo plus tiotropium	Treatment Difference Roflumilast - Placebo
ITT	0.074 (0.012) n = 364 obs = 1653	- 0.007 (0.0011) n = 363 obs = 1735	0.081 (0.015) 95% CI (0.051, 0.110) P < 0.0001

n: number of patients with preFEV1 data available

obs: number of observations
Sources: Tables 17 of section 11.4.2.2.1 in CSR M2-127 and Table 13, section 11.4.2.1.1 in CSR of M2-128.

B. COPD Exacerbations

COPD exacerbations were examined in both trials, but not as primary endpoints as in the pivotal trials. The exacerbation endpoints were also defined and analyzed somewhat differently in trials M2-127 and M2-128 and thus will be discussed separately below wherever necessary.

Mean rate of COPD exacerbations

In trial M2-127, mean rate of all COPD exacerbations (mild, moderate and severe), rather than moderate or severe exacerbations, was defined as the first rank key secondary endpoints in the SAP. Analysis with Poisson regression according to the SAP showed 20% reduction in the rate of all COPD exacerbations in the in the roflumilast-salmeterol (the test) treated group comparing to those of placebo-salmeterol (the control) treated. However the difference was not statistically significant (p=0.1408). Post-hoc analysis showed statistically significant 36.8% (p = 0.0315) reduction of moderate or severe exacerbation in the test group, driven primarily by moderate exacerbations as those in the pivotal trials.

In trial M2-128, mean rate of moderate or severe exacerbation was the second rank key secondary endpoints. Analysis with Poisson regression showed 23% reduction in moderate or severe COPD exacerbations in the roflumilast-tiotropium treated patients comparing to those of placebo-tiotropium treated, however, the difference was not statistically significant (p=0.1957).

Table 33 Mean rate of COPD exacerbations per patient per year

Mean Rate of COPD Exacerbations, M2-127 (SAP and post-hoc Poisson regression, ITT)

COPD exacerbation severity	Rof500 mcg plus salmeterol	Placebo plus salmeterol	Rate Difference (% change) Rate Ratio
Mean Rate of mild, moderate or sever exacerbations per patient per year (SAP)	1.9 N = 131	2.4 N = 159	- 20.7% RR = 0.79 95% CI (0.58, 1.08) P = 0.1408
Mean Rate of moderate or sever exacerbations per patient per year (post-hoc)	0.3 N = 51	0.5 N = 83	- 36.8% RR = 0.63 95% CI (0.42, 0.96) P = 0.0315

Mean Rate of Moderate or Severe COPD Exacerbations, M2-128 (Poisson regression, ITT)

COPD exacerbation severity	Rof500 mcg plus tiotropium	Placebo plus tiotropium	Rate Difference (% change) Rate Ratio (SE)
Mean Rate of moderate or	0.262	0.342	- 23.2 % RR = 0.768 (0.157)

severe exacerbations per patient per year	N = 42	N = 58	95% CI (0.515, 1.146) P = 0.1957

Rate difference: roflumilast plus LABA or LAMA – placebo plus LABA or LAMA. RR = Rate ratio: roflumilast/placebo. SE: standard error
N: number of patients randomized in the respective treatment group.
Sources: Tables 13 and 24 (M2-127) in section 11.4.2.1 and 11.4.2.2.5 respectively in CSR M2-127 and Table 14 (M2-128) of section 11.4.2.1.1 in CSR of M2-128.

Risk of COPD exacerbation per patient per year (log binomial regression)

Risks of COPD exacerbations per patient per year were analyzed using the log binomial regression. In both trials, the overall risk of COPD exacerbations (all category = mild, moderate or severe) were lower in roflumilast treated group comparing to placebo. These differences were mostly driven by reduction in risk of moderate exacerbation in M2-127. The risk ratio of testing drug to placebo was 0.618 (SE=0.107, p=0.0055) for mild exacerbation and 0.582 (SE=0.274, p=0.2505) for severe exacerbation. In trial M2-128, there were no statistically significant differences in the risk of either moderate or severe exacerbation. The risk ratio for moderate and severe exacerbation were 0.735 (SE=0.135, p=0.1121) and 0.623 (SE=0.453, p=0.5151). (Tables 23, section 11.4.2.2.5, CSR of M2-127 and M2-128)

Time to first COPD exacerbation (Cox proportional hazards)

In trial M2-127, analysis on time to first COPD exacerbation showed hazard ratio (roflumilast-salmeterol/placebo-salmeterol) of 0.6 (p=0.0158) in median time to onset of first moderate COPD exacerbation, 0.7 (p=0.3699) for that of first severe exacerbation. Similarly, the hazard ratio for moderate and severe exacerbation was 0.8 (p=0.2055) and 0.7 (p=0.5868) respectively in trial M2-128. Kaplan-Meier plots can be found in Figures 11.4.2.1 in respective sections of CSR of both trials.

Unlike the pivotal trials, subgroup analysis was not performed, nor did the analyses of numbers need to treat (NNT), number of COPD exacerbation days and duration of COPD exacerbation.

Safety Results

The adverse events profile reported in these trials were consistent with findings from other clinical trials. Refer to section 7 for the integrated safety review.

5.3.4 Studies FK1-101 and M2-107 (included a roflumilast 250 mcg once daily dose)

Studies FK1-101 and M2-107 were two of the earlier late Phase 2/3 clinical studies and included a lower dose (250 mcg once daily) of roflumilast than any of the later Phase 3 clinical studies. As such, these two studies represent the roflumilast dose-ranging program. Regarding dosing interval, once daily dosing was used throughout the roflumilast clinical development program based on a single PK study in healthy volunteers, which suggested that roflumilast and its active metabolite (N-oxide) has a respective half lives of 17 and 30 hours. Dosing intervals less than or

greater than 24 hours were not evaluated in COPD clinical trials. Highlights of trials FK1-101 and M2-107 are summarized below.

Trail Number	Trial Period (Total N*)	Countries (# of Centers)
FK1101	Oct 8, 1999 to Feb 12, 2001 (Total N=516)	NON US Germany (17), Hungary (8), South Africa (9) and The Netherlands (1 3)
M2-107	April 5, 2002 to June 17 2003 (Total N=1411)	NON US Australia (9), Austria (9), Belgium (10), Canada (26), France (14), Germany (17), Hungary (10), Ireland (6), South Africa (11), Spain (15) and the UK (32).

Trials M2-107 and FK1-101 had similar designs. Both were double-blind, placebo-controlled, parallel-group multinational studies conducted outside the US. Trial FK1-101 was a phase II/III trial with 2 week run-in followed by 26 week treatment. Trial M2-107 was a phase III trial with 4 week run-in and 24 week treatment.

Co-primary endpoints were pre bronchodilator FEV1 and St. George's Respiratory Questionnaire (SGRQ) in trial FK1-101 and post bronchodilator FEV1 and SGRQ in trial M2-107. SGRQ as primary or key secondary endpoint was the hallmark of earlier COPD trials however it was not evaluated in the pivotal trials.

Treatment groups and dose regimen

The treatment group and dose regimen in trails FK1-101 and M2-107 were different from the other 6 phase III trials discussed earlier. Eligible patients were randomized into 3 treatment groups: roflumilast 500 mcg, roflumilast 250 mcg once daily and placebo once daily at 1:1:1 ratio in trial FK1-101, 2:2:1 ratio in trial M2-107.

Concomitant uses of systemic or inhaled steroids and long acting beta agonists were not permitted. Stable daily dose of anticholinergics (did not specify long or short acting in FK1-101 but had to be short acting in M2-107) were permitted except if taken within 6 hours before spirometry measurement. Uses of other COPD medications were also restricted except rescue salbutamol, which was provided to all eligible subjects as MDI with spacer.

Eligibilities

The entry criteria for these trials were similar to those described for trials M2-111 and M2-112 but included COPD patients across the entire spectrum of disease severity. The main pertinent criteria for inclusion were:

- male or female ages $\geq$ 40 years (also $\leq$ 75 for FK1-101)
- $\geq$12 month history of COPD per GOLD criteria
- Mild, moderate or severe COPD with post bronchodilator FEV1/FVC $\leq$ 70%, FEV1 between 30 and 75% predicted (30-80% for M2-107)
- fixed airflow obstruction (FEV1 increase $\leq$ 12% or $\leq$ 200 mL after receiving 400 mcg salbutamol)

- current or former smoker, with ≥ 10 pack-years history
- absence of concurrent disease that might interfere with study procedure or evaluation

To be eligible for randomization, the patients needed to meet all of the following criteria:
- reconfirm that patients still meet the spirometry requirement defined in eligibility
- medication compliance of 80% to 125% between V0 and V2
- no restrictions on COPD exacerbation during the run-in period (different from most later trials)

The main pertinent exclusions were similar to those described for other trials discussed above. Patients who required ≥ 12 puff per day of rescue inhaler (both trials) or had language or carried diagnosis for psychiatric disorders were excluded (FK1101 only).

In trial FK1-101, patients were not permitted to remain in the study if they met the escape criteria which were as fined as having ether 3 moderate or 1 severe COPD exacerbation. This is different from later trials in which patients were allowed to stay on if the exacerbation occurred during the treatment but not during the run-in.

Study Scheme and Conduct

The scheme and conduct of both trials were similar to those described for others. The trials consisted of 3 periods: a 2 (FK1-101) or 4 (M2-107) week single blind run-in, a 26 2 (FK1-101) or 24 (M2-107) week double blind treatment and an optional safety follow up of needed. Subject visits occurred at 2-4 weeks interval. Assessments included vital status, physical exams, AEs, labs, PFTs, ECGs, COPD symptoms and quality of life assessments. PFTs were conducted according to ATS/ERS guidelines in centralized labs using sponsor provided spirometers. SGRQ and global rating scale (GRS) were evaluated in both trials. SF-36 and exercise tolerance (6 min walk) were evaluated only in FK1-101.

Demographics

Both trials were multinational non US studies. The number of subjects randomized in trials FK1-101 and M2-107 were 516 and 1411, respectively. Similar to other trials discussed above, the study population in both trials was almost exclusively white and predominantly male. In trial FK1-101, the patients were younger and smoked less comparing to M2-107 and other trials reviewed. Baseline pre bronchodilator FEV1 resembled trials with similar FEV1 entry criteria. All other baseline characteristics were well matched between treatment groups within each trial.

Table 34 Demographics and Baseline Characteristics (FK1-101 and M2-107)

	FK1-101 (ITT)			M2-107 (ITT)		
Baseline Characteristics	Roflumilast 500 mcg (N=169)	Roflumilast 250 mcg (N=175)	Placebo (N=172)	Roflumilast 500 mcg (N=555)	Roflumilast 250 mcg (N=578)	Placebo (N=280)
Median Age (range)	61 (42-75)	60 (41-75)	62 (42-75)	64 (42-87)	65 (40-86)	63 (40-82)
Gender, Male, n (%)	122 (72)	121 (69)	129 (43)	410 (73.9)	419 (72.5)	207 (73.9)

Current smoker, n (%) mean pack year +/- SD	88 (52) 36 +/- 18	95 (54) 37 +/- 21	92(53) 38 +/-22	254 (45.8) 41+/- 20.6	267 (46.2) 43+/-24.1	125 (44.6) 43+/-22
preFEV1 mean+/- S(L) (mean % predi+/-SD)	1.53+/-0.43 (52+/-11)	1.55+/-0.42 (52+/-10)	1.48+/-0.40 (51+/-10)	1.41+/-0.49 (51+/-14)	1.40+/-0.47 (50+/-13)	1.45+/-0.48 (51+/-14)
FEV1 reversibility % (SD)	3.2+/-5.9	4.0+/-6.0	3.6+/-5.7	9.1 +/- 13.1	9.6 +/- 12.0	9.6 +/- 13.1

*COPD severity was classified according to the value of post FEV1 as % predicted: mild (%), moderate (%), severe (FEV1 < 50 % and ≥ 30%), very severe (FEV1 < 30%)
N/A, not tabulated in CSR.
Source: Table 5, FK1-101 CSR, pp 64. Table 5, M2-107 CSR, pp93.

Disposition

These trials had randomization and completion rates comparable to other 6-month trials in the program. Nearly 80% patients enrolled were randomized and similar percentage of randomized patients completed the trial (FK1-101: 84-87%, M2-107: 78-89%). In trial FK1-101, similar % of patients discontinued from each treatment group. In contrast, approximately 1.5 times as many subjects in the 250 mcg and twice as much in the 500 mcg roflumilast treated groups discontinued from the trial compared to the placebo.

Table 35 Patient Dispositions (Trials FK1-101 and M2-107)

Disposition, N (%)	FK1-101			M2-107		
Enrolled	657			1792		
Randomized (%)*	516 (78.5)			1413 (78.8)		
Disposition, N (% randomized)	Roflumilast 500 mcg	Roflumilast 250 mcg	Placebo	Roflumilast 500 mcg	Roflumilast 250 mcg	Placebo
Randomized	169	175	172	555	578	280
Completed	145 (85.8)	147 (84.0)	150(87.2)	431 (77.7)	478 (82.7)	248 (88.6)
Premature withdraw	24 (14.2)	28 (16.0)	22 (13.8)	124 (23.3)	100 (17.2)	32 (11.4)
Reasons for premature withdraw, n (% randomized)						
Adverse events	10 (5.9)	10 (5.7)	8 (4.6)	84 (15.1)	54 (9.3)	23 (8.2)
Other medical **	2 (1.2)	7 (4.0)	2 (1.2)	11 (2.0)	8 (1.4)	3 (1.1)
Other non medical	12 (7.1)	11 (6.3)	12 (7.0)	29 (5.2)	38 (6.6)	6 (2.1)

Source: FK1-101 CSR, Table 2 (pp59) and M2-107 CSR, Table 2 (pp87). All % shown here are % of randomized to be consistent with other trials reviewed but different from what's in the original tables. Numbers for patients who completed the study were calculated: # randomized – # total premature withdraw.
* As % enrolled here. All other percentages are % randomized.
** In trial FK1-101, withdraw due to escape reasons (exacerbation) were counted as other medical reasons

Compliance

The overall percentage of patients who had major protocol violations was similar between treatment groups within each trial. However, more patients in M2-107 (21-26%) had at least on major protocol violation compared to trial FK1-101 (15-16%). Different from other trials reviewed, the main reasons for protocol violation were not met entry criteria for FEV1 and or reversibility, rather than use of not allowed medications.

Efficacy Results

These were two of the earlier phase III (or II/III) trials in the COPD development program. Their primary endpoints were similar to each other but different from trials in later phase of the COPD program. Both trials used FEV1 (preFEV1 in trial FK1-101, postFEV1 in trial M2-107) and SGRQ total score as co-primary endpoints, which were different from later phase III trials that used COPD exacerbation instead of SGRQ as a co-primary end point with FEV1 as the other.

The secondary endpoints in both trials included additional pre and post bronchodilator spirometry parameters (FEV1, FVC, FEF_{25-75}, etc), morning peak flow per patient diary, symptom score and rescue medication use, SGRQ component score and global rate scale (GRS). Quality of life (QoL) measurements such as the short form of SF-36 and the 6 minute walk were part of the secondary endpoints in trial FK1-101 but were not accessed in trial M2-107. COPD exacerbations were measured in both trials but differently. Trial FK1-101 had the concept of "escape". Patients who had either 3 moderate or 1 severe COPD exacerbations were to "escape" from the trial (not permitted to remain). This was different from M2-107 and other later phase III trials reviewed; patients who had COPD exacerbation during the treatment period were to remain in the study. Additionally, both number and time to exacerbation were accessed in trial M2-107 but only numbers of exacerbations were measured in trial FK1-101. Symptom and rescue medication free days were secondary endpoints in trial M2-107 but not FK1-101.

Table 36 Primary and Secondary Endpoints in Trials FK1-101 and M2-107

	FK1-101	M2-107
Primary End Points	- Pre bronchodilator FEV1 - SGRQ total score	- Pre bronchodilator FEV1 - SGRQ total score
Secondary End Points (no hierarchy)	- Post bronchodilator FEV1 - Other pre or post bronchodilator spirometry - Morning PEF - Symptom score and rescue medication use - SGRQ component score - SF-36 short form - 6 minute walk - Number of escape - Exacerbation (number only) - GRS	- Pre bronchodilator FEV1 - Other pre or post bronchodilator spirometry - Morning PEF - Symptom score and rescue medication use - SGRQ component score - Exacerbation (number and time to event) - GRS - Symptom free, rescue medication free days

All variables were measured by change at the end of treatment compared to baseline, except the concept of escape which was measured in total number met the escape criteria.

Pre and post bronchodilator FEV1

Change at the end of treatment in pre and post bronchodilator FEV1 from baseline were analyzed with last value ANCOVA. LOCF (last observation carried forward) method was use to replacing missing values for efficacy endpoint analysis. This was different from what was done in the later phase III trials in which mean change in FEV1 during treatment from the baseline was analyzed with repeat measurements ANCOVA.

Of note is that in trial FK1-101, there were no statistically significant differences between the three treatment groups (roflumilast 500 and 250 mcg, and placebo) in pre or post bronchodilator FEV1. This is the only trial of the 8 phase III trials reviewed that failed on FEV1 endpoint. Numerically, the FEV1 between treatment differences (roflumilast versus placebo) in FK1-101 were similar to those reported in other trials and showed trends in favor of the roflumilast treated groups (41 mL-roflumilast 500 mcg versus placebo, 35 mL-roflumilast 250 mcg versus placebo). The likely difference was the decrease in sample size. While trial FK1-101 had about 170 patients in each treatment groups, the other phase III trials had 500 to over 700 patients in each treatment groups.

Trial M2-107 had about 500 patients in each treatment groups and the results for pre and post bronchodilator FEV1 were similar to those reported in other phase III trials reviewed. Patients treated with roflumilast had slight improves in pre and post bronchodilator FEV1 as well as other spirometry parameters. In contrast, the spirometry parameters were largely unchanged in patients received placebo. The differences between roflumilast and placebo treated groups were modest but statistically significant (97 mL-roflumilast 500 mcg versus placebo, 74 mL-roflumilast 250 mcg versus placebo). The roflumilast 500 mcg treated patients did better numerically better than the roflumilast 250 mcg group but there was no significant difference between the two roflumilast groups.

Table 37 Between treatment differences in pre or post bronchodilator FEV1 (trials FK1-101 and M2-107, LOCF, ITT)

FK1-101, pre FEV1 - between-treatment differences in change from baseline to last visit (ITT last-value analysis)

Treatment group	n	LS Mean ± Std Err	95% CI	p-value[a] parametric (non-parametric)
250 µg roflumilast vs placebo	[b]	0.035 ± 0.030	-0.024, 0.094	0.1199 (0.0475)
500 µg roflumilast vs placebo	[b]	0.041 ± 0.030	-0.018, 0.099	0.0884 (0.0471)
500 µg vs 250 µg roflumilast	[b]	0.005 ± 0.030	-0.053, 0.064	0.4284 (0.4980)

[a] one-sided [b] n = 169, 173, 167 for placebo, 250 µg and 500 µg roflumilast, respectively.

Source: FK1-101 CSR synopsis, pp5.

M2-107, post FEV1 - between-treatment differences in change from baseline to last visit (ITT last-value analysis).

Test	Reference	n Test	n Reference	ΔTest – ΔReference LSMean ± SEM	95%CI	p-value[a]
Rof500	Placebo	501	257	0.097 ± 0.018	0.062, 0.131	<0.0001
Rof500	Rof250	501	528	0.023 ± 0.014	-0.006, 0.051	0.1166
Rof250	Placebo	528	257	0.074 ± 0.018	0.039, 0.108	<0.0001

Source: M2-107 CSR synopsis, pp7.

SGRQ total score

SGRQ was the main focus of trials FK1-101 and M2-107. However, both trials failed on this co-primary endpoint. In trial FK1-101, what would be defined as clinically meaningful changes (> -4.0 in total score) were seen at the end of treatment compared to baseline in all three treatment groups with respective changes in total SGRQ of -4.73, -4.41 and -4.45 for the roflumilast 500 mcg, 250 mcg and the placebo group. However, there was no difference between treatments. Similarly, in trial M2-107, significant changes were seen at the end of each treatment comparing to baseline in all three treatment groups. But, again, there was no difference between treatments (Table 38).

Table 38 SGRQ total score -- between treatment differences in trial M2-107 (ITT last-value analysis)

Test	Reference	n Test	n Reference	ΔTest – ΔReference LSMean ± Std Err	95%CI	p-value[a]
Rof500	Placebo	496	267	-1.7 ± 0.9	-3.5, 0.0	0.0532
Rof500	Rof250	496	522	-0.2 ± 0.7	-1.6, 1.3	0.8270
Rof250	Placebo	522	267	-1.6 ± 0.9	-3.3, 0.2	0.0770

[a] p-value for between-treatment differences (ANCOVA), two-sided, significance level 5%.
CI = confidence interval, Δ = within-treatment difference, LS = least squares,
n = number of patients with data available at T0 and T_{last}, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily,
SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).

Source: M2-107 CSR synopsis, p8.

COPD Exacerbations

COPD exacerbations were accessed in these trials but were not the main focus as in the later phase III trials. The definitions for exacerbations were different in these trials compared to the later trials. In study FK1-101, COPD exacerbations were measured as "escape" units (each equal to a patient who was terminated from the study because of either 3 moderate or one severe exacerbation).

In study M2-107, COPD exacerbations were defined as:

- Mild exacerbation: Home management by increased bronchodilator therapy (beta 2-agonists and/or short-acting anticholinergics) without additional health care contact.
- Moderate exacerbation: Home management by initiating an oral glucocorticosteroids therapy and/or unscheduled health care contact required.

- Severe exacerbation: Hospital management (including emergency room treatment).

In trial FK1-101, the number of patients meeting "escape" criteria were three each in the placebo and 250 mcg roflumilast, and two in the 500 mcg roflumilast group. The overall number of exacerbations was lower in the roflumilast 500 mcg compared to the other treatment groups. The respective corresponding numbers of exacerbations and patients with exacerbations were 15 events in 13 patients, 25 events in 19 patients and 26 events in16 for the roflumilast 500 mcg, 250 mcg and the placebo groups, respectively.

In trial M2-107, the Jonckheere-Terpstra test showed a dose dependent reduction of the total number of exacerbations (severe, moderate or mild) with increasing doses of roflumilast. The roflumilast 500 mcg group had a 34% reduction in total number of exacerbation compared to the placebo. However, the reduction was predominantly driven by a reduction of mild exacerbations, the most subjective measurements of all exacerbations.

Other secondary endpoints
There was no difference in other non-spirometry related secondary endpoints examined. This included no difference in SF-36, 6 minute walk, GRS, symptom and rescue medication use, as well as symptom free and rescue medication free days.

Safety Results:

The adverse events profile reported in these trials were consistent with findings from other clinical trials. In general, AE and SAE rates were lower in roflumilast 250 mcg group compared to roflumilast 500 mcg groups. Refer to section 7 for the integrated safety review.

6 Review of Efficacy

Efficacy Summary

6.1 Indication: maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations

6.1.1 Indication

The proposed indication for roflumilast contained in the original NDA submitted on July 15, 2009, is “for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. Subsequently, the FDA was notified on December 4, 2009, of a change in ownership of the NDA from Nycomed to Forest Research Institute. The new Applicant submitted new product labeling in submission dated January 29, 2010 which included a change in the product indication from the above broad “maintenance treatment of COPD” indication to the more limited indication of “reduction of

exacerbations of COPD". Because the regulatory review of an NDA by the FDA is based on the proposed product indication, it should be final at the time of the NDA submission. Thus, this application will be evaluated based on the originally proposed indication "for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.

6.1.2 Methods

The Applicant has proposed two clinical Phase 3 studies as the "pivotal" studies (M2-125 and M2-125) from which approval of roflumilast should be based. However, the clinical development program for roflumilast is extensive and encompasses 18 late phase clinical studies in COPD patients. Therefore, in order to understand the evolution of the roflumilast clinical program over time and understand the totality of the efficacy data for roflumilast, efficacy data will be presented in this section from relevant clinical studies according to endpoint (FEV1, exacerbations, etc.). The primary sources of the data presented are from the 4 one-year studies (Studies M2-111, M2-112, M2-124, and M2-125) which evaluated COPD exacerbations and 4 six-month studies (FLK1-101, M2-107, M2-127, and M2-128) viewed as supportive (see Table of Clinical Studies in Section 5.1). Studies FLK1-101 and M2-107 were conducted relatively early in the roflumilast development program and were two of the few studies to compare the efficacy of 2 roflumilast doses, 250 and 500 mcg once daily, in relatively large numbers of patients with COPD. The data presented for these studies will focus on the treatment differences between the 250 and 500 mcg doses.

All studies were multicenter, multi-national, randomized, double-blind, placebo controlled parallel group trials which included a 2-4 week run-in period followed by a double blind treatment period of 52 (M2-111, M2-112, M2-124, and M2-125,) or 24-26 weeks (FLK1-101, M2-107, M2-127 and M2-128). All studies except M2-107 and FK1-101 (which included both 250 and 500 mcg doses) compared roflumilast 500 mcg once daily to placebo.

The 4 one year-long studies all had lung function as assessed by FEV1 and the rate of COPD exacerbations as co-primary endpoints in patients ≥ 40 years of age with severe COPD (FEV1 ≤ 50%) and nonreversible airway obstruction. After a 4-week run-in period in which patients were taken off prohibited concomitant medications, patients were randomized 1:1 to receive either roflumilast 500 mcg or placebo once daily (see table above for number of patients/group). While generally similar in design, there were some notable differences between the studies. Studies M2-111 and M2-112 evaluated a broad population of patients with severe COPD while M2-124 and M2-125 required patients to have recent histories of chronic bronchitis (cough and sputum production) and COPD exacerbations. Additionally, studies M2-124 and M2-125 allowed concomitant treatment with LABAs (50% of the patients in each study took LABAs) but prohibited the use of inhaled corticosteroids and LAMAs during the treatment period. Conversely, studies M2-111 and M2-112 allowed the use of inhaled corticosteroids however prohibited use of LABAs and LAMAs altogether. The difference in study designs and use of concomitant medications used to treat COPD make inter-study comparisons difficult. It should be noted that in no study was the efficacy of roflumilast evaluated compared to what has become standard of care treatment for patients with COPD, concomitant use of a LABA, LAMA, and an inhaled corticosteroid.

The definition of COPD exacerbations also differed slightly between the year-long studies. In studies M2-111, M2-124, and M2-125, a moderate exacerbation was defined as an exacerbation requiring use of oral or parenteral corticosteroids and a severe exacerbation was defined as an exacerbation which resulted in hospitalization or death. Exacerbations within ten days of each other were merged and counted as a single exacerbation. Study M2-112 differed slightly as it included exacerbations requiring antibiotic treatment and exacerbations leading to death were added post-protocol. Also, in Study 112, exacerbations not separated by one exacerbation free day were merged and counted as a single exacerbation compared to a separation of 10 days in the other 3 year-long studies.

Studies M2-127 and M2-128 were 24-week supportive studies that investigated the benefit of roflumilast treatment in patients with moderate to severe COPD who were receiving maintenance therapy with either salmeterol, administered as Serevent® Diskus 50 mcg twice daily (Study M2-127) or tiotropium18 mcg via HandiHaler (Study M2-128). The focus of these studies was to evaluate if roflumilast adds additional benefit on lung function (FEV1 as primary endpoint) beyond the effects of long-acting bronchodilators. These studies included patients with moderate as well as severe COPD (FEV1 of 40-70% predicted) and were not required to have a history of chronic bronchitis with sputum production bronchitis and/or COPD exacerbations.

The primary dose ranging studies (FK1-101 and M2-107) were both double-blind, placebo-controlled, parallel-group, non-US, multinational studies in patients ≥ 40 years of age with non-reversible airway obstruction across the full range of COPD severity (FEV1 30-75-80% predicted). Study FK1-101 was a 26 weeks phase II/III trial with 2 week run-in followed by 26 week treatment while study M2-107 was a 24 weeks phase III trial with 4 week run-in and 24 week treatment. Patients were randomized 1:1:1 (516 for study FK1-101 and 1411 in study M2-107) to receive either roflumilast 250 or 500 mcg or placebo once daily. Concomitant uses of systemic or inhaled steroids and long acting beta agonists were not permitted. Stable daily dose of short-acting anticholinergics were permitted. Uses of other COPD medications were also restricted except rescue salbutamol, which was provided to all eligible subjects. Co-primary endpoints were pre-bronchodilator FEV1 and the SGRQ in trial FK1-101 and post-bronchodilator FEV1 and SGRQ in trial M2-107. Note that SGRQ as a primary or key secondary endpoint was the hallmark of earlier COPD trials and it was not evaluated in the pivotal trials.

A more detailed description of the design, conduct, and results of these studies are presented in Section 5.3.

6.1.3 Demographics

A summary of demographic data across studies is presented in the table below. The most striking demographic characteristic of the overall population is the predominance of white patients who represent the large majority of patients in the clinical studies. In addition there were more males than females (roughly 70% vs 30%). Within each individual study baseline pulmonary function, smoking history, COPD severity, and LABA use (when allowed) were generally balanced. Patients in studies M2-127 and M2-128 overall had less severe COPD, which is reflective in their higher baseline FEV1 values, and more current smokers than the other studies.

Table 39 Summary of Patient Demographics Across Studies

	M2-124		M2-125		M2-111		M-112		M-127		M2-128	
	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo
N	765	758	772	796	567	606	760	753	466	467	371	372
Age (median yrs)	63	63	64	65	65	64	66	65	65	65	65	65
Sex (% male)	71	71	79	81	68	66	75	76	69	64	71	72
Race (%white)	96	97	72	71	94	93	99	99	96	95	100	100
Height (mean, cm)	170	169	167	167	170	170			169	168	168	169
Weight (mean, kg)	76	75	71	71	75	75	72	72	77	76	78	80
COPD (%)												
Very severe	26	24	34	32	24	27			0	0	1	1
Severe	64	67	59	60	65	65			35	30	34	32
Moderate	11	8	7	7	11	7			65	69	63	65
Mild	0	0	0	0	0	0			0	0	2	3
Smoking (%)												
Current	48	48	35	35	42	44	38	35	61	61	60	61
Former	52	52	65	65	58	56	62	65	40	39	40	39
LABA (%)	49	51	48	51					70	69		
Pre-FEV1** (mean, L)	1.1	1.1	1.0	1.0	1.0	0.9	1.0	1.0	1.4	1.4	1.5	1.5
Post-FEV1 (mean, L)	1.2	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.5	1.5	1.5	1.6
Pre-FEV1 (mean % pred)	35	35	31	32	31	31	37	37	52	52	53	53
Post-FEV1 (mean % pred)	38	38	35	35	37	36	41	41	55	55	56	56

*Pre-FEV1 and Post-FEV1 refer to pre and post-bronchodilator FEV1 measurements, respectively.

6.1.4 Patient Disposition

Patient disposition for the 4 one year studies and supportive 6-month studies is summarized in the following table. In all the four 52-week studies, approximately two thirds of patients completed the study while in the 24-week studies about three quarters of patients completed the studies. Compared to placebo, roflumilast-treated patients had a higher percentage of dropouts in all six studies. The major factor in this difference is the greater number of patients in the roflumilast groups who discontinue due to adverse events. The PDE4 inhibitor class of drugs is known to cause significant gastrointestinal side effects such as nausea and diarrhea. The role of GI side effects on patient discontinuation will be discussed in section 7.3.3. Also of note is the large number of protocol violations across all studies accounting for about 20-30% of the overall study populations. This contributes to the large difference between the ITT and PP study population numbers.

Table 40 Summary of Patient Disposition Across Studies

N or %	M2-124		M2-125		M2-111		M-112		M-127		M2-128	
	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo
Randomized, N	766	759	773	798	568	608	761	753	467	468	372	372
ITT	765	758	772	796	567	606	760	753	466	467	371	372
PP	553	549	528	565	417	468	514	536	360	369	304	302
Completed (%)	65	69	68	69	62	69	71	78	77	82	83	89
Discontinued (% randomized)	35	31	32	31	38	31	29	22	23	18	17	11
Reasons for discontinuation (% randomized)												
Adverse event	16	10	13	10	20	11	14	7	17	10	9	5
Patient decision	16	13	14	13	16	13	-	-	11	8	7	3
Exacerbation	6	9	6	8	6	4	4	3	3	6	1	2
Predefined	1	1	1	1	2	3	-	-	1	3	0.3	1
Lost to follow up	2	2	3	3	2	1	-	-	0.4	0.4	1	1
Other	4	4	4	4	6	7	11	12	2	2	1	2
Protocol violation	28	28	32	29	27	23	33	29	23	21	18	19

Treatment compliance to study treatments was reported to be > 90% for all treatment groups across all six studies (see table 41 below). Mean treatment exposure was 8-30 days less for the roflumilast treatment groups likely due to the increased number of patients dropping out in the roflumilast group compared to placebo.

Table 41 Treatment Compliance and Duration of Exposure Across Studies

	M2-124		M2-125		M2-111		M-112		M-127		M2-128	
	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo
N	765	758	772	796	567	606	760	753	466	467	371	372
Mean Treatment Compliance	94	95	93	96	96	96	99	99	94	96	96	97
Exposure												
≥ 26 wks	76	80	76	80	71*	80*	78*	88*	29†	32†	36†	31†
≥ 52 wks	46	50	48	49	26**	29**	36	40				
Mean Exposure [days]	278	292	282	294	268	298	290	318	142	153	150	158

*> 28 weeks, ** > 52 weeks, † > 24 weeks

6.1.5 Analysis of Primary Endpoint(s)

Each of the 4 one year studies had co-primary endpoints of lung function (pre-bronchodilator FEV1) and the rate of moderate or severe COPD exacerbations while studies M2-127 and M2-128 had the single primary endpoint of pre-bronchodilator FEV1. The definition of COPD exacerbation was based on the decision to treat a patient with systemic corticosteroids, usually prednisone, or hospitalize a patient, presumably for a worsening of their COPD symptoms.

Earlier dose-ranging and Phase 3 studies, most notably studies FK1-101 and M2-107, utilized the SGRQ as a co-primary endpoint rather than COPD exacerbations.

Following are the primary efficacy findings for the pivotal studies M2-124 and M2-125 as well as those for supportive studies. These include pre-bronchodilator FEV1, COPD exacerbations, and in early studies, quality of life as determined by the SGRQ. Unless otherwise stated, all analyses below were conducted on intention to treat (ITT) study populations. More detailed presentations of the efficacy findings for the pivotal and supportive studies can be found in the individual reviews of each study in Section 5.3.

Change in Pre-Bronchodilator FEV1

In the pivotal and supportive studies, patients treated with roflumilast had a statistically significant, albeit quite modest, increase pre-bronchodilator FEV1 compared to placebo. In these studies, the size of the effect ranged from 39 to 80 ml, with an average of 54 mL. This increase in FEV1, although significant statistically, would not constitute a clinically meaningful benefit (about 3-5% increase in FEV1).

Table 42 Change (in mL) from baseline in pre-bronchodilator FEV1 to end of treatment (ITT populations)

Trial Number	Duration (Weeks)	Pre-Bronchodilator FEV1 (ml)				
		Rof500 mcg	Placebo	Difference	P-Value	Pooled Diff
M2-124	52	46 (745)	8 (745)	39	<0.001	48
M2-125	52	33 (730)	-25 (766)	58	<0.001	
M2-111	52	30 (545)	-12 (596)	42	<0.001	51
M2-112	52	49 (737)	-8 (741)	57	<0.001	
M2-127[1]	24	39 (456)	-10 (463)	49	<0.001	
M2-128[2]	24	65 (365)	-16 (364)	80	<0.001	

* pre-bronchodilator FEV1 is one of many secondary endpoints (p-value unadjusted)
1. All patients received salmeterol in addition to roflumilast or placebo
2. All patients received tiotropium in addition to roflumilast or placebo
Diff: difference between roflumilast and placebo.
P-Value: p-value for diff with H_0: Diff = 0.
Number of individuals randomized is provided in parentheses.

The pre-bronchodilator FEV1 data for the 250 and 500 mcg doses of roflumilast studied in studies FK1-101 and M2-107 are shown in table 43 below. Treatment with roflumilast 250 mcg once daily resulted in 35 and 64 mL improvements in FEV1 over placebo for studies FK1-101 and M2-107, respectively. The increases in FEV1 for the 500 mcg dose over the 250 mcg dose were 5 and 24 mL for studies FK1-101 and M2-107, respectively. For study M2-107, much of the benefit for roflumilast over placebo is due to a decrease of 39 mL in FEV1 in the placebo group.

Table 43 Pre-bronchodilator FEV1 in studies with 250 and 500 mcg doses of roflumilast

Trial Number	Duration (Weeks)	Rof500 mcg	Rof250 mcg	Placebo	Difference (ml)		P-Value	
					Rof250-P	R500 - R250	R250-P	R500-R250

FK1-101	26	69 (167)	64 (173)	29 (169)	35	5	0.2398	0.8568
M2-107	24	49 (506)	24 (541)	-39(256)	64	24	<0.0006	0.1024
From individual clinical study reports								

Rate of Exacerbations

While assessing the effect of a drug on COPD exacerbations is viewed as a clinically meaningful endpoint, there is generally a lack of a standardized definition for exacerbation. Most definitions used in clinical trials, including those for roflumilast, are action-driven, i.e., an exacerbation is defined by a decision to treat the patient with additional therapy (generally corticosteroids) or hospitalize the patient. One potential problem with such definitions is that because the decision to initiate extra treatment or hospitalization is investigator-driven, there is room for variations in what would constitute an exacerbation and the severity of the exacerbation. Thus, as much as it is possible, sponsors have been encouraged to standardize their definitions for COPD exacerbations by including criteria that should prompt an investigator to initiate corticosteroid therapy or hospitalize the patient.

The mean rate of moderate or severe COPD exacerbations per patient per year is one of the two primary endpoints for the year-long studies M2-124, M2-125, M2-111, and M2-112 which were specifically designed to assess the effect of roflumilast on the rate of COPD exacerbations.

As stated mentioned above, the definition of an exacerbation in Study M2-112 differed slightly from the other 3 studies as it included exacerbations requiring antibiotics treatment (moderate) and exacerbations leading to death were added post-protocol (severe). Also, exacerbations not separated by one exacerbation free day were merged and counted as a single exacerbation. To facilitate direct comparison of Studies M2-111 and M2-112 with the pivotal studies M2-124 and M2-125, the definitions of moderate and severe exacerbations for studies M2-111 and M2-112 were modified post-hoc by the Applicant to match those of the pivotal studies.

The annual rates of moderate or severe COPD exacerbations in Studies M2-124, M2-125, M2-111, and M2-112 are presented in table 44 below. In these studies, roflumilast numerically reduced the annual rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate (studies M2-124 and M2-125) reaching statistical significance while reduction in exacerbation rates from studies M2-111, and M2-112, were not statistically significant. It is notable that studies M2-111 and M2-112 included a general population of patients with severe COPD while studies M2-124 and M2-125 studied a narrow, more restricted patient population of severe COPD patients who had to have a history of both chronic bronchitis with cough and sputum production and have recent exacerbations of COPD.

To facilitate direct comparison of studies M2-111 and M2-112 with studies M2-124 and M2-125, the definitions of moderate and severe exacerbations for studies M2-111 and M2-112 were modified post-hoc by the sponsor to match those of M2-124 and M2-125. However, without these post hoc changes, the rate ratio comparing roflumilast and placebo was also not significant in either study. The p-value in Study M2-111 would be 0.218 rather than 0.129 and the p-value in Study M2-112 would be 0.4514 rather than 0.085.

Table 44 Rates of moderate or severe exacerbations in the one year studies* (ITT Population)

Trial Number	Duration (Weeks)	Poisson Exacerbation Rate				
		Rof500 mcg	Placebo	Rate Ratio	P-Value	Pooled Rate Ratio
M2-124	52	1.1 (765)	1.3(758)	0.85	0.028	0.83
M2-125	52	1.2 (772)	1.5 (796)	0.82	0.004	
M2-111**	52	0.6 (567)	0.7 (606)	0.86	0.129	0.85
M2-112**	52	0.5 (760)	0.5 (753)	0.85	0.085	

M2-111, M2-112 from report 22/2009_Table 2.7.3-39
* Poisson analysis
** Based on exacerbation definition and analysis method used in Studies 124 and 125

In the PP analysis, the rate of moderate or severe COPD exacerbations per patient year was also lower for roflumilast than for placebo in both studies. However, the rate ratio comparing roflumilast and placebo was not statistical significant in study M2-124.

The frequency of moderate or severe exacerbation for studies M2-124 and M2-125 were also examined (see table 45). The frequency of patients who had one exacerbation was no different in study M2-124 and slightly more in the roflumilast group in study M2-125. However, the frequency of patients experiencing at least 2 (up to 6 in Study M2-124 and up to 9 in Study M2-125) moderate or severe COPD exacerbation was higher in the placebo group compared to the roflumilast group. Approximately half the patients in either of the studies had no exacerbations.

Table 45 Frequency (%) of Moderate or Severe Exacerbations

Frequency	Study 124 (ITT)		Study 125 (ITT)	
	Rof500 mcg N=765	Placebo N=758	Rof500 mcg N=772	Placebo N=796
0	55	49	52	46
1	25	25	26	25
2	11	13	12	14
3	6	7	6	7
4	2	3	3	4
5	1	2	1	2
6	0.1	1	0.4	1
7	1	0.3	0.1	1
8	0	0	0	0.3
9	0	0	0	0.3

Source: FDA statistical analysis

The time to onset of first moderate or severe COPD exacerbation was explored. In both studies M2-124 and M2-125, the median time to first exacerbation (moderate or severe) was approximately 65 days longer in patients who received roflumilast compared to placebo, 244 vs 309 days and 231 vs 295 days for the placebo and roflumilast groups in studies M2-124 and M2-125, respectively. The mean rate of COPD exacerbations per patient year and the time to onset of

first COPD exacerbation for the categories of COPD exacerbations is further described in Section 3.1.2.2 of the statistical briefing document.

Change from Baseline in St. George Respiratory Questionnaire (SGRQ)

The SGRQ is one of the most commonly used measures of the quality of life in patients with COPD. It is comprised of 16 questions that assess disease symptoms, disturbances to patients' daily physical activity, and the impact of the disease on the patient. It is frequently used as a quality of life assessment in clinical trials conducted in drug development programs. Results of the SGRQ are reported because it was used as a co-primary endpoint in several of the earlier dose-ranging and Phase 3 studies (FK1-101, FK1-103, and M2-107, M2-110) and as key or other secondary endpoint in others. In reviewing the SGRQ data note that a lower number is viewed as an improvement and that the defined difference between measurements that is the minimal clinically meaningful effect is -4.0 units.

Change from baseline in total SGRQ score failed to achieve either statistical or clinical significance in any study in which it was utilized.

Table 46 Change from Baseline in SGRQ total score

Trial Number	Duration	Rof500 mcg	Placebo	Difference	P-Value
JP-706	24 weeks	0.31	-1.04	1.35	0.211
FK1-101	26 weeks	-4.7	-4.5	-0.3	0.425
FK1-103	24 weeks	-2.6	-2.9	0.3	0.842
M2-107	24 weeks	-3.5	-1.8	-1.7	0.053
M2-110	24 weeks	-1.2	-1.6	0.47	0.473
M2-111	52 weeks	-1.8	-0.3	-1.5	0.016
M2-112	52 weeks	-3.7	-3.2	-0.5	0.268

Source: individual clinical study reports

6.1.6 Analysis of Secondary Endpoints(s)

Mortality

Mortality rates for the roflumilast and placebo groups for studies M2-124 and M2-125125, which targeted the population in the proposed label indication, were similar with equal numbers of deaths in the placebo and roflumilast groups in both studies (see table 47).

Table 47 Mortality Rates in Studies M2-124 and M2-125

Trial Number	Rof500 mcg		Placebo			
	Deaths	N	Deaths	N	Hazard Ratio*(95% CI)	P-Value
M2-124	17	765	17	758	0.97 (0.49, 1.90)	0.921
M2-125	25	772	25	796	0.82 (0.47,1.45)	0.503

Source: FDA statistical analyses
* derived from a proportional hazards model with concomitant treatment with LABA, age, sex, and smoking

status, stratified by country

Rate of COPD exacerbations in 6-month supportive studies

In studies M2-127 and M2-128, the mean rates of moderate or severe COPD exacerbations per year (same as the primary endpoint for the pivotal studies) were either exploratory (M2-127) or secondary (M2-128) endpoints. Post hoc analyses conducted for study M2-127 demonstrated the rate of COPD exacerbations (moderate or severe) was lower for roflumilast (0.3) than placebo (0.5) with a rate ratio of 0.6. In Study M2-128, the mean rate of COPD exacerbations (moderate or severe) was slightly lower for roflumilast (0.26) than placebo (0.34). However, the rate ratio (0.77) comparing roflumilast and placebo was not statistically significant (see table 48 below).

Table 48 Rates of moderate or severe exacerbations* (ITT Population)

Trial Number	Duration (Weeks)	Poisson Exacerbation Rate			
		R500	Placebo	Rate Ratio	P-Value
M2-127**	24	0.3 (466)	0.5 (467)	0.63	0.032**
M2-128	24	0.3 (371)	0.3 (372)	0.77	0.196

* Poisson analysis
** Post-hoc analysis (p-value unadjusted)

Change in post-bronchodilator FEV1

Change in post-bronchodilator FEV1 from baseline was assessed in most clinical studies conducted in the roflumilast program both as a co-primary endpoint in earlier studies and as a secondary endpoint in the proposed pivotal studies, M2-124 and M2-125. In general, post-bronchodilator FEV1 demonstrated numerical improvement in most, if not all clinical studies. The effect was very similar to that observed for the co-primary endpoint of pre-bronchodilator FEV1 with a difference of about 55 mL (studies M2-124 and M2-125 combined) favoring roflumilast compared to placebo.

Other secondary endpoints

Other secondary endpoints evaluated in studies M2-124 and M2-125 included assessments for dyspnea (BDI/TDI), quality of life measured by the EuroQol, time to mortality, the use of rescue medication, COPD symptom scores, the inflammatory mediator, C-reactive protein, and time to study withdrawal.

For both studies M2-124 and M2-125 there were no meaningful differences between roflumilast and placebo for any of the other secondary endpoints listed above.

Specifically, in study M2-124, the change from baseline TDI was 0.233 (< the clinically meaningful difference of ≥ 1 unit), the change in use of rescue medication was -0.20 puffs/day driven by increased use in the placebo group, and the time to mortality was 214 and 208 days in

the roflumilast and placebo groups, respectively. Time to study withdrawal was 121 and 141 days in the roflumilast and placebo groups, respectively. This difference was driven by a 60% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.

For study M2-125, the change from baseline TDI was 0.286 (< the clinically meaningful difference of ≥ 1 unit), the change in use of rescue medication was -0.43 puffs/day driven by increased use in the placebo group, and the time to mortality was 201 and 215 days in the roflumilast and placebo groups, respectively. Time to study withdrawal was 109 and 146 days in the roflumilast and placebo groups, respectively. This difference was driven by a 40% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose ranging data for the roflumilast clinical program primarily comes from two studies (studies FK1-101 and M2-107) in which two doses of roflumilast (250 and 500 mcg once daily) were compared against placebo. Both trials were double-blind, placebo-controlled, parallel-group, non-US, multinational studies in patients ≥ 40 years of age with non-reversible airway obstruction across the full range of COPD severity (FEV1 30-75-80% predicted). Study FK1-101 was a 26 weeks phase II/III trial with 2 week run-in followed by 26 week treatment while study M2-107 was a 24 weeks phase III trial with 4 week run-in and 24 week treatment. Patients were randomized 1:1:1 (516 in study FK1-101 and 1411 in study M2-107) to receive either roflumilast 250 or 500 mcg or placebo once daily. It is notable that the 500 mcg once daily dose of roflumilast is regarded as the maximally tolerated dose. Concomitant uses of systemic or inhaled steroids and long acting beta agonists were not permitted. Stable daily dose of short-acting anticholinergics were permitted. Uses of other COPD medications were also restricted except rescue salbutamol, which was provided to all eligible subjects. Co-primary endpoints were pre-bronchodilator FEV1 and the SGRQ in trial FK1-101 and post-bronchodilator FEV1 and SGRQ in trial M2-107. Note that although SGRQ as a primary or key secondary endpoint was the hallmark of earlier COPD trials, it was not evaluated in trials designated as pivotal.

For study FK1-101, pre-bronchodilator FEV1 increased by 20 and 24 mL from baseline for the roflumilast 250 and 500 mcg dose groups, respectively while a decrease of 17 mL was noted in the placebo group. With regard to study M2-107, post-bronchodilator FEV1 increased 29 and 51 mL from baseline for the roflumilast 250 and 500 mcg doses respectively while a decrease of 45 mL was noted in the placebo group.

Regarding the other co-primary endpoint, SGRQ, in both studies there was no significant difference in SGRQ between either the 250 or 500 mcg roflumilast dose group and placebo or between each other. Based on the general lack of separation in efficacy parameters between the 250 and 500 mcg doses, dose selection for the roflumilast program appears to have been arrived at by selection of the maximally tolerated dose.

