CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review: Addendum

Date	February 28, 2011
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review Addendum
NDA/BLA # Supplement#	NDA 22-522
Applicant	Forest Laboratories
Date of Submission (original)	July 15, 2009
PDUFA Goal Date	February 28, 2011
Proprietary Name / Established (USAN) names	TRADENAME/roflumilast
Dosage forms / Strength	Oral tablet/500 mcg
Proposed Indication(s)	1. …"to reduce exacerbations of chronic obstructive pulmonary disease associated with chronic bronchitis in patients at risk of exacerbations".
Recommended:	Approval

1. Introduction

This CDTL review addendum is meant to address several review issues that were either outstanding or have changed since the completion of the initial CDTL review dated February 7, 2011. Theses issues include:

- Approval of the roflumilast tradename "Daliresp" by the Division of Medical Error Prevention and Analysis on February 28, 2011.

- In the CDTL review dated February 7, 2011, a postmarketing CMC Commitment to reassess the drug substance particle size distribution (PSD) acceptance criteria after preparation of multiple (e.g., n = 10) commercial batches that are used to produce drug product was recommended.
    - The Applicant was notified of this as a formal CMC PMC by the CMC team and subsequently, on February 8, 2011, responded with a revision of the drug substance particle size specification which tightened the acceptance criteria. This response was felt to be adequate by the CMC team and, as such, the CMC PMC is no longer required.

- The Applicant, Forest Laboratories, submitted a Medication Guide only REMS on April 14, 2010, to inform patients of the potential risk associated with the use of roflumilast in COPD patients including the risk of increased psychiatric adverse events (including suicidality) and weight loss.
    - On February 25, 2011, the FDA made available a draft guidance for industry entitled, "Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)" which clarified that in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes other elements to assure safe use. As the Division's review concluded that no other elements other than the Medication Guide were required to assure safe use of roflumilast, the Medication Guide as part of a REMS was not felt to be necessary.

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/s/

ANTHONY G DURMOWICZ
02/28/2011

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1. Introduction

Nycomed submitted a 505(b)(1) new drug application (NDA 22-522) on July 15, 2009, for the use of roflumilast at a proposed dose of 500 mcg once daily for "the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations". During the course of the review period, the ownership of the NDA was transferred from Nycomed to Forest Laboratories who subsequently desired a change to a more focused disease indication to reduce exacerbations of chronic obstructive pulmonary disease rather than the initial indication to treat the entire COPD disease entity. While the clinical data submitted in the original NDA submission supported the use of roflumilast to reduce the risk of COPD exacerbations in the subpopulation of patients with severe COPD associated with chronic bronchitis and a history of COPD exacerbations, safety concerns over increased psychiatric adverse reactions, including suicide, in patients receiving roflumilast in the clinical trials. (b) (4) , and the need to conduct an evaluation of the potential of roflumilast as a substrate for P-glycoprotein (P-gp), were issues that needed to be addressed before the drug could be considered for approval. During the first review cycle, internal discussion also occurred on whether to require the Applicant to conduct additional clinical trials to determine the efficacy of roflumilast as add-on therapy to a standard COPD therapy, a fixed dose combination product of an inhaled long-acting beta agonist and corticosteroid, prior to approval or postmarketing. Given the known efficacy for roflumilast in a population of hard to treat patients with severe COPD associated with chronic bronchitis and a history of exacerbations and the ability to employ a risk mitigation strategy to fully inform patients of the risks associated with the use of roflumilast, the decision was made for the "add-on" clinical trial to be performed as a postmarketing commitment. Thus, in order to address the deficiencies summarized above and included in the Complete Response letter on May 17, 2010, the Applicant was instructed to:

1. Submit a comprehensive review and evaluation of all roflumilast safety data utilizing an acceptable method, such as the Columbia Classification Algorithm of Suicide Assessment (C-CASA). The assessment should include data from all COPD studies, as well as studies conducted with roflumilast for other indications.

(b) (4)

3. Conduct an in vitro evaluation of the potential of roflumilast as a substrate for P-gp.

In this resubmission, received August 30, 2010, Forest has responded to the three deficiencies identified in the Division's Complete Response Letter. This review will summarize the Division's assessments of the responses provided by the Applicant to the deficiencies outlined in the Complete Response letter, most notably the review of the suicidality and psychiatric system adverse reaction data. Summaries will also be provided for discipline-specific sections

in which previous reviews have recommended approval of roflumilast. For a complete discussion of the drug development program see the reviews of the initial NDA submission from each specific discipline.