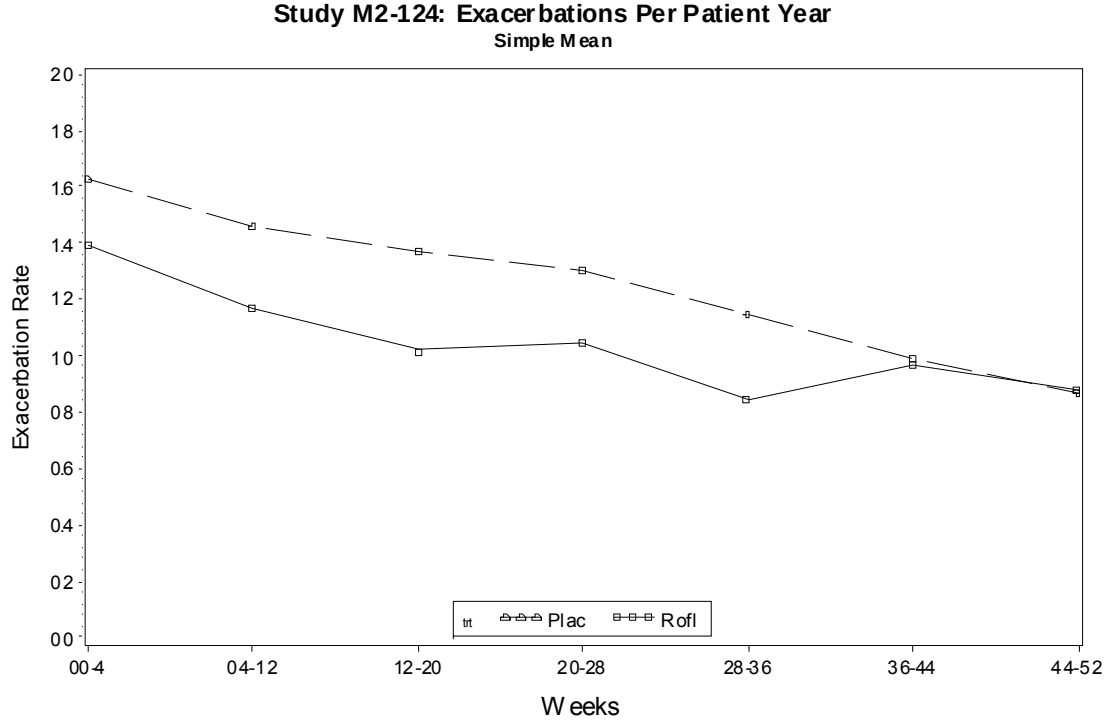
Establishment of a once daily dosing regimen was based on the results of a pharmacokinetic study in healthy volunteers which demonstrated that roflumilast and its active metabolite

(roflumilast-N-oxide) had respective half lives of 17 and 30 hours. Dosing intervals less than or greater than 24 hours were not evaluated in COPD clinical trials.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

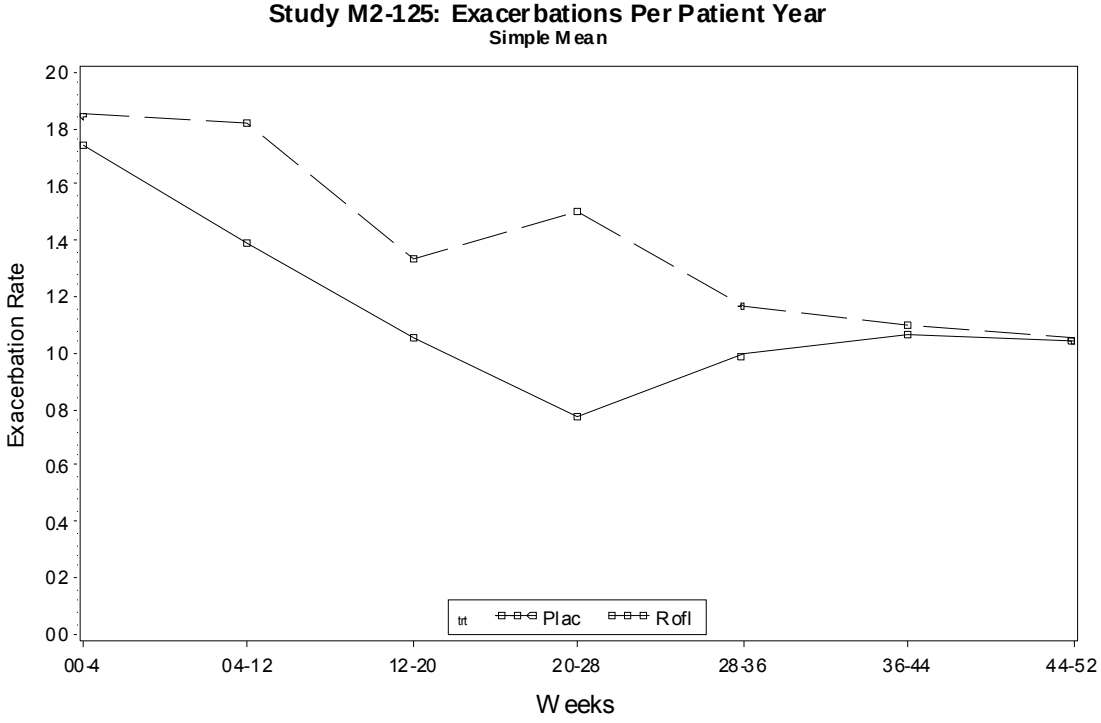
Exploratory analyses evaluating the persistence of efficacy in roflumilast in reducing the rate of COPD exacerbations can be found in Section 3.1.2.2 of the statistical briefing document. These exploratory analyses suggest that the reduction of exacerbation rate by roflumilast compared to placebo may decrease over time (see figures 4 and 5).

Figure 3 Study M2-124 Exacerbations per patient year



Source: FDA statistical analyses

Figure 4 Study M2-125 Exacerbations per patient year



Source: FDA statistical analyses

6.1.9 Conclusions

Patients treated with roflumilast 500 mcg once daily demonstrated a modest statistically significant but not likely clinically meaningful increase in pre-bronchodilator FEV1 compared to placebo. In six large Phase 3 studies (studies M2-124, M2-125, M2-111, M2-112, M2-127 and M2-128), the size of the effect ranged from 39 to 80 ml, with an average of 54 ml or about 3-5% of FEV1.

In the four one-year studies (Studies M2-124, M2-125, M2-111, and M2-112), designed to assess the effect of roflumilast on the rate of COPD exacerbations, roflumilast numerically reduced the annual rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate, from Studies M2-124 and M2-125 statistically significant and with two of the reductions, from Studies M2-111, and M2-112, not statistically significant.

Exploratory analyses by the FDA statistical team suggest that the reduction of exacerbation rate by roflumilast compared to placebo may attenuate or disappear after 8 months. This could potentially be problematic for a long term maintenance indication in which the benefits are expected to be stable and positive over time.

There were no clinically meaningful differences in quality of life as determined by the SGRQ between patients treated with roflumilast compared to placebo.

Other secondary endpoints evaluated in the studies designated as pivotal by the Applicant (M2-124 and M2-125) included assessments for dyspnea (BDI/TDI), quality of life measured by the EuroQol, time to mortality, the use of rescue medication, COPD symptom scores, the inflammatory mediator, C-reactive protein, and time to study withdrawal. For both studies M2-124 and M2-125 there were no meaningful differences between roflumilast and placebo for any of these secondary endpoints.

7 Review of Safety

Safety Summary

GI toxicity, weight loss and psychiatric effects were the main safety concerns. Of the six indications studied, COPD patients accounted for about half of the safety population and represent the cohort of patients with the worst adverse event profile possibly due to their generally older age and increased co-morbidities. For instance, the COPD population had the largest percentage of dropouts and the highest rates of adverse events in nearly all categories. This review will focus on COPD, the proposed indication. Pertinent safety results from other indications will be summarized where appropriate.

Among the almost 12,000 patients included in the COPD safety pool, there were 177 deaths, 84 in the roflumilast 500 mcg group, 86 in the placebo group, and 7 in the roflumilast 250 mcg group. Cardiac disorder and COPD were the most commonly reported AEs associated with fatality. While there were no overall differences in mortality between the 500 mcg roflumilast and the placebo groups, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide and suicide attempt (3 and 2 versus 0) and acute pancreatitis (2 versus 0). Taking into consideration that higher number cases of atrial fibrillation, depression and acute pancreatitis were also reported in the roflumilast group, these rare fatality cases, although small in number are significant.

The overall incidence of serious adverse events (SAE) and adverse events (AEs) in general were similar between the roflumilast 500 mcg and the placebo groups. For the COPD safety pool, the respective SAE rates were 13.5 and 14.2% for the roflumilast 500 mcg and the placebo groups. The roflumilast 500 mcg group reported more severe cases of bronchitis, pneumonia, atrial fibrillation, intractable diarrhea, acute pancreatitis, prostate cancer and acute renal failure. In contrast, the placebo group had more COPD related events, acute respiratory failure, coronary artery disease (angina, myocardial infarction, congestive heart failure) and thromboembolic events (pulmonary embolism, mesenteric, arterial and venous thrombosis).

Approximately 2/3 of patients in the COPD safety pool (roflumilast 500 mcg: 67.2%, placebo 62.8%) had at least one treatment emergent adverse event (abbreviated as adverse events or AEs). The AEs reported at a higher frequency in the roflumilast 500 mcg group, in order of

descending prevalence, included diarrhea, weight loss, nausea, headache, back pain, insomnia, dizziness decreased appetite, depression and anxiety. AEs that occurred at a higher rate in the placebo group included COPD, URI, and hypertension. Nasopharyngitis were common in both groups at equal rates.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The integrated roflumilast safety data base includes information for more than 24,000 subjects from 114 clinical trials dating back to the beginning of the clinical development program in 1996 and through September 25, 2008. Safety and tolerability of oral roflumilast were evaluated in patients with COPD, asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, type II diabetes and in healthy volunteers. More than 14,000 subjects received at least one dose of roflumilast.

While the focus of the safety review was patients with COPD, safety data from other studies in other patient populations were reviewed when a safety signal was detected in the COPD population in order to assess its generalizability.

For the COPD population this safety review focuses on the 14 placebo-controlled Phase 2 and 3 studies which comprise the COPD safety pool. This pool includes approximately 12,000 patients with COPD with approximately of which more than half received roflumilast. With regard to dose and duration of exposure, 5766 (88%) received the proposed, once daily regimen of 500 mcg oral roflumilast, 797 (12%) received roflumilast 250 mcg. Among those who received 500 mcg roflumilast, 1232 were treated for at least one year, 1081 for 6 months to less than 1 year, 2081 for 3 to less than 6 month and 1370 for less than 3 months. The median duration of exposure with 500 mcg roflumilast was 167 days.

7.1.2 Adequacy of Data

In general, the data presented are adequate to assess the safety of roflumilast 500 mcg once daily in the COPD population.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The studies in the integrated summary of safety were pooled according to their indication, duration of drug exposure and study designs. The follow safety pools were formed:

For COPD:

- Pivotal studies pool
    - Trials M2 124 and M2-125

- COPD safety pool
    - All 14 of 18 COPD studies that were double blind and placebo controlled

- 1 year studies pool
    - Trials M2-111, M2-112, M2-124 and M2-125

- 6 month studies pool
    - Trials FK101, FK103 (exclude data from the treatment withdrew arm), M2-107, M2-110. M2-121, M2-127 and M2-128

- 3 month studies pool
    - Trials M2-118, M2-119, IN-108

For asthma:

- asthma safety pool
    - 10 double blind, placebo controlled asthma studies

The safety data from studies that were not double blind, placebo controlled (open label or cross over design), studies in healthy volunteers, and studies in Japan which were conducted under different sponsor for a different regulatory authority were not pooled.

This safety review will focus on the safety data primarily from the large COPD safety pool with reference to other pools (pivotal trials pool, asthma pool) when relevant.

7.2 Adequacy of Safety Assessments

In patients with COPD, safety assessments included adverse events (including COPD exacerbations), clinical laboratories (including hematology, blood chemistry, UA, occult blood and pregnancy), vital signs, physical examinations (including body weight), 12-lead electrocardiograms, 24 Holter and bio-impendence. Body weight, occult blood, 24-hour Holter and bio-impendence were assessed in patients from selected sites in a few studies only.

Safety assessments in patients with other indications were similar to those in the COPD program except that Holter monitoring and bio-impendence were not accessed and that olfactometry was done in one asthma study (FHP003) and hypo/hyperglycemia was evaluated in the diabetes study (M2-401).

Based on positive findings from *in vivo* animal studies, special safety assessments on cardiovascular function, male reproductive function and mental alertness were conducted in healthy volunteers.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Over 6500 COPD patients were exposed to roflumilast in 18 phase II and III COPD trials, 5766 of the patients received at least one 500 mcg dose, 797 patients received at least one 250 mcg dose. Among those who received the 500 mcg dose proposed for registration, 1232 patients

were treated for 1 year or longer, 1081 for 6 months to less than 1 year, 2081 for 3 to less than 6 month and 1370 for less than 3 months. In the pivotal trials M2-124 and M2-125, 1547 patients were treated with 500 mcg of roflumilast with 721 (46%) of them treated for the full 52 week treatment period. Total human exposure for the roflumilast clinical program (COPD safety pool and pooled data from studies M2-124 and M2-125 pool) is shown in table 49 below.

Table 49 Exposure to roflumilast for COPD population (COPD safety pool and pivotal trials pool)

Exposure to study drug	Pivotal COPD studies pool[a]		COPD safety pool[b]		
	Placebo (N=1545) n (%)[c]	Rof500 (N=1547) n (%)[c]	Placebo (N=5491) n (%)[c]	Rof250 (N=797) n (%)[c]	Rof500 (N=5766) n (%)[c]
<1 week	24 (1.6)	36 (2.3)	53 (1.0)	13 (1.6)	119 (2.1)
≥1 week to <4 weeks	48 (3.1)	90 (5.8)	162 (3.0)	23 (2.9)	370 (6.4)
≥4 weeks to <13 weeks	132 (8.5)	164 (10.6)	710 (12.9)	100 (12.5)	883 (15.3)
≥13 weeks to <26 weeks	113 (7.3)	90 (5.8)	2045 (37.2)	549 (68.9)	2081 (36.1)
≥26 weeks to <52 weeks	468 (30.3)	446 (28.8)	1167 (21.3)	112 (14.1)	1081 (18.7)
≥52 weeks	760 (49.2)	721 (46.6)	1354 (24.7)	0 (0.0)	1232 (21.4)
Mean ET per patient (days) [mean ± SD]	293.1 ± 120.6	279.9 ± 134.0	226.5 ± 119.0	148.8 ± 47.9	206.6 ± 125.8
Median ET per patient (days)	363	363	173	168	169
Total ET (patient years)	1240	1186	3405	325	3261

a Includes studies M2-124, M2-125.
b Includes studies FK1 101, FK1 103, IN-108, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, and M2-128.
c Percentages are based on N.
COPD = chronic obstructive pulmonary disease, ET = exposure time, N = number of patients in treatment group, n = number of patients with data available, Rof250 = 250 mcg roflumilast once daily, Rof500 = 500 mcg roflumilast once daily
Source: Table 12, p. 44 of ISS.

It should be noted that the total and mean exposure times were shorter for the roflumilast treated patients than those of placebo treated patients in all pools. This is the result of increased numbers of premature study discontinuations in the roflumilast groups.

Demographics

In general, demographic characteristics such as age, gender, race and smoking status were comparable for trials within the COPD safety pool. COPD disease characteristics and treatment varied from trial to trial according to individual study design.

For study pools of trials that were 6 month or longer in duration, (the pivotal, the 1 year, the 6 month and the overall COPD safety pool), the median age ranged from 63 to 65 years, approximately 35-45% of the patients were older than 65 years, 39-48% were current smokers, 67-76% were male and 88-96% were white. Demographic characteristics were generally matched between treatment groups within each study pool (see table 50).

Table 50 Pooled demographics for one year, 6-month, and total COPD safety pools – age, gender, smoking status and race

Study Pools	Treatments	ITT N	Age (years)*			Male	Current Smoker	Race** N (%N)	
			median	range	N (%> 65)	N (%)	N (%)	White	Asian***
1 Year Pool	Roflumilast 500 mcg	2864	65	40-90	1306 (46)	2108 (74)	1164 (41)	2588 (90)	186 (6.5)
	Placebo	2913	64	40-92	1308 (45)	2160 (74)	1173 (40)	2604 (90)	186 (6.4)
6 Month Pool	Roflumilast 500 mcg	2511	64	25-93	1122 (45)	1713 (68)	1098 (44)	4214 (96)	11 (0.4)
	Roflumilast 250 mcg	751	63	40-86	316 (42)	540 (72)	362 (48)	744 (99)	1 (0.1)
	Placebo	2235	64	40-89	1003 (45)	1504 (67)	962 (43)	2125 (95)	8 (0.4)
COPD Safety pool	Roflumilast 500 mcg	5766	64	25-93	2593 (45)	4158 (72)	2420 (42)	5128 (89)	400 (6.9)
	Roflumilast 250 mcg	797	63	40-86	332 (42)	585 (73)	380 (48)	744 (93)	1 (0.1)
	Placebo	5491	64	40-92	2468 (45)	3979 (73)	2279 (42)	4851 (88)	402 (7.3)

Source: Tables 13 and 14, pp46-47, ISS
* Patients 18-40 years of age were allowed in some early trials.
**Non white, no Asian races were less than 5% in all except the 3 month pool and are not listed in this table.
***Asians in the pivotal pool were predominantly Indians, in 3 the month pool were predominantly Japanese.

7.2.2 Explorations for Dose Response

As part of the roflumilast dose-ranging program, the applicant conducted two large Phase 2/3 double-blind placebo controlled studies in which two doses (250 and 500 mcg once daily) of roflumilast were compared to placebo and each other (studies FK1-101 and M2-107). Both studies were non US, multinational studies. FK1-101 was a 26 week study and M2-107 was a 24 week study. More detailed summaries of studies FK1-101 and M2-107 are summarized in Section 5 of this review.

In these studies an increase in adverse events associated with the gastrointestinal system (diarrhea, nausea), weight loss, and the nervous system (tremor) correlated with the dose of roflumilast with greater numbers in the patients who received 500 mcg compared to patients who received the lower 250 mcg dose. The incidences of the most common adverse events were 2 to 10 times higher in the roflumilast 500 mcg group compared to the roflumilast 250 mcg group. In addition, the incidence of SAEs and early study withdraw due to AEs was also the highest among patients who were treated with the 500 mcg roflumilast.

7.2.3 Special Animal and/or In Vitro Testing

Carcinogenicity

Roflumilast is carcinogenic in animal species (rodents). Carcinogenicity of roflumilast was evaluated in 2-year studies in hamsters (two studies) and mice. Both roflumilast-treated males and females showed numerical increases in the incidence of undifferentiated carcinomas in the nasal cavity. The FDA Executive Carcinogenicity Assessment Committee (ECAC) reviewed the results and concluded that ADCP N-oxide and its metabolite, ADCP N-oxide epoxide, were responsible for the carcinogenicity of roflumilast in hamsters. ADCP N-oxide was found in human urine (approximately 10.5% of roflumilast dose). These data suggest that the hamster tumor data could be relevant to humans.

Gastrointestinal Tract Toxicity

Gastrointestinal toxicities are a known class effect of PDE4 inhibitors. Roflumilast treatment-related effects on the gastrointestinal (GI) tract were observed in rats, dogs and monkeys; but not in mice and hamsters. At an 8.0-mg/kg/day dose for 4 weeks, serositis (inflammation in jejunum), peritonitis, and stomach erosion were seen in Wistar rats. In monkeys, minimal acute inflammation or inflammation foci were noted in the pyloric region of the stomach following up to 42 weeks of roflumilast treatment at up to 0.5 mg/kg/day. The respective NOAELs for GI effects of roflumilast in rats, and monkeys were 2.5 and 0.25 mg/kg/day. The safety margin at the proposed human dose of 500 mcg per day is at least 5.

Fertility and Reproductive Toxicity

Effects on male fertility

A fertility study in Wistar rats showed that roflumilast decreased fertility in male rats. The high dose (1.8 mg/kg) group showed a statistically significant decrease in fertility rate ($P < 0.05$). (The respective male fertility rate was 89.2%, 100%, 92.3% and 64.2% in the control, the lower, mid and high groups) respectively. Morphological changes were also observed in the mid and high roflumilast dose groups. The changes in the high dose group included prostate and testicular atrophy, oligospermia and spermatogenic granuloma. Additionally, slight increase in the incidence of sperm stasis was found in the testes of mice received 36-mg/kg/day roflumilast.

These nonclinical findings of the effects of roflumilast on male fertility have been addressed clinically. A 3-month clinical trial (Report 98/2002) was conducted in over 300 healthy male volunteers to study the effects of roflumilast on male fertility in humans. It appeared that roflumilast at 500 mcg per day had little or no effects on sperm and fertility.

Effects on Pregnancy

Effects of roflumilast on female reproductive system, on embryo and fetal development were studied in mice, rats, and rabbits. In mice, roflumilast treatment during pregnancy resulted in dose-dependent increases in stillborns and maternal deaths, decreases in pup viability. However, roflumilast was not teratogenic in rats and rabbits.

Cardiovascular Toxicity

Roflumilast affected the cardiovascular system in dogs, mice and monkeys. In a 12 month dog study, cardiac lesions such as focal hemorrhages, hemosiderin deposits and lympho-histiocytic cell infiltration in the right atria/auricles were seen in animals received >0.6-mg/kg/day roflumilast. These findings were considered to be dog specific. Myocarditis was seen in monkeys treated with 0.5-mg/kg/day roflumilast for one month. The respective NOAELs for cardiac lesions in mice, dogs and monkeys were 4, 0.2, and 0.25 mg/kg/day. The proposed 500 mcg daily human dose provides a safety margin of 5 or greater.

7.2.4 Routine Clinical Testing

For patients in the 1 year pivotal COPD trials (M2-124, M2-125), routine clinical assessment of vital signs, body weight, spirometry (PFT), hemoccult, urine analysis and urine pregnancy test (in females) occurred at each visit throughout the entire trial period. Hematology, blood chemistry, ECG, 24 hour Holter (at selected study sites) and blood pregnancy test (in females) were done at the screening, at the 28 week visit and at the end of the study. Routine clinical assessments in other phase 3 trials were similar, except hemoccult and body weight were not routinely assessed in earlier trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic clearance, pharmacokinetics, and drug-drug interactions of roflumilast are briefly summarized in the Summary of Clinical Pharmacology and Biopharmaceutics document in the briefing package.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Roflumilast belongs to the phosphodiesterase inhibitor type 4 (PDE4) class of drugs. While there is no currently approved PDE inhibitor approved for use in the United States or elsewhere, this class of drugs is known to have significant gastrointestinal side effects such as diarrhea, nausea, anorexia, and weight loss. Mesenteric vasculitis was also seen in animal studies with another PDE4 inhibitor, cilomilast but not with roflumilast. However, it is not clear if cilomilast can cause vasculitis in humans as assessments in cilomilast studies used to evaluate for the possibility of gastrointestinal vasculitis were conducted only sporadically. In order to assess for serious gastrointestinal side effects such as mesenteric vasculitis, the applicant included systematic testing of stool for occult blood in late phase clinical trials. Refer to section 7.4.5 for further details.

7.3 Major Safety Results

7.3.1 Deaths

Of the approximately 12,000 patients included in the COPD safety pool, there were 177 deaths, 84 in the roflumilast 500 mcg group, 86 in the placebo group, and 7 in the roflumilast 250 mcg

group. Nearly half of the mortality (84 of 177) occurred in the 52 week pivotal trials M2-124 and M2-125. The respective mortality in the pivotal pool (studies M2-124 and M2-125 only) was also about equal between roflumilast and placebo groups (2.6 % in the roflumilast 500 mcg group and 2.7% in the placebo group). Cardiac disorders and COPD were the most common AEs reported in patients who died during treatment. The table below lists AEs reported in ≥ 0.2% for patients who died and AEs reported more frequently in roflumilast treated patients who died.

Although there were no overall difference in mortality between the 500 mcg roflumilast groups and the placebo groups, more roflumilast treated patients, compared to placebo, died of cardiac arrest (7 versus 1), suicide (3 versus 0) and acute pancreatitis (2 versus 0). These findings were consistent with the overall higher incidence of atrial fibrillation, depression and acute pancreatitis observed among roflumilast treated patients in the COPD safety pool.

Table 51 Adverse Events Reported at a frequency of ≥ 0.2% in any treatment group for patients who died

Most Common AEs Reported in Fatality Cases (≥ 0.2% in any treatment group)

Fatality and Fatality Associated AEs	Pivotal Pool		COPD Safety Pool		
	Rof500 mcg	Placebo	Rof500 mcg	Placebo	Rof250 mcg
Subjects Randomized N	1547	1545	5766	5491	797
Fatality cases n (% N)	42 (2.7)	40 (2.6)	84 (1.5)	86 (1.6)	7 (0.9)
COPD	12 (0.8)	12 (0.8)	20 (0.3)	22 (0.4)	0
Respiratory failure, all types	6 (0.4)	5 (0.3)	11 (0.2)	9 (0.2)	1 (0.1)
Pneumonia	3 (0.2)	3 (0.2)	9 (0.2)	9 (0.2)	1 (0.1)
Cardiac Disorders	15 (1.0)	11 (0.7)	24 (0.4)	29 (0.5)	3 (0.4)
Cardiac arrest	3 (0.2)	0	7 (0.1)	1 (<0.1)	0
Cardiopulmonary failure	3 (0.2)	1 (<0.1)	3 (<0.1)	2 (<0.1)	0
Sudden death	2 (0.1)	4 (0.3)	4 (<0.1)	6 (0.1)	0

AEs Reported More Frequently in Roflumilast Treated Fatality Cases

Fatality Associated AEs	Pivotal Pool		COPD Safety Pool		
	Roflumilast 500 mcg	Placebo	Roflumilast 500 mcg	Placebo	Roflumilast 250 mcg
Suicide	1	0	2	0	1
Acute pancreatitis	0	0	1	0	1
Cardiac arrest	3	0	7	1	0

Source: Table 32, pp75, ISS

Of the three completed suicides, 2 were in patients receiving roflumilast 500 mcg and the third was in patient receiving 250 mcg. There were no suicides in patients received placebo. Suicides and other psychiatric system related AEs will be discussed in detail in Section 7.3.4.

Deaths in asthma patients

Of the 2851 roflumilast treated asthma patients included in the asthma safety pool, there were 2 deaths, one in the roflumilast 250 mcg and the other in the placebo group. The patient in the roflumilast 250 mcg group was a 58 year female suffered from cardiogenic shock.

7.3.2 Nonfatal Serious Adverse Events

Table X displays the most frequently reported serious adverse events (SAEs) in the pivotal and the COPD safety pools. In general, the overall incidence of SAEs was similar between the roflumilast 500 mcg and the placebo groups and reflected the common co-morbidities frequently observed in an older COPD population of patients. For the COPD safety pool, the respective SAE rates were 13.5 and 14.2% for the roflumilast 500 mcg and the placebo groups. The SAE rates were higher in the pivotal pool (19.5 and 21.7% respectively) likely as a result of the more severe COPD population studied in these trials. COPD exacerbations and pneumonia were the most frequent SAEs in all treatment groups. In both pools, the roflumilast 500 mcg group reported more SAEs as a result of bronchitis, pneumonia, atrial fibrillation, intractable diarrhea, acute pancreatitis, prostate cancer and acute renal failure. In contrast, the placebo group had more COPD related events, cerebrovascular events, and lower respiratory tract infections.

Table 52 Most Frequently Reported Serious Adverse Events (≥0.3% in any group)

	Pivotal Pool		COPD Safety Pool		
	Rof500 mcg	Placebo	Rof500 mcg	Placebo	Rof250 mcg
Subjects with SAEs, (%N)	301 (19.5)	336 (21.7)	781 (13.5)	782 (14.2)	57 (7.2)
Subjects withdrew due to AEs	219 (14.2)	177 (11.5)	824 (14.3)	503 (9.2)	71 (8.9)
Common SAEs with Higher Occurrence in the Roflumilast Groups					
Pneumonia	26 (1.7)	21 (1.4)	63 (1.1)	59 (1.1)	3 (0.4)
Atrial fibrillation	10 (0.6)	2 (0.1)	24 (0.4)	9 (0.2)	2 (0.3)
Bronchitis	4 (0.3)	2 (0.1)	11 (0.2)	4 (<0.1)	0
Intractable diarrhea	5 (0.3)	0	10 (0.2)	1 (<0.1)	2 (0.3)
Acute pancreatitis	4 (0.3)	1 (<0.1)	5 (<0.1)	1 (<0.1)	1 (0.1)
Prostate cancer	5 (0.3)	2 (0.1)	12 (0.2)	5 (<0.1)	1 (0.1)
Acute renal failure	4 (0.3)	1 (<0.1)	6 (0.1)	4 (<0.1)	0
Common SAEs with Higher Incidence in the Placebo Groups					
COPD exacerbations	157 (10.1)	203 (13.1)	337 (5.8)	389 (7.1)	15 (1.9)
Cerebrovascular accident	1 (<0.1)	5 (0.3)	6 (0.1)	11 (0.2)	0
Lower respiratory tract infection	1 (<0.1)	4 (0.3)	3 (<0.1)	8 (0.1)	0

Source: Table 33, pp77 and Table 19, pp 56 of ISS.

It appears that the PDE4 class-related side effects are dose-related but it is difficult to make direct comparisons regarding SAEs within the COPD safety pool between the roflumilast 250 mcg and the placebo or the roflumilast 500 mcg groups because of the significantly smaller sample size, higher proportion of patients with milder COPD disease, and shorter duration of drug exposure in patients who were treated with the 250 mcg dose.

The more common SAEs observed in the asthma safety pool are shown in table 53 below. Overall, there were numerically more asthma exacerbations, infections, and GI related SAEs in the roflumilast treated patients compared to placebo.

Table 53 Most Frequently Reported Serious Adverse Events (≥0.2% in any group) in asthma trials

	Rof500 mcg	Rof250 mcg	Rof125 mcg	Placebo

Subjects Randomized N	1567	1063	221	2318
Subjects with SAEs, (%N)	48 (3.1)	23 (2.2)	4 (1.4)	48 (2.1)
Asthma exacerbation	12 (0.8)	6 (0.6)	2 (0.9)	11 (0.5)
Infections/infestations	11 (0.7)	2 (0.2)	0	6 (0.3)
Pneumonia	4 (0.3)	2 (0.2)	0	2 (<0.1)
Gastrointestinal disorders	5 (0.3)	2 (0.2)	0	3 (0.1)
Source: Table 65, pp150 of ISS (24/2009).				

7.3.3 Dropouts and/or Discontinuations

The overall dropout rate for patients receiving roflumilast was approximately 28% compared to about 23% for patients who received placebo. For nearly all phase II and III trials included in the COPD development program, the roflumilast 500 mcg groups had higher early termination rate than the placebo groups, largely driven by the higher number of adverse events that ultimately led to early withdrawal. This is in contrary to the findings from most other COPD drug trials, in which the dropout rates were usually higher for the placebo group because of lack of effect from the placebo treatment. Although COPD exacerbation rates were higher in the placebo groups for roflumilast trials, the differences were not large enough to counter balance the effects of high AE rate in the roflumilast group.

As expected, the dropout rates were higher for longer trials. Among 6 phase III trials (M2-124, M2-125, M2-111, M2-112, M2-127 and M2-128), the dropout rates in the 500 mcg roflumilast treated groups were 28.5-38% for the 52 week trials (M2-124, M2-125, M2-111 and M2-112) and 16.7-22.9% for in the 24 week trials (M2-17 and M2-128). The corresponding dropout rates in the placebo treated groups were 21.7-31.1% for the 52 week trails and 10.5-17.5% for the 24 week trials. (Refer to section 5, review of individual studies for further details). Table 54 below shows the comparison of patients in the pivotal and the COPD safety pools who withdrew early.

Table 54 Patients who withdrew early in the pivotal and COPD safety pools

Disposition Number of patients (% randomized)	Pivotal Pool		COPD Safety Pool		
	Rof500 mcg	Placebo	Rof500 mcg	Placebo	Rof250 mcg
Randomized	1547	1545	5766	5491	797
Completed	1037 (67)	1067 (69.1)	4173 (72.4)	4257 (77.5)	664 (83.3)
Early withdrawal	510 (33)	478 (31.9)	1593 (27.6)	1234 (22.5)	133 (16.7)
Due to AE	220 (14.2)	160 (10.4)	807 (14)	465 (8.5)	66 (8.3)
Due to COPD exacerbation	92 (5.9)	125 (8.7)	188 (3.3)	237 (4.3)	0
Other reasons	327 (21.1)	295 (19.1)	878 (15.2)	766 (14)	64 (8)
Number of reasons for early withdraw	639	590	1890	1482	590
Data source: Table 1.3.5, pp 307 and Table 2.3.5, pp 7940 of ISS (289/2008)					

7.3.4 Significant Adverse Events

Gastrointestinal adverse reactions

Gastrointestinal adverse events such as diarrhea, nausea, a known class effect of PDE4 inhibitors, were the most common adverse events reported from all roflumilast clinical trials and the leading cause for early study termination. The percentage of patients in the COPD safety pool who experienced at least one GI adverse event in the 500 mcg roflumilast treatment groups was 22% compared to 11% for placebo treated patients. Among those in the COPD safety pool who had GI AEs, approximately half experienced diarrhea (10.1%) and 20-25% experienced nausea (5%). In the pivotal trials, about 10% (29/319) of roflumilast treated patient who had GI AEs had intractable diarrhea or nausea that met the criteria for an SAE, which accounted for about 2% of all patients in the roflumilast treated groups in pivotal trials.

Both the frequency and severity of GI AEs appeared to be dose dependent. In the COPD safety pool, which contained 4 independent trials that had a 250 mcg roflumilast treatment arm, the frequency of GI AEs in the 250 mcg groups were about half of what seen in the 500 mcg group but still greater than placebo (see table 55 below).

Table 55 Gastrointestinal Toxicities in patients receiving 250 or 500 mcg of roflumilast

Adverse Events (% randomized)	Pivotal Pool		COPD Safety Pool		
	Rof500 mcg	Placebo	Rof500 mcg	Placebo	Rof250 mcg
Randomized	N=1547	N=1545	N=5766	N=5491	N=797
Any GI toxicity*	319 (20.6)	188 (12.2)	1271 (22)	587 (10.7)	104 (13)
Diarrhea*	130 (8.4)	49 (3.2)	585 (10.1)	143 (2.6)	39 (4.9)
Nausea*	62 (4)	30 (1.9)	297 (5.2)	79 (1.4)	18 (2.3)
Withdrawal due to any GI toxicity**	68 (4.4)	13 (0.8)	294 (5.1)	44 (0.8)	13 (1.6)
Data source: Tables 20* (pp58), 4** (pp80) and 33 (pp77) in ISS (24/2009)					

While nearly 90% of the GI side effects were mild or moderate in intensity, the remaining 10% were severe and met the criteria for an SAE. The more severe GI side effects were intractable diarrhea and pancreatitis. Though small in number, both occurred almost exclusively in roflumilast treatment groups. Among the 13 cases of intractable diarrhea and 7 cases of acute pancreatitis reported in the COPD safety pool, all but one case of each occurred in the roflumilast treated groups. Of the two patients who had acute pancreatitis who died, both were receiving roflumilast 500 mcg at the time of occurrence. Again, occurrence of severe GI side effects appeared to be dose dependent. The risk of developing GI SAEs was low for the roflumilast 250 mcg group, similar to that for the placebo group (see table 56 below).

Table 56 Serious gastrointestinal toxicities (frequency > 0.3% patients in any treatment group)

Adverse Events n (% randomized)	Pivotal Pool		COPD Safety Pool		
	Rof500 mcg	Placebo	Rof500 mcg	Placebo	Rof250 mcg
Randomized	N=1547	N=1545	N=5766	N=5491	N=797
GI toxicity met SAE criteria	30 (1.9)	19 (1.2)	80 (1.4)	49 (0.9)	5 (0.6)
Intractable Diarrhea	5 (0.3)	0	10 (0.2)	1 (<0.1)	2 (0.3)
Acute pancreatitis	4 (0.3)	1 (<0.1)	5 (<0.1)	1 (<0.1)	1 (0.1)
Data source: Table 33 (pp77) in ISS (24/2009)					

Roflumilast-related weight loss

Weight loss was a common adverse event reported in roflumilast clinical trials. Patients of all indications studied were affected, which suggests that roflumilast related weight loss is a drug specific effect.

To better understand how roflumilast associated weight loss affects patients with COPD, a meta analysis was performed using weight measurements collected from trials M2-124, M2-125, M2-111, M2-112, M2-127 and M2-128. Data were analyzed in several pools depending on the length of the clinical trials. As weight was regularly assessed in the pivotal studies, M2-124 and M2-125, and because they were long (one year) in duration, the results from the pivotal COPD weight pool will be discussed here. The results from analysis of other study pools were similar.

Overall, in the pivotal trial pool, 62.4% patients in the roflumilast group and 37.7% patients in the placebo group had measurable weight loss (referred as measured weight loss below baseline). Of note, only a fraction of the measured weight loss was reported as adverse event. In the pivotal trial pool, the reported rates of weight loss as an adverse event (referred as AE weight loss below) were 10.3 and 2.8% respectively for the roflumilast and the placebo treated groups.

The mean weight change for patients in the roflumilast group was - 2.09 kg, which corresponded to a -2.72% reduction in body weight compared to baseline. For patients who received the placebo, the mean body weight increased slightly by +0.08 kg which equaled to a 0.25% increase in body weight from the baseline. Obese patients had most absolute (kg loss from the baseline) and relative (% loss from the baseline) weight loss. The between treatment differences in absolute and relative weight loss were: 2.01 kg or % for underweight patients, 1.76 kg or % for normal weight patients, 2.09 kg for % for overweight patients and 3.11 kg or % for obese patients. Subgroup analysis suggested that mild and moderate weight loss affected COPD patients of all disease severity equally. Severe weight loss disproportionally affected more patients with very severe COPD (FEV1 < 30% predicted) than patients with moderate (FEV1 $\geq$ 50%, < 80% predicted) or severe (FEV1 $\geq$ 30%, < 50% predicted) disease (see table 57 below).

Table 57 Analysis of mean weight loss by patient characteristics at baseline (studies M2-124 and M2-125 pooled data)

Baseline Characteristics	Rof500 mcg			Placebo			Δ Treatment (rof–placebo) kg (%)*
	n (% of N)	mean Wt (kg)	Δ Wt kg (%)	n (% of N)	mean Wt (kg)	Δ Wt kg (%)	
All (Pivotal pool)	1498	73.65	-2.09 (2.8)	1510	73.28	0.08 (1.1)	- 2.17 (2.9)
By baseline BMI category							
Underweight	134 (8.9)	45.60	-.073 (1.6)	127 (8.4)	45.83	1.28 (2.8)	-2.01 (4.4)
Normal weight	572 (38.2)	62.74	-1.64 (2.6)	605 (40.1)	62.43	0.12 (0.19)	-1.76 (2.8)
Over weight	475 (31.7)	78.99	-2.02 (2.6)	462 (30.6)	79.00	0.07 (0.09)	-2.09 (2.6)
Obese	317 (21.2)	97.18	-3.57 (3.7)	316 (20.9)	96.72	-0.46 (0.48)	-3.11 (3.2)
By COPD severity							
Moderate	126 (8.4)	77.6	-1.90 (2.4)	116 (7.7)	74.6	0.06 (0.08)	-1.84 (2.4)
Severe	927 (61.9)	74.7	-2.06 (2.7)	972 (64.4)	74.8	0.10 (0.13)	-1.96 (2.6)
Very severe	444 (29.6)	70.5	-2.19 (3.1)	417 (27.6)	69.4	0.00	-2.19 (3.1)

n (% of N): number of patients in each category (as % randomized to each respective treatment group).
mean Wt (kg): mean body weight at the baseline in kilograms.
Δ Wt kg (%): change in mean body weight from baseline in kilograms (% change in body weight comparing to baseline)
COPD severity: moderate: FEV1 <80% and ≥50%; severe: FEV1<50% and ≥30%; very severe: FEV1 <30%.
Source: Table 10, pp 71 and Table 11, pp 75 of CSR 348/2008

Severity of weight loss was categorized as mild, moderate and severe, which were defined respectively as weight loss of 5% or less, more than 5% but equal or less than10% (> 5% and < 10%) and more than 10% of the baseline weight. In the pivotal pool, 35.2% of the patients in the roflumilast group had mild weight loss, 20.1% had moderate weight loss and 7.1% had severe weight loss. In comparison, 27.5, 8.3 and 1.9% of the patients in the placebo group had mild, moderate and severe weight loss (see table 58).

Table 58 Prevalence by severity of weight loss (studies M2-124 and M2-125 pooled data)

Weight loss categories	Rof500 mcg N=1547, n =1498		Placebo N= 1545, n=1510	
	n	(%)	n	(%)
Any weight loss	935	62.4	569	37.3
Mild (< 5%)	527	35.2	415	27.5
Moderate (> 5% and ≤10%)	302	20.1	125	8.3
Severe (> 10%)	107	7.1	29	1.9

N: number of patients randomized to each treatment group. N: number of patient in each category with body weight data available. (%): as percentage of those with data available.
Source: Table 7, pp 58 of CSR 348/2008.

Reviewer's comments: It should be noted that these ANCOVA analyses do not take into account that there were 3 times more patients in the roflumilast group that had moderate or severe weight loss compared to placebo. Therefore, the mean treatment difference analysis failed to capture the real clinical picture of patients who were most vulnerable to or had most severe weight loss.

Psychiatric adverse events including suicide (completed and attempted)

Adverse events related to the psychiatric system organ class were more common in patients who received roflumilast 500 mcg compared to those who received the 250 mcg dose or placebo. There were a total of 403 (7%) psychiatric adverse events reported in patients who received roflumilast 500 mcg once daily compared to 190 (3.5%) total events in the placebo group. There were 2-3 times greater insomnia, anxiety, and depression related adverse events in the 500 mcg roflumilast group compared to placebo (see table 59). In addition to the increase in psychiatric adverse events, of note is that there were more patients treated with roflumilast 500 mcg that had headache, dizziness, and tremor reported as adverse events compared to placebo [266 (4.6%), 139 (2.4%), and 98 (1.7%) compared to 110 (2%), 65 (1.2%), and 15 (0.3%) for headache, dizziness, and tremor in the roflumilast 500 mcg compared to placebo, respectively.

Table 59 Combined treatment emergent adverse events in the psychiatric SOC reported > once and more in roflumilast treatment groups (COPD safety pool)

Preferred term (MedDRA)	Rof500 mcg N=5677, n (%)	Rof250 mcg N=797, n (%)	Placebo N=5491, n (%)
All psychiatric disorders	403 (7.0)	24 (3.0)	190 (3.5)
Insomnia/Sleep disorder	178 (3.1)	13 (1.6)	61 (1.1)
Anxiety/Anxiety disorder	82 (1.4)	6 (0.8)	44 (0.8)
Depression[1]	80 (1.4)	4 (0.5)	49 (0.9)
Nervousness	8 (0.1)	0	3 (<0.1)
Confusional state	6 (0.1)	0	5 (<0.1)
Restlessness	5 (<0.1)	0	3 (<0.1)
Agitation	4 (<0.1)	0	2 (<0.1)
Mental disorder	3 (<0.1)	0	1 (<0.1)
Suicide (completed)	2 (<0.1)	1 (0.1)	0
Suicide (attempt)	2 (<0.1)	0	0
Crying	2 (<0.1)	0	0
Disorientation	2 (<0.1)	0	0
Hallucination	2 (<0.1)	0	0

1. includes the terms depression, depressed mood, depressive symptom, major depression
Source: Table 2.6.1.3 ae-freq-treat-by217-ss-copd-pdf, p. 13657-13660.

In order to assess whether the incidence of psychiatric AEs was consistent across other disease clinical development programs, psychiatric system organ class AEs were reviewed for COPD studies conducted by a different sponsor in Japan and in asthma and “other” disease indications that roflumilast has been studied (diabetes, allergic rhinitis, rheumatoid arthritis, and osteoarthritis). Review of these data show that an approximately 2-fold increase in psychiatric AEs in patients receiving 500 mcg of roflumilast once daily is persistent across studies in different patient populations and appears to be dose-related (see table 60 below). The types of AEs reported in these studies are consistent with those reported in the COPD population (insomnia, anxiety, depression).

Table 60 Total treatment emergent adverse events in the psychiatric SOC reported across roflumilast clinical programs

Clinical Program	Program Total N (ITT)	Rof500 mcg n (%)	Rof250 mcg n (%)	Rof125 mcg n (%)	Placebo n (%)
COPD	11965	403 (6.0)	24 (2.8)	-	190 (3.0)
JPN-COPD*	752	24 (10)	11 (4.2)	-	16 (6.4)
Asthma	5169	67 (4.3)	27 (2.5)	3 (1.4)	50 (2.2)
Other**	671	16 (4.7)	-	-	2 (0.6)

* Japanese studies JP-706, and JP-708
** Diabetes (M2-401), allergic rhinitis (FHP-013), rheumatoid arthritis (FKE-001), osteoarthritis (FKE-002)
Source: Data submitted by Applicant on 3/8/2010 in response to information request

In addition to the general 2-3 fold increases insomnia, anxiety, and depression, there were a total of 5 completed suicides or suicide attempts reported in the roflumilast COPD safety data base (N=12054 patients) in roflumilast treated patients compared to none in patients treated with placebo. In none of the three completed suicide cases (all males) did the patient have a prior history of depression. In two of the cases the patient had reportedly discontinued roflumilast approximately 20-21 days prior to the suicide event. With regard to the suicide attempts, both females had prior psychiatric histories (depression in one patient and previous suicide attempt in the other). Both patients were receiving roflumilast at the time of the suicide attempt. Brief narratives of the completed and attempted suicides follow:

Completed Suicides

- Patient 66176 (Study M2-111, South Africa): The patient is an 80 year old male enrolled in Study M2-111 who received roflumilast 500 mcg once daily. Medications included salbutamol for COPD initiated on May 5, 2004. The patients had also been treatment for non-insulin dependent diabetes and essential hypertension for years. He had no previous history of depression. Therapy with roflumilast started on June 8, 2004 and the patient committed suicide on (b) (6) after receiving roflumilast for approximately 4 months. He had gone for a drive in his car and apparently "gassed" himself while in the car.

- Patient 96102 (Study M2-125, Spain): The patient is a 76 year old male enrolled in Study M2-125 who received roflumilast 500 mcg once daily. Medications included ipratropium, salmeterol and salbutamol for COPD. He had no previous history of depression or other emotional problems. Five days after being randomized to the roflumilast 500 mcg once daily treatment group the patient started to complain about insomnia, irritability, and anxiety. The patient decided to withdraw from the study and did so on (b) (6) (11 days post-randomization). Five days after stopping therapy (a total of 9 tablets), he suffered from an anxiety crisis and was treated in an emergency room with intramuscular diazepam and prescribed clorazepate which he took twice over the next 4 days. He was subsequently prescribed alprolazolam by his physician. Eleven days after discontinuing roflumilast he took an overdose of alprazolam (7-9, 0.5mg tablets) and was treated in an emergency room. There he was seen by a psychiatrist who prescribed venlafaxin, 75 mg, in addition to alprazolam. Four days later the patient was seen by a private psychologist who referred him to a psychiatrist because of ongoing anxiety and insomnia. He

committed suicide by jumping from the 3rd or 4th floor of an office building on (b) (6), (b) (6), 3 weeks after discontinuing roflumilast.

- Patient 7124 (Study M2-107, Spain): The patient is a 73 year old male enrolled in Study M2-107 who received roflumilast 250 mcg once daily. He had a past medical history of ischemic heart disease and duodenal ulcer. He had no noted past history of depression or other depressive symptoms. Chronic medications included ipratropium for COPD. The patient's last study visit was on (b) (6), at which time he was generally well with some dry cough. On (b) (6) the patient underwent a scheduled repair of a previously repaired inguinal hernia. On discharge from the hospital (b) (6)), the patient was being treated with several additional drugs prescribed peri-operatively including cefuroxime, omeprazole, and ketorolac. He committed suicide on (b) (6) after being treated with roflumilast 250 mcg once daily for approximately 17 weeks. Of note is that upon further investigation the investigator indicated that since the last study visit on (b) (6), the patient had taken 6 tablets of roflumilast (Note: if taken consecutively immediately following that last visit, then the patient committed suicide approximately 20 days after the last dose of roflumilast 250 mcg once daily).

Suicide Attempts

- Patient 84291 (Study M2-124): The patient is a 54 year old female enrolled in Study M2-124 who received roflumilast 500 mcg once daily. She had a past history of depression since 2003 and ileus. Chronic medications included salbutamol and ipratropium for COPD as well as clonazepam and alprazolam. Approximately 11 months (342 days) after beginning roflumilast 500 mcg once daily, the patient attempted suicide by ingestion of clonazepam, alprazolam, and niflumic acid. She was taken to a hospital by ambulance. En route the patient lost consciousness and was intubated. Gastric lavage was performed and she was treated for hypothermia and hyponatremia. She was placed on mechanical ventilation and was successfully extubated on hospital day 2. When stabilized the patient was transferred to an inpatient psychiatric unit. After 5 days she was discharged home on mirtazapine, clonazepam, declofenac, ambroxol, and acetylsalicylic acid and encouraged to continue psychiatric care.

- Patient 71037 (Study M2-127, Belgium): The patient is a 52 year old female enrolled in Study M2-127 who received roflumilast 500 mcg once daily and salmeterol 50 mcg inhaled twice daily as study treatments. She had a past history of gastroesophageal reflux disease treated with pantoprazole, angina pectoris, and osteoporosis. She is noted to have had a previous suicide attempt in (b) (6). After approximately 5 months of roflumilast 500 mcg once daily therapy, the patient tried to commit suicide by ingestion of 600 mg of bromazepam on (b) (6). She was admitted to an intensive care unit with a diagnosis of "coma after intake of bromazepam" where she was kept for one week. During this time the study medication was withheld. She was then transferred to an inpatient psychiatry unit where she was hospitalized for an additional 3.5 weeks and treated with sertraline, acamprosate, disulfiram, and lormetazepam. Study medication

was re-started upon transfer. She was discharged with a diagnosis of "serious depression due to relational difficulties".

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In COPD safety pool, the most common adverse event for both treatment groups was COPD-related (exacerbations of the underline disease the drug intends to treat). The rate of exacerbations was slightly lower in the roflumilast treated patients compared to placebo treated patients (19.8 versus 21.3%). The rates of COPD were lower in the pivotal pool because only exacerbations that met the criteria for SAE were included.

The most prominent non-COPD related adverse events noted in the controlled studies were weight loss, diarrhea, nausea, headache, insomnia and dizziness. These adverse events were 2 to 4 fold more frequent in the roflumilast treated patients compared to the placebo treated patients. The frequency of these adverse events ranged from 7-10% (weight loss, diarrhea) to 2-5% (headache, insomnia and dizziness) in roflumilast 500 mcg treated patients compared to 2-3% (weight loss, diarrhea) to 1% or less (headache, insomnia and dizziness) in placebo treated patients (see table 61 below).

Table 61 Patients with AEs ≥ 2% by system organ class and preferred term (pivotal COPD study pool and COPD safety pool)

System Organ Class Preferred Term (MedDRA)	Pivotal COPD studies pool		COPD safety pool		
	Placebo (N=1545) (ET=1240) n (%)[a]	Rof500 (N=1547) (ET=1186) n (%)[a]	Placebo (N=5491) (ET=3405) n (%)[a]	Rof250 (N=797) (ET=325) n (%)[a]	Rof500 (N=5766) (ET=3261) n (%)[a]
All AEs	**963 (62.3)**	**1040 (67.2)**	**3447 (62.8)**	**484 (60.7)**	**3873 (67.2)**
Infections and infestations	**422 (27.3)**	**424 (27.4)**	**1508 (27.5)**	**188 (23.6)**	**1492 (25.9)**
Nasopharyngitis	97 (6.3)	92 (5.9)	346 (6.3)	50 (6.3)	364 (6.3)
Bronchitis	64 (4.1)	56 (3.6)	192 (3.5)	25 (3.1)	177 (3.1)
Upper respiratory tract infection	59 (3.8)	49 (3.2)	234 (4.3)	32 (4.0)	219 (3.8)
Pneumonia	31 (2.0)	42 (2.7)	110 (2.0)	5 (0.6)	104 (1.8)
Influenza	38 (2.5)	39 (2.5)	132 (2.4)	16 (2.0)	145 (2.5)
Gastrointestinal disorders	**188 (12.2)**	**319 (20.6)**	**587 (10.7)**	**104 (13.0)**	**1271 (22.0)**
Diarrhoea	49 (3.2)	130 (8.4)	143 (2.6)	39 (4.9)	585 (10.1)
Nausea	30 (1.9)	62 (4.0)	79 (1.4)	18 (2.3)	297 (5.2)
Investigations	**181 (11.7)**	**281 (18.2)**	**584 (10.6)**	**55 (6.9)**	**811 (14.1)**
Weight decreased	44 (2.8)	157 (10.1)	101 (1.8)	6 (0.8)	394 (6.8)
Respiratory, thoracic and mediastinal disorders	**327 (21.2)**	**265 (17.1)**	**1607 (29.3)**	**197 (24.7)**	**1476 (25.6)**
COPD[b]	204 (13.2)	157 (10.1)	1271 (23.1)	169 (21.2)	1142 (19.8)
Dyspnoea	28 (1.8)	28 (1.8)	120 (2.2)	18 (2.3)	84 (1.5)
Musculoskeletal and connective tissue disorders	**144 (9.3)**	**181 (11.7)**	**445 (8.1)**	**62 (7.8)**	**590 (10.2)**
Back pain	35 (2.3)	50 (3.2)	117 (2.1)	22 (2.8)	176 (3.1)
Nervous system disorders	**90 (5.8)**	**150 (9.7)**	**304 (5.5)**	**45 (5.6)**	**615 (10.7)**
Headache	25 (1.6)	51 (3.3)	110 (2.0)	28 (3.5)	266 (4.6)
Dizziness	16 (1.0)	30 (1.9)	65 (1.2)	9 (1.1)	139 (2.4)
Metabolism and nutrition disorders	**60 (3.9)**	**104 (6.7)**	**186 (3.4)**	**19 (2.4)**	**311 (5.4)**
Decreased appetite	7 (0.5)	36 (2.3)	22 (0.4)	4 (0.5)	125 (2.2)
Psychiatric disorders	**55 (3.6)**	**98 (6.3)**	**164 (3.0)**	**22 (2.8)**	**344 (6.0)**
Insomnia	20 (1.3)	37 (2.4)	50 (0.9)	11 (1.4)	148 (2.6)
Vascular disorders	**80 (5.2)**	**76 (4.9)**	**229 (4.2)**	**20 (2.5)**	**196 (3.4)**
Hypertension	48 (3.1)	38 (2.5)	136 (2.5)	12 (1.5)	95 (1.6)

[a]Percentages of patients with at least one event in the category.
[b]The preferred term COPD refers to COPD exacerbation. Note, in the pivotal COPD studies only COPD exacerbations fulfilling the criterion of a serious AE were to be recorded in the AE section.
AE = adverse event, COPD = chronic obstructive pulmonary disease, ET = number of patient years of exposure, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in treatment group, n = number of patients with at least one event in the category, Rof250 = 250 µg roflumilast once daily, Rof500 = 500 µg roflumilast once daily
Source data: [289/2008, Tables 1.6.1.3, 1.6.6.3, 2.6.1.3, 2.6.6.3]

7.4.2 Laboratory Findings

As presented in Section 7.2.4, routine laboratory assessments included hematology, blood chemistry, urine analysis and pregnancy tests. Hemoccult testing was not routinely performed during the earlier studies but was added in later trials because of the nonclinical findings of mesenteric vasculitis observed for another PDE4 inhibitor, cilomilast.

More patients in the roflumilast 500 mcg treated group had reduction in hemoglobin from within the normal range at the baseline to below the lower limit of the alert range (LLAR), defined as a hemoglobin level of 7.1 mmol/L or lower, compared to those in the placebo and roflumilast 250 mcg treated groups. In the COPD safety pool, 56 (1%) patients from the roflumilast 500 mcg group had hemoglobin levels below the lower limit of the alert range. Of these 56 patients, 26 (0.5%) had normal levels of hemoglobin at baseline. Thus, 30 patients shifted from above to below the LLAR during the study (see table below). In contrast, 13(0.4%) patients from the placebo group had hemoglobin levels below LLAR at the end of the study of which 5 (0.2%) had normal levels at the baseline.

The Applicant did not provide any further discussion regarding the possible cause for the higher incidence of reduction in hemoglobin in roflumilast 500 mcg treated patients. Nevertheless, these results were consistent with the finding that more roflumilast 500 mcg treated patients had positive hemoccult tests compared to placebo. Follow-up work-ups for positive hemoccult were inconclusive. Refer to discussion in section 7.4.5 on vasculitis.

Table 62 Change in hemoglobin levels from baseline to end of treatment

Hematology variable change from baseline to end of treatment	Pivotal COPD studies pool		COPD safety pool		
	Placebo (N=1545) n (%)[a]	Rof500 (N=1547) n (%)[a]	Placebo (N=5491) n (%)[a]	Rof250 (N=797) n (%)[a]	Rof500 (N=5766) n (%)[a]
Hemoglobin					
Low to below LLAR	6 (0.4)	8 (0.5)	12 (0.2)	2 (0.3)	29 (0.5)
Normal to below LLAR	5 (0.3)	10 (0.6)	10 (0.2)	5 (0.6)	26 (0.5)
N.a. to below LLAR	1 (<0.1)	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)

Source: Table 36, pp 87 of ISS.
LLAR: hemoglobin level ≤ 7.1 mmol/L.

There were no statistically significant differences between the treatments in other hematology parameters including erythrocytes, leukocytes and platelets counts. No patients discontinued from the study or were reported as an AE secondary to a change in a hematology parameter.

There were no clinically relevant changes in blood chemistry noted. Less than 1% patients had any abnormality in blood chemistry at the end of the study compared to baseline and more patients in the placebo group had abnormal blood chemistry (predominantly elevated liver enzymes or blood glucose).

More roflumilast 500 mcg treated patients had positive hemoccult tests compared to placebo. However, there were no conclusive findings on follow up evaluations. Refer to 7.4.5 for further discussion of hemoccult testing.

7.4.3 Vital Signs

Vital signs were evaluated at beginning and end and during selected visit(s) in each trial. Data were analyzed for pivotal COPD pool and the COPD safety pool. Blood pressure and pulse rate were comparable between treatment groups and generally stable over time in both pools.

7.4.4 Cardiac Safety and Electrocardiograms (ECGs)

Patients with COPD have a recognized increased risk of cardiovascular co-morbidities. As a result, electrocardiograms (12-lead ECG) were performed at entry and exit of each COPD trial and at the mid point (28 weeks) of the 52 week pivotal trials.

Patients who had clinically relevant abnormal ECGs at baseline were excluded from the clinical trials. EKG readings performed in the clinical trials were evaluated by cardiologists. In the pivotal trials, the ECG data from participating US sites were transferred to and analyzed in a centralized data center.

ECG findings from the 14 trials included in the COPD safety pool were analyzed in a meta-analysis entitled, “Safety evaluation of roflumilast – cardiac safety” (study report 350/2008). The last visit ECG recordings from all trials were compared to those at the baseline. The pooled data showed a similar percentage of patients in either treatment groups experienced cardiac adverse events. There were essentially no differences between treatment groups regarding the percentage of patients who had serious cardiac adverse events (roflumilast 500 mcg 1.8% versus placebo 2.1%), cardiac adverse events leading to death (roflumilast 500 mcg 0.4% versus placebo 0.5%), or cardiac adverse events leading to study discontinuation (roflumilast 500 mcg 0.9% versus placebo 1.0%).

Further analysis for cardiac adverse events was performed by categorizing cardiac events of interest (cardiac arrhythmias, coronary artery disorders, heart failures and myocardial disorders). The rates for all cardiac events of interests, except arrhythmia, were marginally higher in the placebo group. The slightly higher incidence of cardiac arrhythmia in the roflumilast treated group was attributed to atrial fibrillation (the incidence of atrial fibrillation was 0.8% for roflumilast 500 mcg versus for 0.6% placebo).

In addition, 24-hour Holter ECG monitoring was performed in selected patients from trial M2-125 to study the arrhythmogenic potential of roflumilast when used in combination with long-acting beta agonists (LABA) in patients with COPD. The evaluation consisted of a 24-hour Holter ECGs with 3 channels and was performed with 55 US patients (33 in the roflumilast and 22 in the placebo group) receiving LABA as concomitant medication. In addition to the standard 12-lead centralized ECGs, the 24-hour Holter ECGs were performed at baseline, 6 months, and at the last study visit (which was either the scheduled end of the study or an earlier date if the

patient discontinued the study). The results of the 24-hour Holter ECGs showed no differences in heart rates or occurrence of arrhythmias between the roflumilast and the placebo treated groups.

In addition to assessing for cardiac safety in the clinical studies in COPD patients, the effects of roflumilast on cardiovascular function were investigated in healthy volunteers in 4 phase 1 studies.

Trial CP-069 was a placebo controlled QT study in 80 healthy subjects (54 males, 26 females). A single 400 mcg dose of moxifloxacin was given as positive control 1 day prior to roflumilast administration. Seven or 14 day roflumilast treatment of up to 1000 mcg per day were tested. QT interval was accessed 1 hour after roflumilast dosing. While no QTc change of 30 ms or greater was observed in any subject, review of the study by the FDA QT study review group concluded that the study lacked assay sensitivity and therefore was not conclusive.

Trial FHP007 was a placebo controlled crossover study designed to evaluate the effects of roflumilast on heart rate (HR), blood pressure (BP) and EKG patterns. The study contained two 5 day treatment periods during which once daily 500 mcg of roflumilast or placebo were administered. The washout time between the treatments was 3-5 weeks. Thirteen (13) healthy subjects completed the study. Roflumilast did not affect BP, HR, resting or exercise ECG.

Trials CP-059 and CP-070 studied the possible effect of a potential interaction between roflumilast and formoterol (CP-059) or sildenafil (CP-070) on cardiovascular system. Trial CP-059 was a parallel group study in 27 healthy subjects. One group of subjects started with a daily oral dose of 500 mcg roflumilast for the first10 days and formoterol 24 mcg was added on day 11 as concomitant medication for 7 days. The other treatment group had a reverse dosing regimen with formoterol for the first 7 days followed by concomitant formoterol and roflumilast for 10 days. Administration of roflumilast as mono- or add-on treatment to formoterol had no clinically relevant effect on vital signs, ECG, lab test results and various cardiographic parameters tested.

Trial CP-070 was a randomized, double-blind, placebo controlled 4 way crossover, single dose study in 12 healthy males. The subjects received a single dose of 500 mcg roflumilast or 100 mcg sildenafil each alone or in combination, or placebo. There ere no clinically relevant changes in vitals signs, ECG, or impendence cardiography. Mean QTc-prolongations of 5 to < 20 ms were noted for both the roflumilast and sildenafil treatment and roflumilast alone.

7.4.5 Special Safety Studies/Evaluations

Mesenteric Vasculitis

Mesenteric arteritis was seen in rats during pre-clinical studies with cilomilast. As a screen for potentially serious GI-related side effects, systematic hemoccult testing was performed in 4 COPD and 1 asthma roflumilast trials (M2-124, M2-125, M2-110, M2-111 and M2-023). In pivotal COPD studies M2-124 and M2-125, hemoccult testing was performed throughout the study at each planned study visits. In trials M2-111 and M2-023, hemoccult tests were performed at the beginning (screening and baseline), once at the mid point and at the end of the trials. In trial M2-110, hemoccult tests were only performed at the beginning and the end of the trial.

In general, more roflumilast treated patients had GI symptoms that were of concern and tested positive on hemoccult screening than patients received placebo treatment. A total of 129 patients (of whom 70 received roflumilast 500 mcg, 7 received roflumilast 250 mcg, 52 received placebo) had positive hemoccult tests or other signs of GI bleeding (bloody stool or melena) during the trial treatment periods. GI workups including colonoscopy were performed in the majority but not all positive cases. A total of 116 of the 129 patients from the 5 mentioned roflumilast trials underwent endoscopic examination for positive hemoccult tests, GI bleeds or other reasons. There were no findings that would be consistent with or indicative of ischemic colitis.

In addition to the planned hemoccult tests, a search of ischemic colitis and related diagnoses was performed for all 114 trials within the roflumilast development program. The search was based on a narrow set of 15 standardized MedDRA Query terms including: colitis ischemic, colon gangrene, enterocolitis hemorrhagic, gastrointestinal gangrene, gastrointestinal ischemia, gastrointestinal mucosal necrosis, gastrointestinal necrosis, intestinal angina, intestinal gangrene, intestinal infarction, intestinal ischemia, large intestinal hemorrhage, large intestine perforation, mesenteric vascular insufficiency, and necrotizing colitis.

The search identified two patients with suspected ischemic colitis, one from the roflumilast 500 mcg treated group in trial FK1-007, and the other from the placebo group in trial M2-110. The roflumilast treated case involved a 35-year-old male asthma patient (CRF ID (b) (6)) in trial FK1-007, a 40 week open-label safety study. He underwent an intestinal polypectomy about 4 months into his treatment with 500 mcg roflumilast. Two months later (after more than six months on roflumilast) he suffered from "colon perforation" and was admitted urgently to a hospital. He fully recovered in 3 months.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Limited dose-ranging was performed in the clinical trials with only 2 doses, 250 and 500 mcg once daily, being evaluated in COPD patients. While evaluation of the 250 mcg dose of roflumilast was limited, there appears to be a dose dependent increase in GI, weight loss, and psychiatric adverse events associated with the 500 mcg once daily dose of roflumilast. See sections 7.3.4 and 7.4.1.

7.5.2 Drug-Demographic Interactions

The affects of gender and age on roflumilast PK and PD were studied in 8 phase I trials. In an open label phase I study, PDE4 inhibition was 43% higher in healthy females compared to males. In other trials, elderly subjects generally showed greater systemic exposure to roflumilast compared to younger subjects (19% higher PED4 inhibition was observed in patients 65 year of age or older).

Drug demographic interactions were also analyzed in pooled safety data from COPD trials. The demographic characters investigated included age, gender, COPD disease severity, race, smoking status and geographic location. This safety review will focus on age, gender, COPD severity and smoking status. As overwhelming majority of patients in the clinical trials were white Europeans, safety analysis on race and geographic location were inconclusive and will not be reviewed here.

In general, patients who were elderly (> 65 years of age), were female, and had very severe COPD disease had more SAEs and more early withdrawal because of AEs. See the table 62 for drug demographic interactions for the pivotal COPD pool. Findings for the total COPD safety pool follow the same general trends.

Table 63 Affects of gender, age and COPD severity on adverse events (Studies M2-124 and M2-125 pooled data, ITT)

	N	ET	Patients with AEs [n (%)[a]]				
			All AEs	AEs related to study drug	Deaths	Serious AEs	AELW
Overall							
Placebo	1545	1240	963 (62.3)	73 (4.7)	40 (2.6)	336 (21.7)	177 (11.5)
Rof500	1547	1186	1040 (67.2)	225 (14.5)	42 (2.7)	301 (19.5)	219 (14.2)
Gender							
Male							
Placebo	1180	959	724 (61.4)	50 (4.2)	35 (3.0)	261 (22.1)	134 (11.4)
Rof500	1157	904	765 (66.1)	145 (12.5)	35 (3.0)	240 (20.7)	160 (13.8)
Female							
Placebo	365	281	239 (65.5)	23 (6.3)	5 (1.4)	75 (20.5)	43 (11.8)
Rof500	390	282	275 (70.5)	80 (20.5)	7 (1.8)	61 (15.6)	59 (15.1)
Age							
≤65 years							
Placebo	879	708	521 (59.3)	39 (4.4)	16 (1.8)	178 (20.3)	85 (9.7)
Rof500	882	704	585 (66.3)	107 (12.1)	18 (2.0)	156 (17.7)	92 (10.4)
>65 years							
Placebo	666	532	442 (66.4)	34 (5.1)	24 (3.6)	158 (23.7)	92 (13.8)
Rof500	665	482	455 (68.4)	118 (17.7)	24 (3.6)	145 (21.8)	127 (19.1)
COPD severity							
Very severe							
Placebo	438	329	279 (63.7)	20 (4.6)	21 (4.8)	114 (26.0)	60 (13.7)
Rof500	465	330	332 (71.4)	74 (15.9)	21 (4.5)	106 (22.8)	78 (16.8)
Severe							
Placebo	982	801	617 (62.8)	49 (5.0)	17 (1.7)	207 (21.1)	111 (11.3)
Rof500	951	755	623 (65.5)	131 (13.8)	18 (1.9)	173 (18.2)	124 (13.0)
Moderate							
Placebo	120	105	66 (55.0)	4 (3.3)	2 (1.7)	15 (12.5)	6 (5.0)
Rof500	130	100	84 (64.6)	20 (15.4)	3 (2.3)	22 (16.9)	17 (13.1)
Smoking status							
Current							
Placebo	641	519	386 (60.2)	35 (5.5)	14 (2.2)	120 (18.7)	73 (11.4)
Rof500	638	504	421 (66.0)	88 (13.8)	16 (2.5)	119 (18.7)	83 (13.0)
Former							
Placebo	904	721	577 (63.8)	38 (4.2)	26 (2.9)	216 (23.9)	104 (11.5)
Rof500	909	682	619 (68.1)	137 (15.1)	26 (2.9)	182 (20.0)	136 (15.0)

a. Percentage of patients with at least one event in the category.
Data source: Table 41, pp100 and Table 47, pp111 of ISS.

7.5.3 Drug-Disease Interactions

Safety and tolerability of roflumilast in subjects with severe renal or liver impairment were evaluated in three Phase I trials, FHP020, CP-062 and FHP19. Trial FHP020 was an open label, parallel group study of safety and PK of roflumilast 500 mcg in patients with severe renal insufficiency (defined as creatinine clearance 10 ≤ and ≤ 30 ml/min/1.73 m2 body surface areas). PK parameters were evaluated in 24 subjects (12 healthy and 12 renally impaired) after a single 500 mcg dose of roflumilast.

Trials CP-062 and FHP019 were open label, parallel group studies of safety and PK in subjects liver cirrhosis. In trial CP-062, 24 subjects (8 with Child Pugh A, 9 with Child Pugh B and 8 healthy volunteers) received once daily roflumilast 250 mcg for 14 days. In trial FHP019, 12 subjects with Child Pugh A and 12 healthy subjects received a single 250 mcg dose of roflumilast.

Compared to matching healthy subjects, liver cirrhosis patients had significantly increased PDE4 inhibitory activity. The respective increase in mean total PED4 inhibition following repeat administration of 250 mcg of roflumilast (trial CP-062) were 26 and 46% in patients with Child Pugh A and B liver cirrhosis. In contrast, patients with renal severe insufficiency had little change (9% reduction) in PDE4 inhibitory activity (trial FHP020). No differences in AE profiles were observed from these Phase I trials for patients with liver or renal impairment. However, it should be noted that patients with Child Pugh C disease were excluded from roflumilast trials and that the 250 mcg dose used for cirrhosis trials was half of what is being proposed.

7.5.4 Drug-Drug Interactions

A summary of the drug-drug interaction studies conducted for roflumilast can be found in the Summary of Clinical Pharmacology and Biopharmaceutics Findings briefing document.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Roflumilast has been demonstrated to be carcinogenic in animal species (see the Summary of Nonclinical Pharmacology and Toxicology in the briefing package). As a result, cancer and tumor-related adverse events were identified as a topic of special interest.

In the overall roflumilast clinical development program, a total of 218 tumor events were reported in 208 patients. One hundred thirty one (60%) of the tumors were in patients in the roflumilast group and 86 (40%) of the tumors were in patients in the placebo group. These data are consistent with what was observed in COPD patients where 105 of 185 (57%) and 80 of 185 (43%) of tumors were in the roflumilast and placebo treated groups, respectively. There was more lung and prostate cancer reported for patients treated with roflumilast than those who received placebo (33 and 14 compared to 17 and 7, for lung and prostate cancers in the roflumilast and placebo groups, respectively (see table 63 below).

Table 64 Summary of cancer/tumor types in COPD patients (COPD safety pool)

Tumor type	Rtotal (N=6563)			Placebo (N=5491)			Total (N=12054)		
	n	(%)	n'	n	(%)	n'	n	(%)	n'
All Tumor AEs	**98**	**1.5**	**105**	**72**	**1.3**	**80**	**170**	**1.4**	**185**
Lung cancer	33	0.5	33	17	0.3	17	50	0.4	50
Skin neoplasms	14	0.2	14	12	0.2	12	26	0.2	26
Other and not further specified neoplasms[b]	9 (8)[a]	0.1 (0.1)[a]	9 (8)[a]	16 (13)[a]	0.3 (0.2)[a]	17 (14)[a]	25 (21)[a]	0.2 (0.2)[a]	26 (22)[a]
Prostate cancer	14	0.2	14	7	0.1	7	21	0.2	21
Other gastro-intestinal neoplasms	5	<0.1	6	13	0.2	13	18	0.1	19
Neoplasms of the urinary tract	9	0.1	11	5	<0.1	5	14	0.1	16
Colon and rectal cancer	9	0.1	9	2	<0.1	2	11	<0.1	11
Gynecologic neoplasms	3	<0.1	3	4	<0.1	5	7	<0.1	8
Hematologic neoplasms	5 (6)[a]	<0.1 (<0.1)[a]	5 (6)[a]	1 (4)[a]	<0.1 (<0.1)[a]	1 (4)[a]	6 (10)[a]	<0.1 (0.1)[a]	6 (10)[a]
Neoplasms of the upper respiratory tract	1	<0.1	1	1	<0.1	1	2	<0.1	2

[a] After the safety analyses were completed, it was detected that 4 patients were categorized erroneously into the tumor type 'other and not further specified neoplasms' although they should have been categorized into 'hematologic neoplasms'. The affected patients were: in the roflumilast group: 1 patient (M2-121, CRF 90070) with paraproteinemia; in the placebo group: 1 patient (M2-125, CRF 90215) with paraproteinemia and 2 patients (M2-125, CRF 91041 and 97653) with plasmacytoma [Table 1.4.12]. The adjusted numbers of patients in these tumor type categories are indicated in brackets.
[b] The category 'other and not further specified neoplasms' includes tumors which either occurred in very few patients (bone neoplasm, neuroendocrine carcinoma), or were not-further specified (eg metastasis).
AE = adverse event, N = number of patients in treatment group, n = number of patients with at least one event in the category, n' = number of events in the category, po = per os, % = percentage of patients with at least one event in the category based on N, Rtotal = both treatment groups combined (Roflumilast 250 µg once daily and Roflumilast 500 µg once daily po), PBO = Placebo once daily po.
Source data: [Tables: 1.4.1.2, 1.4.1.3, 1.4.1.4, 1.4.2 and 1.4.3].

7.6.2 Human Reproduction and Pregnancy Data

Females

Effects of roflumilast on the reproductive system and embryofetal development were studied in mice, rats, and rabbits. Roflumilast administration to animals during pregnancy resulted in dose-related increases in stillborns, maternal deaths, and decreases in pup viability in mice.

Clinical studies to assess the affects of roflumilast during pregnancy have not been conducted. While pregnancy was a criterion of exclusion for participating in roflumilast clinical trials, as of December 9, 2008, a total 20 females (16 in the 500 mcg group, 3 in the 250 mcg group and 1 in the 125 mcg group) who received roflumilast became pregnant (all indications). The estimated duration of in utero drug exposure was 2 to 65days. The pre-pregnancy drug exposure was between 2 days and 5 months.

Of the 20 pregnancies in roflumilast treated woman, 11 resulted in healthy neonates, 2 spontaneously aborted, 3 ended with elective abortion, 2 terminated medically (one due to severe maternal hypertension) and 2 lost to follow up.

There is no human experience regarding roflumilast use in lactating women as such individuals were excluded from participation in clinical trials. Excretion of roflumilast and/or its metabolites into human milk has not been studied. However, roflumilast has been found in the milk of lactating rats.

Males

In animal studies, a statistically significant decrease in male rat fertility rate (64.2% compared to control at 89.2%) was observed at the 1.8 mg/kg/day roflumilast dose level. Therefore, the effects of roflumilast on male fertility have been addressed clinically. Trial FHP035 was a double-blind, placebo-controlled, parallel-group study in 351 healthy men. The study began with a 12 week active treatment period followed by a 12 week, off treatment follow up. The subjects received once daily dosing of roflumilast 500 mcg or placebo for 12 weeks during the active treatment. Sperm concentration, progressive motility and male reproductive hormones (testosterone, FSH, LH, inhibin B) were measured at the baseline as well as during the treatment and follow-up period. There were no between treatment differences noted between roflumilast and placebo treated groups.

7.6.3 Overdose, Drug Abuse Potential, Withdrawal and Rebound

While there are no experiences with accidental overdose, early single dose, dose escalation studies with roflumilast administered to healthy volunteers demonstrated significant toxicities at doses ≥ 2500 mcg. AEs after administration of 2500 mcg dose were headache, gastrointestinal complaints (diarrhea, nausea and lower abdominal pain), dizziness, palpitation and clamminess. Additionally, decreased systolic and diastolic blood pressure were noted in subjects who received single 2500 mcg or 5000 mcg doses of roflumilast.

There is no evidence for abuse potential for roflumilast or other PDE4 inhibitors.

No independent study was conducted to evaluate any withdrawal or rebound effects after long term roflumilast use. Nevertheless, trial FK1-103 included a roflumilast withdrawal arm, in which 12 weeks of roflumilast treatment was followed by 12 weeks of placebo treatment. Patients in the roflumilast withdrawal arm were compared to patients in the 24 weeks roflumilast

or placebo treatment arms for efficacy and tolerability. There was no evidence of any effect on vital signs, ECG, lab values or physical exams from roflumilast withdrawal.

7.7 Conclusions

Serious safety issues have been noted with roflumilast. This PDE4 inhibitor causes significant and at times severe gastrointestinal adverse events (diarrhea, nausea, and pancreatitis) and weight loss in many, if not most, of the patients that have received it. The effects are dose-related with greater frequency observed in patients receiving the proposed 500 mcg dose. While this dose was what was felt to be the maximally tolerated dose for chronic use in healthy subjects the high frequency of adverse events in patients with COPD suggests the highest tolerable dose for that older population with other co-morbidities may be lower than 500 mcg once daily. In addition to gastrointestinal side effects, patients treated with roflumilast demonstrate a 2-3 times increased occurrence of psychiatric adverse events such as anxiety, depression, and insomnia. Five patients in the COPD program have attempted (2) or had completed suicides (3) compared to no subjects who were treated with placebo. The increased occurrence of psychiatric adverse events observed in COPD patients also extends to other patient populations who have received roflumilast (diabetes, arthritis, allergic rhinitis) which suggests this is a direct drug effect. Roflumilast is carcinogenic in animals. Of note is that there is a 20% greater occurrence of cancer in patients who have received roflumilast compared to placebo suggestive of human carcinogenicity.

8 Postmarketing Experience

Roflumilast is not currently marketed for any indication.

PULMONARY - ALLERGY DRUGS ADVISORY COMMITTEE MEETING

April 7, 2010

STATISTICAL BRIEFING DOCUMENT

NDA22-522

Daxas [500 µg oral tablet once daily]
for maintenance treatment of chronic obstructive pulmonary disease associated with chronic bronchitis in patients at risk of exacerbation

Primary Reviewer: Robert Abugov, Ph.D.

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1. EXECUTIVE SUMMARY

Forest Research Institute, Inc. has proposed Daxas®, a film coated tablet of roflumilast, for "the maintenance treatment of chronic obstructive pulmonary disease associated with chronic bronchitis in patients at risk of exacerbation." Efficacy and safety data from six studies, 124, 125, 111, 112, 127, and 128 were analyzed for the proposed use of roflumilast 500 µg oral tablet once daily (QD) in COPD patients.

Two Studies, 124 and 125, conducted for 52 weeks on the population proposed for indicated use, provide evidence that roflumilast increases pre-bronchodilator FEV1 by approximately 48 milliliters, and demonstrate a statistically significant reduction compared to placebo in rate of moderate or severe exacerbations, with a rate ratio of 0.83, and with an absolute rate reduction of 0.3 moderate or severe exacerbations per patient per year.

The primary analysis employed by the Applicant compares exacerbation rates between treatments averaged over the entire course of the study. This analysis does not explicitly examine potential changes of treatment effect over time, a potentially important consideration when assessing maintenance therapy for long-term administration. Exploratory analyses of the data suggest that the reduction in exacerbation rate by roflumilast compared to placebo appears to attenuate eight months after commencement of treatment.

2. INTRODUCTION

2.1 Overview

Chronic obstructive pulmonary disease (COPD) is characterized by limitations of airflow which are not fully reversible. It is usually progressive and associated with abnormal inflammatory responses to noxious particles or gases.

The Applicant, Nycomed Gmbh, has developed roflumilast, a phosophodiesterase-4 (PDE4) inhibitor, for the maintenance treatment of chronic obstructive pulmonary disease associated with chronic bronchitis in patients at risk of exacerbation. The Applicant expects that inhibition of PDE4, a major enzyme for metabolizing cyclic adenosine monophosphate (cAMP), should increase cAMP concentrations and consequently reduce the inflammatory responses and bronchiolar constrictions which produce COPD.

The clinical development plan was introduced to the Division of Pulmonary and Allergy Products by Nycomed Gmbh (formerly Altana Pharma AG) via IND 57,883 (February 12, 1999) and discussed during several meetings, as well as written correspondences. Some of the statistical issues discussed or provided written comments concerned the choice of primary endpoints (i.e. pre-bronchodilator FEV1 and exacerbation), consistent definition of exacerbation across studies, the analysis population (i.e. intent-to-treat population), multiplicity consideration for the analyses of primary and secondary endpoints (i.e. gatekeeping approach), as well as performing efficacy analyses stratified by randomization factors.

Sixteen phase 2 and 3 (placebo-controlled, randomized, double-blind, parallel group) studies were performed in patients with COPD to establish the therapeutic dose and to assess the efficacy and safety of roflumilast compared to placebo (Table 1, in chronological order). After conducting subgroup analyses on Studies 111 and 112, Nycomed Gmbh concluded that greatest reduction in exacerbation rates would be seen among patients with severe COPD, chronic bronchitis and a prior history of exacerbations. The design of Studies 124 and 125 were based on this finding.

The Applicant submitted this application on July 15, 2009 (NDA 22-522) in support of the proposed indication for Daxas (roflumilast) for the indication maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. The submission included 4 one-year studies (Studies 124, 125, 111, 112) and 7 six-month studies (Studies 101, 103, 107, 110, 121, 127, and 128). The Applicant also provided reports (English translation) from Studies JP-706 and JP-708 conducted under a different sponsor.

On December 4, 2009, the Applicant, Nycomed Gmbh informed the Agency in a letter the transfer ownership of NDA 22-522 to Forest Research Institute, Inc. who assumed responsibility as the Sponsor of the NDA.

Of the 11 studies submitted by the Applicant, this statistical review focuses on Studies 124, 125,

111, 112, 127 and 128. Studies 124 and 125 were 52-week, double-blind, placebo-controlled studies evaluating roflumilast 500 μg QD, and were conducted in the US, Europe, South Africa, Australia, New Zealand, Canada, and India. Both studies allowed concomitant treatment with long-acting β2-agonists (LABA) and 50% of the patients in each study took such medication. Studies M2-111 and M2-112 were similar in design to studies 124 and 125, but included a similar yet slightly different patient population (i.e. patients in Studies M2-111 and M2-112 were not required to have a history of exacerbations and chronic bronchitis). Studies 124, 125, 111, and 112 investigated the effect of roflumilast on exacerbations and lung function in patients with severe to very severe COPD. Studies 127 and 128 were 24-week trials that investigated the benefit of roflumilast treatment in patients with moderate to severe COPD who were receiving maintenance therapy with either salmeterol (Study 127) or tiotropium (Study 128). The focus of these studies was to evaluate if roflumilast adds additional benefit on lung function beyond the effects of long-acting bronchodilators.

Table 1: Randomized, double blind, placebo controlled, parallel arm phase 3 clinical trials conducted to assess the effect of roflumilast, in chronological order.

Study	COPD	Dose	Primary Endpoints	Weeks	N
FK1 101	Mod – Sev	250, 500	Pre-bronchodilator FEV1 SGRQ	26	516
FK1 103	Mod – Sev	500	Post-bronchodilator FEV1 SGRQ	24	581
IN-108	Mod – Sev	250, 500	(safety)	12	118
M2-107	Mod – Sev	250, 500	Post-bronchodilator FEV1 SGRQ	24	1411
M2-110	Mod – Sev	500	Post-bronchodilator FEV1	24	909
M2-111	Sev – V Sev	500	Mod/Sev Exacerb Pre-bronchodilator FEV1	52	1173
M2-112	Sev – V Sev	500	Mod/Sev Exacerb Post-bronchodilator FEV1	52	1513
M2-118	Mod – Sev	500	Endurance	12	250
M2-119	Mod – Sev	500	Post-bronchodilator FEV1	12	410
M2-121	Mod – V Sev	500	Post-bronchodilator FRC Post-bronchodilator FEV1	24	600
JP 706	Mod – Sev	250, 500	Post-bronchodilator FEV1	24	600
JP 708	Mod – Sev	250, 500	safety extension JP-706	28	152
M2-124	Sev – V Sev Bronchitis	500	Pre-bronchodilator FEV1 Mod/Sev Exacerb	52	1523
M2-125	Sev – V Sev Bronchitis	500	Pre-bronchodilator FEV1 Mod/Sev Exacerb	52	1568
M2-127[1.]	Mod – Sev	500 + S	Pre-bronchodilator FEV1	24	933
M2-128[2.]	Mod – Sev	500 + T	Pre-bronchodilator FEV1	24	743

1. Treatment and placebo receive salmeterol 50µg bid
2. Treatment and placebo receive tiotropium 18µg qd
Mod: moderate
Sev: severe
V Sev : very severe
SGRQ: St. Georges's Respiratory Questionnaire

2.2 Data Sources

Documents reviewed were accessed from the CDER document room at:
\\...\CDSESUB1\EVSPROD\NDA022522

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design, Efficacy Endpoints, and Statistical Methodologies

3.1.1.1 Efficacy Studies (Studies 124, 125, 111, 112, 127 and 128)

Studies 124 and 125 were conducted from 2006 to 2008, as randomized, parallel arm double-blind, placebo-controlled international studies.

The objective of each study was to evaluate the efficacy and safety of roflumilast 500 µg tablet once daily (QD) compared to placebo in patients with COPD. After a four week run-in period during which patients were removed from all prohibited COPD medications and received a single blind placebo, compliant symptomatic patients without exacerbations during the run-in period with severe or very severe COPD and bronchitis were randomized to receive either placebo or roflumilast, stratified by smoking status and use of concomitant treatment with long-acting $ß_2$ agonists (LABA). All patients were at least 40 years of age and had a smoking history of at least 20 pack years.

Investigational site (clinic) visits were scheduled every two weeks during the run-in period, every four weeks after randomization up to week 12 (post-randomization) and, every eight weeks thereafter until 52 weeks elapsed since randomization.

During the run-in and treatment periods, patients were provided with albuterol for use as rescue medication. Because spirometry was conducted during clinic visits, patients were instructed to withhold the use of rescue medications for four hours prior to the clinic visit, anticholinergics for six hours, and LABAs for 12 hours.

In both studies, a moderate exacerbation was defined as an exacerbation requiring use of oral or parenteral glucocorticosteroids, and a severe exacerbation was defined as an exacerbation which resulted in hospitalization or death. Exacerbations within ten days of each other were merged and counted as a single exacerbation.

The primary efficacy endpoints for these studies were mean change in pre-bronchodilator forced expiratory volume in 1 second (FEV_1 [L]) from baseline of at each post-randomization visit and rate of moderate or severe COPD exacerbations. In both studies, the primary efficacy endpoints were tested in hierarchical manner, with rate of COPD exacerbations tested at the two-sided 0.05 level of significance only if pre-bronchodilator FEV1 was significant at the two-sided 0.05 level.

All analyses were conducted on the intent-to-treat population, defined as all randomized patients (primary) and per-protocol population defined as valid cases only without any major protocol violations (secondary).

The primary analysis for treatment effect on mean change in pre-bronchodilator FEV_1 from baseline to each visit of used a repeated measure analysis of covariance (ANCOVA) with baseline pre-bronchodilator FEV_1 value, age, sex, smoking status, concomitant treatment with LABA, and country, and with fixed effects time and time-by-treatment interaction. The default analysis above was to employ restricted maximum likelihood (REML) with an unstructured covariance matrix. If the default analyses failed to converge, the sponsor planned to employ, in order, maximum likelihood (ML) rather than REML, a compound symmetry covariance matrix with REML, and a compound symmetry covariance matrix with maximum likelihood. If the above models failed to converge, factors would be excluded individually from the statistical model in the following order: country, concomitant treatment with LABA, smoking status, and sex. Statistical significance was to be declared if the two-sided, unadjusted p-value at the last measurement is less than 0.05. In this analysis, no replacement of missing values was performed.

In addition to the repeated measurements model, a further ANCOVA was performed as change from baseline to each post-randomization visit as well as last visit for the primary endpoint pre-bronchodilator FEV1. In this analysis, last observed value is carried forward to replace missing value.

The primary analysis for the effect of roflumilast on rate of moderate or severe exacerbations was a Poisson regression model with log-link and with the log of each patient's time in study as an offset variable. The model included treatment, country, smoking status, percent predicted FEV1, gender, and age. A Pearson chi-square correction for scale was applied to account for potential overdispersion. A negative binomial regression model was also performed as secondary analysis for the mean rate of moderate or severe COPD exacerbations per patient per year.

The Applicant performed analyses on several secondary endpoints they classified as 'key'. This includes (in the following order)

1. mean change in post-bronchodilator FEV1 [L] from baseline to each post-randomization visit during the treatment period
2. time to mortality due to any reason
3. natural log-transformed CRP (C-reactive protein) [mg/L] (mean change from baseline to last scheduled study visit)
4. mean Transition Dyspnea Index (TDI) focal score during the treatment period

For the post-bronchodilator FEV1 and TDI focal score, a repeated measurements ANCOVA model was used to evaluate within- and between-treatment differences. Time to mortality due to any reason was analyzed using the Cox-proportional hazards regression. In terms of CRP, an ANCOVA was performed using a natural log-transformed CRP at the last study visit. The dependent variable was the mean ratio of the natural log-transformed CRP to baseline. This was derived as the difference between the last study visit naturally log-transformed CRP value and the naturally log-transformed CRP baseline value. In this analysis, last observed value is carried forward to replace missing value at the end of study visit.

The key-secondary endpoints were tested in a confirmatory manner two-sided at a significance level of 5% if and only if both primary endpoints were statistically significant at the 5%

significance level. According to the Applicant, in the case that the test for a key-secondary endpoint could not be performed on a confirmatory basis, because a test with higher priority had failed, this test was performed in an exploratory manner.

Studies 111 and 112

The patient populations for Studies 111 and 112 were similar to those for Studies 124 and 125 described above. However, although patients had severe or very severe COPD, a history of bronchitis and of COPD exacerbations was neither requested nor required, and 10 rather than 20 pack years of smoking was required for enrollment. In Study 111, but not in Study 112, the randomization was stratified by smoking status and use of inhaled corticosteroids pre-treatment.

As in Studies 124 and 125, investigational site (clinic) visits were scheduled every two weeks during the run-in period, every four weeks after randomization up to week 12 (post-randomization) and, every eight weeks thereafter until 52 weeks elapsed since randomization.

The primary efficacy endpoints were the mean change from baseline to the end of treatment in FEV1 (pre-bronchodilator FEV1 in Study 111 and post-bronchodilator FEV1 in Study 112), and the number of moderate or severe COPD exacerbations per patient-year. Analysis of FEV1 in Study 112 used an analysis of covariance rather than a repeated measures analysis at study endpoint. In Study 111, as in Studies 124 and 125, exacerbations requiring oral or parenteral glucocorticosteroids or hospitalization and/or leading to death were considered primary evaluation of exacerbations. Study 112 differed slightly as it included exacerbations requiring antibiotics treatment and exacerbations leading to death were added post-protocol. Unlike Studies 124 and 125, beginning and end time of exacerbations were recorded by use of drugs or hospital admission or death rather than by time of exacerbation as experienced by the patient. In Study 112, exacerbations not separated by one exacerbation free day were merged and counted as a single exacerbation, and in Study 111, exacerbations not separated by ten exacerbation free days were merged and counted as a single exacerbation.

In both studies, a moderate exacerbation was defined as an exacerbation requiring use of oral or parenteral glucocorticosteroids, with Study 112 additionally including an exacerbation requiring antibiotics. In Study 111, a severe exacerbation was defined as an exacerbation which resulted in hospitalization or death, while in Study 112, a severe exacerbation was originally defined as an exacerbation which resulted in hospitalization, with death added post protocol. Unlike Studies 124 and 125, beginning and end time of exacerbations were recorded by use of drugs or hospital admission or death rather than by time of exacerbation as experienced by the patient. In Study 112, exacerbations not separated by one exacerbation free day were merged and counted as a single exacerbation, and in Study 111, exacerbations not separated by ten exacerbation free days were merged and counted as a single exacerbation.
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In both studies, all analyses were conducted on the intent-to-treat population, defined as all randomized patients (primary) and per-protocol population defined as valid cases only without any major protocol violations (secondary).

In Study 111, the primary analysis for treatment effect on lung function (FEV1) is similar to that used in Studies 124 and 125, that is, a repeated measure ANCOVA, but with inhaled corticosteroids (ICS) pre-treatment replacing concomitant treatment with LABA as covariate, and having pre-treatment with ICS used as stratification factor in randomization. The primary analysis for exacerbation in Study 111 was also similar to that used in Studies 124 and 125, using a Poisson regression model with overdispersion. Pretreatment ICS and history of COPD classified by presence or absence of bronchitis and emphysema were added as covariates in the regression model.

In Study 112, the primary analysis for treatment effect on change from baseline to endpoint (i.e. landmark analysis) in post-bronchodilator FEV1 used an ANCOVA with covariates baseline value, age, sex, smoking status, pre-treatment treatment with inhaled corticosteroids, and country. In this analysis, last observed value is carried forward to replace missing value (i.e. LOCF approach). A repeated measure ANCOVA was also performed as secondary analysis for the primary variable post-bronchodilator FEV1.

In Study 112, the primary analysis for the effect of roflumilast on frequency of moderate or severe exacerbations used an unstratified Wilcoxon Rank Sum Test. A poisson regression with overdispersion was also performed as secondary analysis for the frequency of moderate or severe COPD exacerbations.

In Study 111, the Applicant performed analyses on several secondary endpoints they classified as 'key'. This includes (in the following order)

1. mean change in post-bronchodilator FEV1 [L] from baseline to each post-randomization visit during the treatment period
2. The number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids or severe COPD exacerbations per patient per year in the following population (in order):
    a. patients with post-bronchodilator FEV1 <30% of predicted at T0
    b. patients with a medical history of chronic bronchitis with or without a medical history of emphysema
    c. patients with a cough score of ≥2 in the week before randomization
    d. patients with a cough score of ≥1 in the week before randomization
    e. patients with a history of at least one moderate or severe COPD exacerbation in the year prior to baseline
3. The number of moderate COPD exacerbations treated with oral or parenteral glucocorticosteroids and/or antibiotics or severe COPD exacerbations per patient per year.
4. The number of mild or moderate or severe COPD exacerbations per patient per year.

The secondary variable (1) was analyzed with a repeated measure ANCOVA analogous to the primary variable of pre-bronchodilator FEV1 and secondary variables (2) to (4) were analyzed with a Poisson regression model analogous to that of the primary variable of COPD exacerbations

The decision rule using hierarchical approach to control the family-wise type 1 error was similar to that in Studies 124 and 125.

Change (endpoint minus baseline value) in total score of SGRQ was the only 'key' secondary variable in Study 112, using the same analysis approach as the primary variable post-bronchodilator FEV1 (i.e. landmark analysis). The decision rule in Study 112 uses a hierarchical approach with both primary endpoints tested simultaneously first, and if both are significant, the secondary endpoint (SGRQ) will then be tested.

Studies 127 and 128

The patient population for 24 week Studies 127 and 128 were similar to those for Studies 124 and 125 described above. However, patients in these studies had moderate or severe COPD rather than severe or very severe COPD, did not necessarily have a history of bronchitis and or COPD exacerbations, and had a minimum of 10 rather than 20 pack years of smoking. In addition, patients in Study 128 had to receive tiotropium for at least three months before the run in phase of the trial. Further, to be eligible for randomization, patients in Study 128 had to use 28 puffs of rescue medication during the week preceding randomization. Randomization of patients in Study 127 was stratified by smoking status. In both studies, patients were withdrawn if they had a severe exacerbation or a second moderate exacerbation after commencement of treatment.

Investigational site (clinic) visits were scheduled every 2 weeks, during the four week run in period, and every 4 weeks on post-randomization (i.e. weeks 4, 8, 12, 18, and 24). Throughout the baseline and treatment periods, all patients in Study 127 were assigned to receive salmeterol (Serevent® Diskus) administered 50 μg bid in the morning and evening as recommended for use in COPD, and all patients in 128 were assigned to receive one inhalation of tiotropium 18 μg via Handihaler each morning.

The primary efficacy endpoint for these studies was mean change in pre-bronchodilator FEV1 from baseline to each post-randomization visit during the treatment period.

For both studies, the primary analysis for treatment effect on change from baseline to study endpoint of pre-bronchodilator FEV1 used a repeated measures ANCOVA with covariates baseline value, age, sex, smoking status, and country, and with fixed effects time and time by treatment interaction similar to Studies 124, 125 and 111.

The Applicant performed analyses on several secondary endpoints they classified as 'key'. In Study 127, this includes (in the following order)

1. mean rate of COPD exacerbations (mild, moderate, or severe) per patient year
2. mean Transition Dyspnea Index (TDI) focal score during the treatment period
3. mean change in the Shortness of Breath Questionnaire (SOBQ) from baseline to each post-randomization visit during the treatment period

In Study 128, this includes (in the following order)

1. mean change in post-bronchodilator FEV1 [L] from baseline to each post-randomization visit during the treatment period
2. mean rate of COPD exacerbations (moderate, or severe) per patient year

COPD Exacerbation is defined as follows:

- mild exacerbation: increase in rescue medication of three or more puffs/day on at least two consecutive days during the double-blind treatment period;
- moderate exacerbation: management by initiating an oral or parenteral glucocorticosteroid therapy
- severe exacerbation: hospitalization and/or death

The secondary variables (1) in Study 127 and (2) in Study 128 were analyzed with a Poisson regression model analogous to that of the primary variable of COPD exacerbations in Studies 111, 125 and 125. Secondary variables (2) and (3) in Study 127 and (1) in Study 128 were analyzed with a repeated measure ANCOVA analogous to the primary variable of pre-bronchodilator FEV1.

The decision rule using hierarchical approach to control the family-wise type 1 error was similar to that in Studies 111, 124 and 125.

3.1.2 Results and Conclusions

3.1.2.1 Patient Disposition, Demographic and Baseline Characteristics

The focus of this review will be on the four 52-week studies (Studies 124, 125, 111, and 112) and two 24-week studies (Studies 127 and 128). In terms of endpoints, my focus will be on the pre-bronchodilator FEV1 endpoint and the rate of moderate or severe exacerbation endpoint. I will only briefly describe the results of other secondary endpoints (e.g. mortality and SGRQ) in this review.

In all four 52-week studies, more than 60% of patients completed the study (Table 2). In the 24-week studies, more than 75% of patients completed the study. Compared to placebo, roflumilast-treated patients had a higher percentage of dropouts in all six studies. The two most common reasons for discontinuation were adverse event and patient request/unwillingness to continue. Compared to placebo, roflumilast-treated patients had a higher percentage of dropouts due to adverse event, as well as due to patient decision. In contrast, placebo-treated patients had a higher percentage of dropouts due to COPD exacerbation compared to roflumilast-treated patients in four out of six studies.

Table 2: Summary of Patient Disposition

	Study 124		Study 125		Study 111		Study 112		Study 127		Study 128	
	Rof	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**
Randomized	766	759	773	798	568	608	761	753	467	468	372	372
ITT	765	758	772	796	567	606	760	753	466	467	371	372
PP	553	549	528	565	417	468	514	536	360	369	304	302
Completed (%)	65	69	68	69	62	69	71	78	77	82	83	89
Discontinued (% randomized)	35	31	32	31	38	31	29	22	23	18	17	11
Adverse event (%)	16	10	13	10	20	11	14	7	17	10	9	5
Patient decision (%)	16	13	14	13	16	13	-	-	11	8	7	3
COPD exacerbation (%)	6	9	6	8	6	4	4	3	3	6	1	2
Predefined discontinuation (%)	1	1	1	1	2	3	-	-	1	3	0.3	1
Lost to follow up (%)	2	2	3	3	2	1	-	-	0.4	0.4	1	1
Other (%)	4	4	4	4	6	7	11	12	2	2	1	2
Protocol violation (%)	28	28	32	29	27	23	33	29	23	21	18	19

Note: Results from Study Reports

In all studies, the demographic and baseline disease characteristics were generally well balanced and comparable between the treatment groups (Table 3). Overall, the median age was 65 years. The majority of patients were Caucasian and approximately two-thirds of patients were male. In Studies 127 and 128, more than 60% of patients had COPD severity of 'moderate' compared to 30% of patients in the other four studies. Patients enrolled in Studies 127 and 128 had 'moderate' or 'severe' COPD compared to patients in Studies 111, 112, 124, and 125, who were enrolled with 'severe' or 'very severe' COPD (Table 1). Also, a higher proportion of patients are current smokers in these two studies compared to the other studies. In addition, patients in Studies 127 and 128 have a higher baseline mean pre-bronchodilator and post-bronchodilator FEV1 and % predicted FEV1 compared to the other studies.

Table 3: Summary of Patient Disposition

	Study 124		Study 125		Study 111		Study 112		Study 127		Study 128	
	Rof	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**
N	765	758	772	796	567	606	760	753	466	467	371	372
Age [a] [years] (median)	63	63	64	65	65	64	66	65	65	65	65	65
Sex [a,c] [male] %	71	71	79	81	68	66	75	76	68	64	71	72
Race [a,c] [white] %	96	97	72	71	94	93	99	99	95	95	100	100
Height [a] [cm] (mean)	170	169	167	167	170	170			169	168	168	169
Weight [b] [kg] (mean)	76	75	71	71	75	75	72	72	77	76	78	80
BMI [b] [kg/m^2] (mean)	26	26	25	25	26	26						
COPD [a,c] (%)												
Very severe	26	24	34	32	24	27			0	0	1	1
Severe	64	67	59	60	65	65			35	30	34	32
Moderate	11	8	7	7	11	7			65	69	63	65
Mild	0	0	0	0	0	0			0	0	2	3
Smoking [a,c] (%)												
Current	48	48	35	35	42	44	38	35	61	61	60	61
Former	52	52	65	65	58	56	62	65	40	39	40	39
LABA[d] (%)	49	51	48	51					70 [g]	69 [g]		
ICS [e] (%)	44	44	40	41			62[f]	63[f]				
Pre-bron FEV1[b] (mean)	1.1	1.1	1.0	1.0	1.0	0.9	1.0	1.0	1.4	1.4	1.5	1.5
Post-bron FEV1[b] (mean)	1.2	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.5	1.5	1.5	1.6
Pre-bron FEV1 [b] % predicted (mean)	35	35	31	32	31	31	37	37	52	52	53	53
Post-bron FEV1 [b] % predicted (mean)	38	38	35	35	37	36	41	41	55	55	56	56
SGRQ (mean)					48	49						

Note: Results from study reports.

[a] measurements were taken at V0

[b] measurements were taken at baseline (last measurement prior to randomization)

[c] percentages are based on the number of patients in the respective treatment group

[d] based on whether the patient had used LABA at least once within the time period start of treatment period (including) up to end of treatment period (including)

[e] based on whether the patient had used ICS at least once within visit V0 + 1 day up to the day preceding randomization, i.e. randomization date – 1 day, including both delimiting days

[f] based on whether patient had concomitant use of ICS treatment

[g] based on whether patient had pre-treatment of LABA

The average percentage of compliance to the study treatment was above 90% in all six studies (Table 4) and generally well balanced between roflumilast and placebo groups.

Table 4: Treatment Compliance and Duration of Exposure

	Study 124		**Study 125**		**Study 111**		**Study 112**		**Study 127**		**Study 128**	
	Rof	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**
N	765	758	772	796	567	606	760	753	466	467	371	372
Mean Treatment Compliance	94	95	93	96	96	96	99	99	94	96	96	97
Exposure												
≥ 26 weeks	76	80	76	80	71*	80*	78*	88*	29†	32†	36†	31†
≥ 52 weeks	46	50	48	49	26**	29**	36	40				
Mean Exposure [days]	278	292	282	294	268	298	290	318	142	153	150	158

*> 28 weeks
** > 52 weeks
† > 24 weeks

3.1.2.1 Change in Pre-Bronchodilator FEV1

Unless otherwise stated, all analyses below were conducted on intention to treat (ITT) study populations.

The primary analysis for treatment effect on mean change in pre-bronchodilator FEV_1 from baseline to each visit of used a repeated measure analysis of covariance (ANCOVA). Patients treated with roflumilast have a statistically significant effect on pre-bronchodilator FEV1 compared to placebo. In these studies, the size of the effect ranged from 39 to 80 ml, with an average of 54 ml.

Table 5: Change from Baseline in Pre-bronchodilator FEV1 to End of Treatment (ITT population)

Study	Weeks	Pre-Bronchodilator FEV1 (ml)				
		R500	Placebo	Diff	P-Value	Pooled Diff
M2-124	52	46 (745)	8 (745)	39	<0.001	48
M2-125	52	33 (730)	-25 (766)	58	<0.001	
M2-111	52	30 (545)	-12 (596)	42	<0.001	51
M2-112	52	49 (737)	-8 (741)	57	<0.001	
M2-127[1]	24	39 (456)	-10 (463)	49	<0.001	
M2-128[2]	24	65 (365)	-16 (364)	80	<0.001	

* pre-bronchodilator FEV1 is one of many secondary endpoints (p-value unadjusted)
1. All patients received salmeterol in addition to roflumilast or placebo
2. All patients received tiotropium in addition to roflumilast or placebo
Measurements in milliliters
Diff: difference between roflumilast and placebo.
P-Value: p-value for diff with H_0: Diff = 0.
Number of individuals randomized is provided in parentheses.

3.1.2.2 Rate of Exacerbation

Except in Studies 127 and 128, the mean rate of moderate or severe COPD exacerbations per patient per year is one of the two primary endpoints for Studies 124, 125, 111 and 112. In these four studies, the primary efficacy endpoints were tested in hierarchical manner, with rate of COPD exacerbations tested at the two-sided 0.05 level of significance only if pre-bronchodilator FEV1 was significant at the two-sided 0.05 level. As stated in Section 3.1.1.1, the definition of exacerbation in Study 112 differed slightly with the other studies as it included exacerbations requiring antibiotics treatment (moderate) and exacerbations leading to death were added post-protocol (severe). Also, exacerbations not separated by one exacerbation free day were merged and counted as a single exacerbation. To facilitate direct comparison of Studies 111 and 112 with Studies 124 and 125, the definitions of moderate and severe exacerbations were modified post-hoc by the Applicant to match those of 124 and 125. In addition, the analysis method, in particular the covariates included in the model, used in Studies 124 and 125 were applied to Studies 111 and 112 post-hoc.

The annual rates of moderate or severe exacerbation in Studies 124, 125, 111, and 112 are presented in Table 6. In these studies, roflumilast numerically reduced the annual rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate, from Studies 124 and 125 statistically significant and with two of the reductions, from Studies 111, and 112, not statistically significant. To facilitate direct comparison of Studies 111 and 112 with studies 124 and 125, the definitions of moderate and severe exacerbations in Table 6 were modified post-hoc by the sponsor to match those of 124 and 125. Without these post-hoc changes, the rate ratio comparing roflumilast and placebo was also not significant in both studies. The p-value for the Poisson analysis in Study 111 was 0.218 rather than 0.129 and the p-value for the for the Wilcoxon rank-sum test in Study 112 was 0.4514 rather than 0.085.

Table 6: Poisson Rates of Moderate or Severe Exacerbations in Studies 124, 125, 111, and 112 (ITT Population)

Study	Weeks	Poisson Exacerbation Rate					
		R500	Placebo	Rate Ratio	P-Value	Pooled	Rate Ratio
124	52	1.1 (765)	1.3 (758)	0.85	0.028	0.83	
125	52	1.2 (772)	1.5 (796)	0.82	0.004		
111*	52	0.6 (567)	0.7 (606)	0.86	0.129	0.85	
112*	52	0.5 (760)	0.5 (753)	0.85	0.085		

M2-111, M2-112 from report 22/2009_Table 2.7.3-39
Measurements under columns R500 and Placebo provided are the exponentiated mean log of the number of exacerbations per person per year.
* Based on exacerbation definition and analysis method used in Studies 124 and 125

In Study 127, the mean rate of COPD exacerbations (mild, moderate or severe) per patient year is one of the three the Applicant considered 'key' secondary endpoints and is the second test of the confirmatory testing procedure. The mean rate of moderate or severe COPD exacerbations is one of 'other' secondary endpoints and the Applicant has considered this endpoint 'exploratory'. Based on the analyses by the Applicant, the rate of COPD exacerbation (mild, moderate or severe) was lower for roflumilast (1.9) than placebo (2.4). However, the rate ratio (0.8) comparing roflumilast and placebo was not statistically significant. The confirmatory testing procedure ended with this test. Post-hoc analysis of moderate or severe COPD exacerbations in this study was conducted by the Applicant. The rate of COPD exacerbation (moderate or severe) was lower for roflumilast (0.3) than placebo (0.5) and the rate ratio is 0.6. In Study 128, the mean rate of COPD exacerbations (moderate or severe) per patient year is one of the two the Applicant considered 'key' secondary endpoints and is the second test of the confirmatory testing procedure. Based on the analyses by the Applicant, the rate of COPD exacerbation (moderate or severe) was slightly lower for roflumilast (0.26) than placebo (0.34). However, the rate ratio (0.77) comparing roflumilast and placebo was not statistically significant (Table 7).

Table 7: Poisson Rates of Moderate or Severe Exacerbations in Studies 127 and 128 (ITT Population)

Study	**Weeks**	**Poisson Exacerbation Rate**			
		R500	**Placebo**	**Rate Ratio**	**P-Value**
127*	24	0.3 (466)	0.5 (467)	0.63	0.032*
128	24	0.3 (371)	0.3 (372)	0.77	0.196

From datasets dm, xe, ds, dv, see pgm mainline efficacy poisson exacerbation rate 2010 02 09
* Post-hoc analysis (p-value unadjusted)

The statistical significance of reductions in exacerbation rate provided by roflumilast compared to placebo in Studies 124 and 125 were re-examined in Table 8 using a negative-binomial distribution (which has more flexibility in handling overdispersion). The rate ratios were nearly the same as in the original Poisson analysis.

Table 8: Negative binomial rates of moderate or severe exacerbations (ITT population)

Study	Weeks	Negative Binomial Exacerbation Rate			
		R500	Placebo	Rate Ratio	P-Value
M2-124	52	1.124 (765)	1.323 (758)	0.850	0.038
M2-125	52	1.268 (772)	1.556 (796)	0.815	0.007

From datasets dm, xe, ds, dv, see pgm mainline efficacy poisson exacerbation rate 2010 02 09
Measurements under columns R500 and Placebo provided are the exponentiated mean log of the number of exacerbations per person per year.

The frequency of moderate or severe exacerbation is presented in Table 9. Overall, a higher proportion of patients in the placebo experienced at least one moderate or severe COPD exacerbation compared to the roflumilast group. The frequency of patients experiencing at least 2 (up to 6 in Study 124 and up to 9 in Study 125) moderate or severe COPD exacerbation was higher in the placebo group compared to the roflumilast group.

Table 9: Frequency (in %) of Moderate or Severe Exacerbation

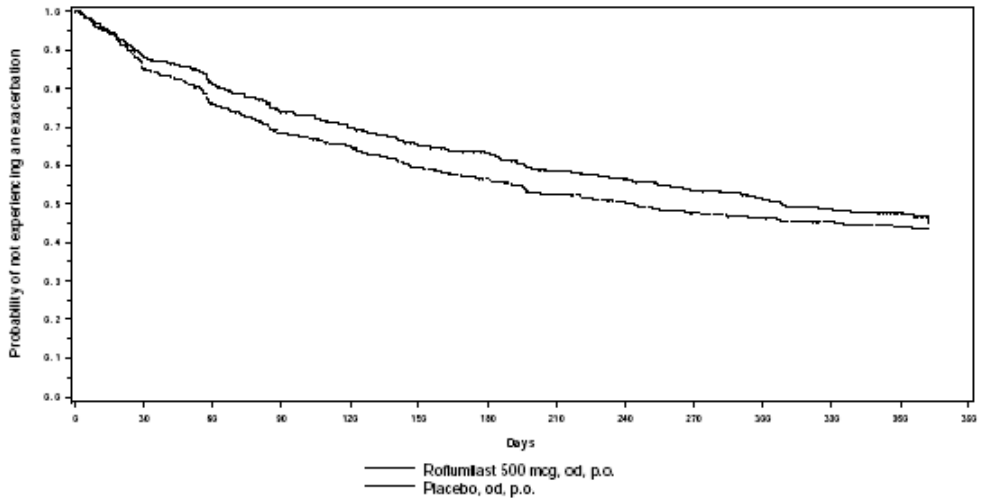
	Study 124		Study 125	
Frequency	ITT		ITT	
	Rof	Pbo	Rof	Pbo
N	765	758	772	796
0	**55**	**49**	**52**	**46**
1	25	25	26	25
2	11	13	12	14
3	6	7	6	7
4	2	3	3	4
5	1	2	1	2
6	0.1	1	0.4	1
7	1	0.3	0.1	1
8			0	0.3
9			0	0.3

The time to onset of first moderate or severe COPD exacerbation is explored. In Study 124, median time to first exacerbation (moderate or severe) was 244 days in the placebo group and 309 days in the roflumilast group (Figure 1). Similarly, in Study 125, median time to first

exacerbation was 227 days in the placebo group and 290 days in the roflumilast group (Figure 2). This implies a 65-day delay in the time to first COPD exacerbation (moderate or severe) in the roflumilast group compared to placebo.

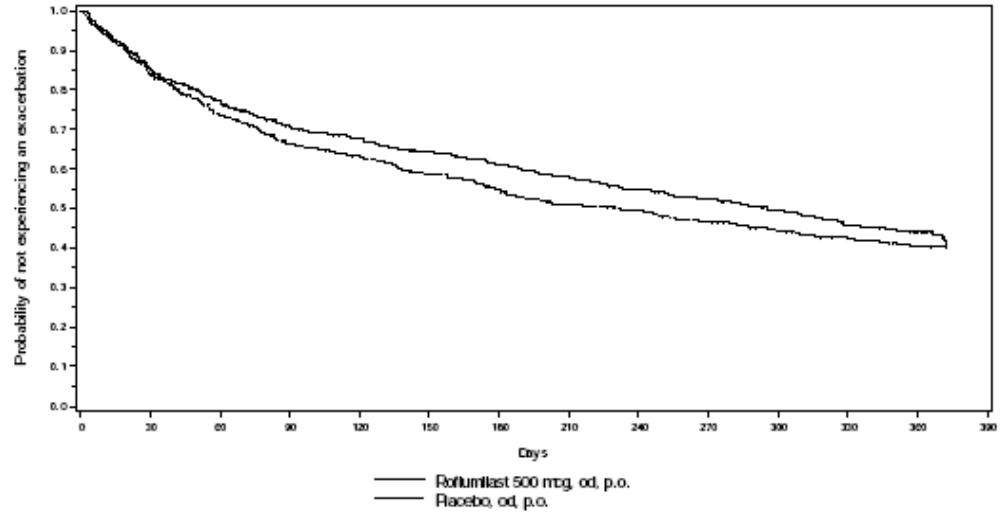
The mean rate of COPD exacerbations per patient year and the time to onset of first COPD exacerbation for different categories of COPD exacerbations are presented in Table 10. In general, the mean rate of COPD exacerbations and the proportion of patients with COPD exacerbations are numerically smaller in the roflumilast group compared to the placebo group for the different categories of COPD exacerbations in both studies. The largest treatment effect appears to be in patients with moderate COPD exacerbation in Study 124, where the 95% confidence limits for rate and hazard ratios do not include one, and in patients with severe COPD exacerbation in Study 125, where the 95% confidence interval for both rate ratio and hazard ratio include one (i.e. the null value), suggesting uncertainty in the difference in risk. In both studies, reduction in exacerbation rates appears to be similar for moderate exacerbations and for exacerbation treated with systemic steroids and/or antibiotics. Meanwhile, the hazard ratios appear to be similar for different categories of COPD exacerbation and numerically favor the roflumilast group.

Figure 1: Time to Onset of First Moderate or Severe COPD Exacerbation (Kaplan-Meier estimates, ITT population) Study 124



The plots only show events up to Day 372 (52-week study).
Source: Figure 3, Study Report 218/2008

Figure 2: Time to Onset of First Moderate or Severe COPD Exacerbation (Kaplan-Meier estimates, ITT population) Study 125



The plot only shows events up to Day 372 (52-week study).
Source: Figure 3, Study Report 219/2008

Table 10: Mean rate of COPD exacerbation per patient-year (Poisson regression) and Time to onset of first COPD exacerbation (Cox Proportional Hazards Regression)

Type of Exacerbation	**Study 124**				**Study 125**			
	Rof N=765 n (%) rate	**Pbo N=758 n (%) rate**	**Rate Ratio* 95%CI**	**Hazard Ratio** 95%CI**	**Rof N=772 n (%) rate**	**Pbo N=796 n (%) rate**	**Rate Ratio* 95%CI**	**Hazard Ratio** 95%CI**
Moderate	299 (39) 0.9	343 (45) 1.1	0.84 (0.7, 0.99)	0.87 (0.7, 1.0)	325 (44) 1.0	380 (50) 1.3	0.82 (0.7, 0.9)	0.89 (0.8, 1.0)
Severe	69 (9) 0.1	81 (11) 0.1	0.89 (0.6, 1.3)	0.90 (0.7, 1.2)	88 (10) 0.1	117 (12) 0.2	0.77 (0.5, 1.1)	0.85 (0.6, 1.1)
Moderate or Severe	**344 (45) 1.1**	**389 (51) 1.3**	**0.85 (0.7, 0.98)**	**0.88 (0.76, 1.0)**	**373 (50) 1.2**	**432 (56) 1.5**	**0.82 (0.7, 0.9)**	**0.89 (0.8, 1.0)**
Mild, moderate or severe	455 (60) 3.9	508 (67) 4.4	0.89 (0.8, 1.0)	0.89 (0.8, 1.0)	495 (64) 4.3	563 (71) 5.4	0.81 (0.7, 0.9)	0.90 (0.8, 1.1)
Treated with Systemic steroids and/or antibiotics	336 (44) 1.1	382 (50) 1.3	0.85 (0.7, 0.98)	0.87 (0.7, 1.0)	364 (49) 1.2	416 (54) 1.4	0.83 (0.7, 0.9)	0.92 (0.8, 1.1)
Treated with antibiotics only	62 (8) 0.1	73 (10) 0.1	0.95 (0.7, 1.4)	0.87 (0.6, 1.2)	63 (6) 0.1	72 (6) 0.1	0.93 (0.7, 1.3)	0.97 (0.7, 1.4)
Hospitalized	52 (7) 0.2	55 (7) 0.3	0.94 (.6,1.4)	0.82 (0.6,1.2)	59 (8) 0.3	70 (9) 0.3	0.84 (0.5,1.3)	0.86 (0.6,1.2)

pgm mainline efficacy Poisson&Cox exacerbation rate hosp 2010 03 03.sas

* Mean rate of COPD exacerbation: Rate ratio calculated using Poisson regression

** Time to first COPD exacerbation: Hazard ratio calculated using Cox regression mod

The Poisson and negative binomial analyses provided in Table 7 and Table 8 assess the effect of roflumilast on exacerbation rate averaged over the entire course of the study, but they do not explicitly examine potential changes in its effect over time. However, the proposed 'maintenance treatment' indication implies that roflumilast will be effective when administered for an extended period, and it therefore seems worthwhile to perform exploratory analyses to assess whether its effect is constant.

For the exploratory analyses, I broke the study into time intervals, similar to those used by the Applicant for the FEV1 analyses, and examined the mean number of exacerbations per patient year. The simple means are presented in Figure 3 and Figure 4.

The reduction of exacerbation rate by roflumilast compared to placebo appears to attenuate or even disappear after 8 months (Table 11, and shown graphically in Figure 3 and Figure 4). This may be problematic for a long term maintenance indication in which the benefits are expected to be stable and positive over time.

Table 11: Number of exacerbations per patient year, calculated from simple means

Study	Interval	Roflumilast				Placebo				Diff
	(weeks)	N Pat	Exac	PYr	ExPPYr	N Pat	Exac	PYr	ExPPYr	
M2-124	00–04	765	80	57.3	1.4	758	93	57.2	1.6	-0.2
	04–12	732	119	101.7	1.2	736	156	107.0	1.5	-0.3
	12–20	632	96	94.5	1.0	676	136	99.0	1.4	-0.4
	20–28	606	94	90.0	1.0	628	123	94.0	1.3	-0.3
	28–36	575	72	85.1	0.8	600	102	88.7	1.1	-0.3
	36–44	547	78	80.6	1.0	571	83	84.1	1.0	0.0
	44–52	518	68	77.5	0.9	541	71	81.6	0.9	0.0
M2-125	00–04	772	100	57.6	1.7	796	110	59.6	1.8	-0.1
	04–12	731	143	102.5	1.4	763	205	112.6	1.8	-0.4
	12–20	641	100	95.0	1.1	717	141	105.2	1.3	-0.2
	20–28	607	70	90.0	0.8	671	150	99.8	1.5	-0.7
	28–36	578	86	86.6	1.0	640	110	94.0	1.2	-0.2
	36–44	560	90	84.6	1.1	598	98	88.9	1.1	0.0
	44–52	546	85	81.7	1.0	572	90	85.8	1.0	0.0

pgm mainline repeated measures exacerbation 2010 03 01.sas
N_Pat: Number of patients
Exac: Number of exacerbations
PYr: Patient years accumulated during interval
EXPPYr: Number of exacerbations per patient year.

Figure 3: Number of exacerbations per patient year, Study M2-124

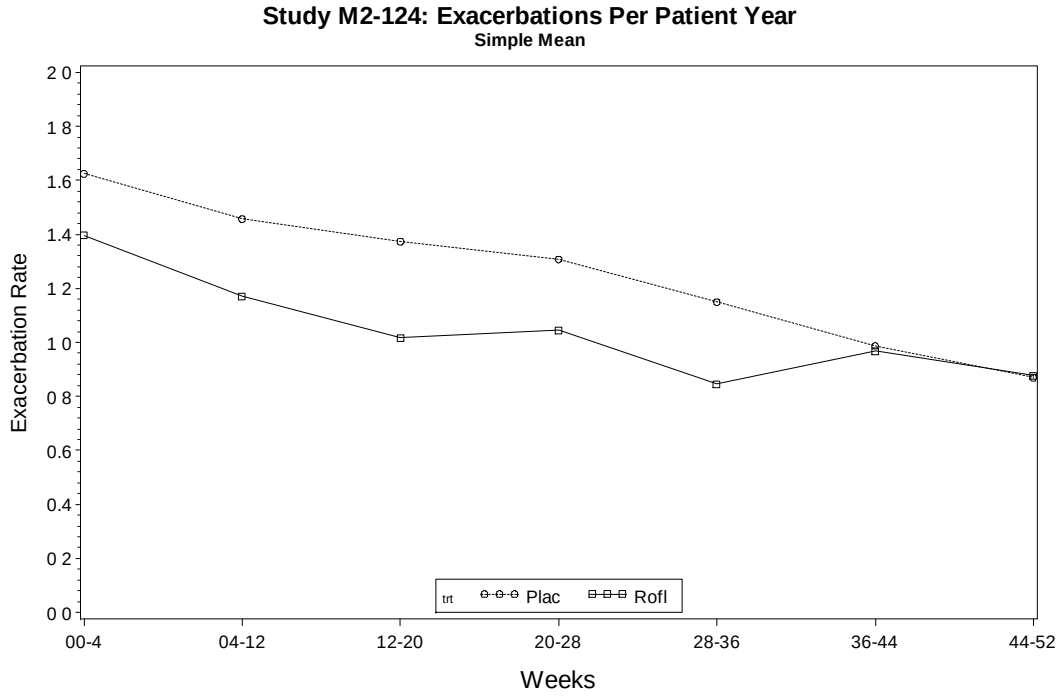
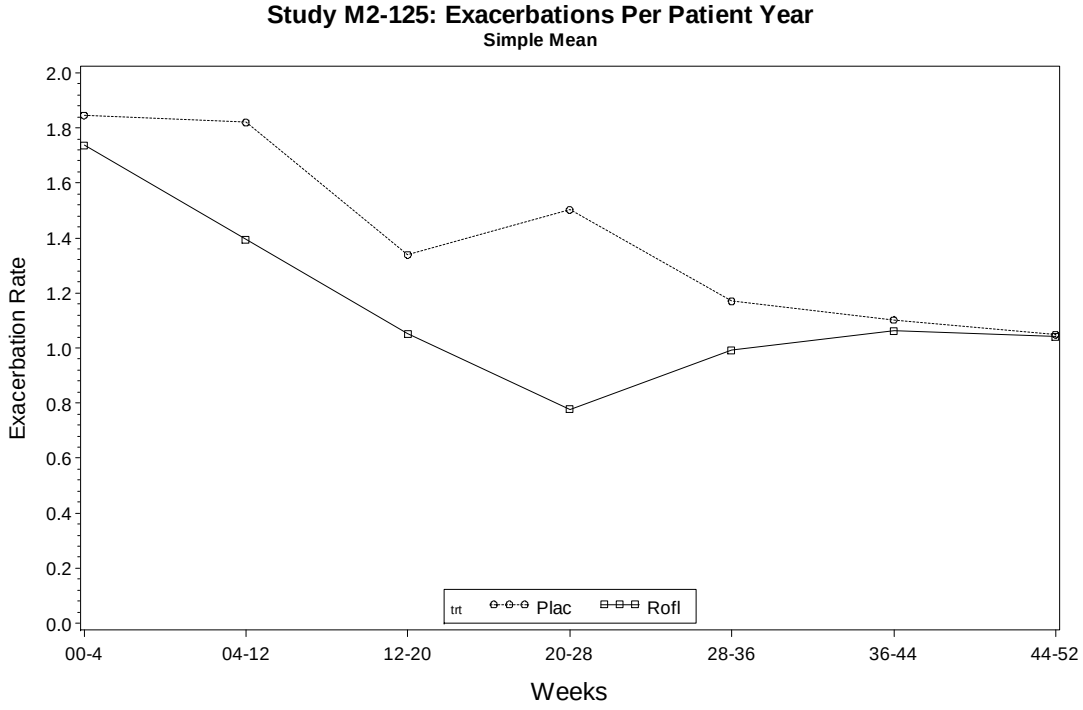


Figure 4: Number of exacerbations per patient year, Study M2-124



An integrated analysis for Studies 124 and 125 to examine exacerbations per patient year by time interval is provided in Table 12 with approximate confidence limits and p-values calculated

using a Poisson regression model with explanatory variables pre-bronchodilator FEV_1 value, age, sex, smoking status, concomitant treatment with LABA, and country, interval, and interval by treatment interaction. The analyses should be considered only as approximate because, as already noted, exacerbation rates were changing between time periods and would therefore be expected to change within time periods, albeit somewhat less. Estimates of mean exacerbation rates and their differences in Table 12 represent geometric means and so, even without the inclusion of explanatory variables, would be expected to differ somewhat from the simple means given in Table 11 above.

Like the results from individual studies, the integrated analysis suggests that roflumilast reduced exacerbation rates relative to placebo between weeks 4 to 28, with the effect attenuating during the interval of weeks 28 and 36 (or around month 8) and disappearing by week 36.

Table 12: Exacerbation rates per patient year. Integrated analysis for Studies 124 and 125

Weeks	Roflumilast	Placebo	Diff
00–04	1.6	1.8	0.2 (-0.1,0.3)
04–12	1.3	1.7	0.4 (0.1,0.4)
12–20	1.1	1.4	0.3 (0.1,0.4)
20–28	1.0	1.5	0.5 (0.2,0.6)
28–36	1.0	1.2	0.2 (0.0,0.4)
36–44	1.1	1.1	0.0 (-0.2,0.2)
44–52	1.0	1.0	0.0 (-0.2,0.2)

pgm mainline exacerbation by period with cl 2010 03 03.sas
Diff: difference between placebo and roflumilast
Lower and upper confidence 95% bounds in parentheses

3.1.2.3 SGRQ

Six studies in the submission examined changes from baseline of the St. George's Respiratory Questionnaire (SGRQ) as a primary or secondary effectiveness variable. None of these studies showed statistically significant differences in mean SGRQ between patients in the roflumilast and placebo arms (Table 13).

Table 13: Changes from baseline of the Saint George's Respiratory Questionnaire total score.

Study	Roflumilast	Placebo	Diff	P-Value
JP-706	0.31	-1.04	1.35	0.211
FK1101	-4.7	-4.5	-0.3	0.425
FK1103	-2.6	-2.9	0.3	0.842
M2-107	-3.5	-1.8	-1.7	0.053
M2-110	-1.2	-1.6	0.47	0.473
M2-112	-3.7	-3.2	-0.5	0.268

Lower scores indicate better patient-perceived health status.

3.1.3.4 Mortality

Roflumilast did not affect overall mortality rates in Studies 124 or 125, which targeted the population in the proposed label indication. Hazard ratios, provided from a proportional hazards model with concomitant treatment with LABA, age, sex, and smoking status, stratified by country, are presented in Table 14.

Table 14: Mortality Rates in Studies 124 and 125

Study	Roflumilast		Placebo			
	Deaths	N	Deaths	N	Hazard Ratio 95% CI	P-Value
M2-124	17	765	17	758	0.97 (0.49, 1.90)	0.921
M2-125	25	772	25	796	0.82 (0.47,1.45)	0.503

pgm mainline cox mortality 2010 03 02.sas
Est: Point estimate
Lower and upper 95% confidence bounds in parentheses ( ).

3.2 Statistical Issues and Findings

Issues

During my review of the application, I identified one issue warranting further consideration. In particular, because the maintenance therapy indication implies long-term administration, it seems important that benefits remain positive for an extended period of time, at least throughout the duration of the studies conducted. The exacerbation analyses provided by the Applicant did not explicitly examine potential attenuations in treatment effect; of the four statistical models presented, the Poisson and the negative binomial models only assessed roflumilast's effect averaged over the entire course of each study, while the proportional hazards and the log-rank tests only assess times to onset of exacerbations in each study, without including all exacerbation recurrences.

To address this issue, I conducted exploratory analyses which broke studies into time intervals, similar to those used by the Applicant for the FEV1 analyses, and examined for each time interval the mean number of exacerbations per patient year.

Findings

Roflumilast has a statistically significant effect on pre-bronchodilator FEV1 compared to placebo. In the six studies reviewed (Studies 124, 125, 111, 112, 127 and 128), the size of the effect ranged from 39 to 80 ml, with an average of 54 ml.

In the four one-year studies (Studies 124, 125, 111, and 112), roflumilast numerically reduced the average rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate, from Studies 124 and 125 statistically significant and with two of the reductions, from Studies 111, and 112, not statistically significant. With an explicit requirement for recent bronchitis and exacerbations, the entrance criteria for Studies 124 and 125 more closely matched the proposed label indication than the entrance criteria for Studies 111 and 112.

Exploratory analyses on Studies 124 and 125 suggest that the reduction of exacerbation rate by roflumilast compared to placebo may attenuate or even disappear after 8 months. This could be problematic for a long term maintenance indication in which benefits are expected to be positive for an extended period of time.

Nonclinical Considerations of Roflumilast

Nonclinical safety evaluations including general toxicity, genetic toxicity, carcinogenicity, and reproductive and developmental toxicity studies are an essential part of drug safety evaluation. Goals of the studies are primarily to identify the target organs of toxicity of the drug, to determine the relevance of the animal findings to humans, and to determine the margin of safety for the drug at the intended clinical dose.

The determination of the relevance of animal toxicity findings to humans includes assessments of the differences in test species anatomy, physiology, and metabolism compared to humans. These differences may render some drug effects in some species more or less relevant to humans than others. Generally, an animal species exhibiting a similar drug profile (pharmacology and pharmacokinetics) to that of humans will be given more consideration.

The margin of safety is determined after a No-Observed-Adverse-Effect-Level (NOAEL) is identified in animals and compared to the expected clinical doses in humans. The safety margin can be determined on the basis of body weight (mg/kg/day), body surface area (mg/m^2/day), or plasma drug levels defined as the area under the curve (AUC). A smaller safety margin suggests that the drug might be more likely to cause similar changes in humans at the recommended doses than a larger one.

The nonclinical evaluation also determines the exposure ratios between animals and humans for a particular pregnancy, fertility and carcinogenesis finding. These ratios are used in drug product labeling. The ratios provide physicians the likelihood that a particular event observed in animals may also occur in humans. A small ratio suggests that an event is more likely to occur. Conversely, a large ratio suggests that the event is less likely to occur in humans.

The roflumilast application has completed all required toxicity studies. The following sections discuss carcinogenicity, reproductive toxicity, cardiovascular toxicity and gastrointestinal toxicity of roflumilast in animals. For general toxicities, the AUC was used to determine the margin of safety. For pregnancy, fertility and carcinogenesis findings in animals, exposure ratios were determined for the expected clinical dose.

Carcinogenicity

Carcinogenicity of roflumilast was evaluated in 2-year studies in hamsters (two studies) and mice. Roflumilast at daily doses of 8 and 16 mg/kg/day caused statistically significant increases in the incidence of nasal tumors in hamsters. Nasal tumors were not observed in mice at doses up to 18 mg/kg/day.

In the first hamster study, oral gavage doses of roflumilast at 0.25, 1, 4 and 8 mg/kg/day were administered for 103 weeks. Females showed a statistically significant increase in incidence of undifferentiated carcinomas in the nasal cavity (6.7% compared to controls). Males showed no remarkable neoplastic findings in any of the roflumilast-treated groups. In the second two year study, hamsters were treated with oral gavage doses of 16 or 0-mg/kg/day roflumilast. Both roflumilast-treated males and females showed numerical increases in the incidence of undifferentiated carcinomas in the nasal cavity compared to controls (8.3% for both males and females), but these were statistically insignificant (P-values of 0.0587 and 0.081 for males and females, respectively). Taking the data from the two hamster studies together, the total tumor prevalence was 3.3% in males (8 mg/kg/day) and 12.5% in females at (16 mg/kg/day).

The Agency's Executive Carcinogenicity Assessment Committee (ECAC) reviewed the results and interpretation of the roflumilast carcinogenicity on May 10, 2005. The ECAC concluded that roflumilast was carcinogenic in hamsters and determined that ADCP N-oxide and its metabolite, ADCP N-oxide epoxide, were responsible for these nasal tumors. Additionally, the nasal findings were deemed not relevant to humans based on the lack of ADCP N-oxide formation in humans. However, upon review of the recently submitted human pharmacokinetic data, ADCP N-oxide has been identified in human plasma and urine and accounts for 10.5% (urine data) of the roflumilast dose. In light of these new data, the ECAC amended its initial determination on January 19, 2010 and concluded that the ADCP-N-oxide metabolite does not appear to be rodent-specific and the hamster nasal tumor is no longer considered rodent specific.

Relevance of the hamster tumor findings to humans is unknown due to differences in tissue ADCP N-oxide concentrations between rodents and humans. In the rodent nasal cavity Cytochrome P450 enzyme CYP2G1 converts ADCP to ADCP N-oxide and then to ADCP N-oxide epoxide intermediate, which will deplete intracellular glutathione and result in protein cross-links. Human nasal tissues apparently lack active enzymes to convert ADCP to ADCP N-oxide, but ADCP N-oxide is found in human plasma and urine. Tissues and enzymes involved in the production and metabolism of ADCP N-oxide in humans are unknown.

Exposure ratios between rodents and humans for roflumilast and its 3 major metabolites were determined based on available data (Table 1). Roflumilast N-oxide plasma AUC in humans is approximately 10 times that of roflumilast. ADCP and ADCP N-oxide level in humans are lower than roflumilast; they are, however, of special interest because of their roles in tumorigenicity in roflumilast carcinogenicity studies. Data on plasma AUCs of ADCP and ADCP N-oxide in humans were very limited.

Table 1 Exposure Ratios for Carcinogenicity Studies in Rats and Mice

	Exposure Ratios [a]			
	Rat [b]			Mouse (F)
Roflumilast (mg/kg/day, PO)	4	8	16	12
Tumor Prevalence (%)	0	3.3	12.5	0
Roflumilast (plasma)	1.2	1.8	15.8	20.2
Roflumilast N-oxide	3.1	8.0	32.3	6.1
ADCP	32.2	143.0	104.6	32.7
ADCP N-oxide	34.7	78.1	96.0	54.6

a. These ratios were calculated based on AUC data from healthy human subjects and animal carcinogenicity studies.

b. These estimates are did not consider the potential accumulation factor of ADCP N-oxide in humans. Accumulation of ADCP N-oxide apparently occurred in hamsters, but was unknown in humans.

Fertility and Reproductive Toxicity

Nonclinical assessments of roflumilast effects on fertility were completed in male and female Wistar rats up to doses of 1.8 mg/kg/day. A statistically significant (P-value < 0.05) decrease in male rat fertility rate (64.2% compared to control at 89.2%) was observed at the 1.8 mg/kg/day. The NOAEL for male fertility effects was 0.6 mg/kg. The plasma AUC data were not evaluated in the study.

The effects of roflumilast on male fertility have been addressed clinically. A 3-month clinical trial (Report 98/2002) was completed to study the effects of roflumilast on male fertility in humans. It appears that roflumilast at 500 μg/patient/day had no effects on sperm and fertility parameters evaluated.

Roflumilast affected male organ morphology in rats, dogs and mice; but not in hamsters and monkeys. Rats treated with roflumilast doses ⩾1.5 mg/kg/day showed morphological changes in the prostate (atrophy), testes (tubular atrophy degeneration and atrophy, spermatogenic disturbances), epididymides (oligospermia, spermatogenic Granuloma), and seminal vesicles (atrophy). Dogs at roflumilast doses ≥1.8-mg/kg/day showed testis degeneration and atrophy. Mice treated with 36-mg/kg/day roflumilast showed a slight increase in the incidence of sperm stasis in the testes. The NOAELs for reproductive organ morphology were 12, 0.8, 16, 1 and 0.5 mg/kg/day in mice, rats, hamsters, dogs and monkeys, respectively. Table 2 presents the safety margins of the male reproductive effects of roflumilast.

Table 2 Safety Margins for the Male Reproductive Effects of Roflumilast

Species		Mice	Rat	Hamster	Dog	Monkey
Report #		33/2002	14/96	252/98	94/96	232/2001
NOAEL	mg/kg/day	12	0.8	16	1	0.5
	AUC (μg.h/L)	689.7	30.7	106.3	588.5	816.7
Safety Margin [a]		21.0	0.90	3.2	17.9	24.9

a. Derived by dividing AUC at NOAEL in animals by the expected human AUC of 32.8 μg.h/L at the recommended dose of 500 μg/day.

The relevance of the effects of roflumilast on nonclinical test species male reproductive parameters to humans is unknown. Rats were especially sensitive to the male reproductive toxicity of roflumilast. The applicant argues that increased sensitivity was attributed to anatomical differences in efferent ductile formation in epididymides between rodent and non-rodent species. However, rats showed fertility effects while mice did not, which fails to support the sponsor's argument.

Effects on Pregnancy

Effects of roflumilast on the reproductive system and embryofetal development were studied in mice, rats, and rabbits. Roflumilast treatment during pregnancy resulted in dose-related increases in stillborns, maternal deaths, and decreases in pup viability in mice. Roflumilast given during pregnancy and delivery can cause significant harm to fetuses and dams, especially during the late stage of pregnancy (Table 3). This effect was attributed to the tocolytic effect of roflumilast. Roflumilast was not teratogenic in rats and rabbits.

Table 3 Temporal Effects of Roflumilast on Pregnancy Outcome

	C	G2	G3	G4
Roflumilast (mg/kg/day)	0	12	12	12
Treatment Time (Gestation days)	6-16	6-16	15-18	18 [a]
Dam data				
Dams dead or pre-maturely sacrificed	0	0	0	3
Dams with deliver problems	0	0	0	7
Dams with live born #	10	10	6	6
Dams completing delivery #	10	12	10	6
Dams with stillborn pups [#, (%)]	0 (0)	4 (33.3)	9 (90)**	6 (100)**
Litter data				
Pup livered (total #)	116	93	89	71
Live born#	116	75**	39**	39**
Still born [#, (%)]	0 (0)	18 (19)**	50 (56)**	32 (45)**
Died in lactation day 1 - 4	1 (0.9)	10 (13)**	31 (80)**	29 (74)**
Viability index (%, day 4)	99.1	86.7**	20.5**	25.6**

a. The dosing time on day 18 for G4 was much late than G3. *, $p < 0.05$; **, $p < 0.01$.

Cardiovascular Toxicity

Roflumilast affected the cardiovascular system in dogs, mice and monkeys. Dogs treated with >0.6-mg/kg/day roflumilast for 12 months showed cardiac lesions such as focal hemorrhages, hemosiderin deposits and lympho-histiocytic cell infiltration in the right atria/auricles Male mice treated with ≥12-mg/kg/day roflumilast for 6-months showed moderate peri-arteritis in the heart. Monkeys treated with 0.5-mg/kg/day roflumilast for a month showed myocarditis. The respective NOAELs for cardiac lesions in mice, dogs and monkeys were 4, 0.2, and 0.25 mg/kg/day on nominal doses and 153.1, 203.7 and 251.3 μg.h/L in plasma AUCs. These AUC values provided safety margins of at least 5, a value greater than the usual requirement of 2 for drugs similar to roflumilast.

Gastrointestinal Tract Toxicity

Roflumilast treatment-related effects on the gastrointestinal (GI) tract were observed in rats, dogs and monkeys; but not in mice and hamsters. Wistar rats treated with 8.0-mg/kg/day roflumilast for 4 weeks showed serositis/inflammation in jejunum, peritonitis, and stomach erosion. No GI findings were observed at roflumilast doses up to 2.5 mg/kg/day in a 6-month rat study. In monkeys, minimal acute inflammation or inflammation foci were noted in the pyloric region of the stomach after roflumilast treatment up to 0.5 mg/kg/day for up to 42 weeks. The respective NOAELs for GI effects of roflumilast in rats and monkeys were 2.5 and 0.25 mg/kg/day on nominal doses and 78.7 and 251.3 µg.h/L in plasma AUCs. These AUC values provided safety margins of at least 5, a value greater than the usual requirement of 2.

Summary

Nonclinical toxicities of roflumilast and/or its metabolites included carcinogenicity, reproductive toxicity, and cardiovascular and GI toxicities. Roflumilast metabolite (ADCP N-oxide) induced nasal tumor formation in hamsters. Although first thought to be a rodent specific metabolite, this metabolite has been observed in human plasma and urine. Therefore, the metabolite related nasal tumors observed in hamsters may be relevant to humans. Roflumilast showed adverse fertility effects in male rats but these effects where not replicated in clinical trials. Structural damage to male reproductive organs was observed in rats, mice and dogs, but not in hamsters and monkeys. Reproductive effects of roflumilast included stillbirths and pup deaths in mice attributed to a tocolytic effect of the drug. Cardiac toxicities were observed in dogs, mice, and monkeys including cardiac lesions, periarteritis, and myocarditis. Additionally, GI toxicities were observed in rats, dogs and monkeys that included inflammation and erosion of the mucosa.

Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Daxas® (roflumilast) is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. Roflumilast is a phosphodiesterase-4 (PDE4) inhibitor.

Daxas was evaluated in 19 *in vitro* studies in human biomaterials, 10 biopharmaceutics studies, 65 Phase 1 clinical studies, and 18 Phase II and III COPD studies. These clinical studies were designed to evaluate the pharmacokinetics in healthy subjects and COPD patients and intrinsic and extrinsic factors. Fifteen *in vitro* studies and 65 clinical pharmacology and biopharmaceutics studies were reviewed. The remaining studies were not reviewed because they were either exploratory or did not provide additional information. The proposed dosage for COPD patients is one oral table of 500 µg per day, with or without food.

Pharmacokinetics in Healthy Subjects

Absorption

The absolute bioavailability of roflumilast following a 500 µg oral dose is 79%. The median time to reach maximum plasma concentrations of roflumilast (t_{max}) is one hour, while t_{max} of roflumilast N-oxide (the major active metabolite of roflumilast) is eight hours in the fasted state. Food intake delays t_{max} of roflumilast by one hour and reduces C_{max} by 40%; however, C_{max} and t_{max} of roflumilast N-oxide are unaffected. The exposure (AUC and Cmax) of roflumilast and roflumilast N-oxide is dose-proportional over the roflumilast dose range of 250 to 1000 µg.

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is 99% and 97%, respectively.

Metabolism and Elimination

Roflumilast is extensively metabolized via Phase 1 (cytochrome P450) and Phase II (conjugation) reactions. Roflumilast N-oxide is the major metabolite observed in human plasma. The plasma AUC of roflumilast N-oxide, on average, is about 10-fold greater than that of roflumilast. *In vitro* studies and clinical drug-drug interaction studies suggested that the metabolism of roflumilast to roflumilast N-oxide was mediated by CYP1A2 and CYP3A4. Following an oral dose of roflumilast, the median plasma effective half-lives of roflumilast and roflumilast N-oxide were 17 and 30 hours, respectively. Steady state plasma concentrations were reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing of roflumilast. Following once daily oral administration of roflumilast at 500 µg in healthy subjects, the accumulation index was about 1.8 for roflumilast and 2.0 for roflumilast N-oxide. After intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

Pharmacokinetics in COPD Patients

The PK of roflumilast in COPD patients was evaluated in studies IN108 and M2-110. As compared to healthy subjects, roflumilast exposure in COPD patients based on mean observed data was about 60% higher for AUC (up to 9 hours) and 6% higher for C_{max}; roflumilast N-oxide exposure in COPD patients was about 30% higher for AUC (up to 9 hours) and 37% higher for C_{max}. Based on a population PK analysis, COPD patients have a 65% higher AUC for roflumilast and about 8% higher AUC for roflumilast N-oxide compared to healthy subjects.

Pharmacokinetics in Special Populations

Age

The age effect on the PK of roflumilast and roflumilast N-oxide was evaluated in study CP-050. The exposure between young (18-45 years old) and middle-aged (45-65 years old) subjects was comparable for both roflumilast and roflumilast N-oxide. However, the exposure in elderly (>65 years old) was 27% higher for AUC and 16% higher for C_{max} for roflumilast and 19% higher for AUC and 13% higher for C_{max} for roflumilast-N-oxide than that in young subjects.

Gender

Women exhibited higher exposures of both roflumilast and roflumilast N-oxide when compared with men (Study CP-050). As compared to male subjects, the AUC of roflumilast was increased by 40%, 79%, and 28%, respectively, for young, middle-aged, and elderly female subjects. The C_{max} of roflumilast was comparable between male and female subjects. As compared to male subjects, the AUC of roflumilast N-oxide was increased by 33%, 52%, and 45%, respectively, for young, middle-aged, and elderly female subjects; the C_{max} of roflumilast N-oxide was increased by 30%, 53%, and 47%, respectively, for young, middle-aged, and elderly female subjects.

Race

The exposure difference between Caucasians and Japanese was assessed in study CP-048. African American, Hispanic, and Caucasian healthy subjects were enrolled in several drug-drug interaction studies (CP-044, CP-066, CP-067, and CP-068). The impact of subjects being African American and Hispanic on exposure was assessed using the combined dataset from these four studies.

As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 25%, 47%, and 15% higher AUC, respectively, for roflumilast, and 69%, 51%, and 16% higher AUC, respectively, for roflumilast N-oxide. As compared to Caucasians, the African Americans, Hispanics, and Japanese showed 15%, 31%, and 17% higher C_{max}, respectively, for roflumilast, and 17%, 9%, and 5% higher C_{max}, respectively, for roflumilast N-oxide.

Renal Impairment

The effect of renal impairment on the exposure of roflumilast and roflumilast N-oxide was examined after a single dose of 500 µg roflumilast to patients with severe renal impairment as compared to healthy subjects (Study FHP020). As compared to healthy subjects, the roflumilast exposure in severe renal impairment patients was 21% lower for AUC and 16% lower for Cmax. The roflumilast N-oxide exposure in severe renal impairment patients was 7% lower for AUC and was 13% lower for Cmax as compared to healthy subjects.

Hepatic Impairment

The effect of hepatic impairment on the exposure of roflumilast and roflumilast N-oxide was examined after 14 days of oral administration of roflumilast at 250 µg once daily in 16 subjects with mild to moderate hepatic impairment (Child-Pugh category A (6) and Child-Pugh category B (6)) and compared to healthy subjects (Study CP-062). As compared to healthy subjects, the AUC and C_{max} of roflumilast were 51% and 3% higher for patients with Child-Pugh A, respectively; and 92% and 26% higher for patients with Child-Pugh B, respectively. As compared to healthy subjects, the AUC and C_{max} of roflumilast N-oxide were 24% and 26% higher for patients with Child-Pugh A, respectively; and 42% and 40% higher for patients with Child-Pugh B, respectively.

The effect of intrinsic factors on the exposure of roflumilast and roflumilast N-oxide is shown in the Figures 1 and 2, respectively.

Drug-Drug Interactions

In vitro metabolism studies using human liver microsomes and *in vivo* drug-drug interaction studies indicated that roflumilast is mainly metabolized by CYP3A4 and CYP1A2 and did not inhibit or induce the activity of the major CYP P450 enzymes. *In vitro* study showed that roflumilast did not inhibit P-gp transport.

Drug-drug interaction studies were conducted with the following drugs: midazolam, erythromycin, ketoconazole, rifampicin, fluvoxamine, digoxin, Maalox, salbutamol, formoterol, budesonide, theophylline, cimetidine, warfarin, enoxacin, sildenafil, minulet, montelukast. No significant interactions were observed with midazolam, salbutamol, formoterol, budesonide, warfarin, sildenafil, Maalox, digoxin and montelukast. Coadministration of roflumilast with the rest compounds significantly changed the exposure of roflumilat and/or roflumilst N-oxide (Figures 3 and 4).

Figure 1. The effect of intrinsic factors on roflumilast exposure.

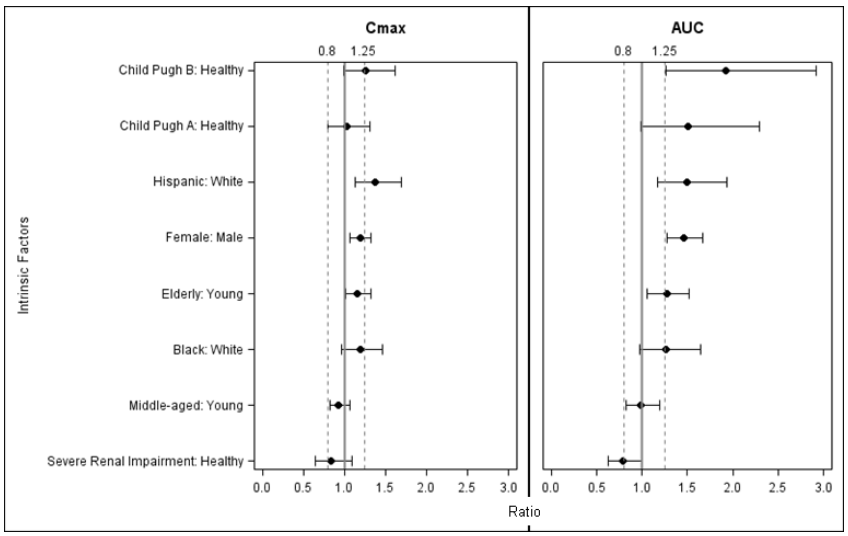


Figure 2. The effect of intrinsic factors on roflumilast N-oxide exposure.

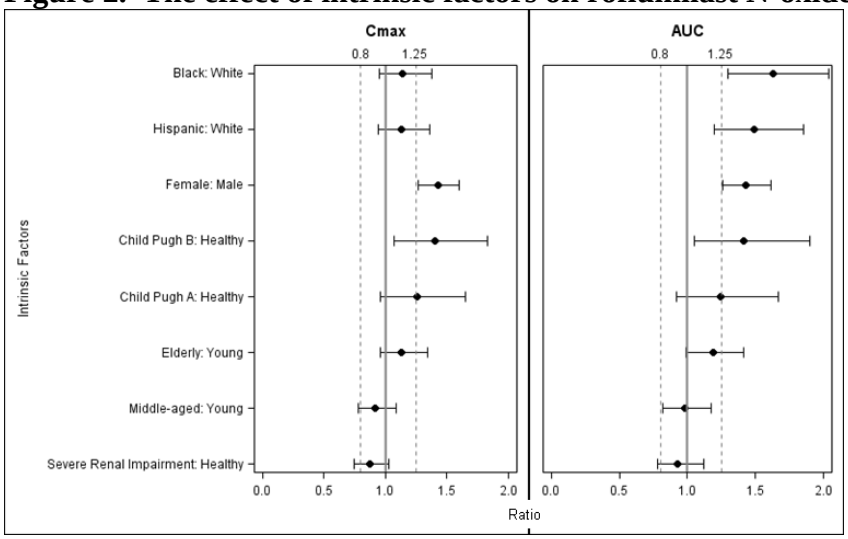


Figure 3. The effect of extrinsic factors on roflumilast exposure.

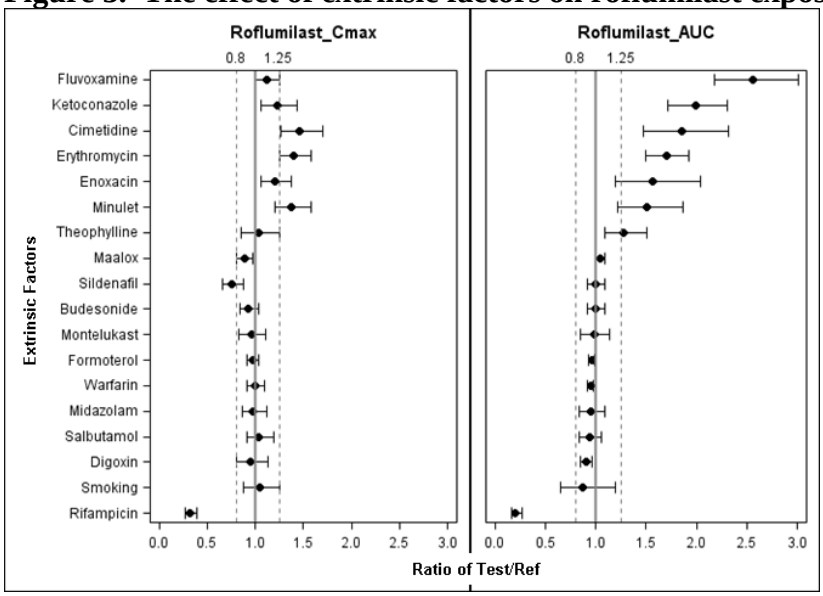
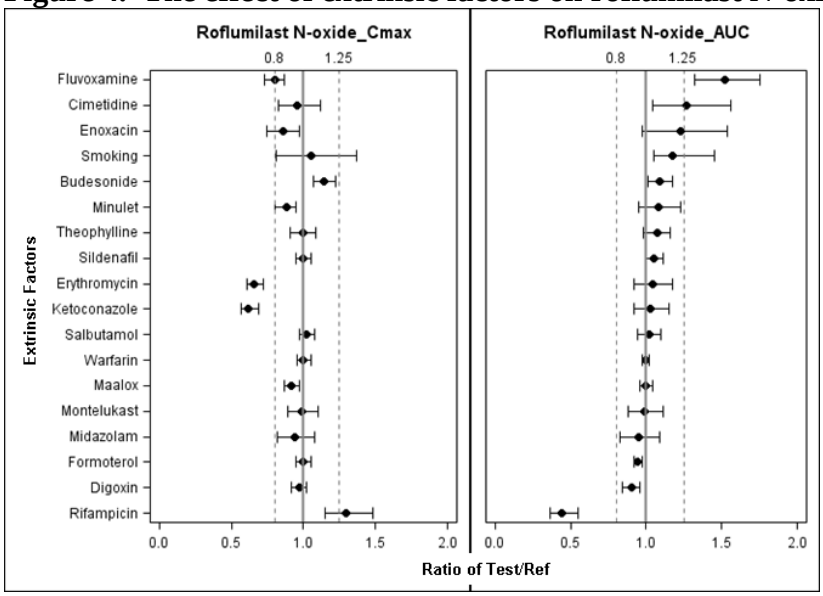


Figure 4. The effect of extrinsic factors on roflumilast N-oxide exposure.



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Daxas® safely and effectively. See full prescribing information for Daxas.

Daxas (roflumilast) film-coated tablets
Initial U.S. Approval: 20XX

---------- INDICATIONS AND USAGE ----------
Daxas is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. (1)

-------- DOSAGE AND ADMINISTRATION---------
The recommended dosage for patients with COPD is 1 tablet per day, with or without food. (2)

------- DOSAGE FORMS AND STRENGHTS -------
Daxas film-coated tablet: 500 mcg (3)

----------CONTRAINDICATIONS ----------
The use of Daxas is contraindicated in patients with known hypersensitivity to any component of the formulation. (4)

--------- WARNINGS AND PRECAUTIONS ---------
- Acute bronchospasms: Do not use for the relief of acute bronchospasms. (5.1)
- Weight decrease: In case of unexplained and pronounced weight decrease, discontinue Daxas, if deemed necessary. (5.2)

---------- ADVERSE REACTIONS----------
Most common adverse reactions (≥3%) are diarrhoea, weight decrease, nausea, headache, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (*phone # and Web address*) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
- Strong cytrochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin): May reduce therapeutic effectiveness of Daxas. (7.2)

--------- USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Should not use. (8.1)
- Labor and Delivery: Should not use. (8.2)
- Nursing Mothers: Should not use. (8.3)
- Pediatric use: Safety and effectiveness not established in patients less than 18 years of age. (8.4)
- Hepatic impairment: Not recommended in patients with severe hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Daxas is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

2 DOSAGE AND ADMINISTRATION

The recommended dosage for patients with COPD is 1 tablet per day, with or without food.

3 DOSAGE FORMS AND STRENGHTS

Yellow, D-shaped, film-coated tablet, embossed with "D" on one side, containing 500 microgram (mcg) roflumilast.

4 CONTRAINDICATIONS

The use of Daxas is contraindicated in patients with known hypersensitivity to any component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Treatment of Acute COPD Symptoms

Roflumilast is an anti-inflammatory substance indicated for maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasms.

5.2 Weight Decrease

In the event of an unexplained and pronounced weight decrease, patients should consult a healthcare professional. Further intake of Daxas should be stopped, if deemed necessary.

In 1-year studies (M2-124, M2-125), a decrease of body weight occurred in 62% of patients treated with Daxas compared to 38% of placebo-treated patients. Weight decrease was irrespective of the BMI. The mean absolute weight change over the 1-year period was -2.1 kg in Daxas-treated patients. After discontinuation of Daxas, the majority of patients had regained body weight after 3 months.

6 ADVERSE REACTIONS

The data described below reflect exposure to Daxas in 6,563 COPD patients studied in placebo-controlled trials, including 4,138 exposed for up to 6 months, 1,193 exposed for up to one year, and 1,232 exposed for one year or longer. The population was 25 to 93 years old (median age 64), 72% were male, and 89% were white. Most patients received Daxas doses of 500 mcg once daily.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In general, Daxas has been demonstrated to be well tolerated in short-term and long-term trials. The most common adverse reactions with incidence rates of 4% or more were: diarrhea, weight decrease, nausea and headache. These adverse reactions in patients on treatment with Daxas in clinical trials mainly occurred within the first weeks of therapy and mostly resolved on continued treatment.

6.1 Adverse Reactions in Clinical Trials

Table 1 lists the adverse events reported in 1% or more of Daxas-treated patients with COPD from 14 double-blind, placebo-controlled Phase II/III studies of up to 12 months that administered 250 mcg or 500 mcg roflumilast per day.

Table 1 Treatment-Emergent Adverse Events* Reported by ≥ 1% of Daxas-Treated COPD Patients in 14 Phase II/III, Placebo-Controlled Studies

	% incidence	
Study event	Daxas (N=6563)	Placebo (N=5491)
Diarrhea	10	3
Weight decreased	6	2
Nausea	5	1
Headache	4	2
Back pain	3	2
Abdominal pain	2	1
Decreased appetite	2	0
Dizziness	2	1
Tremor	2	0
Insomnia	2	1
Gastritis	1	0

* A treatment-emergent adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related, for which the incidence rate for Daxas exceeds the rate for placebo.

Additional clinically significant treatment-emergent adverse reactions occurring in these clinical trials involving Daxas with an incidence of less than 1% and at a greater incidence with Daxas than with placebo include the following: abdominal discomfort, frequent bowel movements, asthenia, anorexia and pruritus.

7 DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP 3A4 and CYP 1A2. Both roflumilast and roflumilast N-oxide have intrinsic phosphodiesterase 4 (PDE4) inhibitory activity. Therefore, following administration of Daxas, the total PDE4 inhibition is considered to be the combined effect of both roflumilast and roflumilast N-oxide *[See Clinical Pharmacology (12.3)]*.

No clinically relevant interactions with the following drugs were observed: inhaled salbutamol, formoterol, budesonide, oral theophylline, montelukast, digoxin, warfarin, sildenafil, midazolam and an oral contraceptive containing gestodene and ethinyl estradiol. Co-administration with an antacid did not alter the absorption or pharmacokinetics of roflumilast or its N-oxide.

7.1 Drugs That Inhibit Cytochrome P450 (CYP) Enzymes

Clinical drug-drug interaction studies with CYP 3A4 inhibitors (erythromycin and ketoconazole) did not result in increases of total PDE4 inhibitory activity (i.e. total exposure to roflumilast and roflumilast N-oxide). Interaction studies with CYP 1A2 inhibitor fluvoxamine, and dual CYP 3A4/1A2 inhibitors enoxacin and cimetidine resulted in increases in total PDE4 inhibitory activity. Therefore, an increase in the total PDE4 inhibition of 20% to 60% should be

expected when Daxas is concomitantly taken with strong CYP 1A2 inhibitors, such as fluvoxamine, while no alteration should be expected with strong CYP 3A4 inhibitors such as ketoconazole. No clinically relevant drug interactions are expected.

7.2 Drugs That Induce Cytochrome P450 (CYP) Enzymes

Administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in total PDE4 inhibitory activity by about 60% and use of strong cytochrome P450 inducers (e.g. phenobarbital, carbamazepine, phenytoin) may reduce the therapeutic effect of Daxas.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Roflumilast was not teratogenic in rats and rabbits following oral administration up to the highest doses of 1.8 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. Administered at the same doses, roflumilast has been shown to induce mild retardation of embryo-fetal development (incomplete ossification) in the rat, but not in the rabbit. Exposure of pregnant rats to unbound roflumilast and roflumilast N-oxide was 1.7 and 10.8 times higher, respectively, than exposure of women at the 500 mcg roflumilast dose. In one of three rat studies on fertility and embryo-fetal-development, post-implantive losses were observed at oral doses of 0.6 mg/kg/day and 1.8 mg/kg/day. Post-implantive losses were not seen in rabbits up to doses of 0.8 mg/kg/day. Rat and rabbit fetuses were exposed to roflumilast and the permeability of the placental barrier for drug-related material increased with the progression of pregnancy.

There are no adequate and well-controlled studies of Daxas in pregnant women. Data on a limited number (20) of exposed pregnancies indicate no adverse effects of Daxas on pregnancy or on the health of the fetus or new-born child. Nonetheless, the safe use during pregnancy is not established and Daxas should not be used during pregnancy.

8.2 Labor and Delivery

Signs of tocolytic activity resulting in delivery retardation and decreased postnatal survival were observed in the mouse at oral doses of 2 mg/kg/day and above.

There are no human studies that have investigated effects of Daxas on preterm labor or labor at term. Daxas should not be used during labor and delivery.

8.3 Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or metabolites into human milk is probable. Daxas should not be used during breast-feeding.

8.4 Pediatric Use

Safety and effectiveness of Daxas in children and adolescents below 18 years of age have not been established. Daxas is not recommended in this population.

8.5 Geriatric Use

In clinical studies with Daxas, there were no overall differences in safety and effectiveness of Daxas in the elderly compared to younger patients with COPD. Therefore, no dose adjustment is necessary *[See Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

The pharmacokinetics of Daxas 250 mcg once-daily was tested in patients with mild-to-moderate hepatic impairment classified as Child-Pugh A and B. In these patients, the total PDE4 inhibitory activity was increased by about 30% in patients with Child-Pugh A and about 50% in patients with Child-Pugh B. Simulations suggest dose proportionality between Daxas 250 and 500 mcg in patients with mild-to-moderate hepatic impairment. Therefore, no dose adjustment is necessary in these patients. The pharmacokinetics of Daxas in patients with severe hepatic impairment (Child-Pugh Class C) was not tested, and therefore the use of Daxas is not recommended in these patients *[See Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Total PDE4 inhibitory activity was decreased by 9% in patients with severe renal impairment (creatinine clearance 10–30 mL/min). No dose adjustment is necessary *[See Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

10.1 Human Experience

No case of overdose has been reported in clinical studies with Daxas. During the Phase I studies of Daxas the following symptoms were observed at an increased rate after single oral doses of 2,500 mcg and one single dose of 5,000 mcg (ten times the recommended dose): headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

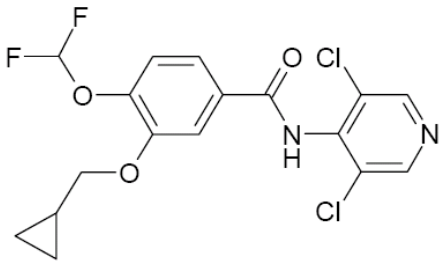
10.2 Management of Overdose

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, haemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

11 DESCRIPTION

The active ingredient in Daxas film-coated tablets is roflumilast. The chemical name of roflumilast is N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22.

The chemical structure is:



The drug substance is poorly soluble in water.

Daxas is supplied as a yellow, D-shaped film-coated tablet, embossed with “D” on one side that contains 500 mcg of roflumilast. Each film-coated tablet of Daxas for oral administration contains the following inactive ingredients: lactose monohydrate, maize starch, povidone and magnesium stearate. In addition, the film-coat contains: hypromellose, Macrogol 4000, titanium dioxide and yellow iron oxide.

12 CLINICAL PHARMACOLGY

12.1 Mechanism of Action

Roflumilast is a phosphodieserase 4 (PDE4) inhibitor. It is a non-steroid, anti-

inflammatory agent designed to target both the systemic and pulmonary inflammation associated with chronic obstructive pulmonary disease. The mechanism of anti-inflammatory action of roflumilast is the inhibition of PDE4, a major cAMP-metabolizing enzyme found in structural and inflammatory cells important to the pathogenesis of COPD. Roflumilast targets the PDE4A, 4B and 4D splicing variants with similar potency in the nanomolar range. The affinity to the PDE4C splicing variants is 5 to 10-fold lower. This mechanism of action and the selectivity also apply to roflumilast N-oxide, which is the major active metabolite of roflumilast.

12.2 Pharmacodynamics

Inhibition of PDE4 leads to elevated intracellular cAMP levels and mitigates COPD-related malfunctions of leukocytes, airway and pulmonary vascular smooth muscle cells, endothelial and airway epithelial cells and fibroblasts. Based on this mechanism, roflumilast in experimental animals suppressed the release of inflammatory mediators, i.e. cytokines and reactive oxygen species from cells and lung tissue *in vitro* and *in vivo*. In addition, roflumilast inhibited the infiltration of leukocytes, in particular neutrophils, into the lungs of experimental animals. Roflumilast also reduced the smoke-induced destruction of lung parenchyma and prevented lung fibrotic and vascular remodeling in animal models *in vivo*. It stimulated bronchial ciliary activity *in vitro* and inhibited the formation of MUC5AC, a goblet cell-derived gel-forming mucin, in human airway epithelial cells and in animal experiments. These effects also apply to roflumilast N-oxide and respective *in vitro* and *in vivo* data concur with its PDE4 inhibitory potency.

In patients with COPD, Daxas reduced sputum neutrophils. Furthermore, Daxas attenuated influx of neutrophils and eosinophils into the airways of endotoxin challenged healthy volunteers.

12.3 Pharmacokinetics

Roflumilast is extensively metabolized in humans, with the formation of a major pharmacodynamically active metabolite, roflumilast N-oxide. Since both roflumilast and roflumilast N-oxide contribute to PDE4 inhibitory activity *in vivo* (see Biotransformation below), pharmacokinetic considerations are based on total PDE4 inhibitory activity (i.e. total exposure to roflumilast and roflumilast N-oxide).

Absorption

The absolute bioavailability of roflumilast following a 500 mcg oral dose is approximately 80%. Maximum plasma concentrations of roflumilast typically occur approximately one hour after dosing (ranging from 0.5 to 2 hours) in the fasted state while plateau-like maximum concentrations of the N-oxide metabolite are reached after about eight hours (ranging from 4 to 13 hours). Food intake does not affect the total PDE4 inhibitory activity, but delays time to maximum concentration (t_{max}) of roflumilast by one hour and reduces C_{max} by approximately 40%. However, C_{max} and t_{max} of roflumilast N-oxide are unaffected.

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for single dose 500 mcg roflumilast is about 2.9 L/kg. Studies in rats with radiolabeled roflumilast indicate low penetration across the blood-brain barrier.

Biotransformation

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the major metabolite observed in the plasma of humans. The plasma AUC of the N-oxide metabolite on average is about 10-fold greater than the plasma AUC of roflumilast. Thus, the N-oxide metabolite is considered to be the main contributor to the total PDE4 inhibitory activity *in vivo*.

In vitro studies and clinical drug-drug interaction studies suggest that the metabolism of roflumilast to its N-oxide metabolite is mediated by CYP 1A2 and 3A4. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of roflumilast and roflumilast N-oxide do not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or

4A9/11. Therefore, there is a low probability of relevant interactions with substances metabolized by these P450 enzymes. In addition, *in vitro* studies demonstrated no induction of the CYP 1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP 2B6 by roflumilast.

Elimination

The plasma clearance after short-term intravenous infusion of roflumilast is on average about 9.6 L/h. Following an oral dose, the median plasma effective half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state plasma concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing. Following intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

Linearity/Non-linearity

The pharmacokinetics of roflumilast and its N-oxide metabolite are dose-proportional over a range of doses from 250 mcg to 1,000 mcg.

Special Populations

Renal Impairment

In patients with severe renal impairment, total PDE4 inhibitory activity was slightly decreased. These differences are not considered to be clinically relevant. Dosage modifications are not required.

Hepatic Impairment

In patients with mild-to-moderate hepatic impairment classified as Child-Pugh A or B total PDE4 inhibitory activity was increased. These differences are not considered to be clinically relevant. Dosage modifications are not required in patients with mild-to-moderate hepatic impairment. There are no data on the pharmacokinetics of roflumilast in patients with severe hepatic impairment (Child-Pugh C). Therefore, Daxas is not recommended in patients with severe hepatic impairment.

Age

In elderly, total PDE4 inhibitory activity was increased. These differences are not considered to be clinically relevant. Dosage modifications are not required.

Gender

In women, total PDE4 inhibitory activity was increased when compared with men. These differences are not considered to be clinically relevant. Dosage modifications are not required.

Smoking

In smokers, total PDE4 inhibitory activity was slightly decreased. However, the effectiveness was comparable irrespective of the current smoking status.

Race

In African Americans and Hispanics, simulations suggest that total PDE4 inhibitory activity is higher than in Caucasians. These differences are not considered to be clinically relevant. Dosage modifications are not required.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Roflumilast was administered by gavage to male and female B6C3F1 mice at doses up to 12 mg/kg/day (males), and 18 mg/kg/day (females) over two years. No compound-related tumors occurred. In the 2-year hamster carcinogenicity studies at doses up to 16 mg/kg/day, nasal neoplasms were caused by a drug metabolite, which is absent in humans. No other treatment-related neoplastic findings were observed. Overall, the tumor-free level in the animals was 4 mg/kg/day.

Mutagenesis

Roflumilast did not reveal a genotoxic potential in a standard battery of genotoxicity assays *in vitro* and *in vivo* assessing different genetic endpoints.

Impairment of Fertility

There was no effect on female fertility up to the highest roflumilast dose of 1.5 mg/kg/day in rats. Slight reduction in male fertility was seen in conjunction with epididymal toxicity in rats dosed with 1.8 mg/kg/day (about 2.2 and 8.8 times human exposure to unbound roflumilast and roflumilast N-oxide, respectively). No epididymal toxicity or changes in semen parameters or fertility was present in any other rodent or non-rodent species including monkeys in spite of higher drug exposure. In a human spermatogenesis study, roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period.

13.2 Animal Toxicology and/or Pharmacology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. Furthermore, there is no evidence of immunotoxic, skin sensitizing or phototoxic potential.

14 CLINICAL STUDIES

14.1 Chronic Obstructive Pulmonary Disease (COPD)

The main clinical registration program consisted of two replicate one-year trials (M2-124 and M2-125) and two supplementary six-month trials (M2-127 and M2-128), all randomized, parallel-design, double-blind and placebo-controlled, with a total number of 4,768 randomized and treated patients of whom 2,374 were treated with Daxas.

Studies M2-124 and M2-125 included patients with a history of COPD associated with chronic bronchitis for at least 12 months prior to baseline, with symptoms at baseline as determined by cough and sputum score, non-reversible airway obstruction (FEV_1/FVC ratio of $\leq$70%), an $FEV_1 \leq 50\%$ of predicted and at least one documented COPD exacerbation in the previous year.

In the one-year trials, long-acting beta-2 agonists (LABA) were allowed and used in approximately 50% of the study population. The use of inhaled corticosteroids was terminated at randomization. Lung function (pre-bronchodilator forced expiratory volume in one second, FEV_1) and the rate of moderate exacerbations (requiring intervention with systemic glucocorticosteroids) or severe exacerbations (resulting in hospitalization and/or leading to death) were primary endpoints. Secondary endpoints in both studies included further evaluation of exacerbations and lung function parameters, dyspnea, and use of reliever medication.

In a pooled analysis of the replicate one-year studies M2-124 and M2-125, Daxas 500 mcg once daily significantly improved lung function compared to placebo, on average by 48 mL (pre-bronchodilator FEV_1, primary endpoint, $p<0.0001$), and by 55 mL (post-bronchodilator FEV_1, $p<0.0001$). Pre-bronchodilator forced vital capacity (FVC) was significantly greater with Daxas than placebo in both studies by 89 mL ($p<0.0001$) in M2-124 and 108 mL ($p<0.0001$) in M2-125. Similar significant improvements were seen in post-bronchodilator FVC and pre-bronchodilator mid-expiratory flow. These changes in lung function were similar irrespective of concomitant treatment with or without LABA. In the pooled analysis, Daxas 500 mcg increased mean pre-bronchodilator FEV_1 by 46 mL ($p<0.0001$), as compared to placebo with concomitant LABA treatment, and by 50 mL ($p<0.0001$) without concomitant LABA treatment.

In a pooled analysis, the endpoint of moderate or severe exacerbations was reduced by 17% (primary endpoint; $p=0.0003$). Numbers of patients needed to treat (NNT) to avoid one moderate or severe exacerbation per patient per year were 5.3 (M2-124) and 3.6 (M2-125). The number of patients experiencing a moderate exacerbation in the Daxas group was 624 vs. 723 in the placebo

group (Risk Ratio: 0.88; p=0.0011). The number of patients experiencing a severe exacerbation in the Daxas group was 157 vs. 198 in the placebo group (Risk Ratio: 0.84; p=0.0715). Furthermore, the transitional dyspnea index (TDI) improved with Daxas 500 mcg by on average 0.25 (p<0.0009) as compared to placebo.

The six-month studies M2-127 and M2-128 included patients with a history of COPD for at least 12 months prior to baseline. In study M2-128 in addition, documentation of chronic bronchitis and high reliever medication use was required. Both studies included patients with a non-reversible airway obstruction (FEV_1/FVC <70%) and a FEV_1 of 40% to 70% of predicted. Daxas or placebo treatment was added to continuous treatment with a long-acting bronchodilator, in particular salmeterol in study M2-127 or tiotropium in study M2-128.

In these two studies, pre-bronchodilator FEV_1 was significantly improved by 49 mL (primary endpoint, p<0.0001) beyond the bronchodilator effect of concomitant treatment with salmeterol in study M2-127 and by 80 mL (primary endpoint, p<0.0001) incremental to concomitant treatment with tiotropium in study M2-128. The corresponding post-bronchodilator values were 60 mL (p<0.0001) and 81 mL (p<0.0001) in studies M2-127 and M2-128, respectively.

These six-month studies were neither designed nor powered to show a statistically significant effect on exacerbations. However, analysis of data indicated that the reduction in the rate of moderate or severe exacerbations with Daxas reached the level of statistical significance in study M2-127 (reduction by 37%; p=0.0315, post-hoc analysis), but not in study M2-128 (reduction by 23%; p=0.1957). In study M2-128 the TDI focal score improved in Daxas treated patients by 0.4 (p=0.0032) beyond the bronchodilator effect of tiotropium.

In both the one-year and six-month studies, the improvement in lung function was sustained over the treatment period. Improvements in lung function and reduction of exacerbations was independent of underlying treatment with long-acting bronchodilators. Smoking status did not influence the improvement in lung function or reduction in exacerbations. Effects were similar, independent of previous treatment with inhaled corticosteroids.

In a pooled post-hoc analysis of two previous one-year studies (M2-111 and M2-112) including patients with a history of COPD associated with chronic bronchitis and emphysema, improvements in lung function was also shown to be independent of concomitant treatment with inhaled corticosteroids.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Daxas is supplied as 500 mcg yellow, D-shaped film-coated tablets, embossed with “D” on one side.

Daxas tablets are available in polyethylene (PE) bottles with a polypropylene (PP) screw cap containing 30 tablets (NDC XXXX-XXXX-XX) or 90 tablets (NDC XXXX-XXXX-XX).

16.2 Storage and Handling

Store Daxas 500 mcg film-coated tablets at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature]. The drug product shelf life is 24 months.

17 PATIENT COUNSELING INFORMATION

17.1 Not for Acute Bronchospasms

Patients should be informed that Daxas is indicated for maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasms.

17.2 Weight Decrease

Patients should be informed that in the event of an unexplained and pronounced weight decrease, they should consult a healthcare professional.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DAXAS® safely and effectively. See full prescribing information for DAXAS.

DAXAS (roflumilast) film-coated tablets
Initial U.S. Approval: 20XX

----------INDICATIONS AND USAGE----------

DAXAS is an anti-inflammatory agent indicated for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dosage for patients with COPD is one 500 mcg tablet per day, with or without food. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: film-coated 500 mcg (3)

----------CONTRAINDICATIONS----------

- Moderate to severe liver impairment (Child-Pugh B or C) (4)
- Hypersensitive to any component of this product (4)

----------WARNINGS AND PRECAUTIONS----------

- Acute bronchospasm: Do not use for the relief of acute bronchospasm. (5.1)
- Weight decrease: Patients should have their weight monitored. (5.2)
- Neuropsychiatric Events: Patients should be instructed to notify their prescriber if these events occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment DAXAS if such events occur. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥2%) are diarrhea, weight decrease, nasal pharyngitis, nausea, headache, insomnia, back pain, influenza, decreased appetite and dizziness. (6.3)

To report SUSPECTED ADVERSE REACTIONS, Contact Forest Laboratories, Inc. at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong cytrochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) may reduce therapeutic effectiveness of DAXAS. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use if potential benefit justifies potential risk to the fetus. (8.1)
- Labor and Delivery: Should not be used. (8.2)
- Nursing Mothers: Should not be used. (8.3)
- Pediatric use: Safety and effectiveness not established in patients less than 18 years of age. Not recommended for use. (8.4)
- Hepatic impairment: Not recommended for use in patients with moderate or severe hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATON

REVISED XX/2010

1

FULL PRESCRIBING INFORMATION: CONTENTS*

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3. DOSAGE FORMS AND STRENGTHS
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DAXAS is indicated as maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

2 DOSAGE AND ADMINISTRATION

The recommended dose of DAXAS is one 500 microgram (mcg) tablet per day, with or without food.

3 DOSAGE FORMS AND STRENGTHS

DAXAS is supplied as a yellow, D-shaped, film-coated tablet, embossed with "D" on one side containing 500 mcg of roflumilast.

4 CONTRAINDICATIONS

The use of DAXAS is contraindicated in the following conditions:

- Moderate to severe liver impairment (Child-Pugh B or C) [see *Clinical Pharmacology (12.3)* and *Use in Special Populations (8.6)*].
- Known hypersensitivity to any component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Treatment of Acute COPD Symptoms

DAXAS is an anti-inflammatory substance indicated for maintenance treatment of COPD, and is not a steroid. It is not indicated for the relief of acute bronchospasm.

5.2 Weight Decrease

Weight loss was reported as an adverse event in the COPD safety pool by 7% of patients in the roflumilast group and 2% in the placebo group as shown in Table 1. A measured weight decrease of ≥ 10 % was observed in the pivotal one-year placebo-controlled studies in 8% percent of patients on roflumilast and 2% of patients on placebo. Patients who reported weight loss as an adverse event regained on average half of the weight lost within a 3-month follow-up period. Patients treated with DAXAS should have their weight monitored.

5.3 Neuropsychiatric Events

In clinical studies an increased number of neuropsychiatric events such as anxiety, depression, insomnia, sleep disorders, dizziness, headache, tremor, and rare instances of suicidal thinking and behavior (including suicide) were reported in DAXAS treated patients by comparison to placebo treated patients.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment DAXAS if such events occur.

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Studies

DAXAS was evaluated in studies which involved greater than 14,000 patients exposed to DAXAS, of which 6,563 were COPD patients. Of these, 3,689 patients were exposed for up to 6

months and 2,874 patients were exposed for up to one year. A total of 5,766 COPD patients received DAXAS at a dose of 500 mcg once daily.

Within the overall clinical experience, DAXAS was evaluated in two pivotal double-blind placebo controlled Phase III studies (M2-124 and M2-125) including 3,092 COPD patients (1,547 treated with DAXAS and 1,545 treated with placebo) for treatment period up to 12 months. The population had a median age of 64 years, 76% were male, and 84% were Caucasian.

In addition, DAXAS was evaluated in two 6-month double-blind placebo controlled studies, in combination with salmeterol (M2-127) or tiotropium (M2-128), including 933 COPD patients in M2-127 (466 treated with DAXAS and 467 treated with placebo) and 743 COPD patients in M2-128 (374 treated with DAXAS and 369 treated with placebo). In studies M2-127 and M-128, the population had a median age of 65 years, 70% were male, and 98% were Caucasian.

A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.2 Adverse Reactions Leading to Discontinuation

In studies M2-124 and M2-125, 14% of 1,547 patients treated with DAXAS 500 mcg once daily compared to 11% of 1,545 patients treated with placebo discontinued due to an adverse reaction. The most common adverse reactions that led to discontinuation of DAXAS were nausea (1%) and diarrhea (1%). In studies M2-127 and M2-128, the number of patients on DAXAS 500 mcg once daily experienced a similar profile and frequency of adverse events leading to discontinuation as in studies M2-124 and M2-125.

6.3 Most Common Adverse Reactions

Table 1 lists the most common adverse reactions experienced in four one-year Phase III clinical studies consisting of 5,766 patients receiving DAXAS 500 mcg daily and 5,491 patients receiving placebo.

Table 1 Adverse Events Occurring in ≥ 2% of Patients Treated with Roflumilast at an Incidence Greater Than in Patients Treated with Placebo

TEAE ≥ 2% COPD Safety Pool		
Preferred Term	Roflumilast	Placebo
	N=5766	N=5491
Study Event	%	%
Diarrhea	10	3
Weight decreased	7	2
Nasopharyngitis	6	6
Nausea	5	1
Headache	5	2
Insomnia	3	1
Influenza	3	2
Back pain	3	2
Decreased appetite	2	0
Dizziness	2	1

6.4 Other Adverse Reactions Observed During Clinical Studies of DAXAS

The following is a list of those treatment-emergent adverse reactions occurring on one or more occasion in at least 1/1000 patients exposed to DAXAS for periods up to 1 year. The listing does not include those events already listed in Table 1, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. These reports do not necessarily indicate a causative relationship with DAXAS. These adverse reactions are categorized by body system and listed in order of decreasing frequency:

Gastrointestinal disorders - abdominal pain, gastritis, vomiting, gastro-esophageal reflux disease, dyspepsia
Infections and infestations – pneumonia
Musculoskeletal and connective tissue disorders - muscle spasms, weakness
Nervous system disorders - tremor, vertigo, myalgia
Psychiatric disorders - anxiety, depression, suicidality
Immune system disorders - hypersensitivity
General disorders and administration site conditions - malaise, asthenia, fatigue
Skin and subcutaneous tissue disorders - rash

7 DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP 3A4 and CYP 1A2. Both roflumilast and roflumilast N-oxide have intrinsic phosphodiesterase 4 (PDE4) inhibitory activity. Therefore, following administration of 500 mcg roflumilast, the total PDE4 inhibition is considered to be the combined effect of both roflumilast and roflumilast N-oxide *[See Clinical Pharmacology (12.3)]*.

Drugs that have been shown not to produce any pharmacokinetic or pharmacodynamic interaction with 500 mcg oral roflumilast are albuterol, antacid such as magnesium aluminum hydroxide, budesonide, digoxin, formoterol, oral and intravenous midazolam, montelukast, sildenafil, and warfarin.

Theophylline

Co-administration of theophylline (375 mg twice daily for 10 days) and 500 mcg oral roflumilast did not alter the pharmacokinetics of theophylline, roflumilast or roflumilast N-oxide to a clinically relevant extent.

Oral Contraceptive containing gestodene and ethinyl estradiol

Concomitant administration of a once daily oral dose of 500 mcg roflumilast with repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol caused a 38% increase and 12 % decrease in C_{max} of roflumilast and roflumilast N-oxide, respectively. Roflumilast and roflumilast N-oxide AUC were increased by 51% and 14%, respectively. This interaction is unlikely to be clinically important, as the major active moiety (roflumilast N-oxide) is not altered significantly. The effect of roflumilast on the pharmacokinetics of gestodene and ethinyl estradiol was not evaluated.

7.1 Drugs That Inhibit Cytochrome P450 (CYP) Enzymes

Clinical drug-drug interaction studies of 500 mcg roflumilast with CYP 3A4 inhibitor erythromycin (500 mg three times daily with meals, for 13 days) resulted in 40% and 70% increase in C_{max} and AUC of roflumilast, respectively and a 34% decrease and a 4% increase in C_{max} and AUC of roflumilast N-oxide. Similarly, co-administration of a strong CYP 3A4 inhibitor

ketoconazole (200 mg twice daily for 13 days) with 500 mcg roflumilast increased roflumilast C_{max} and AUC by 23% and 101%, respectively, reduced roflumilast N-oxide C_{max} by 38% and increased AUC by 3%.

Drug interaction studies with CYP 1A2 inhibitor fluvoxamine (50 mg daily for 14 days) and 500 mcg oral roflumilast showed a 12% and 156% increase in roflumilast C_{max} and AUC along with a 21% decrease and 52% increase in roflumilast N-oxide C_{max} and AUC, respectively.

Co-administration of dual CYP 3A4/1A2 inhibitor enoxacin (400 mg twice daily for 12 days) increased the C_{max} and AUC of roflumilast by 20% and 56%, respectively. Roflumilast N-oxide C_{max} was decreased by 14% while roflumilast N-oxide AUC was increased by 23%.

When cimetidine, a dual CYP 3A4/1A2 inhibitor (400 mg twice daily for 7 days), was co-administered with single dose 500 mcg roflumilast, a 46% and 85% increase in roflumilast C_{max} and AUC; and a 4% decrease in roflumilast N-oxide C_{max} and 27% increase in AUC were noted.

Interactions with CYP 3A4 or CYP 1A2 inhibitors are unlikely to be clinically important as the AUC of roflumilast N-oxide is not altered significantly.

7.2 Drugs That Induce Cytochrome P450 (CYP) Enzymes

Co-administration of 500 mcg roflumilast and the cytochrome P450 enzyme inducer rifampicin (600 mg once daily for 11 days) reduced roflumilast C_{max} and AUC by 68% and 79%, respectively; increased roflumilast N-oxide C_{max} by 30% and reduced roflumilast N-oxide AUC by 56%. Use of strong cytochrome P450 inducers (e.g. phenobarbital, carbamazepine, and phenytoin) may reduce the therapeutic effect of DAXAS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

DAXAS has been shown to induce mild retardation of embryo-fetal development (incomplete ossification) in the rat at exposures of unbound roflumilast and roflumilast N-oxide approximately 2 and 11 times higher, respectively, than exposures in women at the 500 mcg roflumilast dose. Roflumilast was not teratogenic in rats and rabbits following oral administration up to the highest doses of 1.8 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. In one of three rat studies on fertility and embryo-fetal-development, post-implantation losses were observed at oral doses of 0.6 mg/kg/day and 1.8 mg/kg/day. Post-implantation losses were not seen in rabbits up to doses of 0.8 mg/kg/day. Permeability of the placental barrier for drug-related material increased with the progression of pregnancy in rats and rabbits, exposing fetuses to increasing concentrations of roflumilast. There are no adequate and well controlled studies in pregnant women. DAXAS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

Signs of tocolytic activity resulting in delivery retardation and decreased postnatal survival were observed in the mouse at oral doses of 2 mg/kg/day and above. There are no human studies that have investigated effects of DAXAS on preterm labor or labor at term. DAXAS should not be used during labor and delivery.

8.3 Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. DAXAS should not be used during breast-feeding.

8.4 Pediatric Use

Safety and effectiveness of DAXAS in children and adolescents below 18 years of age have not been established. Therefore, DAXAS is not recommended in this population.

8.5 Geriatric Use

Of the total number of COPD subjects in Phase II/III clinical studies (6,563), 1,472 were ≥ 65 years of age, while 414 were ≥ 75 years of age who were exposed to DAXAS for up to 12 months. No overall difference was observed in safety, including adverse event experience, or efficacy between these groups as compared to those less than age 65. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted *[See Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DAXAS 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DAXAS to patients who have mild liver impairment (Child-Pugh A). DAXAS is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[See Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. These differences are not considered to be clinically relevant. No dosage adjustment is necessary for patients with any degree of renal impairment *[See Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

10.1 Human Experience

No case of overdose has been reported in clinical studies with DAXAS. During the Phase I studies of DAXAS the following symptoms were observed at an increased rate after a single oral dose of 2,500 mcg and a single dose of 5,000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

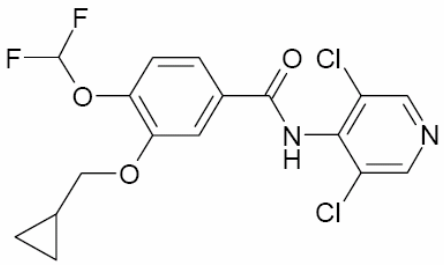
10.2 Management of Overdose

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

11 DESCRIPTION

The active ingredient in DAXAS film-coated tablets is roflumilast. The chemical name of roflumilast is N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22.

The chemical structure is:



The drug substance is a white to off-white non-hygroscopic powder with a melting point of 160°C. It is practically insoluble in water and hexane, sparingly soluble in ethanol and freely soluble in acetone.

DAXAS is supplied as a yellow, D-shaped film-coated tablet, embossed with "D" on one side that contains 500 mcg of roflumilast.

Each film-coated tablet of DAXAS for oral administration contains the following inactive ingredients: lactose monohydrate, corn starch, polyvinylpyrrolidone and magnesium stearate. In addition, the film-coat contains: hydroxypropyl methylcellulose, Macrogol 4000, titanium dioxide E171 and yellow iron oxide E172.

12 CLINICAL PHARMACOLGY

12.1 Mechanism of Action

Roflumilast and its active metabolite (roflumilast N-oxide) are potent and selective phosphodiesterase 4 (PDE4) inhibitors. Roflumilast is an anti-inflammatory agent that targets both the systemic and pulmonary inflammation associated with chronic obstructive pulmonary disease. Roflumilast and roflumilast N-oxide inhibition of PDE4 (a major cyclic-3′, 5′-adenosine monophosphate (cyclic AMP)-metabolizing enzyme) activity leads to accumulation of intracellular cyclic AMP known to inhibit the production of multiple pro-inflammatory factors which may contribute to the pathogenesis of COPD. In preclinical studies with human neutrophils, monocytes/macrophages, lymphocytes, airway smooth muscle cells, lung fibroblasts, endothelial and alveolar epithelial cells, roflumilast and roflumilast N-oxide have been shown to inhibit different cellular functions contributing to lung inflammation, pulmonary remodeling and mucociliary malfunction.

12.2 Pharmacodynamics

In experimental animal models of COPD, roflumilast blocked the infiltration of neutrophils and other leukocytes into the lung. Roflumilast also reduced the smoke-induced destruction of lung parenchyma, bleomycin-induced lung fibrosis and monocrotaline and hypoxia-induced vascular remodeling. In COPD patients, 4 week treatment with DAXAS 500 mcg oral once daily reduced sputum neutrophils and eosinophils by 31%, and 42%, respectively. In a separate 4 week pharmacodynamic study in healthy volunteers, DAXAS 500 mcg once daily significantly reduced

the number of total cells, neutrophils and eosinophils found in bronchoalveolar lavage fluid following segmental pulmonary LPS challenge by 35%, 38% and 73%, respectively.

12.3 Pharmacokinetics

Roflumilast is extensively metabolized in humans, with the formation of a major pharmacodynamically active metabolite, roflumilast N-oxide. Roflumilast is three times more potent than roflumilast N-oxide at inhibition of the PDE4 enzyme *in vitro*. Both moieties contribute to PDE4 inhibitory activity *in vivo*, however the main contribution to the activity is related to roflumilast N-oxide metabolite because the concentrations of this metabolite are about 10-fold higher than roflumilast (see Biotransformation below).

Absorption

The absolute bioavailability of roflumilast following a 500 mcg oral dose is approximately 80%. Maximum plasma concentrations (C_{max}) of roflumilast typically occur approximately one hour after dosing (ranging from 0.5 to 2 hours) in the fasted state while plateau-like maximum concentrations of the N-oxide metabolite are reached in approximately eight hours (ranging from 4 to 13 hours). Food has no affect on total drug absorption, but delays time to maximum concentration (T_{max}) of roflumilast by one hour and reduces C_{max} by approximately 40%, however, C_{max} and T_{max} of roflumilast N-oxide are unaffected.

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for single dose 500 mcg roflumilast is about 2.9 L/kg. Studies in rats with radiolabeled roflumilast indicate low penetration across the blood-brain barrier.

Biotransformation

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the only major metabolite observed in the plasma of humans. Together, roflumilast and roflumilast N-oxide account for the majority (87.5%) of total dose administered in plasma. In urine, roflumilast was not detectable while roflumilast N-oxide was only a trace metabolite (less than 1%). Other conjugated metabolites such as roflumilast N-oxide glucuronide were detected in urine.

The plasma AUC of the N-oxide metabolite on average is about 10-fold greater than the plasma AUC of roflumilast. Thus, the N-oxide metabolite is considered to be the main contributor to the *in vivo* activity.

In vitro studies and clinical drug-drug interaction studies suggest that the biotransformation of roflumilast to its N-oxide metabolite is mediated by CYP 1A2 and 3A4. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of roflumilast and roflumilast N-oxide do not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A9/11. Therefore, there is a low probability of relevant interactions with substances metabolized by these P450 enzymes. In addition, *in vitro* studies demonstrated no induction of the CYP 1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP 2B6 by roflumilast.

Elimination

The plasma clearance after short-term intravenous infusion of roflumilast is on average about 9.6 L/h. Following an oral dose, the median plasma effective half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state plasma

concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing. Following intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

Linearity/Non-linearity

The pharmacokinetics of roflumilast and its N-oxide metabolite are dose-proportional over a range of doses from 250 mcg to 1,000 mcg.

Special Populations

Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUC of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DAXAS 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DAXAS to patients who have mild liver impairment (Child-Pugh A). DAXAS is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C).

Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, roflumilast and roflumilast N-oxide AUCs were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. These differences are not considered to be clinically relevant. No dosage adjustment is necessary for patients with any degree of renal impairment.

Age

In elderly subjects (≥ 65 years of age), roflumilast and roflumilast N-oxide AUCs were greater by 26% and 18%, respectively, as compared to healthy adult subjects (18-65 years old). These differences are not considered to be clinically relevant. No dosage adjustment is necessary for elderly patients.

Gender

In a Phase I study evaluating the effect of age and gender on the pharmacokinetics of roflumilast and roflumilast N-oxide, a 49% and 43% increase in roflumilast and roflumilast N-oxide AUC were noted in healthy female subjects as compared to healthy male subjects, however, these differences are not considered to be clinically relevant. Therefore, no dosage adjustment is necessary based on gender.

Smoking

The pharmacokinetics of roflumilast and roflumilast N-oxide were not significantly altered in smokers as compared to non-smokers. Also, effectiveness was comparable irrespective of the current smoking status.

Race

In African-Americans (n=27) and Hispanics (n=15), population pharmacokinetic analyses suggest that roflumilast pharmacokinetics are not altered by comparison to Caucasians. No dosage adjustment is necessary for race.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Roflumilast was administered by gavage to male and female B6C3F1 mice at doses up to 18 mg/kg/day (males, up to 29 times the expected human clinical exposure for roflumilast and 11 times for roflumilast N-oxide) and doses up to 12 mg/kg/day (females up to 16 times the expected human clinical exposure for roflumilast and 5 times for roflumilast N-oxide) over two years. No compound-related tumors occurred. In the 2-year hamster carcinogenicity studies at doses up to 16 mg/kg/day (16 times the expected human clinical exposure for roflumilast and 32 times for roflumilast N-oxide), no clinically relevant neoplastic findings were observed.

Mutagenesis

Roflumilast was not mutagenic in the Ames test, HPRT test, *in vitro* micronucleus test and chromosomal aberration test in human lymphocytes. There was a slight increase in polychromatic erythrocytes with micronuclei at doses of 300 and 900 mg/kg/d in the *in vivo* mouse micronucleus test (the no observed effect level was 100 mg/kg/d or 168 times the expected human clinical exposure for roflumilast, and 40 times for roflumilast N-oxide). Roflumilast N-oxide was not mutagenic in the Ames and V79 *in vitro* micronucleus tests.

Impairment of Fertility

There was no effect on female fertility up to the highest roflumilast dose of 1.5 mg/kg/day in rats (approximately 2 and 11 times human exposure to unbound roflumilast and roflumilast N-oxide, respectively). Slight reduction in male fertility was seen in conjunction with epididymal toxicity in rats dosed with 1.8 mg/kg/day (approximately 2 and 11 times human exposure to unbound roflumilast and roflumilast N-oxide, respectively). No epididymal toxicity or changes in semen parameters or fertility was present in any other rodent or non-rodent species including monkeys in spite of higher drug exposure. In a human spermatogenesis study, roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period.

13.2 Animal Toxicology and/or Pharmacology

Non-clinical data provided no evidence of immunotoxic, skin sensitizing or phototoxic potential.

14 CLINICAL STUDIES

14.1 Chronic Obstructive Pulmonary Disease (COPD)

In two replicate 1-year pivotal double-blind placebo controlled Phase III studies (M2-124 and M2-125) and two additional six-month randomized, parallel-design, double-blind, placebo-controlled studies (M2-127 and M2-128), a total number of 2,387 patients were treated with DAXAS 500 mcg once daily.

Studies M2-124 and M2-125 included patients with a history of COPD associated with chronic bronchitis for at least 12 months prior to baseline, with symptoms at baseline as determined by cough and sputum score, non-reversible airway obstruction (FEV_1/FVC ratio of $\leq$70%), an FEV_1 $\leq$ 50% of predicted and at least one documented COPD exacerbation in the previous year.

In the 1-year studies, long-acting beta-2 agonists (LABA) or short-acting muscarinic antagonists (SAMA) were used concomitantly by 44% and 35% of patients treated with DAXAS and 45% and 37% of patients on placebo respectively. The use of inhaled corticosteroids was terminated at randomization. Rate of moderate exacerbations (requiring intervention with systemic glucocorticosteroids) or severe exacerbations (resulting in hospitalization and/or leading to death) and lung function (pre-bronchodilator forced expiratory volume in one second, FEV_1) were primary endpoints.

In a pooled analysis, the rate of moderate or severe exacerbations per patient-year was reduced by 16.9%. Table 2 shows a significant reduction in the rate of exacerbations over one year in studies M2-124 and M2-125 in patients with moderate or severe exacerbations on DAXAS 500 mcg once daily compared to placebo.

Table 2 Rate of Moderate or Severe Exacerbation (M2-124 and M2-125)

Study	Placebo		DAXAS		DAXAS versus Placebo			
	N	Rate	N	Rate	%Change	Rate ratio	95% CI	p-value[a]
M2-124	758	1.266	765	1.077	-14.9	0.851	0.737, 0.982	0.0278
M2-125	796	1.485	772	1.210	-18.5	0.815	0.710, 0.935	0.0035

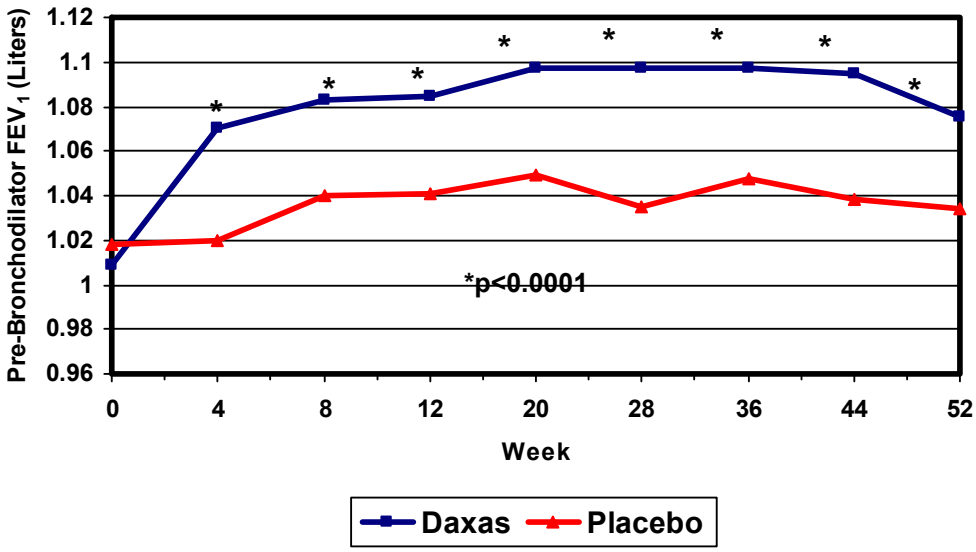
[a] 2-sided based on Poison regression model
CI = confidence interval, N = number of patients

The median time to first moderate or severe COPD exacerbation was delayed from 244 days in the placebo group to 309 days in the DAXAS group based on Study M2-124 and from 232 days in the placebo group to 295 days in the DAXAS group based on M2-125. Averaged over both studies, patients treated with DAXAS had a median time to first COPD exacerbation which was 64 days longer than placebo.

In studies M2-124 and M2-125, reduction of exacerbations was independent of concomitant treatment. Effects were similar, and were also independent of previous treatment with inhaled corticosteroids. Smoking status did not influence reduction of exacerbations.

In a pooled analysis of studies M2-124 and M2-125, DAXAS 500 mcg once daily significantly improved lung function compared to placebo, on average by 48 mL (pre-bronchodilator FEV_1, primary endpoint, $p<0.0001$), and by 55 mL (post-bronchodilator FEV_1, $p<0.0001$). Similarly in a pooled analysis in studies M2-124 and M2-125, DAXAS 500 mcg once daily significantly improved pre-bronchodilator and post-bronchodilator forced vital capacity (FVC) compared to placebo, on average by 98 mL ($p<0.0001$) and by 101 mL ($p<0.0001$), respectively. These changes in lung function were irrespective of concomitant treatment. DAXAS increased mean pre-bronchodilator FEV_1 by 46 mL ($p<0.0001$), as compared to placebo with concomitant LABA treatment, and by 50 mL ($p<0.0001$) without concomitant LABA treatment. The treatment effect of DAXAS on lung function was independent of smoking status or prior use of ICS. Figure 1 shows the sustained improvement in the pre-bronchodilator FEV_1 over one year in the pooled DAXAS 500 mcg once daily patients compared to the placebo group.

Figure 1: Measurements of Pre-Bronchodilator FEV_1 over one year in studies M2-124 and M2-125



Studies M2-127 and M2-128 included patients with a history of COPD for at least 12 months prior to baseline. In study M2-128 documentation of chronic bronchitis and high reliever medication use was also required. Both studies included patients with a non-reversible airway obstruction (FEV_1/FVC <70%) and a FEV_1 of 40% to 70% of predicted. DAXAS or placebo treatment was added to continuous treatment with a long-acting bronchodilator, salmeterol in study M2-127 or tiotropium in study M2-128.

In study M2-127, DAXAS with salmeterol significantly improved pre-bronchodilator FEV_1 by 49 mL ($p<0.0001$) compared to salmeterol alone. In study M2-128, DAXAS with tiotropium significantly improved pre-bronchodilator FEV_1 by 80 mL ($p<0.0001$) compared to tiotropium alone. The improvement in lung function was sustained over the treatment period. Although the studies were not designed to test for exacerbations, moderate or severe exacerbations were analyzed (post-hoc) consistent with the 1-year pivotal studies. Reduction in the rate of moderate or severe exacerbations was observed in patients treated with DAXAS 500 mcg once daily by 37% ($p=0.03$) in study M2-127 and 23% ($p=0.20$) in study M2-128.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DAXAS is supplied as 500 mcg yellow, D-shaped film-coated tablets, embossed with “D” on one side.

DAXAS tablets are available in bottles containing 30 tablets - NDC XXXX-XXXX-XX or 90 tablets - NDC XXXX-XXXX-XX. DAXAS is also available as a 10 X 10 Unit Dose - NDC XXXX-XXXX-XX.

16.2 Storage and Handling

Store DAXAS 500 mcg film-coated tablets at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

17.1 Bronchospasm

DAXAS is indicated for maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasm. Patients should not stop therapy with DAXAS without physician/ provider guidance since symptoms may recur after discontinuation.

17.2 Weight Decrease

Weight loss was reported as an adverse event in the COPD safety pool by 7% of patients in the roflumilast group and 2% in the placebo group as shown in Table 1. A measured weight decrease of ≥ 10 % was observed in the pivotal one-year placebo-controlled studies in 8% percent of patients on roflumilast and 2% of patients on placebo. Patients who reported weight loss as an adverse event regained on average half of the weight lost within a 3-month follow-up period. Patients treated with DAXAS should have their weight monitored [see *Section Warnings and Precautions* (5)].

17.3 Neuropsychiatric Events

In clinical studies an increased number of neuropsychiatric events such as anxiety, depression, insomnia, sleep disorders, dizziness, headache, tremor, and rare instances of suicidal thinking and behavior (including suicide) were reported in DAXAS treated patients by comparison to placebo treated patients.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment DAXAS if such events occur.

Manufactured by:

Nycomed GmbH
Production Site Oranienburg
Lehnitzstrasse 70 – 98
16515 Oranienburg
Germany

Manufactured for:

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

Component Code Number: Rev. XX/2010

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADVAIR DISKUS safely and effectively. See full prescribing information for ADVAIR DISKUS.

ADVAIR DISKUS 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)
ADVAIR DISKUS 250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)
ADVAIR DISKUS 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)
FOR ORAL INHALATION

Initial U.S. Approval: 2000

WARNING: RISK OF ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. A US study showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 out of 13,179 patients on placebo). (5.1)**
- **When treating patients with asthma, only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. (1.1, 5.1)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Reduction in Bone Mineral Density (5 13) March 2009

----------INDICATIONS AND USAGE----------

ADVAIR DISKUS is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist indicated for:

- Maintenance treatment of asthma in patients aged 4 years and older. (1.1)
- Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1.2)

Important limitations:

- Not indicated for patients whose asthma can be managed by inhaled corticosteroids with occasional use of inhaled short-acting beta$_2$-agonists. (1.1)
- Not indicated for the relief of acute bronchospasm. (1.1, 1.2)

---------- DOSAGE AND ADMINISTRATION ----------

For oral inhalation only.

- Maintenance treatment of asthma in patients ≥12 years: 1 inhalation of ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily. Starting dosage is based on asthma severity. (2.1)
- Maintenance treatment of asthma in patients aged 4 to 11 years: 1 inhalation of ADVAIR DISKUS 100/50 twice daily. (2.1)
- Maintenance treatment of COPD: 1 inhalation of ADVAIR DISKUS 250/50 twice daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

DISKUS device containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as an oral inhalation powder. (3)

----------CONTRAINDICATIONS----------

- Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Asthma-related death: Long-acting beta$_2$-adrenergic agonists may increase the risk. Prescribe only for recommended patient populations. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta$_2$-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to ADVAIR DISKUS. (5.7)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ADVAIR DISKUS slowly. (5.8)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid and cardiovascular effects. Use not recommended with ADVAIR DISKUS. (5.9)
- Paradoxical bronchospasm: Discontinue ADVAIR DISKUS and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation. (5.12)
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter. (5.13)
- Effects on growth: Monitor growth of pediatric patients. (5.14)
- Glaucoma and cataracts: Close monitoring is warranted. (5.15)
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.16, 5.18)
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.17)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥3%) are:

- Asthma: upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting. (6.1)
- COPD: pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use not recommended. May cause systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of salmeterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

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ADD:6PI

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS®, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 2 maintenance therapies. 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 an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Asthma

ADVAIR DISKUS is indicated for the long-term, twice-daily, maintenance treatment of asthma in patients aged 4 years and older.

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death *[see Warnings and Precautions (5.1)]*. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 2 maintenance therapies.

Important Limitations of Use:

- ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.
- ADVAIR DISKUS is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting beta$_2$-agonists.

1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

ADVAIR DISKUS 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. ADVAIR DISKUS 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR DISKUS 250/50 twice daily is the only approved dosage for the treatment of COPD because an efficacy advantage of the higher strength ADVAIR DISKUS 500/50 over ADVAIR DISKUS 250/50 has not been demonstrated.

Important Limitations of Use: ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

ADVAIR DISKUS should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing *[see Patient Counseling Information (17.4)]*.

More frequent administration or a higher number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of ADVAIR DISKUS is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. Patients using ADVAIR DISKUS should not use additional long-acting beta$_2$-agonists for any reason. *[See Warnings and Precautions (5.3, 5.12).]*

2.1 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Adult and Adolescent Patients Aged 12 Years and Older: For patients aged 12 years and older, the dosage is 1 inhalation twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for ADVAIR DISKUS for patients aged 12 years and older are based upon patients' asthma severity. For patients not currently on inhaled corticosteroids whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, or patients inadequately controlled on an inhaled corticosteroid, the recommended starting dosage is ADVAIR DISKUS 100/50 or 250/50 twice daily.

The maximum recommended dosage is ADVAIR DISKUS 500/50 twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Improvement in asthma control following inhaled administration of ADVAIR DISKUS can occur within 30 minutes of beginning treatment, although maximum benefit may not be achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of ADVAIR DISKUS with a higher strength may provide additional improvement in asthma control.

If a previously effective dosage regimen of ADVAIR DISKUS fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g., replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional inhaled corticosteroid, initiating oral corticosteroids) should be considered.

Pediatric Patients Aged 4 to 11 Years: For patients with asthma aged 4 to 11 years who are symptomatic on an inhaled corticosteroid, the dosage is 1 inhalation of ADVAIR DISKUS 100/50 twice daily (morning and evening, approximately 12 hours apart).

2.2 Chronic Obstructive Pulmonary Disease

The recommended dosage for patients with COPD is 1 inhalation of ADVAIR DISKUS 250/50 twice daily (morning and evening, approximately 12 hours apart).

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

3 DOSAGE FORMS AND STRENGTHS

Disposable purple device with 60 blisters containing a combination of fluticasone propionate (100, 250, or 500 mcg) and salmeterol (50 mcg) as an oral inhalation powder formulation. An institutional pack containing 14 blisters is also available.

4 CONTRAINDICATIONS

The use of ADVAIR DISKUS is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Severe hypersensitivity to milk proteins *[see Warnings and Precautions (5.11), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Asthma-Related Death With Long-Acting Beta$_2$-Adrenergic Agonists

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS 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 2 maintenance therapies.

A large placebo-controlled US study that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting beta$_2$-agonist–naive patients with asthma to assess the safety of salmeterol (SEREVENT Inhalation Aerosol) 42 mcg twice daily over 28 weeks compared with placebo when added to usual asthma therapy. A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355), which led to premature termination of the study. The results of the interim analysis showed that patients receiving salmeterol were at increased risk for fatal asthma events (see Table 1 and Figure 1). In the total population, a higher rate of asthma-related death occurred in patients treated with salmeterol than those treated with placebo (0.10% vs. 0.02%, relative risk 4.37 [95% CI: 1.25, 15.34]).

Post-hoc subpopulation analyses were performed. In Caucasians, asthma-related death occurred at a higher rate in patients treated with salmeterol than in patients treated with placebo (0.07% vs. 0.01%, relative risk 5.82 [95% CI: 0.70, 48.37]). In African Americans also, asthma-related death occurred at a higher rate in patients treated with salmeterol than those

treated with placebo (0.31% vs. 0.04%, relative risk 7.26 [95% CI: 0.89, 58.94]). Although the relative risks of asthma-related death were similar in Caucasians and African Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African Americans because there was a higher overall rate of asthma-related death in African American patients (see Table 1). Given the similar basic mechanisms of action of beta$_2$-agonists, it is possible that the findings seen in the SMART study represent a class effect.

The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other active ingredient in ADVAIR DISKUS, or other asthma-controller therapy modifies the risk of asthma-related death.

Table 1. Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART)

	Salmeterol n (%[a])	Placebo n (%[a])	Relative Risk[b] (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients[c] (95% Confidence Interval)
Total Population[d] Salmeterol: N = 13,176 Placebo: N = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Salmeterol: N = 9,281 Placebo: N = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Salmeterol: N = 2,366 Placebo: N = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

[a] Life-table 28-week estimate, adjusted according to the patients' actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.

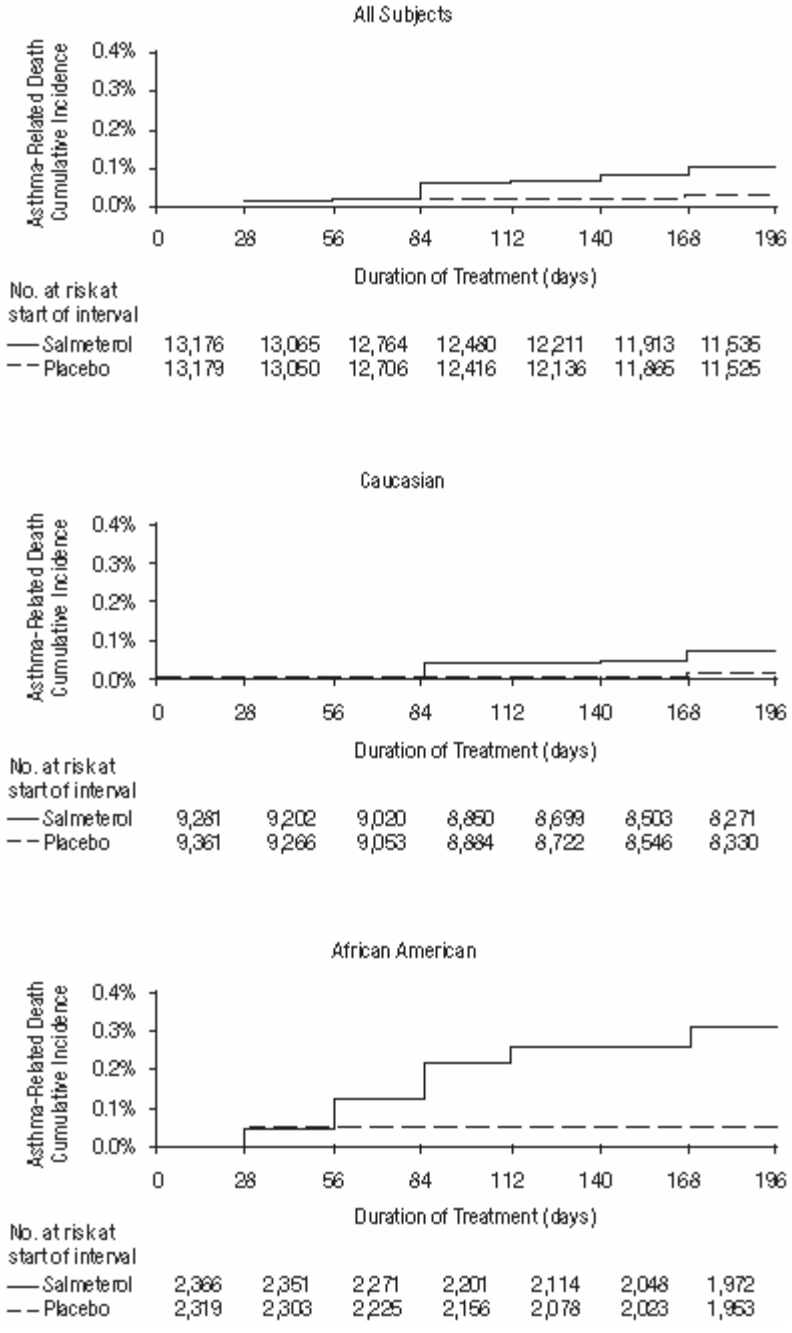
[b] Relative risk is the ratio of the rate of asthma-related death in the salmeterol group and the rate in the placebo group. The relative risk indicates how many more times likely an asthma-related death occurred in the salmeterol group than in the placebo group in a 28-week treatment period.

[c] Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.

[d] The Total Population includes the following ethnic origins listed on the case report form: Caucasian, African American, Hispanic, Asian, and "Other." In addition, the Total Population includes those patients whose ethnic origin was not reported. The results for Caucasian and African American subpopulations are shown above. No asthma-related deaths occurred in the

Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was not reported (salmeterol n = 130, placebo n = 127).

Figure 1. Cumulative Incidence of Asthma-Related Deaths in the 28-Week Salmeterol Multi-center Asthma Research Trial (SMART), by Duration of Treatment



A 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study, showed results similar to the SMART study. In the SNS study, the rate of asthma-related death was numerically, though not statistically significantly, greater in patients with asthma treated with salmeterol (42 mcg twice daily) than those treated with albuterol (180 mcg 4 times daily) added to usual asthma therapy.

The SNS and SMART studies enrolled patients with asthma. No studies have been conducted that were primarily designed to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists.

5.2 Deterioration of Disease and Acute Episodes

ADVAIR DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. ADVAIR DISKUS has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of ADVAIR DISKUS in this setting is not appropriate.

Serious acute respiratory events, including fatalities, have been reported when salmeterol, a component of ADVAIR DISKUS, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (e.g., patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, previous life-threatening acute asthma exacerbations) and in some patients with acutely deteriorating asthma (e.g., patients with significantly increasing symptoms; increasing need for inhaled, short-acting beta$_2$-agonists; decreasing response to usual medications; increasing need for systemic corticosteroids; recent emergency room visits; deteriorating lung function). However, these events have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of ADVAIR DISKUS with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily (morning and evening) of ADVAIR DISKUS.

ADVAIR DISKUS should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms such as shortness of breath. When prescribing ADVAIR DISKUS, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of ADVAIR DISKUS.

When beginning treatment with ADVAIR DISKUS, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.3 Excessive Use of ADVAIR DISKUS and Use With Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, ADVAIR DISKUS should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta$_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ADVAIR DISKUS should not use an additional long-acting beta$_2$-agonist (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or COPD.

5.4 Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with ADVAIR DISKUS. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with ADVAIR DISKUS continues, but at times therapy with ADVAIR DISKUS may need to be interrupted. Patients should rinse the mouth after inhalation of ADVAIR DISKUS.

5.5 Pneumonia

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD following the inhaled administration of corticosteroids, including fluticasone propionate and ADVAIR DISKUS. In 2 replicate 12-month studies of 1,579 patients with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR DISKUS 250/50 (7%) than in those receiving salmeterol 50 mcg (3%). The incidence of pneumonia in the patients treated with ADVAIR DISKUS was higher in patients over 65 years of age (9%) compared with the incidence in patients less than 65 years of age (4%). *[See Adverse Reactions (6.2), Use in Specific Populations (8.5).]*

In a 3-year study of 6,184 patients with COPD, there was a higher incidence of pneumonia reported in patients receiving ADVAIR DISKUS 500/50 compared with placebo (16% with ADVAIR DISKUS 500/50, 14% with fluticasone propionate 500 mcg, 11% with salmeterol 50 mcg, and 9% with placebo). Similar to what was seen in the 1-year studies with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in patients over 65 years of age (18% with ADVAIR DISKUS 500/50 vs. 10% with placebo) compared with patients less than 65 years of age (14% with ADVAIR DISKUS 500/50 vs. 8% with placebo). *[See Adverse Reactions (6.2), Use in Specific Populations (8.5).]*

5.6 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such

children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

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

5.7 Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although ADVAIR DISKUS may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ADVAIR DISKUS. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with ADVAIR DISKUS. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or ADVAIR DISKUS may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Fluticasone propionate, a component of ADVAIR DISKUS, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of ADVAIR DISKUS in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing ADVAIR DISKUS.

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

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of ADVAIR DISKUS should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

The use of strong CYP 3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug interactions (7.1), Clinical Pharmacology (12.3)]*.

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, ADVAIR DISKUS can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ADVAIR DISKUS, it should be treated immediately with an inhaled, short-acting bronchodilator, ADVAIR DISKUS should be discontinued immediately, and alternative therapy should be instituted. Upper airway symptoms of laryngeal spasm, irritation, or swelling, such as

stridor and choking, have been reported in patients receiving fluticasone propionate and salmeterol.

5.11 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of ADVAIR DISKUS, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm. There have been reports of anaphylactic reactions in patients with severe milk protein allergy; therefore, patients with severe milk protein allergy should not take ADVAIR DISKUS *[see Contraindications (4)]*.

5.12 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10)]*. Therefore, ADVAIR DISKUS, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol, a component of ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post-menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating ADVAIR DISKUS and periodically thereafter. If significant reductions in BMD are seen and ADVAIR DISKUS is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

2-Year Fluticasone Propionate Study: A 2-year study of 160 patients (females aged 18 to 40 years, males 18 to 50) with asthma receiving CFC-propelled fluticasone propionate

inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

3-Year Bone Mineral Density Study: Effects of treatment with ADVAIR DISKUS 250/50 or salmeterol 50 mcg on BMD at the L_1-L_4 lumbar spine and total hip were evaluated in 186 patients with COPD (aged 43 to 87 years) in a 3-year double-blind study. Of those enrolled, 108 patients (72 males and 36 females) were followed for the entire 3 years. BMD evaluations were conducted at baseline and at 6-month intervals. Conclusions cannot be drawn from this study regarding BMD decline in patients treated with ADVAIR DISKUS versus salmeterol due to the inconsistency of treatment differences across gender and between lumbar spine and total hip.

In this study there were 7 non-traumatic fractures reported in 5 patients treated with ADVAIR DISKUS and 1 non-traumatic fracture in 1 patient treated with salmeterol. None of the non-traumatic fractures occurred in the vertebrae, hip, or long bones.

3-Year Survival Study: Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on BMD was evaluated in a subset of 658 patients (females and males aged 40 to 80 years) with COPD in the 3-year survival study. BMD evaluations were conducted at baseline and at 48, 108, and 158 weeks. Conclusions cannot be drawn from this study because of the large number of drop outs (>50%) before the end of the follow-up and the maldistribution of covariates among the treatment groups that can affect BMD.

Fracture risk was estimated for the entire population of patients with COPD in the survival study (N = 6,184). The probability of a fracture over 3 years was 6.3% for ADVAIR DISKUS, 5.4% for fluticasone propionate, 5.1% for salmeterol, and 5.1% for placebo.

5.14 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving ADVAIR DISKUS routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms. *[See Dosage and Administration (2.1), Use in Specific Populations (8.4).]*

5.15 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a subset of 658 patients with COPD in the 3-year survival study. Ophthalmic examinations were

conducted at baseline and at 48, 108, and 158 weeks. Conclusions about cataracts cannot be drawn from this study because the high incidence of cataracts at baseline (61% to 71%) resulted in an inadequate number of patients treated with ADVAIR DISKUS 500/50 who were eligible and available for evaluation of cataracts at the end of the study (n = 53). The incidence of newly diagnosed glaucoma was 2% with ADVAIR DISKUS 500/50, 5% with fluticasone propionate, 0% with salmeterol, and 2% with placebo.

5.16 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.17 Coexisting Conditions

ADVAIR DISKUS, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.18 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2)]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with ADVAIR DISKUS at recommended doses.

6 ADVERSE REACTIONS

Long-acting $beta_2$-adrenergic agonists, such as salmeterol, may increase the risk of asthma-related death. 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 an increase in asthma-related deaths in patients receiving salmeterol *[see Warnings and Precautions (5.1)]*. Salmeterol is a component of ADVAIR DISKUS. However, the data from this study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma-controller therapy modifies the risk of asthma-related death.

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Pneumonia in patients with COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Growth effects *[see Warnings and Precautions (5.14)]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Asthma

Adult and Adolescent Patients Aged 12 Years and Older: The incidence of adverse reactions associated with ADVAIR DISKUS in Table 2 is based upon 2 placebo-controlled, 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with ADVAIR DISKUS (100/50- or 250/50-mcg doses), fluticasone propionate inhalation powder (100- or 250-mcg doses), salmeterol inhalation powder 50 mcg, or placebo. The average duration of exposure was 60 to 79 days in the active treatment groups compared with 42 days in the placebo group.

Table 2. Adverse Reactions With ≥3% Incidence With ADVAIR DISKUS in Adult and Adolescent Patients With Asthma

Adverse Event	ADVAIR DISKUS 100/50 (N = 92) %	ADVAIR DISKUS 250/50 (N = 84) %	Fluticasone Propionate 100 mcg (N = 90) %	Fluticasone Propionate 250 mcg (N = 84) %	Salmeterol 50 mcg (N = 180) %	Placebo (N = 175) %
Ear, nose, & throat						
Upper respiratory tract infection	27	21	29	25	19	14
Pharyngitis	13	10	7	12	8	6
Upper respiratory inflammation	7	6	7	8	8	5
Sinusitis	4	5	6	1	3	4
Hoarseness/dysphonia	5	2	2	4	<1	<1
Oral candidiasis	1	4	2	2	0	0
Lower respiratory						
Viral respiratory infections	4	4	4	10	6	3
Bronchitis	2	8	1	2	2	2
Cough	3	6	0	0	3	2
Neurology						
Headaches	12	13	14	8	10	7
Gastrointestinal						
Nausea & vomiting	4	6	3	4	1	1
Gastrointestinal discomfort & pain	4	1	0	2	1	1
Diarrhea	4	2	2	2	1	1
Viral gastrointestinal infections	3	0	3	1	2	2
Non-site specific						
Candidiasis unspecified site	3	0	1	4	0	1
Musculoskeletal						
Musculoskeletal pain	4	2	1	5	3	3

The types of adverse reactions and events reported in Study 3, a 28-week, non-US clinical study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily with ADVAIR DISKUS 500/50, fluticasone propionate inhalation powder 500 mcg and salmeterol inhalation powder 50 mcg used concurrently, or fluticasone propionate inhalation powder 500 mcg, were similar to those reported in Table 2.

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by patients with asthma treated with ADVAIR DISKUS compared with patients treated with placebo include the following: lymphatic signs and symptoms; muscle injuries; fractures; wounds and lacerations; contusions and hematomas; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; keratitis and conjunctivitis; dental discomfort and pain; gastrointestinal signs and symptoms; oral ulcerations; oral discomfort and pain; lower respiratory signs and symptoms; pneumonia; muscle stiffness, tightness, and rigidity; bone and cartilage disorders; sleep disorders; compressed nerve syndromes; viral infections; pain; chest symptoms; fluid retention; bacterial infections; unusual taste; viral skin infections; skin flakiness and acquired ichthyosis; disorders of sweat and sebum.

Pediatric Patients Aged 4 to 11 Years: The safety data for pediatric patients aged 4 to 11 years is based upon 1 US trial of 12 weeks' treatment duration. A total of 203 patients (74 females and 129 males) who were receiving inhaled corticosteroids at study entry were randomized to either ADVAIR DISKUS 100/50 or fluticasone propionate inhalation powder 100 mcg twice daily. Common adverse reactions (≥3% and greater than placebo) seen in the pediatric patients but not reported in the adult and adolescent clinical trials include: throat irritation and ear, nose, and throat infections.

Laboratory Test Abnormalities: Elevation of hepatic enzymes was reported in ≥1% of patients in clinical trials. The elevations were transient and did not lead to discontinuation from the studies. In addition, there were no clinically relevant changes noted in glucose or potassium.

6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

Short-Term (6 Months to 1 Year) Trials: The short-term safety data are based on exposure to ADVAIR DISKUS 250/50 twice daily in one 6-month and two 1-year clinical trials. In the 6-month trial, a total of 723 adult patients (266 females and 457 males) were treated twice daily with ADVAIR DISKUS 250/50, fluticasone propionate inhalation powder 250 mcg, salmeterol inhalation powder, or placebo. The mean age of the patients was 64, and the majority (93%) was Caucasian. In this trial, 70% of the patients treated with ADVAIR DISKUS reported an adverse reaction compared with 64% on placebo. The average duration of exposure to ADVAIR DISKUS 250/50 was 141.3 days compared with 131.6 days for placebo. The incidence of adverse reactions in the 6-month study is shown in Table 3.

Table 3. Overall Adverse Reactions With ≥3% Incidence With ADVAIR DISKUS 250/50 in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis

Adverse Event	ADVAIR DISKUS 250/50 (N = 178) %	Fluticasone Propionate 250 mcg (N = 183) %	Salmeterol 50 mcg (N = 177) %	Placebo (N = 185) %
Ear, nose, & throat				
Candidiasis mouth/throat	10	6	3	1
Throat irritation	8	5	4	7
Hoarseness/dysphonia	5	3	<1	0
Sinusitis	3	8	5	3
Lower respiratory				
Viral respiratory infections	6	4	3	3
Neurology				
Headaches	16	11	10	12
Dizziness	4	<1	3	2
Non-site specific				
Fever	4	3	0	3
Malaise & fatigue	3	2	2	3
Musculoskeletal				
Musculoskeletal pain	9	8	12	9
Muscle cramps & spasms	3	3	1	1

In the two 1-year studies, ADVAIR DISKUS 250/50 was compared with salmeterol in 1,579 patients (863 males and 716 females). The mean age of the patients was 65, and the majority (94%) was Caucasian. To be enrolled, all of the patients had to have had a COPD exacerbation in the previous 12 months. In this trial, 88% of the patients treated with ADVAIR DISKUS and 86% of the patients treated with salmeterol reported an adverse event. The most common events that occurred with a frequency of >5% and more frequently in the patients treated with ADVAIR DISKUS were nasopharyngitis, upper respiratory tract infection, nasal congestion, back pain, sinusitis, dizziness, nausea, pneumonia, candidiasis, and dysphonia. Overall, 55 (7%) of the patients treated with ADVAIR DISKUS and 25 (3%) of the patients treated with salmeterol developed pneumonia.

The incidence of pneumonia was higher in patients over 65 years of age, 9% in the patients treated with ADVAIR DISKUS compared with 4% in the patients treated with ADVAIR DISKUS less than 65 years of age. In the patients treated with salmeterol, the incidence of pneumonia was the same (3%) in both age-groups. *[See Warnings and Precautions (5.5.), Use in Specific Populations (8.5).]*

Long-Term (3-Year) Trial: The safety of ADVAIR DISKUS 500/50 was evaluated in a randomized, double-blind, placebo-controlled, multicenter, international, 3-year study in 6,184 adult patients with COPD (4,684 males and 1,500 females). The mean age of the patients was 65, and the majority (82%) was Caucasian. The distribution of adverse events was similar to that seen in the 1-year trials with ADVAIR DISKUS 250/50. In addition, pneumonia was reported in a significantly increased number of patients treated with ADVAIR DISKUS 500/50 and fluticasone propionate 500 mcg (16% and 14%, respectively) compared with patients treated with salmeterol 50 mcg or placebo (11% and 9%, respectively). When adjusted for time on treatment, the rates of pneumonia were 84 and 88 events per 1,000 treatment-years in the groups treated with fluticasone propionate 500 mcg and with ADVAIR DISKUS 500/50, respectively, compared with 52 events per 1,000 treatment-years in the salmeterol and placebo groups. Similar to what was seen in the 1-year studies with ADVAIR DISKUS 250/50, the incidence of pneumonia was higher in patients over 65 years of age (18% with ADVAIR DISKUS 500/50 vs. 10% with placebo) compared with patients less than 65 years of age (14% with ADVAIR DISKUS 500/50 vs. 8% with placebo). *[See Warnings and Precautions (5.5), Use in Specific Populations (8.5).]*

Additional Adverse Reactions: Other adverse reactions not previously listed, whether considered drug-related or not by the investigators, that were reported more frequently by patients with COPD treated with ADVAIR DISKUS compared with patients treated with placebo include the following: syncope; ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection; hypothyroidism; dry eyes; eye infections; gastrointestinal signs and symptoms; oral lesions; abnormal liver function tests; bacterial infections; edema and swelling; viral infections.

Laboratory Abnormalities: There were no clinically relevant changes in these trials. Specifically, no increased reporting of neutrophilia or changes in glucose or potassium was noted.

6.3 Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during worldwide use of any formulation of ADVAIR, fluticasone propionate, and/or salmeterol regardless of indication. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ADVAIR DISKUS, fluticasone propionate, and/or salmeterol or a combination of these factors.

Cardiac Disorders: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia.

Endocrine Disorders: Cushing syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism.

Eye Disorders: Glaucoma.

Gastrointestinal Disorders: Abdominal pain, dyspepsia, xerostomia.

Immune System Disorders: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction). Very rare anaphylactic reaction in patients with severe milk protein allergy.

Metabolic and Nutrition Disorders: Hyperglycemia, weight gain.

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis.

Nervous System Disorders: Paresthesia, restlessness.

Psychiatric Disorders: Agitation, aggression, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

Reproductive System and Breast Disorders: Dysmenorrhea.

Respiratory, Thoracic, and Mediastinal Disorders: Chest congestion; chest tightness; dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin and Subcutaneous Tissue Disorders: Ecchymoses, photodermatitis.

Vascular Disorders: Pallor.

7 DRUG INTERACTIONS

ADVAIR DISKUS has been used concomitantly with other drugs, including short-acting $beta_2$-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD, without adverse drug reactions. No formal drug interaction studies have been performed with ADVAIR DISKUS.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of ADVAIR DISKUS, are substrates of CYP 3A4. The use of strong CYP 3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

Ritonavir: *Fluticasone Propionate:* A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations *[see Clinical Pharmacology (12.3)]*. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression.

Ketoconazole: *Fluticasone Propionate:* Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

Salmeterol: In a drug interaction study in 20 healthy subjects, coadministration of inhaled salmeterol (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to salmeterol (AUC increased 16-fold and C_{max} increased 1.4-fold). Three (3) subjects were withdrawn due to $beta_2$-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

ADVAIR DISKUS should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system may be potentiated by these agents.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but may produce severe bronchospasm in patients with reversible obstructive airways disease. Therefore, patients with asthma and COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Diuretics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies with ADVAIR DISKUS in pregnant women. ADVAIR DISKUS was teratogenic in mice and not in rats, although it lowered fetal weight in rats. Fluticasone propionate alone was teratogenic in mice, rats, and rabbits, and salmeterol alone was teratogenic in rabbits and not in rats. From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol when compared with toxicity data from the components administered separately.

ADVAIR DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVAIR DISKUS: In the mouse reproduction assay, fluticasone propionate by the subcutaneous route at a dose approximately 3/5 the maximum recommended human daily

inhalation dose (MRHD) on a mg/m^2 basis combined with oral salmeterol at a dose approximately 410 times the MRHD on a mg/m^2 basis produced cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses of fluticasone propionate subcutaneously up to approximately 1/6 the MRHD on a mg/m^2 basis and oral doses of salmeterol up to approximately 55 times the MRHD on a mg/m^2 basis. In rats, combining fluticasone propionate subcutaneously at a dose equivalent to the MRHD on a mg/m^2 basis and an oral dose of salmeterol at approximately 810 times the MRHD on a mg/m^2 basis produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when combining fluticasone propionate subcutaneously at a dose less than the MRHD on a mg/m^2 basis and an oral dose of salmeterol at approximately 80 times the MRHD on a mg/m^2 basis.

Fluticasone Propionate: Subcutaneous studies in the mouse at a dose less than the MRHD on a mg/m^2 basis and in the rat at a dose equivalent to the MRHD on a mg/m^2 basis revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose less than the MRHD on a mg/m^2 basis. However, no teratogenic effects were reported at oral doses up to approximately 5 times the MRHD on a mg/m^2 basis. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration *[see Clinical Pharmacology (12.3)]*.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol: No teratogenic effects occurred in rats at oral doses approximately 160 times the MRHD on a mg/m^2 basis. In Dutch rabbits administered oral doses approximately 50 times the MRHD based on comparison of the AUCs, salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose approximately 20 times the MRHD based on comparison of the AUCs.

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose approximately 1,600 times the MRHD on a mg/m^2 basis. Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans.

8.2 Labor and Delivery

There are no well-controlled human studies that have investigated effects of ADVAIR DISKUS on preterm labor or labor at term. Because of the potential for beta-agonist interference

with uterine contractility, use of ADVAIR DISKUS during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

8.3 Nursing Mothers

Plasma levels of salmeterol, a component of ADVAIR DISKUS, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a component of ADVAIR DISKUS, is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of tritiated fluticasone propionate resulted in measurable radioactivity in milk.

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

Caution should be exercised when ADVAIR DISKUS is administered to a nursing woman.

8.4 Pediatric Use

Use of ADVAIR DISKUS 100/50 in patients aged 4 to 11 years is supported by extrapolation of efficacy data from older patients and by safety and efficacy data from a study of ADVAIR DISKUS 100/50 in children with asthma aged 4 to 11 years *[see Adverse Reactions (6.1), Clinical Studies (14.1)]*. The safety and effectiveness of ADVAIR DISKUS in children with asthma less than 4 years of age have not been established.

Inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause a reduction in growth velocity in children and adolescents *[see Warnings and Precautions (5.14)]*. The growth of pediatric patients receiving orally inhaled corticosteroids, including ADVAIR DISKUS, should be monitored.

A 52-week placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder (FLOVENT® ROTADISK®) at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4 to 11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (N = 76), 6.07 cm/year in the 50-mcg group (N = 98), and 5.66 cm/year in the 100-mcg group (N = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). In children aged 8.5 years, the mean age of children in this study, the range for expected growth velocity is: boys – 3^{rd} percentile = 3.8 cm/year, 50^{th} percentile = 5.4 cm/year, and 97^{th} percentile = 7.0 cm/year; girls – 3^{rd} percentile = 4.2 cm/year, 50^{th} percentile = 5.7 cm/year, and 97^{th} percentile = 7.3 cm/year. The clinical relevance of these growth data is not certain.

If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including ADVAIR DISKUS, each patient should be titrated to the lowest strength that effectively controls his/her asthma *[see Dosage and Administration (2.1)]*.

8.5 Geriatric Use

Clinical studies of ADVAIR DISKUS for asthma did not include sufficient numbers of patients aged 65 years and older to determine whether older patients with asthma respond differently than younger patients.

Of the total number of patients in clinical studies receiving ADVAIR DISKUS for COPD, 1,621 were aged 65 years or older and 379 were aged 75 years or older. Patients with COPD aged 65 years and older had a higher incidence of serious adverse events compared with patients less than 65 years of age. Although the distribution of adverse events was similar in the 2 age-groups, patients over 65 years of age experienced more severe events. In two 1-year studies, the excess risk of pneumonia that was seen in patients treated with ADVAIR DISKUS compared with those treated with salmeterol was greater in patients over 65 years of age than in patients less than 65 years of age *[see Adverse Reactions (6.2)]*. As with other products containing $beta_2$-agonists, special caution should be observed when using ADVAIR DISKUS in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for ADVAIR DISKUS or its active components, no adjustment of dosage of ADVAIR DISKUS in geriatric patients is warranted.

No relationship between fluticasone propionate systemic exposure and age was observed in 57 patients with COPD (aged 40 to 82 years) given 250 or 500 mcg twice daily.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with renal impairment.

10 OVERDOSAGE

No human overdosage data has been reported for ADVAIR DISKUS.

No deaths occurred in rats given an inhaled single-dose combination of salmeterol 3.6 mg/kg (approximately 290 and 140 times the MRHD for adults and children, respectively, on a mg/m^2 basis) and 1.9 mg/kg of fluticasone propionate (approximately 15 and 35 times the MRHD for adults and children, respectively, on a mg/m^2 basis).

Fluticasone Propionate: Chronic overdosage with fluticasone propionate may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.7)]*. Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at dosages of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

No deaths were seen in mice given an oral dose of 1,000 mg/kg (4,100 and 9,600 times the MRHD dose for adults and children, respectively, on a mg/m^2 basis). No deaths were seen in rats given an oral dose of 1,000 mg/kg (8,100 and 19,200 times the MRHD for adults and children, respectively, on a mg/m^2 basis).

Salmeterol: The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following: seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of salmeterol.

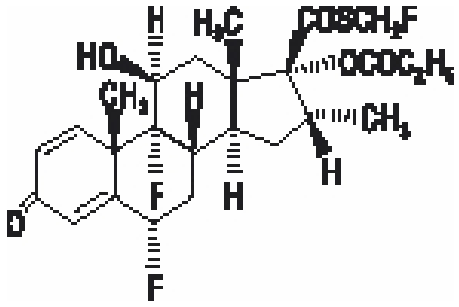
Treatment consists of discontinuation of salmeterol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is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

No deaths were seen in rats given salmeterol at an inhalation dose of 2.9 mg/kg (approximately 240 and 110 times the MRHD for adults and children, respectively, on a mg/m^2 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately 190 and 90 times the MRHD for adults and children, respectively, on a mg/m^2 basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately 6,100 and 2,900 times the MRHD for adults and children, respectively, on a mg/m^2 basis) and in rats at 1,000 mg/kg (approximately 81,000 and 38,000 times the MRHD for adults and children, respectively, on a mg/m^2 basis).

11 DESCRIPTION

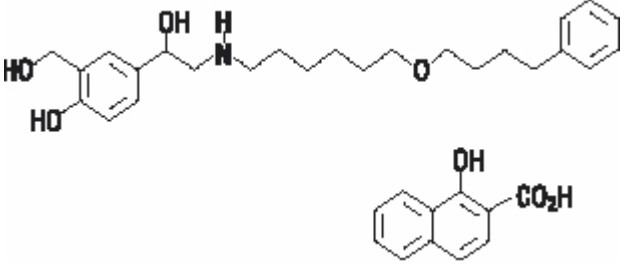
ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of ADVAIR DISKUS is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of ADVAIR DISKUS is salmeterol xinafoate, a beta$_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate, and it has the following chemical structure:



Salmeterol xinafoate is a white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \bullet C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and ADVAIR DISKUS 500/50 are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins). Each blister contains 1 complete dose of both medications. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, ADVAIR DISKUS delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister from ADVAIR

DISKUS 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean FEV_1 20% to 30% of predicted), mean peak inspiratory flow (PIF) through a DISKUS® inhalation device was 82.4 L/min (range, 46.1 to 115.3 L/min).

Inhalation profiles for adolescent (N = 13, aged 12 to 17 years) and adult (N = 17, aged 18 to 50 years) patients with asthma inhaling maximally through the DISKUS device show mean PIF of 122.2 L/min (range, 81.6 to 152.1 L/min). Inhalation profiles for pediatric patients with asthma inhaling maximally through the DISKUS device show a mean PIF of 75.5 L/min (range, 49.0 to 104.8 L/min) for the 4-year-old patient set (N = 20) and 107.3 L/min (range, 82.8 to 125.6 L/min) for the 8-year-old patient set (N = 20).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ADVAIR DISKUS: Since ADVAIR DISKUS contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to ADVAIR DISKUS. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor agonist) that have different effects on clinical and physiological indices.

Fluticasone Propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Inflammation is also a component in the pathogenesis of COPD. In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone propionate when used apart from ADVAIR DISKUS are not indicated for the treatment of COPD.

Salmeterol Xinafoate: Salmeterol is a selective, long-acting $beta_2$-adrenergic agonist. In vitro studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial

smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10% to 50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

12.2 Pharmacodynamics

ADVAIR DISKUS: *Healthy Subjects: Cardiovascular Effects:* Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four (4) studies were conducted in healthy adult subjects: (1) a single-dose crossover study using 2 inhalations of ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, or fluticasone propionate powder 500 mcg given alone, (2) a cumulative dose study using 50 to 400 mcg of salmeterol powder given alone or as ADVAIR DISKUS 500/50, (3) a repeat-dose study for 11 days using 2 inhalations twice daily of ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, or salmeterol powder 50 mcg, and (4) a single-dose study using 5 inhalations of ADVAIR DISKUS 100/50, fluticasone propionate powder 100 mcg alone, or placebo. In these studies no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as ADVAIR DISKUS, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in ADVAIR DISKUS. The potential effect of salmeterol on the effects of fluticasone propionate on the HPA axis was also evaluated in these studies.

HPA Axis Effects: No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in ADVAIR DISKUS in healthy subjects.

Asthma: Adults and Adolescent Patients: Cardiovascular Effects: In clinical studies with ADVAIR DISKUS in adult and adolescent patients aged 12 years and older with

asthma, no significant differences were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as ADVAIR DISKUS. In 72 adolescent and adult patients with asthma given either ADVAIR DISKUS 100/50 or ADVAIR DISKUS 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

HPA Axis Effects: In a 28-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 500/50 twice daily was compared with the concurrent use of salmeterol powder 50 mcg plus fluticasone propionate powder 500 mcg from separate inhalers or fluticasone propionate powder 500 mcg alone. No significant differences across treatments were observed in serum cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week study in adolescent and adult patients with asthma, ADVAIR DISKUS 250/50 twice daily was compared with fluticasone propionate powder 250 mcg alone, salmeterol powder 50 mcg alone, and placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with ADVAIR DISKUS. One patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing, compared with 2 patients (6%) who received placebo, 2 patients (6%) who received fluticasone propionate 250 mcg, and no patients who received salmeterol.

In a repeat-dose, 3-way crossover study, 1 inhalation twice daily of ADVAIR DISKUS 100/50, FLOVENT® DISKUS® 100 mcg (fluticasone propionate inhalation powder, 100 mcg), or placebo was administered to 20 adolescent and adult patients with asthma. After 28 days of treatment, geometric mean serum cortisol AUC over 12 hours showed no significant difference between ADVAIR DISKUS and FLOVENT DISKUS or between either active treatment and placebo.

Pediatric Patients: HPA Axis Effects: In a 12-week study in patients with asthma aged 4 to 11 years who were receiving inhaled corticosteroids at study entry, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg administered twice daily via the DISKUS. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

Chronic Obstructive Pulmonary Disease: Cardiovascular Effects: In clinical studies with ADVAIR DISKUS in patients with COPD, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between ADVAIR DISKUS, the individual components of ADVAIR DISKUS, and placebo. In a study of ADVAIR DISKUS 250/50, 8 patients (2 [1.1%] in the group given ADVAIR DISKUS 250/50, 1 [0.5%] in the fluticasone propionate 250-mcg group, 3 [1.7%] in the salmeterol group, and 2 [1.1%] in the placebo group) had QTc intervals >470 msec at least 1 time during the treatment period. Five (5) of these 8 patients had a prolonged QTc interval at baseline.

In a 24-week study, 130 patients with COPD received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg, salmeterol powder 50 mcg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with ADVAIR DISKUS 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given ADVAIR DISKUS 500/50 experienced heart block. There were 3 cases of nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500-mcg treatment groups).

In 24-week clinical studies in patients with COPD, the incidence of clinically significant electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for patients who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 mcg or ADVAIR DISKUS) compared with placebo (3%, 10 of 370 patients).

No significant differences with salmeterol 50 mcg alone or in combination with fluticasone propionate as ADVAIR DISKUS 500/50 were observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (N = 183) and after 12 weeks of therapy (N = 149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo.

HPA Axis Effects: Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 patients with COPD receiving twice-daily ADVAIR DISKUS 250/50, fluticasone propionate powder 250 mcg, salmeterol powder 50 mcg, or placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with ADVAIR DISKUS 250/50. One (1) patient (3%) who received ADVAIR DISKUS 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by high-performance liquid chromatography) after dosing, compared with 2 patients (9%) who received fluticasone propionate 250 mcg, 2 patients (7%) who received salmeterol 50 mcg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early discontinuation from study.

After 36 weeks of dosing, serum cortisol concentrations in a subset of patients with COPD (n = 83) were 22% lower in patients receiving ADVAIR DISKUS 500/50 and 21% lower in patients receiving fluticasone propionate 500 mcg than in patients receiving placebo.

Other Fluticasone Propionate Products: *Asthma: HPA Axis Effects:* In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL assessed by radioimmunoassay) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out with the DISKHALER® inhalation device in

64 patients with mild, persistent asthma (mean FEV_1 91% of predicted) randomized to fluticasone propionate 500 mcg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 mcg/dL). With a peak cortisol threshold of <35 mcg/dL, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Chronic Obstructive Pulmonary Disease: HPA Axis Effects: After 4 weeks of dosing, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of patients with COPD (n = 86) randomized to twice-daily fluticasone propionate inhalation powder via the DISKUS 500 mcg, fluticasone propionate inhalation powder 250 mcg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval. Serum cortisol concentrations following 250- and 500-mcg twice-daily dosing were 10% and 21% lower than placebo, respectively, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

Other Salmeterol Xinafoate Products: *Asthma: Cardiovascular Effects:* Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium *[see Warnings and Precautions (5.12, 5.18)]*. The cardiovascular effects (heart rate, blood pressure) associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 mcg administered as inhalation aerosol resulted in heart rate increases of 3 to 16 beats/min, about the same as albuterol dosed at 180 mcg by inhalation aerosol (4 to 10 beats/min). Adolescent and adult patients receiving 50-mcg doses of salmeterol inhalation powder (N = 60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted.

Concomitant Use of ADVAIR DISKUS With Other Respiratory Medications: *Short-Acting $Beta_2$-Agonists:* In clinical trials with patients with asthma, the mean daily need for albuterol by 166 adult and adolescent patients aged 12 years and older using ADVAIR DISKUS was approximately 1.3 inhalations/day, and ranged from 0 to 9 inhalations/day. Five percent (5%) of patients using ADVAIR DISKUS in these trials averaged 6 or more inhalations per day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations per day.

In a COPD clinical trial, the mean daily need for albuterol for patients using ADVAIR DISKUS 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using ADVAIR DISKUS 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations of albuterol per day.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by adult and adolescent patients aged 12 years and older receiving ADVAIR DISKUS has not been completely evaluated. In clinical trials with patients with asthma, 39 patients receiving ADVAIR DISKUS 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 patients receiving ADVAIR DISKUS without theophylline. Similar results were observed in patients receiving salmeterol 50 mcg plus fluticasone propionate 500 mcg twice daily concurrently with a theophylline product (n = 39) or without theophylline (n = 132).

In a COPD clinical trial, 17 patients receiving ADVAIR DISKUS 250/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 161 patients receiving ADVAIR DISKUS without theophylline. Based on the available data, the concomitant administration of methylxanthines with ADVAIR DISKUS did not alter the observed adverse event profile.

Fluticasone Propionate Nasal Spray: In adult and adolescent patients aged 12 years and older taking ADVAIR DISKUS in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients who were taking FLONASE® (fluticasone propionate) Nasal Spray, 50 mcg concurrently (n = 46) and those who were not (n = 130).

12.3 Pharmacokinetics

Absorption: *Fluticasone Propionate: Healthy Subjects:* Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed.

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of fluticasone propionate were achieved in 1 to 2 hours. In a single-dose crossover study, a higher-than-recommended dose of ADVAIR DISKUS was administered to 14 healthy adult subjects. Two (2) inhalations of the following treatments were administered: ADVAIR DISKUS 500/50, fluticasone propionate powder 500 mcg and salmeterol powder 50 mcg given concurrently, and fluticasone propionate powder 500 mcg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/mL, respectively, indicating no significant changes in systemic exposures of fluticasone propionate.

In 15 healthy subjects, systemic exposure to fluticasone propionate from 4 inhalations of ADVAIR® HFA 230/21 (fluticasone propionate 230 mcg and salmeterol 21 mcg) Inhalation Aerosol (920/84 mcg) and 2 inhalations of ADVAIR DISKUS 500/50 (1,000/100 mcg) were similar between the 2 inhalers (i.e., 799 vs. 832 pg•hr/mL, respectively), but approximately half the systemic exposure from 4 inhalations of fluticasone propionate CFC inhalation aerosol 220 mcg (880 mcg, AUC = 1,543 pg•hr/mL). Similar results were observed for peak fluticasone propionate plasma concentrations (186 and 182 pg/mL from ADVAIR HFA and ADVAIR

DISKUS, respectively, and 307 pg/mL from the fluticasone propionate CFC inhalation aerosol). Absolute bioavailability of fluticasone propionate was 5.3% and 5.5% following administration of ADVAIR HFA and ADVAIR DISKUS, respectively.

Asthma and COPD Patients: Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (N = 11) ranged from undetectable to 266 pg/mL after a 500-mcg twice-daily dose of fluticasone propionate inhalation powder using the DISKUS device. The mean fluticasone propionate plasma concentration was 110 pg/mL.

Full pharmacokinetic profiles were obtained from 9 female and 16 male patients with asthma given fluticasone propionate inhalation powder 500 mcg twice daily using the DISKUS device and from 14 female and 43 male patients with COPD given 250 or 500 mcg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Peak steady-state fluticasone propionate plasma concentrations in patients with COPD averaged 53 pg/mL (range, 19.3 to 159.3 pg/mL) after treatment with 250 mcg twice daily (N = 30) and 84 pg/mL (range, 24.3 to 197.1 pg/mL) after treatment with 500 mcg twice daily (N = 27) via the fluticasone propionate DISKUS device. In another study in patients with COPD, peak steady-state fluticasone propionate plasma concentrations averaged 115 pg/mL (range, 52.6 to 366.0 pg/mL) after treatment with 500 mcg twice daily via the fluticasone propionate DISKUS device (N = 15) and 105 pg/mL (range, 22.5 to 299.0 pg/mL) via ADVAIR DISKUS (N = 24).

Salmeterol Xinafoate: Healthy Subjects: Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Following administration of ADVAIR DISKUS to healthy adult subjects, peak plasma concentrations of salmeterol were achieved in about 5 minutes.

In 15 healthy subjects receiving ADVAIR HFA 230/21 Inhalation Aerosol (920/84 mcg) and ADVAIR DISKUS 500/50 (1,000/100 mcg), systemic exposure to salmeterol was higher (317 vs. 169 pg•hr/mL) and peak salmeterol concentrations were lower (196 vs. 223 pg/mL) following ADVAIR HFA compared with ADVAIR DISKUS, although pharmacodynamic results were comparable.

Asthma Patients: Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 mcg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 mcg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5 to 45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes and no accumulation with repeated doses.

Distribution: *Fluticasone Propionate:* Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Salmeterol: The percentage of salmeterol bound to human plasma proteins averages 96% in vitro over the concentration range of 8 to 7,722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism: *Fluticasone Propionate:* The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP 3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Salmeterol: Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

An in vitro study using human liver microsomes showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by CYP 3A4. Ketoconazole, a strong inhibitor of CYP 3A4, essentially completely inhibited the formation of α-hydroxysalmeterol in vitro.

Elimination: *Fluticasone Propionate:* Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites. Terminal half-life estimates of fluticasone propionate for ADVAIR HFA, ADVAIR DISKUS, and fluticasone propionate CFC inhalation aerosol were similar and averaged 5.6 hours.

Salmeterol: In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days. No terminal half-life estimates were calculated for salmeterol following administration of ADVAIR DISKUS.

Special Populations: A population pharmacokinetic analysis was performed for fluticasone propionate and salmeterol utilizing data from 9 controlled clinical trials that included 350 patients with asthma aged 4 to 77 years who received treatment with ADVAIR DISKUS, the combination of HFA-propelled fluticasone propionate and salmeterol inhalation aerosol (ADVAIR HFA), fluticasone propionate inhalation powder (FLOVENT DISKUS), HFA-propelled fluticasone propionate inhalation aerosol (FLOVENT® HFA), or CFC-propelled fluticasone propionate inhalation aerosol. The population pharmacokinetic analyses for

fluticasone propionate and salmeterol showed no clinically relevant effects of age, gender, race, body weight, body mass index, or percent of predicted FEV_1 on apparent clearance and apparent volume of distribution.

Age: When the population pharmacokinetic analysis for fluticasone propionate was divided into subgroups based on fluticasone propionate strength, formulation, and age (adolescents/adults and children), there were some differences in fluticasone propionate exposure. Higher fluticasone propionate exposure from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg was observed in adolescents and adults (ratio 1.52 [90% CI: 1.08, 2.13]). However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in adolescents and adults, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed. Similar fluticasone propionate exposure was observed from ADVAIR DISKUS 500/50 and FLOVENT DISKUS 500 mcg (ratio 0.83 [90% CI: 0.65, 1.07]) in adolescents and adults.

Steady-state systemic exposure to salmeterol when delivered as ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, or ADVAIR HFA 115/21 (fluticasone propionate 115 mcg and salmeterol 21 mcg) Inhalation Aerosol was evaluated in 127 patients aged 4 to 57 years. The geometric mean AUC was 325 pg•hr/mL [90% CI: 309, 341] in adolescents and adults.

The population pharmacokinetic analysis included 160 patients with asthma aged 4 to 11 years who received ADVAIR DISKUS 100/50 or FLOVENT DISKUS 100 mcg. Higher fluticasone propionate exposure (AUC) was observed in children from ADVAIR DISKUS 100/50 compared with FLOVENT DISKUS 100 mcg (ratio 1.20 [90% CI: 1.06, 1.37]). Higher fluticasone propionate exposure (AUC) from ADVAIR DISKUS 100/50 was observed in children compared with adolescents and adults (ratio 1.63 [90% CI: 1.35, 1.96]). However, in clinical studies of up to 12 weeks' duration comparing ADVAIR DISKUS 100/50 and FLOVENT DISKUS 100 mcg in both adolescents and adults and in children, no differences in systemic effects of corticosteroid treatment (e.g., HPA axis effects) were observed.

Exposure to salmeterol was higher in children compared with adolescents and adults who received ADVAIR DISKUS 100/50 (ratio 1.23 [90% CI: 1.10, 1.38]). However, in clinical studies of up to 12 weeks' duration with ADVAIR DISKUS 100/50 in both adolescents and adults and in children, no differences in systemic effects of $beta_2$-agonist treatment (e.g., cardiovascular effects, tremor) were observed.

Gender: The population pharmacokinetic analysis involved 202 males and 148 females with asthma who received fluticasone propionate alone or in combination with salmeterol and showed no gender differences for fluticasone propionate pharmacokinetics.

The population pharmacokinetic analysis involved 76 males and 51 females with asthma who received salmeterol in combination with fluticasone propionate and showed no gender differences for salmeterol pharmacokinetics.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using ADVAIR DISKUS have not been conducted in patients with hepatic or renal impairment. However, since both fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism,

impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Drug Interactions: In the repeat- and single-dose studies, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given as ADVAIR DISKUS. The population pharmacokinetic analysis from 9 controlled clinical trials in 350 patients with asthma showed no significant effects on fluticasone propionate or salmeterol pharmacokinetics following co-administration with beta$_2$-agonists, corticosteroids, antihistamines, or theophyllines.

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone Propionate: Fluticasone propionate is a substrate of CYP 3A4. Coadministration of fluticasone propionate and the strong CYP 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Fluticasone Propionate: In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Salmeterol: In a placebo-controlled, crossover drug interaction study in 20 healthy male and female subjects, coadministration of salmeterol (50 mcg twice daily) and the strong CYP 3A4 inhibitor ketoconazole (400 mg once daily) for 7 days resulted in a significant increase in plasma salmeterol exposure as determined by a 16-fold increase in AUC (ratio with and without ketoconazole 15.76 [90% CI: 10.66, 23.31]) mainly due to increased bioavailability of the swallowed portion of the dose. Peak plasma salmeterol concentrations were increased by 1.4-fold [90% CI: 1.23, 1.68]. Three (3) out of 20 subjects (15%) were withdrawn from salmeterol and ketoconazole coadministration due to beta-agonist–mediated systemic effects (2 with QTc prolongation and 1 with palpitations and sinus tachycardia). Coadministration of salmeterol and ketoconazole did not result in a clinically significant effect on mean heart rate, mean blood potassium, or mean blood glucose. Although there was no statistical effect on the mean QTc, coadministration of salmeterol and ketoconazole was associated with more frequent increases in QTc duration compared with salmeterol and placebo administration.

Erythromycin: Fluticasone Propionate: In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol: In a repeat-dose study in 13 healthy subjects, concomitant administration of erythromycin (a moderate CYP 3A4 inhibitor) and salmeterol inhalation aerosol resulted in a 40% increase in salmeterol C_{max} at steady state (ratio with and without erythromycin 1.4 [90% CI: 0.96, 2.03], p = 0.12), a 3.6-beat/min increase in heart rate ([95% CI: 0.19, 7.03], p<0.04), a 5.8-msec increase in QTc interval ([95% CI: -6.14, 17.77], p = 0.34), and no change in plasma potassium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone Propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 4 and 10 times the MRHD for adults and children, respectively, on a mg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (less than and approximately equivalent to the MRHD for adults and children, respectively, on a mg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats at subcutaneous doses up to 50 mcg/kg (less than the MRHD on a mg/m^2 basis). Prostate weight was significantly reduced.

Salmeterol: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the MRHD for adults and children based on comparison of the plasma AUCs) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. No tumors were seen at 0.2 mg/kg (approximately 3 times the MRHD for adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times the MRHD for adults and children, respectively, on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times the MRHD for adults and children, respectively, on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test. No effects on fertility were identified in rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the MRHD for adults on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

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

Reproductive Toxicology Studies: *ADVAIR DISKUS:* In mice, combining 150 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m^2 basis) with 10 mg/kg orally of salmeterol (approximately 410 times the MRHD on a mg/m^2 basis) produced cleft palate, fetal death, increased implantation loss, and delayed ossification. No such effects were observed at combination subcutaneous doses up to 40 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m^2 basis) and up to 1.4 mg/kg orally doses of salmeterol (approximately 55 times the MRHD on a mg/m^2 basis).

In rats, combining 100 mcg/kg subcutaneously of fluticasone propionate (equivalent to the MRHD on a mg/m^2 basis) and 10 mg/kg orally of salmeterol (approximately 810 times the MRHD on a mg/m^2 basis) produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were observed at combination doses up to 30 mcg/kg subcutaneously of fluticasone propionate (less than the MRHD on a mg/m^2 basis) and up to 1 mg/kg orally of salmeterol (approximately 80 times the MRHD on a mg/m^2 basis).

Fluticasone Propionate: Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg (less than and equivalent to the MRHD on a mg/m^2 basis), respectively, revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the MRHD on a mg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 5 times the MRHD on a mg/m^2 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration *[see Clinical Pharmacology (12.3)]*.

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

Salmeterol: No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the MRHD on a mg/m^2 basis).

In Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times and above the MRHD based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the MRHD based on comparison of the AUCs). New Zealand White rabbits were less

sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1,600 times the MRHD on a mg/m^2 basis).

Salmeterol crossed the placenta following oral administration to mice and rats.

14 CLINICAL STUDIES

14.1 Asthma

Adult and Adolescent Patients Aged 12 Years and Older: In clinical trials comparing ADVAIR DISKUS with its individual components, improvements in most efficacy endpoints were greater with ADVAIR DISKUS than with the use of either fluticasone propionate or salmeterol alone. In addition, clinical trials showed similar results between ADVAIR DISKUS and the concurrent use of fluticasone propionate plus salmeterol at corresponding doses from separate inhalers.

Studies Comparing ADVAIR DISKUS to Fluticasone Propionate Alone or Salmeterol Alone: Three (3) double-blind, parallel-group clinical trials were conducted with ADVAIR DISKUS in 1,208 adolescent and adult patients (≥12 years, baseline FEV_1 63% to 72% of predicted normal) with asthma that was not optimally controlled on their current therapy. All treatments were inhalation powders given as 1 inhalation from the DISKUS device twice daily, and other maintenance therapies were discontinued.

Study 1: Clinical Trial With ADVAIR DISKUS 100/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 100/50 with its individual components, fluticasone propionate 100 mcg and salmeterol 50 mcg. The study was stratified according to baseline asthma maintenance therapy; patients were using either inhaled corticosteroids (N = 250) (daily doses of beclomethasone dipropionate 252 to 420 mcg; flunisolide 1,000 mcg; fluticasone propionate inhalation aerosol 176 mcg; or triamcinolone acetonide 600 to 1,000 mcg) or salmeterol (N = 106). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 100/50, 2.17 L; fluticasone propionate 100 mcg, 2.11 L; salmeterol, 2.13 L; and placebo, 2.15 L.

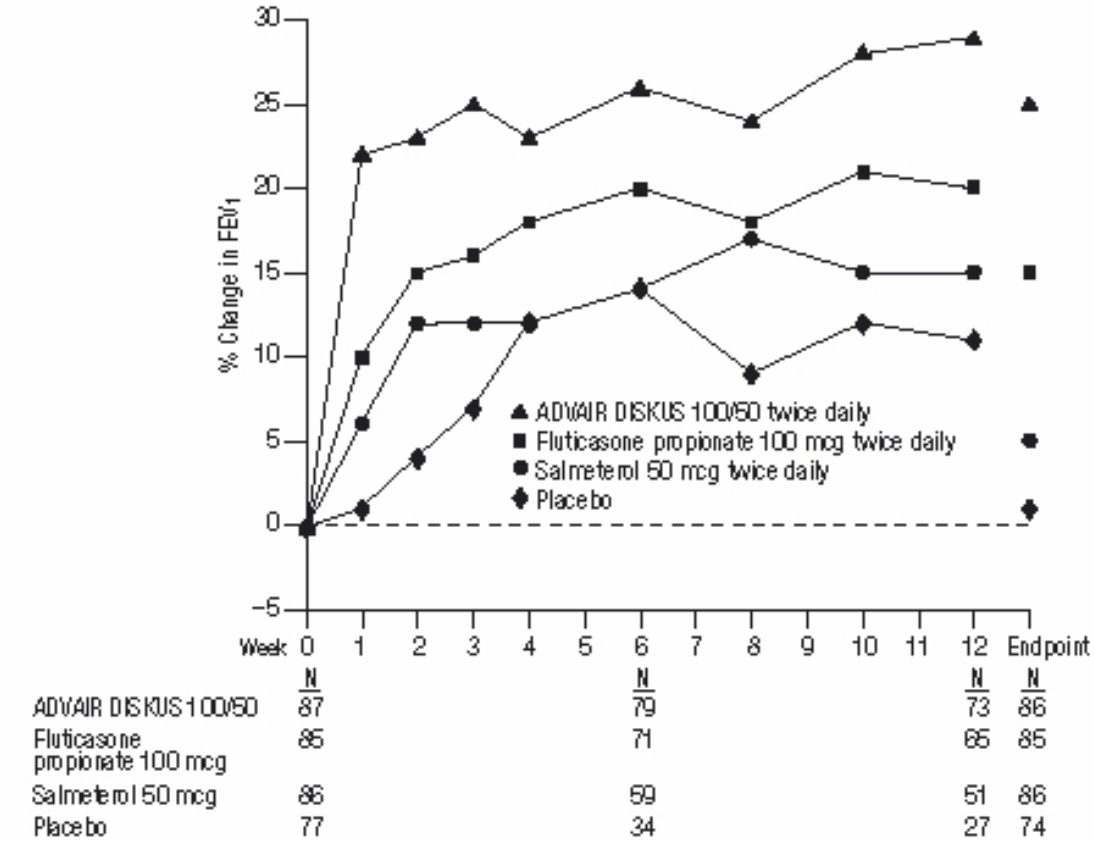
Predefined withdrawal criteria for lack of efficacy, an indicator of worsening asthma, were utilized for this placebo-controlled study. Worsening asthma was defined as a clinically important decrease in FEV_1 or PEF, increase in use of VENTOLIN® (albuterol, USP) Inhalation Aerosol, increase in night awakenings due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. As shown in Table 4, statistically significantly fewer patients receiving ADVAIR DISKUS 100/50 were withdrawn due to worsening asthma compared with fluticasone propionate, salmeterol, and placebo.

Table 4. Percent of Patients Withdrawn Due to Worsening Asthma in Patients Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
3%	11%	35%	49%

The FEV_1 results are displayed in Figure 2. Because this trial used predetermined criteria for worsening asthma, which caused more patients in the placebo group to be withdrawn, FEV_1 results at Endpoint (last available FEV_1 result) are also provided. Patients receiving ADVAIR DISKUS 100/50 had significantly greater improvements in FEV_1 (0.51 L, 25%) compared with fluticasone propionate 100 mcg (0.28 L, 15%), salmeterol (0.11 L, 5%), and placebo (0.01 L, 1%). These improvements in FEV_1 with ADVAIR DISKUS were achieved regardless of baseline asthma maintenance therapy (inhaled corticosteroids or salmeterol).

Figure 2. Mean Percent Change From Baseline in FEV_1 in Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)



The effect of ADVAIR DISKUS 100/50 on morning and evening PEF endpoints is shown in Table 5.

Table 5. Peak Expiratory Flow Results for Patients With Asthma Previously Treated With Either Inhaled Corticosteroids or Salmeterol (Study 1)

Efficacy Variable[a]	ADVAIR DISKUS 100/50 (N = 87)	Fluticasone Propionate 100 mcg (N = 85)	Salmeterol 50 mcg (N = 86)	Placebo (N = 77)
AM PEF (L/min)				
Baseline	393	374	369	382
Change from baseline	53	17	-2	-24
PM PEF (L/min)				
Baseline	418	390	396	398
Change from baseline	35	18	-7	-13

[a]Change from baseline = change from baseline at Endpoint (last available data).

The subjective impact of asthma on patients' perception of health was evaluated through use of an instrument called the Asthma Quality of Life Questionnaire (AQLQ) (based on a 7-point scale where 1 = maximum impairment and 7 = none). Patients receiving ADVAIR DISKUS 100/50 had clinically meaningful improvements in overall asthma-specific quality of life as defined by a difference between groups of ≥0.5 points in change from baseline AQLQ scores (difference in AQLQ score of 1.25 compared with placebo).

Study 2: Clinical Trial With ADVAIR DISKUS 250/50: This placebo-controlled, 12-week, US study compared ADVAIR DISKUS 250/50 with its individual components, fluticasone propionate 250 mcg and salmeterol 50 mcg, in 349 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 462 to 672 mcg; flunisolide 1,250 to 2,000 mcg; fluticasone propionate inhalation aerosol 440 mcg; or triamcinolone acetonide 1,100 to 1,600 mcg). Baseline FEV_1 measurements were similar across treatments: ADVAIR DISKUS 250/50, 2.23 L; fluticasone propionate 250 mcg, 2.12 L; salmeterol, 2.20 L; and placebo, 2.19 L.

Efficacy results in this study were similar to those observed in Study 1. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in FEV_1 (0.48 L, 23%) compared with fluticasone propionate 250 mcg (0.25 L, 13%), salmeterol (0.05 L, 4%), and placebo (decrease of 0.11 L, decrease of 5%). Statistically significantly fewer patients receiving ADVAIR DISKUS 250/50 were withdrawn from this study for worsening asthma (4%) compared with fluticasone propionate (22%), salmeterol (38%), and placebo (62%). In addition, ADVAIR DISKUS 250/50 was superior to fluticasone propionate, salmeterol, and placebo for improvements in morning and evening PEF. Patients receiving ADVAIR DISKUS 250/50 also

had clinically meaningful improvements in overall asthma-specific quality of life as described in Study 1 (difference in AQLQ score of 1.29 compared with placebo).

Study 3: Clinical Trial With ADVAIR DISKUS 500/50: This 28-week, non-US study compared ADVAIR DISKUS 500/50 with fluticasone propionate 500 mcg alone and concurrent therapy (salmeterol 50 mcg plus fluticasone propionate 500 mcg administered from separate inhalers) twice daily in 503 patients with asthma using inhaled corticosteroids (daily doses of beclomethasone dipropionate 1,260 to 1,680 mcg; budesonide 1,500 to 2,000 mcg; flunisolide 1,500 to 2,000 mcg; or fluticasone propionate inhalation aerosol 660 to 880 mcg [750 to 1,000 mcg inhalation powder]). The primary efficacy parameter, morning PEF, was collected daily for the first 12 weeks of the study. The primary purpose of weeks 13 to 28 was to collect safety data.

Baseline PEF measurements were similar across treatments: ADVAIR DISKUS 500/50, 359 L/min; fluticasone propionate 500 mcg, 351 L/min; and concurrent therapy, 345 L/min. Morning PEF improved significantly with ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg over the 12-week treatment period. Improvements in morning PEF observed with ADVAIR DISKUS 500/50 were similar to improvements observed with concurrent therapy.

Onset of Action and Progression of Improvement in Asthma Control: The onset of action and progression of improvement in asthma control were evaluated in the 2 placebo-controlled US trials. Following the first dose, the median time to onset of clinically significant bronchodilatation (≥15% improvement in FEV_1) in most patients was seen within 30 to 60 minutes. Maximum improvement in FEV_1 generally occurred within 3 hours, and clinically significant improvement was maintained for 12 hours (see Figure 3). Following the initial dose, predose FEV_1 relative to Day 1 baseline improved markedly over the first week of treatment and continued to improve over the 12 weeks of treatment in both studies. No diminution in the 12-hour bronchodilator effect was observed with either ADVAIR DISKUS 100/50 (Figures 3 and 4) or ADVAIR DISKUS 250/50 as assessed by FEV_1 following 12 weeks of therapy.

Figure 3. Percent Change in Serial 12-hour FEV_1 in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

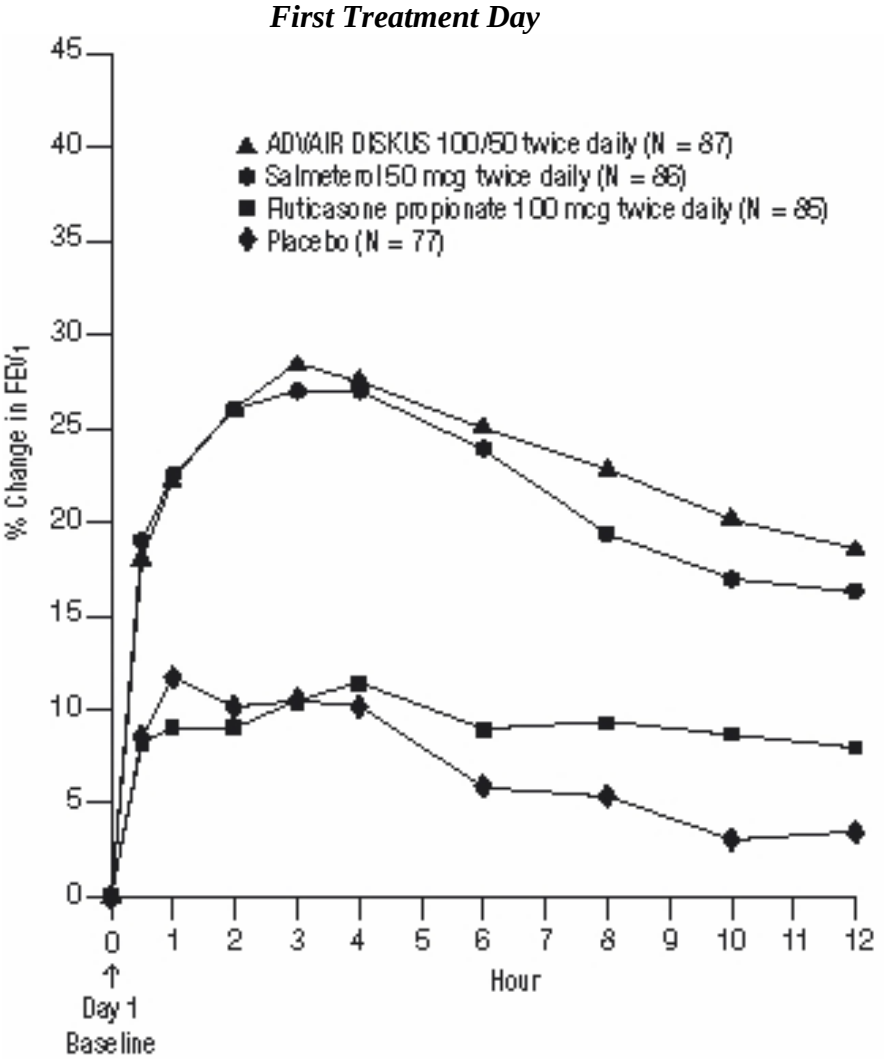
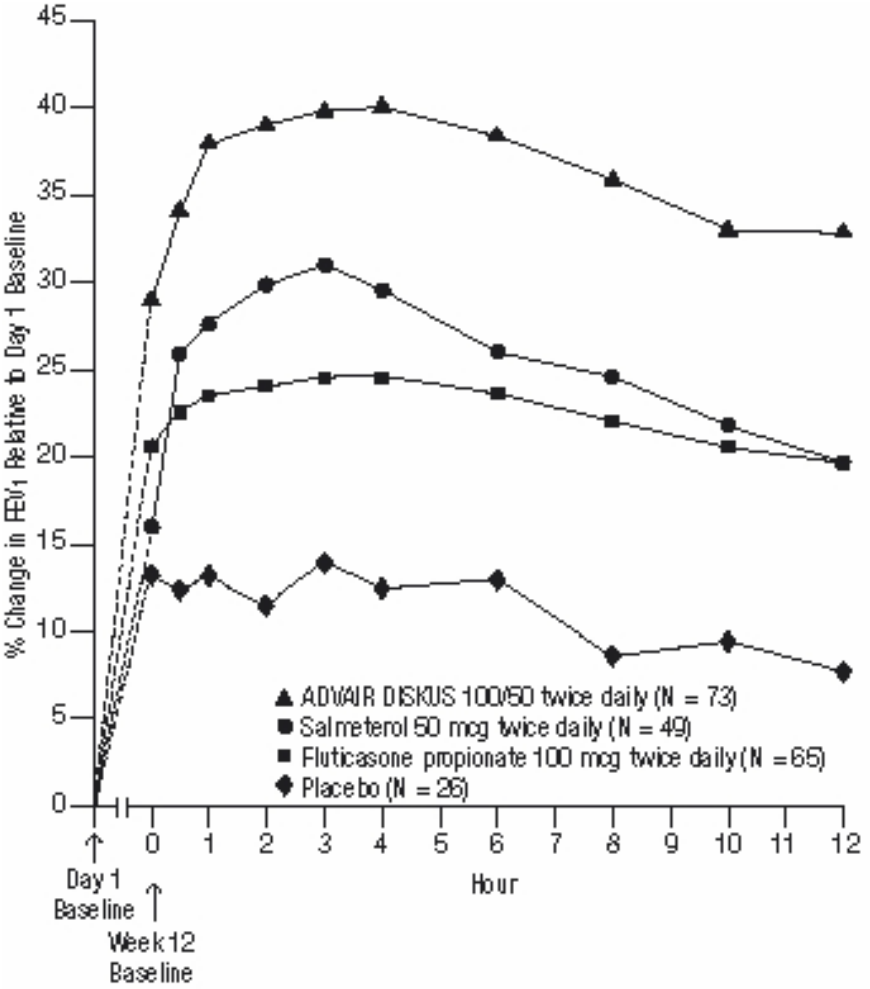


Figure 4. Percent Change in Serial 12-hour FEV_1 in Patients With Asthma Previously Using Either Inhaled Corticosteroids or Salmeterol (Study 1)

Last Treatment Day (Week 12)



Reduction in asthma symptoms, use of rescue VENTOLIN Inhalation Aerosol, and improvement in morning and evening PEF also occurred within the first day of treatment with ADVAIR DISKUS, and continued to improve over the 12 weeks of therapy in both studies.

Pediatric Patients: In a 12-week US study, ADVAIR DISKUS 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 mcg twice daily in 203 children with asthma aged 4 to 11 years. At study entry, the children were symptomatic on low doses of inhaled corticosteroids (beclomethasone dipropionate 252 to 336 mcg/day; budesonide 200 to 400 mcg/day; flunisolide 1,000 mcg/day; triamcinolone acetonide 600 to 1,000 mcg/day; or fluticasone propionate 88 to 250 mcg/day). The primary objective of this study was to determine the safety of ADVAIR DISKUS 100/50 compared with fluticasone propionate inhalation powder

100 mcg in this age-group; however, the study also included secondary efficacy measures of pulmonary function. Morning predose FEV_1 was obtained at baseline and Endpoint (last available FEV_1 result) in children aged 6 to 11 years. In patients receiving ADVAIR DISKUS 100/50, FEV_1 increased from 1.70 L at baseline (N = 79) to 1.88 L at Endpoint (N = 69) compared with an increase from 1.65 L at baseline (N = 83) to 1.77 L at Endpoint (N = 75) in patients receiving fluticasone propionate 100 mcg.

The findings of this study, along with extrapolation of efficacy data from patients aged 12 years and older, support the overall conclusion that ADVAIR DISKUS 100/50 is efficacious in the maintenance treatment of asthma in patients aged 4 to 11 years.

14.2 Chronic Obstructive Pulmonary Disease

The efficacy of ADVAIR DISKUS 250/50 and ADVAIR DISKUS 500/50 in the treatment of patients with COPD was evaluated in 6 randomized, double-blind, parallel-group clinical trials in adult patients aged 40 years and older. These trials were primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function (3 trials), exacerbations (2 trials), and survival (1 trial).

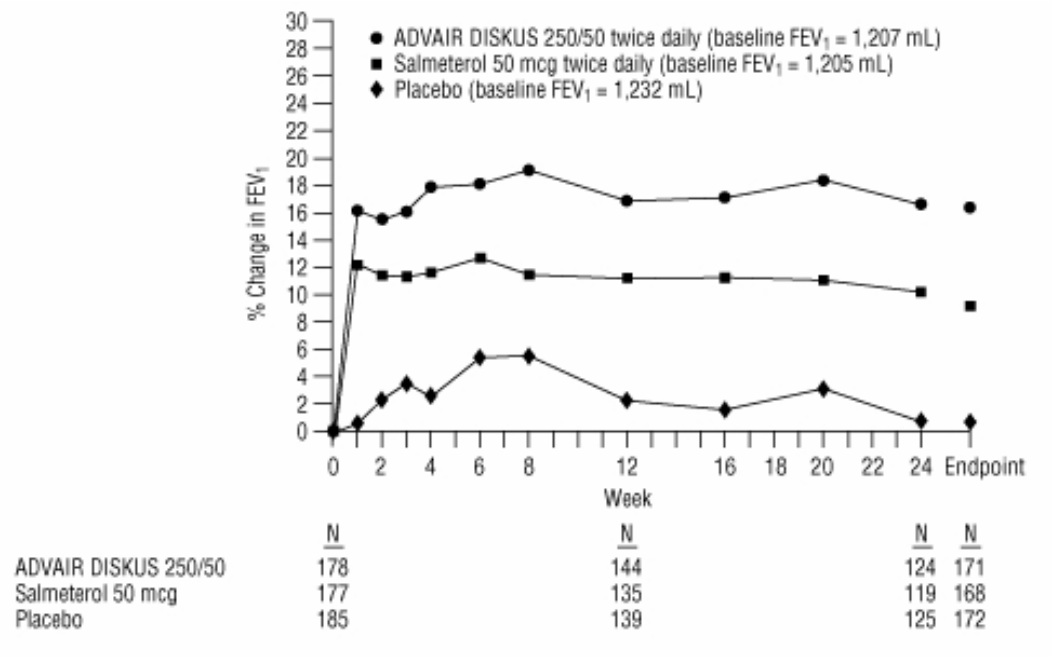
Lung Function: Two of the 3 clinical trials primarily designed to evaluate the efficacy of ADVAIR DISKUS on lung function were conducted in 1,414 patients with COPD associated with chronic bronchitis. In these 2 trials, all the patients had a history of cough productive of sputum that was not attributable to another disease process on most days for at least 3 months of the year for at least 2 years. The trials were randomized, double-blind, parallel-group, 24-week treatment duration. One trial evaluated the efficacy of ADVAIR DISKUS 250/50 compared with its components fluticasone propionate 250 mcg and salmeterol 50 mcg and with placebo, and the other trial evaluated the efficacy of ADVAIR DISKUS 500/50 compared with its components fluticasone propionate 500 mcg and salmeterol 50 mcg and with placebo. Study treatments were inhalation powders given as 1 inhalation from the DISKUS device twice daily. Maintenance COPD therapies were discontinued, with the exception of theophylline. The patients had a mean pre-bronchodilator FEV_1 of 41% and 20% reversibility at study entry. Percent reversibility was calculated as 100 times (FEV_1 post-albuterol minus FEV_1 pre-albuterol)/FEV_1 pre-albuterol.

Improvements in lung function (as defined by predose and postdose FEV_1) were significantly greater with ADVAIR DISKUS than with fluticasone propionate, salmeterol, or placebo. The improvement in lung function with ADVAIR DISKUS 500/50 was similar to the improvement seen with ADVAIR DISKUS 250/50.

Figures 5 and 6 display predose and 2-hour postdose, respectively, FEV_1 results for the study with ADVAIR DISKUS 250/50. To account for patient withdrawals during the study, FEV_1 at Endpoint (last evaluable FEV_1) was evaluated. Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in predose FEV_1 at Endpoint (165 mL, 17%) compared with salmeterol 50 mcg (91 mL, 9%) and placebo (1 mL, 1%), demonstrating the contribution of fluticasone propionate to the improvement in lung function with ADVAIR DISKUS (Figure 5). Patients receiving ADVAIR DISKUS 250/50 had significantly greater improvements in postdose FEV_1 at Endpoint (281 mL, 27%) compared with fluticasone

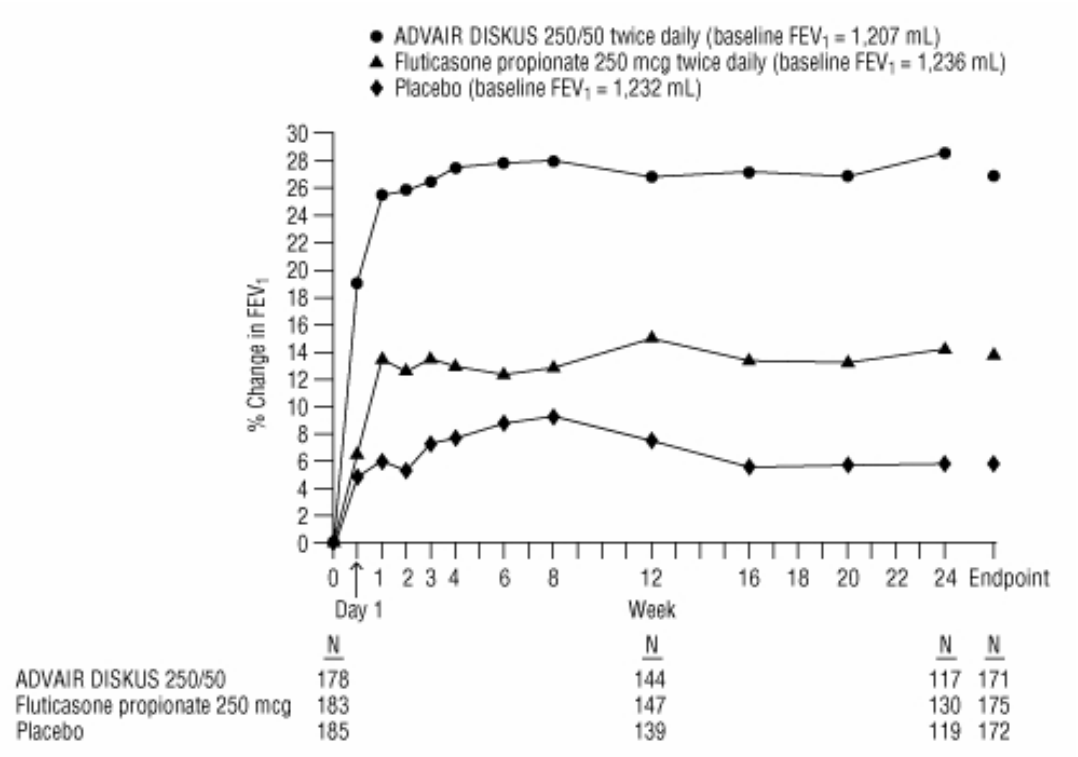
propionate 250 mcg (147 mL, 14%) and placebo (58 mL, 6%), demonstrating the contribution of salmeterol to the improvement in lung function with ADVAIR DISKUS (Figure 6).

Figure 5. Predose FEV_1: Mean Percent Change From Baseline in Patients With Chronic Obstructive Pulmonary Disease



	N		N		N	N
ADVAIR DISKUS 250/50	178		144		124	171
Salmeterol 50 mcg	177		135		119	168
Placebo	185		139		125	172

Figure 6. Two-Hour Postdose FEV_1: Mean Percent Changes From Baseline Over Time in Patients With Chronic Obstructive Pulmonary Disease



The third trial was a 1-year study that evaluated ADVAIR DISKUS 500/50, fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo in 1,465 patients. The patients had an established history of COPD and exacerbations, a pre-bronchodilator FEV_1 <70% of predicted at study entry, and 8.3% reversibility. The primary endpoint was the comparison of pre-bronchodilator FEV_1 in the groups receiving ADVAIR DISKUS 500/50 or placebo. Patients treated with ADVAIR DISKUS 500/50 had greater improvements in FEV_1 (113 mL, 10%) compared with fluticasone propionate 500 mcg (7 mL, 2%), salmeterol (15 mL, 2%), and placebo (-60 mL, -3%).

Exacerbations: Two studies were primarily designed to evaluate the effect of ADVAIR DISKUS 250/50 on exacerbations. In these 2 studies, exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotics was required and were considered severe if hospitalization was required.

Exacerbations were also evaluated as a secondary outcome in the 1- and 3-year trials with ADVAIR DISKUS 500/50. There was not a symptomatic definition of exacerbation in these 2

trials. Exacerbations were defined in terms of severity requiring treatment with antibiotics and/or systemic corticosteroids (moderately severe) or requiring hospitalization (severe).

The 2 exacerbation trials with ADVAIR DISKUS 250/50 were identical studies designed to evaluate the effect of ADVAIR DISKUS 250/50 and salmeterol 50 mcg, each given twice daily, on exacerbations of COPD over a 12-month period. A total of 1,579 patients had an established history of COPD (but no other significant respiratory disorders). Patients had a pre-bronchodilator FEV_1 of 33% of predicted, a mean reversibility of 23% at baseline, and a history of ≥1 COPD exacerbation in the previous year that was moderate or severe. All patients were treated with ADVAIR DISKUS 250/50 twice daily during a 4-week run-in period prior to being assigned study treatment with twice-daily ADVAIR DISKUS 250/50 or salmeterol 50 mcg. In both studies, treatment with ADVAIR DISKUS 250/50 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (30.5% reduction [95% CI: 17.0, 41.8], $p<0.001$) in the first study and (30.4% reduction [95% CI: 16.9, 41.7], $p<0.001$) in the second study. Patients treated with ADVAIR DISKUS 250/50 also had a significantly lower annual rate of exacerbations requiring treatment with oral corticosteroids compared with patients treated with salmeterol (39.7% reduction [95% CI: 22.8, 52.9], $p <0.001$) in the first study, and (34.3% reduction [95% CI: 18.6, 47.0], $p<0.001$) in the second study. Secondary endpoints including pulmonary function and symptom scores improved more in patients treated with ADVAIR DISKUS 250/50 than with salmeterol 50 mcg in both studies.

Exacerbations were evaluated in the 1- and the 3-year trials with ADVAIR DISKUS 500/50 as 1 of the secondary efficacy endpoints. In the 1-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with placebo (25.4% reduction compared with placebo [95% CI: 13.5, 35.7]) but not when compared with its components (7.5% reduction compared with fluticasone propionate [95% CI: -7.3, 20.3] and 7% reduction compared with salmeterol [95% CI: -8.0, 19.9]). In the 3-year trial, the group receiving ADVAIR DISKUS 500/50 had a significantly lower rate of moderate and severe exacerbations compared with each of the other treatment groups (25.1% reduction compared with placebo [95% CI: 18.6, 31.1], 9.0% reduction compared with fluticasone propionate [95% CI: 1.2, 16.2], and 12.2% reduction compared with salmeterol [95% CI: 4.6, 19.2]).

There were no studies conducted to directly compare the efficacy of ADVAIR DISKUS 250/50 with ADVAIR DISKUS 500/50 on exacerbations. Across studies, the reduction in exacerbations seen with ADVAIR DISKUS 500/50 was not greater than the reduction in exacerbations seen with ADVAIR DISKUS 250/50.

Survival: A 3-year multicenter, international study evaluated the efficacy of ADVAIR DISKUS 500/50 compared with fluticasone propionate 500 mcg, salmeterol 50 mcg, and placebo on survival in 6,112 patients with COPD. During the study patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids and long-acting bronchodilators. The patients were aged 40 to 80 years with an established history of COPD, a pre-bronchodilator FEV_1 <60% of predicted at study entry, and <10% of predicted reversibility. Each patient who

withdrew from double-blind treatment for any reason was followed for the full 3-year study period to determine survival status. The primary efficacy endpoint was all-cause mortality. Survival with ADVAIR DISKUS 500/50 was not significantly improved compared with placebo, or the individual components (all-cause mortality rate 12.6% ADVAIR DISKUS vs. 15.2% placebo). The rates for all-cause mortality were 13.5% and 16.0% in the groups treated with salmeterol 50 mcg and fluticasone propionate 500 mcg, respectively. Secondary outcomes, including pulmonary function (post-bronchodilator FEV_1), improved with ADVAIR DISKUS 500/50, salmeterol, and fluticasone propionate 500/50 compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

ADVAIR DISKUS 100/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-00). ADVAIR DISKUS 100/50 is also supplied in an institutional pack of 1 disposable purple device containing 14 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0695-04).

ADVAIR DISKUS 250/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-00). ADVAIR DISKUS 250/50 is also supplied in an institutional pack of 1 disposable purple device containing 14 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0696-04).

ADVAIR DISKUS 500/50 is supplied as a disposable purple device containing 60 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-00). ADVAIR DISKUS 500/50 is also supplied in an institutional pack of 1 disposable purple device containing 14 blisters. The DISKUS inhalation device is packaged within a purple, plastic-coated, moisture-protective foil pouch (NDC 0173-0697-04).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F), in a dry place away from direct heat or sunlight. Keep out of reach of children. The DISKUS inhalation device is not reusable. The device should be discarded 1 month after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads “0”), whichever comes first. Do not attempt to take the device apart.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.6).

17.1 Asthma-Related Death

Patients with asthma should be informed that salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. They should also be informed that data are not adequate to determine whether the concurrent use of

inhaled corticosteroids, such as fluticasone propionate, the other component of ADVAIR DISKUS, or other asthma-controller therapy modifies this risk.

17.2 Not for Acute Symptoms

ADVAIR DISKUS is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol. (The physician should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
- Significant decrease in lung function as outlined by the physician

Patients should not stop therapy with ADVAIR DISKUS without physician/provider guidance since symptoms may recur after discontinuation.

17.3 Do Not Use Additional Long-Acting $Beta_2$-Agonists

When patients are prescribed ADVAIR DISKUS, other long-acting $beta_2$-agonists for asthma and COPD should not be used.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with ADVAIR DISKUS, but at times therapy with ADVAIR DISKUS may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

Hypercorticism and Adrenal Suppression: Patients should be advised that ADVAIR DISKUS may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to ADVAIR DISKUS.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS, may cause

a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy

Patients should be informed of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.6 Medication Guide

MEDICATION GUIDE

ADVAIR [*ad′vair*] DISKUS® 100/50
(fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS® 250/50
(fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder)

ADVAIR DISKUS® 500/50
(fluticasone propionate 500 mcg and salmeterol 50 mcg inhalation powder)

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

What is the most important information I should know about ADVAIR DISKUS?

- **ADVAIR DISKUS contains 2 medicines:**
  - **fluticasone propionate (the same medicine found in FLOVENT®)**, an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
  - **salmeterol (the same medicine found in SEREVENT®)**, a long-acting $beta_2$-agonist medicine or LABA. LABA medicines are used in patients with asthma and chronic obstructive pulmonary disease (COPD). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.

- **In patients with asthma, LABA medicines, such as salmeterol (one of the medicines in ADVAIR DISKUS), may increase the chance of death from asthma problems.** In a large asthma study, more patients who used salmeterol died from asthma problems compared with patients who did not use salmeterol. It is not known whether fluticasone propionate, the other medicine in ADVAIR DISKUS, changes your chance of death from asthma problems seen

with salmeterol. Talk with your healthcare provider about this risk and the benefits of treating your asthma with ADVAIR DISKUS.

- **ADVAIR DISKUS does not relieve sudden symptoms. Always have a short-acting beta$_2$-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**

- **Do not stop using ADVAIR DISKUS unless told to do so by your healthcare provider because your symptoms might get worse.**

- **ADVAIR DISKUS should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.**

- **Call your healthcare provider if breathing problems worsen over time while using ADVAIR DISKUS. You may need different treatment.**

- **Get emergency medical care if:**
  - **breathing problems worsen quickly, and**
  - **you use your short-acting beta$_2$-agonist medicine, but it does not relieve your breathing problems.**

What is ADVAIR DISKUS?
ADVAIR DISKUS combines an inhaled corticosteroid medicine, fluticasone propionate (the same medicine found in FLOVENT) and a long-acting beta$_2$-agonist medicine, salmeterol (the same medicine found in SEREVENT). ADVAIR DISKUS is used for asthma and chronic obstructive pulmonary disease (COPD) as follows:

Asthma
ADVAIR DISKUS is used long term, twice a day to control symptoms of asthma and to prevent symptoms such as wheezing in adults and children ages 4 and older.

ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). Because LABA medicines, such as salmeterol, may increase the chance of death from asthma problems, ADVAIR DISKUS is not for adults and children with asthma who:
- are well controlled with another asthma-controller medicine such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta$_2$-agonist medicines once in awhile

Chronic Obstructive Pulmonary Disease

COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. ADVAIR DISKUS 250/50 is used long term, twice a day to help improve lung function for better breathing in adults with COPD. ADVAIR DISKUS 250/50 has been shown to decrease the number of flare-ups and worsening of COPD symptoms (exacerbations).

Who should not use ADVAIR DISKUS?

Do not use ADVAIR DISKUS:

- to treat sudden, severe symptoms of asthma or COPD
- if you have a severe allergy to milk proteins. Ask your doctor if you are not sure.

What should I tell my healthcare provider before using ADVAIR DISKUS?

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

- **have heart problems**
- **have high blood pressure**
- **have seizures**
- **have thyroid problems**
- **have diabetes**
- **have liver problems**
- **have osteoporosis**
- **have an immune system problem**
- **are pregnant or planning to become pregnant.** It is not known if ADVAIR DISKUS may harm your unborn baby.
- **are breastfeeding.** It is not known if ADVAIR DISKUS passes into your milk and if it can harm your baby.
- **are allergic to any of the ingredients in ADVAIR DISKUS, any other medicines, or food products. See the end of this Medication Guide for a complete list of the ingredients in ADVAIR DISKUS.**
- **are exposed to chickenpox or measles**

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. ADVAIR DISKUS and certain other medicines may interact with each other. This may cause serious side effects. Especially, tell your healthcare provider if you take ritonavir. The anti-HIV medicines NORVIR® (ritonavir capsules) Soft Gelatin, NORVIR (ritonavir oral solution), and KALETRA® (lopinavir/ritonavir) Tablets contain ritonavir.

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

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

- Children should use ADVAIR DISKUS with an adult's help, as instructed by the child's healthcare provider.

- Use ADVAIR DISKUS exactly as prescribed. **Do not use ADVAIR DISKUS more often than prescribed.** ADVAIR DISKUS comes in 3 strengths. Your healthcare provider will prescribe the one that is best for your condition.

- The usual dosage of ADVAIR DISKUS is 1 inhalation twice a day (morning and evening). The 2 doses should be about 12 hours apart. Rinse your mouth with water after using ADVAIR DISKUS.

- If you take more ADVAIR DISKUS than your doctor has prescribed, get medical help right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.

- If you miss a dose of ADVAIR DISKUS, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.

- Do not use a spacer device with ADVAIR DISKUS.

- Do not breathe into ADVAIR DISKUS.

- **While you are using ADVAIR DISKUS twice a day, do not use other medicines that contain a long-acting beta$_2$-agonist or LABA for any reason. Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.**

- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.

- Make sure you always have a short-acting beta$_2$-agonist medicine with you. Use your short-acting beta$_2$-agonist medicine if you have breathing problems between doses of ADVAIR DISKUS.

- **Call your healthcare provider or get medical care right away if:**
  - your breathing problems worsen with ADVAIR DISKUS

- you need to use your short-acting beta$_2$-agonist medicine more often than usual
- your short-acting beta$_2$-agonist medicine does not work as well for you at relieving symptoms
- you need to use 4 or more inhalations of your short-acting beta$_2$-agonist medicine for 2 or more days in a row
- you use 1 whole canister of your short-acting beta$_2$-agonist medicine in 8 weeks' time
- your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
- you have asthma and your symptoms do not improve after using ADVAIR DISKUS regularly for 1 week

What are the possible side effects with ADVAIR DISKUS?

- **ADVAIR DISKUS contains salmeterol (the same medicine found in SEREVENT). In patients with asthma, LABA medicines, such as salmeterol, may increase the chance of death from asthma problems.** See "What is the most important information I should know about ADVAIR DISKUS?"
- Patients with COPD have a higher chance of getting pneumonia. ADVAIR DISKUS may increase the chance of getting pneumonia. **Call your healthcare provider if you notice any of the following symptoms:**
  - increase in mucus (sputum) production
  - change in mucus color
  - fever
  - chills
  - increased cough
  - increased breathing problems.

Other possible side effects with ADVAIR DISKUS include:

- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction, including:
  - rash
  - hives
  - swelling of the face, mouth, and tongue
  - breathing problems
- **increased blood pressure**
- **a fast and irregular heartbeat**
- **chest pain**
- **headache**
- **tremor**
- **nervousness**
- **weakened immune system and a higher chance of infections**

- **lower bone mineral density.** This may be a problem for people who already have a higher chance of low bone density (osteoporosis).
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using ADVAIR DISKUS.
- **slowed growth in children.** A child's growth should be checked often.

The most common side effects with ADVAIR DISKUS include:
Asthma in adults and children:
- upper respiratory tract infection
- throat irritation
- hoarseness and voice changes
- thrush in the mouth and throat
- bronchitis
- cough
- headache
- nausea and vomiting

In children with asthma, infections in the ear, nose, and throat are also common.

COPD:
- thrush in the mouth and throat
- throat irritation
- hoarseness and voice changes
- viral respiratory infections
- headache
- muscle and bone pain

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with ADVAIR DISKUS. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store ADVAIR DISKUS?
- Store ADVAIR DISKUS at room temperature between 68° to 77° F (20° to 25° C). Keep in a dry place away from heat and sunlight.
- Safely discard ADVAIR DISKUS 1 month after you remove it from the foil pouch, or after the dose indicator reads "0", whichever comes first.
- **Keep ADVAIR DISKUS and all medicines out of the reach of children.**

General Information about ADVAIR DISKUS

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use ADVAIR DISKUS for a condition for which it was not prescribed. Do not give your ADVAIR DISKUS to other people, even if they have the same condition. It may harm them.

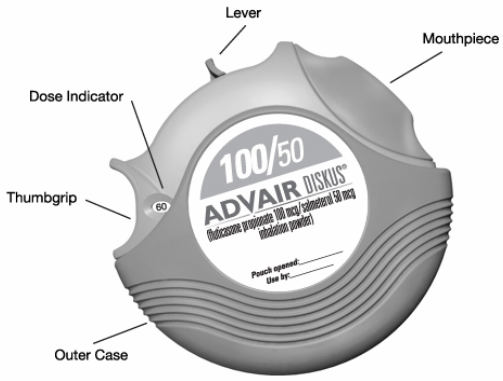
This Medication Guide summarizes the most important information about ADVAIR DISKUS. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ADVAIR DISKUS that was written for healthcare professionals. You can also contact the company that makes ADVAIR DISKUS (toll free) at 1-888-825-5249 or at www.advair.com.

What are the ingredients in ADVAIR DISKUS?

Active ingredients: fluticasone propionate, salmeterol xinafoate
Inactive ingredient: lactose (contains milk proteins)

Instructions for Using ADVAIR DISKUS

Follow the instructions below for using your ADVAIR DISKUS. **You will breathe in (inhale) the medicine from the DISKUS®.** If you have any questions, ask your healthcare provider or pharmacist.



Take ADVAIR DISKUS out of the box and foil pouch. Write the **"Pouch opened"** and **"Use by"** dates on the label on top of the DISKUS. **The "Use by" date is 1 month from date of opening the pouch.**

- The DISKUS will be in the closed position when the pouch is opened.
- The **dose indicator** on the top of the DISKUS tells you how many doses are left. The dose indicator number will decrease each time you use the DISKUS. After you have used 55 doses from the DISKUS, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left *(see Figure 1)*. If you are using a "sample" DISKUS, the numbers 5 to 0 will appear in red after 9 doses.

Figure 1

Taking a dose from the DISKUS requires the following 3 simple steps: Open, Click, Inhale.

1. **OPEN**

   Hold the DISKUS in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position *(see Figure 2)*.

Figure 2

2. **CLICK**

   Hold the DISKUS in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** *(see Figure 3)*. The DISKUS is now ready to use.

Figure 3

Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the DISKUS is ready:**

- **Do not close the DISKUS.**
- **Do not tilt the DISKUS.**
- **Do not play with the lever.**
- **Do not move the lever more than once.**

3. INHALE

Before inhaling your dose from the DISKUS, breathe out (exhale) fully while holding the DISKUS level and away from your mouth *(see Figure 4)*. **Remember, never breathe out into the DISKUS mouthpiece.**

Figure 4

Put the mouthpiece to your lips *(see Figure 5)*. Breathe in quickly and deeply through the DISKUS. Do not breathe in through your nose.

Figure 5

Remove the DISKUS from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly.

The DISKUS delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the DISKUS if you do not feel or taste the medicine.

Rinse your mouth with water after breathing-in the medicine. Spit the water out. Do not swallow.

4. **Close the DISKUS when you are finished taking a dose so that the DISKUS will be ready for you to take your next dose.** Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go *(see Figure 6)*. The DISKUS will click shut. The lever will automatically return to its original position. The DISKUS is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4.)

Figure 6

Remember:

- Never breathe into the DISKUS.
- Never take the DISKUS apart.
- Always ready and use the DISKUS in a level, flat position.
- Do not use the DISKUS with a spacer device.
- After each dose, rinse your mouth with water and spit the water out. Do not swallow.
- Never wash the mouthpiece or any part of the DISKUS. **Keep it dry.**
- Always keep the DISKUS in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.

October 2008 ADD:5MG

This Medication Guide has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPIRIVA HandiHaler safely and effectively. See full prescribing information for SPIRIVA HandiHaler.

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)
Capsules for Respiratory Inhalation

DO NOT Swallow SPIRIVA Capsules
FOR ORAL INHALATION ONLY with the HandiHaler Device

Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2009
Dosage and Administration (2)	12/2009
Contraindications (4)	12/2009
Warnings and Precautions,	
Immediate Hypersensitivity Reactions (5.2)	12/2009
Worsening of Narrow-Angle Glaucoma (5.4)	12/2009
Worsening of Urinary Retention (5.5)	12/2009
Renal Impairment (5.6)	12/2009

----------INDICATIONS AND USAGE----------

SPIRIVA HandiHaler is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations (1)

----------DOSAGE AND ADMINISTRATION----------

DO NOT swallow SPIRIVA capsules (2)
For Use with the HandiHaler Device ONLY (2)
For Oral Inhalation ONLY (2)

- Two inhalations of the powder contents of a single SPIRIVA capsule (18 mcg) once daily (2)

----------DOSAGE FORMS AND STRENGTHS----------

SPIRIVA capsules for oral inhalation: 18 mcg tiotropium powder, for use with HandiHaler device (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to ipratropium or tiotropium (4)

----------WARNINGS AND PRECAUTIONS----------

- Not for acute use: Not for use as a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA HandiHaler at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, occur. Use with caution in patients with severe hypersensitivity to milk proteins. (5.2)
- Paradoxical bronchospasm: Discontinue SPIRIVA HandiHaler and consider other treatments if paradoxical bronchospasm occurs (5.3)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs. (5.4)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to consult a physician immediately if this occurs. (5.5)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (>5% incidence in the 1-year placebo-controlled trials) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Not recommended for use with other anticholinergics since this has not been studied (7.2)

----------USE IN SPECIFIC POPULATIONS----------

Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects (2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA HandiHaler is indicated to reduce exacerbations in COPD patients.

2 DOSAGE AND ADMINISTRATION

DO NOT SWALLOW SPIRIVA CAPSULES
FOR USE WITH HANDIHALER DEVICE ONLY

FOR ORAL INHALATION ONLY

SPIRIVA capsules must not be swallowed as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules are only for oral inhalation and should only be used with the HandiHaler device [*see Overdosage (10)*]**.**

The recommended dose of SPIRIVA HandiHaler is two inhalations of the powder contents of one SPIRIVA capsule, once-daily, with the HandiHaler device [*see Patient Counseling Information (17.6)*].

For administration of SPIRIVA HandiHaler, a SPIRIVA capsule is placed into the center chamber of the HandiHaler device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HandiHaler device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece [*see Patient Counseling Information (17.6)*].

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA HandiHaler should be monitored closely for anticholinergic effects [*see Warnings and Precautions (5.6), Use in Specific Populations (8.5, 8.6, 8.7), and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

SPIRIVA HandiHaler consists of SPIRIVA capsules and a HandiHaler device. SPIRIVA capsules contain 18 mcg dry powder formulation of tiotropium in a light green, hard gelatin capsule with TI 01 printed on one side and Boehringer Ingelheim company logo on the other side. Supplied with a HandiHaler device.

4 CONTRAINDICATIONS

SPIRIVA HandiHaler is contraindicated in patients with a hypersensitivity to ipratropium or tiotropium. In clinical trials and postmarketing experience with SPIRIVA HandiHaler, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Acute Use

SPIRIVA HandiHaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., rescue therapy).

5.2 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash may occur after administration of SPIRIVA HandiHaler. If such a reaction occurs, therapy with SPIRIVA HandiHaler should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to SPIRIVA HandiHaler. In addition, SPIRIVA HandiHaler should be used with caution in patients with severe hypersensitivity to milk proteins.

5.3 Paradoxical Bronchospasm

Inhaled medicines, including SPIRIVA HandiHaler, may cause paradoxical bronchospasm. If this occurs, treatment with SPIRIVA HandiHaler should be stopped and other treatments considered.

5.4 Worsening of Narrow-Angle Glaucoma

SPIRIVA HandiHaler should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.5 Worsening of Urinary Retention

SPIRIVA HandiHaler should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.6 Renal Impairment

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [*see Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Immediate hypersensitivity reactions [*see Warnings and Precautions (5.2)*]
- Paradoxical bronchospasm [*see Warnings and Precautions (5.3)*]
- Worsening of narrow-angle glaucoma [*see Warnings and Precautions (5.4)*]
- Worsening of urinary retention [*see Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6-Month to 1-Year Trials

The data described below reflect exposure to SPIRIVA HandiHaler in 2663 patients. SPIRIVA HandiHaler was studied in two 1-year placebo-controlled trials, two 1-year active-controlled trials, and two 6-month placebo-controlled trials in patients with COPD. In these trials, 1308 patients were treated with SPIRIVA HandiHaler at

the recommended dose of 18 mcg once a day. The population had an age ranging from 39 to 87 years with 65% to 85% males, 95% Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) percent predicted of 39% to 43%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. An additional 6-month trial conducted in a Veteran's Affairs setting is not included in this safety database because only serious adverse events were collected.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, tachycardia, blurred vision, glaucoma (new onset or worsening), dysuria, and urinary retention.

Four multicenter, 1-year, placebo-controlled and active-controlled trials evaluated SPIRIVA HandiHaler in patients with COPD. Table 1 shows all adverse reactions that occurred with a frequency of ≥3% in the SPIRIVA HandiHaler group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HandiHaler group exceeded placebo by ≥1%. The frequency of corresponding reactions in the ipratropium-controlled trails is included for comparison.

Table 1 Adverse Reactions (% Patients) in One-Year COPD Clinical Trials

Body System (Event)	**Placebo-Controlled Trials**		**Ipratropium-Controlled Trials**	
	SPIRIVA (n = 550)	**Placebo (n = 371)**	**SPIRIVA (n = 356)**	**Ipratropium (n = 179)**
Body as a Whole				
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (Upper)				
Upper Respiratory Tract Infection	41	37	43	35
Sinusitis	11	9	3	2
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Epistaxis	4	2	1	1
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the SPIRIVA HandiHaler treatment group, but were <1% in excess of the placebo group.

Other reactions that occurred in the SPIRIVA HandiHaler group at a frequency of 1% to 3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole* allergic reaction, leg pain; *Central and Peripheral Nervous System* dysphonia, paresthesia; *Gastrointestinal System Disorders* gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders* hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders* skeletal pain; *Cardiac Events* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder* depression; *Infections* herpes zoster; *Respiratory System Disorder (Upper)* laryngitis; *Vision Disorder* cataract. In addition, among the adverse reactions observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age [*see Use in Specific Populations (8.5)*].

Two multicenter, 6-month, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. The adverse reactions and the incidence rates were similar to those seen in the 1-year controlled trials.

4-Year Trial

The data described below reflect exposure to SPIRIVA HandiHaler in 5992 COPD patients in a 4-year placebo-controlled trial. In this trial, 2986 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age range from 40 to 88 years, was 75% male, 90% Caucasian, and had COPD with a mean pre-bronchodilator FEV_1 percent predicted of 40%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. When the adverse reactions were analyzed with a frequency of ≥3% in the SPIRIVA HandiHaler group where the rates in the SPIRIVA HandiHaler group exceeded placebo by ≥1%, adverse reactions included (SPIRIVA HandiHaler, placebo): pharyngitis (12.5%, 10.8%), sinusitis (6.5%, 5.3%), headache (5.7%, 4.5%), constipation (5.1%, 3.7%), dry mouth (5.1%, 2.7%), depression (4.4%, 3.3%), insomnia (4.4%, 3.0%), and arthralgia (4.2%, 3.1%).

Additional Adverse Reactions

Other adverse reactions not previously listed that were reported more frequently in COPD patients treated with SPIRIVA HandiHaler than placebo include: dehydration, skin ulcer, stomatitis, gingivitis, oropharyngeal candidiasis, dry skin, skin infection, and joint swelling.

6.2 Postmarketing Experience

Adverse reactions have been identified during worldwide post-approval use of SPIRIVA HandiHaler. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

7 DRUG INTERACTIONS

7.1 Sympathomimetics, Methylxanthines, Steroids
SPIRIVA HandiHaler has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids without increases in adverse drug reactions.

7.2 Anticholinergics
The co-administration of SPIRIVA HandiHaler with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.

7.3 Cimetidine, Ranitidine
No clinically significant interaction occurred between tiotropium and cimetidine or ranitidine [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects, Pregnancy Category C.
There are no adequate and well-controlled studies in pregnant women. SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to approximately 660 and 6 times the recommended human daily inhalation dose (RHDID) on a mg/m^2 basis, respectively. However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 35 times the RHDID on a mg/m^2 basis. In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 360 times the RHDID on a mg/m^2 basis. Such effects were not observed at inhalation doses of approximately 4 and 80 times the RHDID on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

8.2 Labor and Delivery
The safety and effectiveness of SPIRIVA HandiHaler has not been studied during labor and delivery.

8.3 Nursing Mothers
Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA HandiHaler is administered to a nursing woman.

8.4 Pediatric Use
SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with COPD and for the reduction of COPD exacerbations. COPD does not normally occur in children. The safety and effectiveness of SPIRIVA HandiHaler in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of patients who received SPIRIVA HandiHaler in the 1-year clinical trials, 426 were <65 years, 375 were 65 to 74 years, and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HandiHaler and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HandiHaler group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HandiHaler group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were –0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA HandiHaler dosage in geriatric patients is warranted [*see Clinical Pharmacology (12.3)*].

8.6 Renal Impairment
Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [*see Dosage and Administration (2), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment
The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

10 OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Accidental Ingestion
Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from postmarketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HandiHaler was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7300, 120,000, and 850 times the recommended human daily inhalation dose on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

11 DESCRIPTION

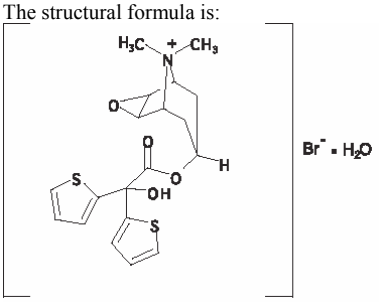
SPIRIVA HandiHaler consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation only with the HandiHaler device.

Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins) as the carrier.

The dry powder formulation within the SPIRIVA capsule is intended for oral inhalation only.

The active component of SPIRIVA HandiHaler is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2ß, 4ß, 5α, 7ß)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is:



Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br \bullet H_2O$.

The HandiHaler device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2 L total). In a study of 26 adult patients with COPD and severely compromised lung function [mean FEV_1 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16% to 65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

12.2 Pharmacodynamics

Cardiovascular Effects

In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the SPIRIVA HandiHaler group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with SPIRIVA HandiHaler did not detect an effect of the drug on QTc intervals.

The effect of SPIRIVA HandiHaler on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received SPIRIVA HandiHaler 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for SPIRIVA HandiHaler 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

12.3 Pharmacokinetics

Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. The effect of food on tiotropium's bioavailability has not been studied. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation.

Distribution

Tiotropium shows a volume of distribution of 32 L/kg indicating that the drug binds extensively to tissues. The human plasma protein binding for tiotropium is 72%. At steady state, peak tiotropium plasma levels in COPD patients were 17 to 19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 mcg dose and decreased in a multi-compartmental manner. Steady-state trough plasma concentrations were 3 to 4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Metabolism

The extent of metabolism appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol *N*-methylscopine and dithienylglycolic acid, neither of which bind to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver

microsomes showed that tiotropium in supra-therapeutic concentrations did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination
The terminal elimination half-life of tiotropium was between 5 and 6 days following inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium was mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion was 14% of the dose, the remainder being mainly non-absorbed drug in the gut which was eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2 to 3 weeks with no accumulation thereafter.

Drug Interactions
An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC_{0-4h}, a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium.

Specific Populations
Geriatric Patients
As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in AUC_{0-4} after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability [*see Dosage and Administration (2) and Use in Specific Populations (8.5)*].

Renal Impairment
Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (creatinine clearance of 50 to 80 mL/min), which is often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in AUC_{0-4} after intravenous infusion). In COPD patients with moderate to severe renal impairment (creatinine clearance of <50 mL/min), the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4}), which was confirmed by plasma concentrations after dry powder inhalation. Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [*see Dosage and Administration (2), Warnings and Precautions (5.4), and Use in Specific Populations (8.6)*].

Hepatic Impairment
The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to approximately 25, 35, and 0.5 times the recommended human daily inhalation dose (RHDID) on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDID on a mg/m^2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDID on a mg/m^2 basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDID on a mg/m^2 basis). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

13.2 Animal Toxicology and Pharmacology
Reproductive Toxicology Studies
No evidence of fetal structural alteration was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the RHDID on a mg/m^2 basis, respectively. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥0.078 mg/kg (approximately 35 times the RHDID on a mg/m^2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDID on a mg/m^2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDID on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

14 CLINICAL STUDIES

The SPIRIVA HandiHaler (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2663 patients with COPD (1308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a forced expiratory volume in one second (FEV_1) less than or equal to 60% or 65% of predicted, and a ratio of FEV_1/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (FEV_1), with peak effect occurring within 3 hours following the first dose.

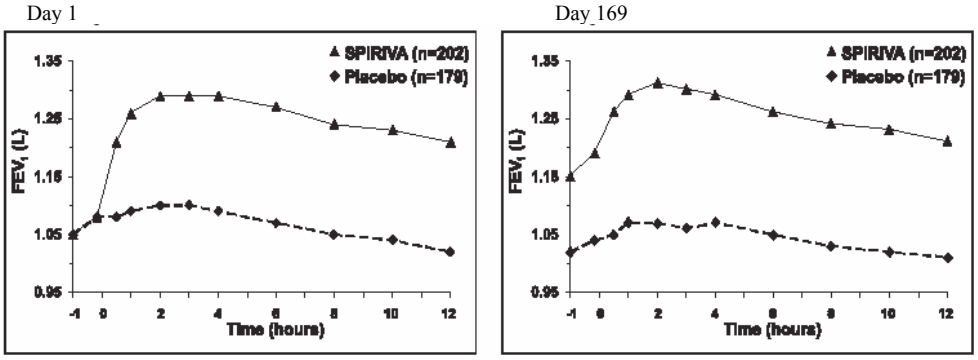
Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5992 COPD patients. Long-term effects on lung function and other outcomes were also evaluated in the 4-year multicenter trial.

6-Month to 1-Year Effects on Lung Function
In the 1-year, placebo-controlled trials, the mean improvement in FEV_1 at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to

baseline after the first dose (Day 1). Further improvements in FEV_1 and forced vital capacity (FVC) were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV_1, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV_1 values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV_1) with SPIRIVA HandiHaler, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

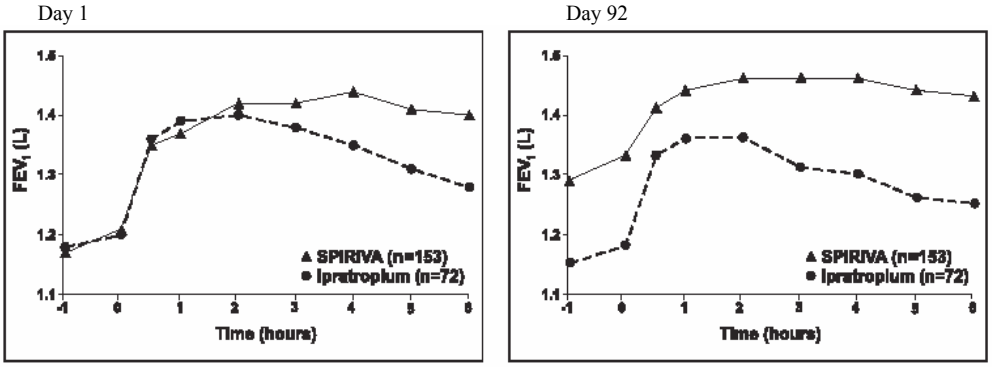
Figure 1 Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HandiHaler and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

Results of each of the 1-year ipratropium-controlled trials were similar to the results of the 1-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV_1 Over Time (0 to 6 hours post-dose) on Days 1 and 92, Respectively for One of the Two Ipratropium-Controlled Studies*



*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HandiHaler and ipratropium groups, respectively, completed through 3 months of observation. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HandiHaler was administered in the morning or in the evening.

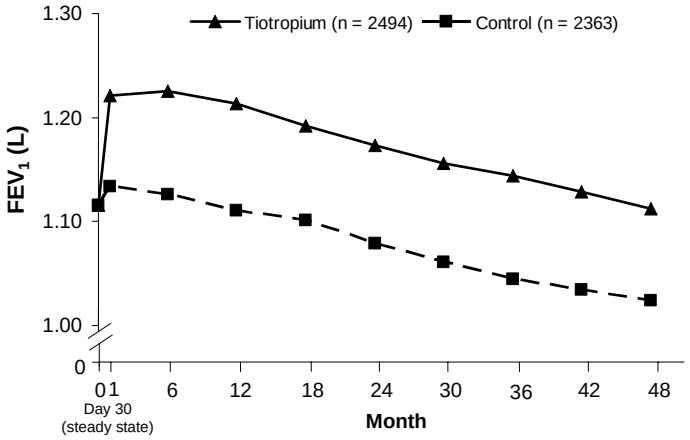
Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HandiHaler had a reduced requirement for the use of rescue short-acting $beta_2$-agonists. Reduction in the use of rescue short-acting $beta_2$-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

4-Year Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5992 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HandiHaler on disease progression (rate of decline in FEV_1). Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age, 75% male, and 90% Caucasian with a diagnosis of COPD and a mean pre-bronchodilator FEV_1 of 39% predicted (range = 9% to 76%) at study entry. There was no difference between the groups in either of the co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV_1, as demonstrated by similar slopes of FEV_1 decline over time (Figure 3).

SPIRIVA HandiHaler maintained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87 to 103 mL) throughout the 4 years of the study (Figure 3).

Figure 3 Trough (pre-dose) FEV_1 Mean Values at Each Time Point



Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV_1 (observed mean) = 1.12. Patients with ≥3 acceptable pulmonary function tests after Day 30 and non-missing baseline value were included in the analysis.

Exacerbations
The effect of SPIRIVA HandiHaler on COPD exacerbations was evaluated in two clinical trials: a 4-year clinical trial described above and a 6-month clinical trial of 1829 COPD patients in a Veterans Affairs setting. In the 6-month trial, COPD exacerbations were defined as a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics, systemic steroids, or hospitalization. The population had an age ranging from 40 to 90 years with 99% males, 91% Caucasian, and had COPD with a mean pre-bronchodilator FEV_1 percent predicted of 36% (range = 8% to 93%). Patients were permitted to use respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. In the 6-month trial, the co-primary endpoints were the proportion of patients with COPD exacerbation and the proportion of patients with hospitalization due to COPD exacerbation. SPIRIVA HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo (27.9% vs 32.3%, respectively; Odds Ratio (OR) (tiotropium/placebo) = 0.81; 95% CI = 0.66, 0.99; p = 0.037). The proportion of patients with hospitalization due to COPD exacerbations in patients who used SPIRIVA HandiHaler compared to placebo was 7.0% vs 9.5%, respectively; OR = 0.72; 95% CI = 0.51, 1.01; p = 0.056.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids. SPIRIVA HandiHaler significantly reduced the risk of an exacerbation by 14% (Hazard Ratio (HR) = 0.86; 95% CI = 0.81, 0.91; p<0.001) and reduced the risk of exacerbation-related hospitalization by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p<0.002) compared to placebo. The median time to first exacerbation was delayed from 12.5 months (95% CI = 11.5, 13.8) in the placebo group to 16.7 months (95% CI = 14.9, 17.9) in the SPIRIVA HandiHaler group.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIRIVA HandiHaler consists of SPIRIVA capsules and the HandiHaler device. SPIRIVA capsules contain 18 mcg of tiotropium and are light green, with the Boehringer Ingelheim company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HandiHaler device is gray colored with a green piercing button. It is imprinted with SPIRIVA HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo, and the Pfizer company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HandiHaler device and that the HandiHaler device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:
- carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HandiHaler inhalation device (NDC 0597-0075-75)
- carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-41)
- carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-47)

Storage
Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store SPIRIVA capsules in the HandiHaler device.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (17.6)

17.1 Instructions for Administering SPIRIVA HandiHaler
It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler device [*see Patient Counseling Information (17.6)*]. Patients should be instructed that SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications. **The contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed**.

SPIRIVA capsules should always be stored in sealed blisters. Only one SPIRIVA capsule should be removed immediately before use or its effectiveness may be reduced. Additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use) should be discarded.

17.2 Paradoxical Bronchospasm
Patients should be informed that SPIRIVA HandiHaler can produce paradoxical bronchospasm. If paradoxical bronchospasm occurs, patients should discontinue SPIRIVA HandiHaler.

17.3 Urinary Retention
Difficulty passing urine and dysuria may be symptoms of new or worsening prostatic hyperplasia or bladder outlet obstruction. Patients should be instructed to consult a physician immediately should any of these signs or symptoms develop.

17.4 Visual Effects
Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Patients should be told to consult a physician immediately should any of these signs and symptoms develop. Miotic eye drops alone are not considered to be effective treatment.

Patients should be told that care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

17.5 Acute Exacerbation
Patients should understand that SPIRIVA HandiHaler is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems (i.e., as a rescue medication).

17.6 FDA-approved Patient Labeling
Patient Information and Patient's Instructions for Use are supplied as tear-off leaflets following the full prescribing information and should be dispensed with each new prescription and refill.

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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos. RE38,912, RE39,820, 5,478,578, 6,777,423, 6,908,928, 7,070,800, and 7,309,707 with other patents pending. The HandiHaler® inhalation device is covered by U.S. Design Patent No. D355,029 with other patents pending.

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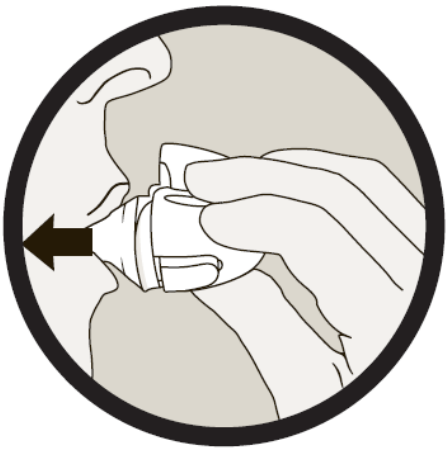
Patient Information

SPIRIVA® (speh REE vah) HandiHaler®
(tiotropium bromide inhalation powder)

Do NOT swallow SPIRIVA capsules.



After putting the SPIRIVA capsule into the HandiHaler device, breathe in your medicine through your mouth.

<u>Important Information:</u> Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device. SPIRIVA HandiHaler should only be inhaled by mouth (oral inhalation).

Read the information that comes with your SPIRIVA HandiHaler before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SPIRIVA HandiHaler?

SPIRIVA HandiHaler is a prescription medicine that you use one time every day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD). SPIRIVA HandiHaler helps make your lungs work better for 24 hours. SPIRIVA HandiHaler relaxes your airways and helps keep them open. You may start to feel like it is easier to breathe on the first day, but it may take longer for you to feel the full effects of the medicine. SPIRIVA HandiHaler works best and may help make it easier to breathe when you use it every day.

SPIRIVA HandiHaler also reduces the likelihood of flare-ups and worsening of COPD symptoms (COPD exacerbations). A COPD exacerbation is defined as an increase or new onset of more than one COPD symptom such as cough, mucus, shortness of breath, and wheezing that requires medicine beyond your rescue medicine.

SPIRIVA HandiHaler is **not** a rescue medicine and should not be used for treating sudden breathing problems. Your doctor may give you other medicine to use for sudden breathing problems.

SPIRIVA HandiHaler has not been studied in children.

Who should not take SPIRIVA HandiHaler?

Do not use SPIRIVA HandiHaler if you:

- are allergic to tiotropium. See the end of this leaflet for a complete list of ingredients.
- have had an allergic reaction to ipratropium (Atrovent®).

Allergic reactions may include itching, rash, or swelling of the lips, tongue, or throat (trouble swallowing).

What should I tell my doctor before using SPIRIVA HandiHaler?

Before taking SPIRIVA HandiHaler, tell your doctor about all your medical conditions, including if you:

- have kidney problems.
- have glaucoma. SPIRIVA HandiHaler may make your glaucoma worse.
- have an enlarged prostate, problems passing urine, or a blockage in your bladder. SPIRIVA HandiHaler may make

these problems worse.
- are pregnant or plan to become pregnant. It is not known if SPIRIVA HandiHaler could harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if SPIRIVA HandiHaler passes into breast milk. You and your doctor will decide if SPIRIVA HandiHaler is right for you while you breast-feed.
- have a severe allergy to milk proteins. Ask your doctor if you are not sure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and eye drops, vitamins, and herbal supplements. Some of your other medicines or supplements may affect the way SPIRIVA HandiHaler works. SPIRIVA HandiHaler is an anticholinergic medicine. You should not take other anticholinergic medicines while using SPIRIVA HandiHaler, including ipratropium. Ask your doctor or pharmacist if you are not sure if one of your medicines is an anticholinergic.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take SPIRIVA HandiHaler?

- Use SPIRIVA HandiHaler exactly as prescribed. Use SPIRIVA HandiHaler one time every day.
- Read the "Patient's Instructions for Use" at the end of this leaflet before you use SPIRIVA HandiHaler. Talk with your doctor if you do not understand the instructions.
- **Do not swallow SPIRIVA capsules.**
- **Only use SPIRIVA capsules with the HandiHaler device.**
- **Do not use the HandiHaler device to take any other medicine**.
- SPIRIVA HandiHaler comes as a powder in a SPIRIVA capsule that fits the HandiHaler device. Each SPIRIVA capsule, containing only a small amount of SPIRIVA powder, is one full dose of medicine.
- Separate one blister from the blister card. Then take out one of the SPIRIVA capsules from the blister package right before you use it.
- After the capsule is pierced, take a complete dose of SPIRIVA HandiHaler by breathing in the powder by mouth two times, using the HandiHaler device (take 2 inhalations from one SPIRIVA capsule). See the "Patient's Instructions for Use" at the end of this leaflet.
- Throw away any SPIRIVA capsule that is not used right away after it is taken out of the blister package. Do not leave the SPIRIVA capsules open to air; they may not work as well.
- If you miss a dose, take it as soon as you remember. Do not use SPIRIVA HandiHaler more than one time every 24 hours.
- If you use more than your prescribed dose of SPIRIVA HandiHaler, call your doctor or a poison control center.

What should I avoid while using SPIRIVA HandiHaler?

Do not let the powder from the SPIRIVA capsule get into your eyes. Your vision may get blurry and the pupil in your eye may get larger (dilate). If this happens, call your doctor.

What are the possible side effects of SPIRIVA HandiHaler?

SPIRIVA HandiHaler can cause serious side effects. If you get any of the following side effects, stop taking SPIRIVA HandiHaler and get medical help right away.

- **Allergic reaction.** Symptoms may include**:** itching, rash, swelling of the lips, tongue, or throat (trouble swallowing).
- **Sudden narrowing and blockage of the airways into the lungs (bronchospasm).** Your breathing suddenly gets worse.
- **New or worsened increased pressure in the eyes (acute narrow-angle glaucoma).** Symptoms of acute narrow-angle glaucoma may include: eye pain, blurred vision, seeing halos (visual halos) or colored images along with red eyes.
- **New or worsened urinary retention.** Symptoms of blockage in your bladder and/or enlarged prostate may include: difficulty passing urine, painful urination.

Other side effects with SPIRIVA HandiHaler include:

- upper respiratory tract infection
- dry mouth
- sinus infection
- sore throat
- non-specific chest pain
- urinary tract infection

- indigestion
- runny nose
- constipation
- increased heart rate
- blurred vision

These are not all the possible side effects with SPIRIVA HandiHaler. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SPIRIVA HandiHaler?

- **Do not store SPIRIVA capsules in the HandiHaler device.**
- Store SPIRIVA capsules in the sealed blister package at room temperature between 68°F–77°F (20°–25°C).
- Keep SPIRIVA capsules away from heat and cold (do not freeze).
- Store SPIRIVA capsules in a dry place. Throw away any unused SPIRIVA capsules that have been open to air.

Ask your doctor or pharmacist if you have any questions about storing your SPIRIVA capsules.

Keep SPIRIVA HandiHaler, SPIRIVA capsules, and all medicines out of the reach of children.

General information about SPIRIVA HandiHaler

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use SPIRIVA HandiHaler for a purpose for which it has not been prescribed. Do not give SPIRIVA HandiHaler to other people even if they have the same symptoms that you have. It may harm them.

For more information about SPIRIVA HandiHaler, talk with your doctor. You can ask your doctor or pharmacist for information about SPIRIVA HandiHaler that is written for health professionals.

For more information about SPIRIVA HandiHaler, you may call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in SPIRIVA HandiHaler?

Active ingredient: tiotropium
Inactive ingredient: lactose monohydrate

What is COPD (Chronic Obstructive Pulmonary Disease)?

COPD is a serious lung disease that includes chronic bronchitis, emphysema, or both. Most COPD is caused by smoking. When you have COPD, your airways become narrow. So, air moves out of your lungs more slowly. This makes it hard to breathe.

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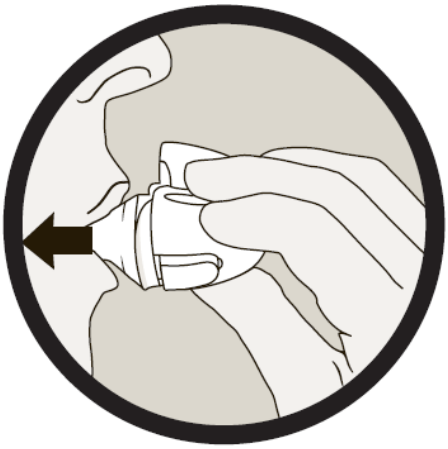
Patient's Instructions for Use

SPIRIVA® HandiHaler®
(tiotropium bromide inhalation powder)

Do NOT swallow SPIRIVA capsules.



Step 1: Put the SPIRIVA capsule into the HandiHaler device.
Step 2: Inhale the medicine through your mouth.

<u>Important Information:</u> Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device. SPIRIVA HandiHaler should only be inhaled through your mouth (oral inhalation).

First read the Patient Information that comes with SPIRIVA HandiHaler for important information about using SPIRIVA HandiHaler.

Read these Patient's Instructions for Use before you start to use SPIRIVA HandiHaler and each time you refill your prescription. There may be new information.

For more information, ask your doctor or pharmacist.

SPIRIVA HandiHaler comes with SPIRIVA capsules and a HandiHaler device. The HandiHaler device is an inhalation device that is for use only with SPIRIVA capsules. Do not use the HandiHaler device to take any other medicine.

Becoming familiar with SPIRIVA HandiHaler:

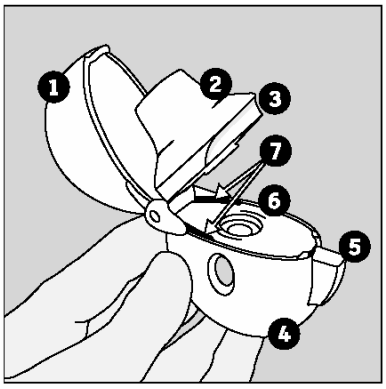
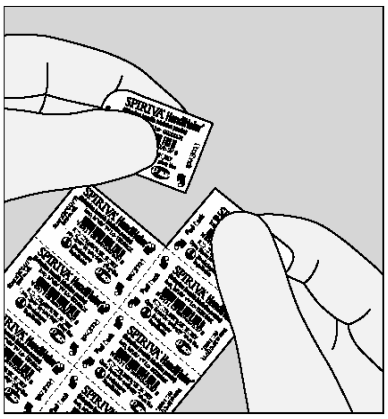


Figure A

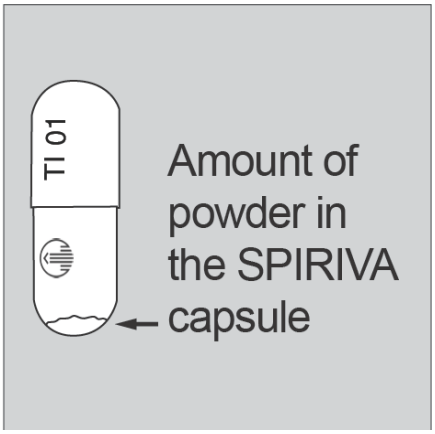
Remove the HandiHaler device from the pouch and become familiar with its components. (Figure A)

1. dust cap
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. center chamber
7. air intake vents



Each SPIRIVA capsule is packaged in a blister. Each blister can be separated from the blister card by tearing along the perforation. (Figure B)

Figure B



Do not open the SPIRIVA capsule before you insert it into the HandiHaler device. If you open the SPIRIVA capsule, it may not work. Each SPIRIVA capsule contains only a small amount of powder. (Figure C) This is one full dose. The product was designed this way.

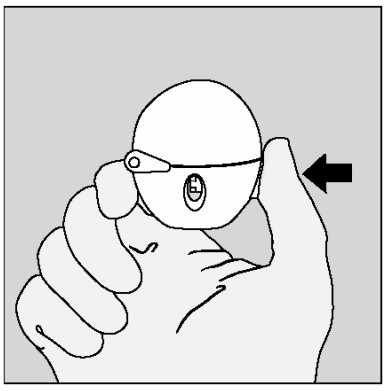
Figure C

How do I inhale the contents of the SPIRIVA capsule using the HandiHaler device?

Taking your dose of medicine using the HandiHaler device has four main steps:
1. **Open** the HandiHaler device and the blister
2. **Insert** the SPIRIVA capsule
3. **Press** the green piercing button
4. **Breathe in (inhale)** your medicine

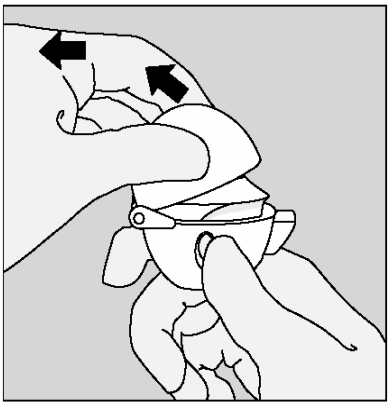
(See below for details)

Opening the HandiHaler device:



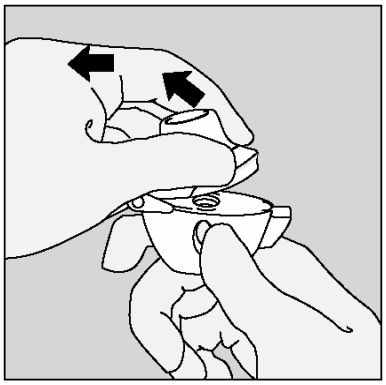
1. Open the dust cap by pressing the green piercing button. (Figure 1)

Figure 1



Pull the dust cap upwards to expose the mouthpiece. (Figure 2)

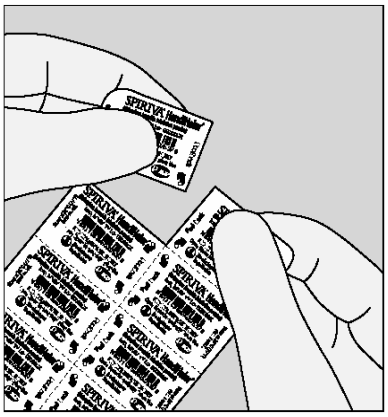
Figure 2



Open the mouthpiece by pulling the mouthpiece ridge upwards away from the base. (Figure 3)

Figure 3

Removing a SPIRIVA capsule:



Before removing a SPIRIVA capsule from the blister, separate one of the blisters from the blister card by tearing along the perforation. (Figure 4)

Do not swallow SPIRIVA capsules.

Always store SPIRIVA capsules in the sealed blisters. Remove only one SPIRIVA capsule from the blister right before use. Do not store SPIRIVA capsules in the HandiHaler device. Inhale the contents of the SPIRIVA capsule using the HandiHaler device right away after the blister packaging of an individual SPIRIVA capsule is opened, or else it may not work as well.

Figure 4

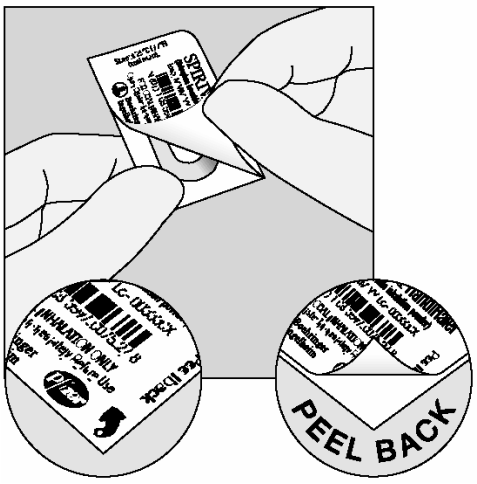


Figure 5

Right before you are ready to use your SPIRIVA HandiHaler:

Bend back and forth one of the corners of the blister that has an arrow and then with your finger separate the aluminum foil layers. Carefully peel back the printed foil until you can see the whole SPIRIVA capsule. (Figure 5)

Turn the blister upside down and tip the SPIRIVA capsule out, tapping the back of the blister, if needed.

Do not cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.

If more SPIRIVA capsules are opened to air, they should not be used and should be thrown away.

Inserting the SPIRIVA capsule into the HandiHaler device:

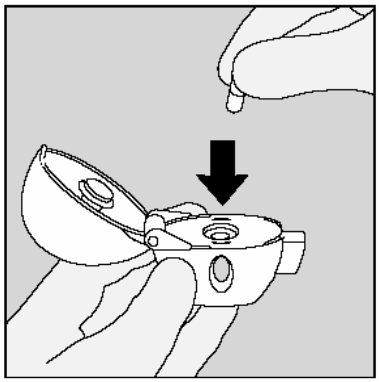


Figure 6

2. Insert (put) the SPIRIVA capsule in the center chamber of the HandiHaler device. It does not matter which end of the SPIRIVA capsule you put in the chamber. (Figure 6)

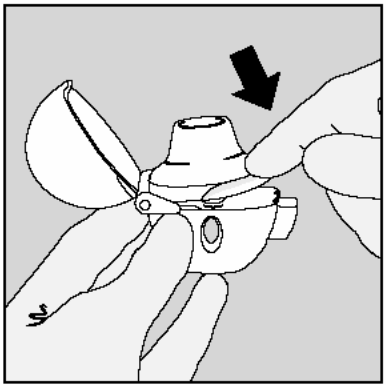


Figure 7

Close the mouthpiece **until you hear a click**, but leave the dust cap open. (Figure 7)

Be sure that you have the mouthpiece sitting firmly against the gray base.

Taking your dose using the HandiHaler device:

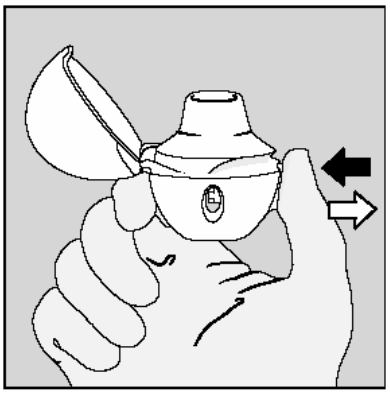


Figure 8

Hold the HandiHaler device with the mouthpiece upright. It is important that you hold the HandiHaler device in an upright position (Figure 8) when pressing the green piercing button.

3. Press the green piercing button until it is flat (flush) against the base, and release. This is how you make holes in the SPIRIVA capsule so that you get the medicine when you breathe in.

Do not press the green button more than one time.

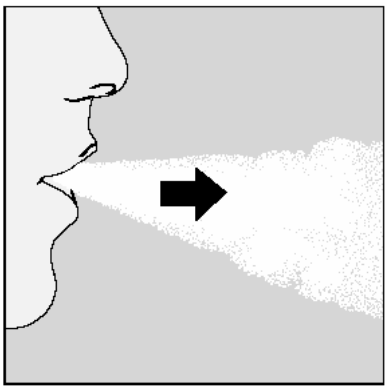


Figure 9

Breathe out completely. (Figure 9)

Important: Do not breathe (exhale) into the mouthpiece of the HandiHaler device at any time.

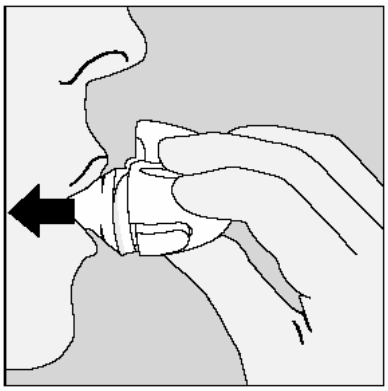


Figure 10

4. Breathe in (inhale)

- Hold the HandiHaler device by the gray base. Do not block the air intake vents.
- Raise the HandiHaler device to your mouth and close your lips tightly around the mouthpiece.
- **Keep your head in an upright position. The HandiHaler device should be in a horizontal position.** (Figure 10)
- Breathe in **slowly and deeply** so that you **hear or feel the SPIRIVA capsule vibrate.**
- Breathe in until your lungs are full.
- Hold your breath as long as is comfortable and at the same time take the HandiHaler device out of your mouth. Breathe normally again.

To make sure you get the full dose, you must breathe out completely, and inhale again as in step 4 above (Figure 10). *Do not press the green piercing button again.*

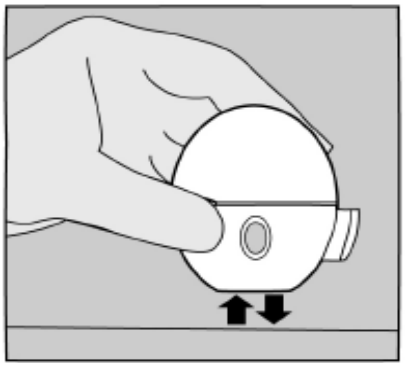


Figure 11

If you do not hear or feel the SPIRIVA capsule vibrate, **do not press the green piercing button again.** Instead, hold the HandiHaler device in an upright position and tap the HandiHaler device gently on a table. (Figure 11)

Check to see that the mouthpiece is completely closed. Then, breathe in again – slowly and deeply.

If you still do not hear or feel the SPIRIVA capsule vibrate after repeating the above steps, throw away the SPIRIVA capsule. Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule (SPIRIVA capsule fragments). SPIRIVA capsule fragments in the center chamber can cause a SPIRIVA capsule not to vibrate. Turn the HandiHaler device upside down and gently tap to remove the SPIRIVA capsule fragments. Call your doctor for instructions.

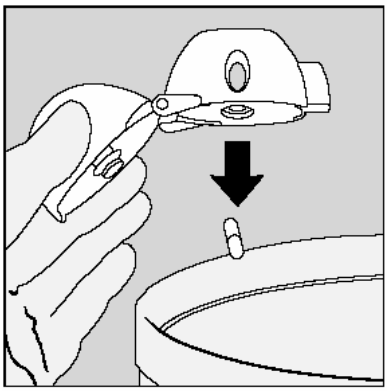


Figure 12

After you finish taking your daily dose of SPIRIVA HandiHaler, open the mouthpiece again. Tip out the used SPIRIVA capsule and throw it away. (Figure 12)

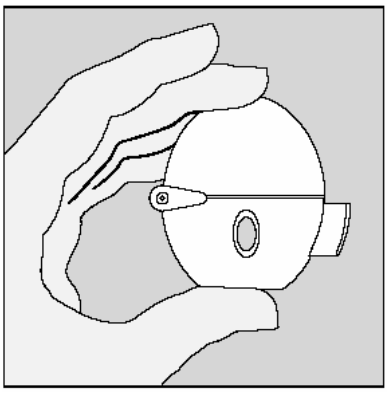
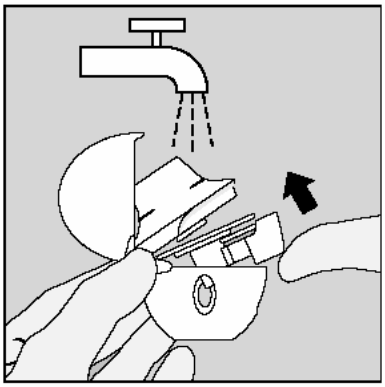


Figure 13

Close the mouthpiece and dust cap for storage of your HandiHaler device. (Figure 13)

Do not store used or unused SPIRIVA capsules in the HandiHaler device.

When and how should I clean my HandiHaler device?



Clean the HandiHaler device one time each month or as needed. (Figure 14)

- Open the dust cap and mouthpiece.
- Open the base by lifting the green piercing button.
- Look at the center chamber for SPIRIVA capsule fragments or powder residue.
- Rinse the HandiHaler device with warm water. Check that any powder buildup or SPIRIVA capsule fragments are removed.
- Do not use cleaning agents or detergents.
- Do not place the HandiHaler device in the dishwasher for cleaning.
- Dry the HandiHaler device well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open.

Figure 14

- Do not use a hair dryer to dry the HandiHaler device.
- **It takes 24 hours to air dry, so clean the HandiHaler device right after you use it so that it will be ready for your next dose.**
- Do not use the HandiHaler device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

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