2. Background

Roflumilast is a new molecular entity and a selective phosphodiesterase type 4 (PDE 4) inhibitor proposed as a treatment to reduce exacerbations 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, and formoterol as well as anti-muscarinic agents such as ipratropium and tiotropium) that are used to treat reversible bronchoconstriction associated with COPD. Tiotropium (Spiriva) and Advair® 250/50, a salmeterol (50 mcg) and fluticasone propionate (250 mcg) combination product that contains both a long-acting beta agonist (LABA) and inhaled corticosteroid are currently 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.

Although none have been approved for use, other specific PDE 4 inhibitors have been developed and studied in clinical trials. One, cilomilast was shown to have little effect as a bronchodilator as demonstrated by the 30-40 mL increase from baseline in FEV1 compared to placebo that was observed in cilomilast phase 3 clinical trials. Cilomilast and other specific PDE 4 inhibitors have also demonstrated dose-dependent class-related toxicities related to the gastrointestinal system in clinical studies, including nausea, vomiting, diarrhea, anorexia, and weight, which have affected drug tolerability.

The regulatory history for roflumilast is long 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. During this time, the development program has changed ownership several times, most recently to Forest Laboratories. The large clinical program and phase 3 trials are a reflection that the design, endpoints, and patient populations of the COPD clinical program evolved substantially over time (see Table 1) with earlier Phase 2/3 dose-ranging and Phase 3 studies focused on a commonly used patient reported pulmonary disease outcome measure, the St. George Respiratory Questionnaire (SGRQ) and lung function (FEV1) as endpoints with later Phase 3 studies assessing COPD exacerbations and lung function as endpoints.

3. CMC/Device

The primary CMC review was conducted by Craig Bertha, Ph.D. His review has concluded that from a CMC perspective, the application is recommended for approval pending inspection of the (b) (4) manufacturing site scheduled on February 14, 2011.

The drug substance is roflumilast (USAN), a phosphodiesterase type 4 inhibitor. The chemical name is 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4- (difluoromethoxy)benzamide (IUPAC). All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The formulation of the drug product contains 500 mcg of roflumilast with standard compendial excipients. (b) (4) Currently the proposed expiration dating period for the drug product is 24 months.

In this resubmission, the Applicant has agreed to a CMC post-marketing commitment to reassess the drug substance particle size distribution (PSD) acceptance criteria after preparation of multiple (e.g., n = 10) commercial batches that are used to produce drug product and to make adjustments that will reflect the PSD data.

4. Nonclinical Pharmacology/Toxicology

The applicant has submitted all required nonclinical data and studies needed to characterize the nonclinical safety profile of roflumilast and support its approval from the nonclinical perspective. Nonclinical toxicities of roflumilast and/or its metabolites included carcinogenicity, fertility, reproductive toxicity, and cardiovascular and GI toxicities. Following is a brief summary of the relevant toxicities with emphasis on the carcinogenic potential of roflumilast.

Carcinogenicity
Roflumilast at daily doses of 8 and 16 mg/kg/day for 2 years caused statistically significant increases in the incidence of nasal tumors in hamsters but not in mice. 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. At that time the nasal findings were deemed not relevant to humans based on the lack of ADCP N-oxide formation in humans. However, human pharmacokinetic data have demonstrated the presence of ADCP N-oxide in human plasma and urine. 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. Of the thirteen PDE-4 inhibitors that FDA has nonclinical toxicology data on, one other PDE-4 inhibitor, piclamilist, which also forms the ADCP metabolites, has demonstrated nasal toxicities in rats and mice and nasal tumors in rats.

The exact 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, resulting in very high local exposure to the carcinogens. Human nasal tissues apparently lack active enzymes to convert ADCP to ADCP N-oxide but as mentioned above, ADCP N-oxide can be found in human urine.

Fertility
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 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. As a result of the fertility studies, the effects of roflumilast on human male fertility were evaluated in a 3-month clinical trial (Report 98/2002). In that study roflumilast at 500 μg/patient/day had no effects on sperm and fertility parameters evaluated.

Reproductive toxicity
Effects of roflumilast on the reproductive system and embryofetal development were studied in mice, rats, and rabbits. Roflumilast treatment of 12 mg/kg/day during pregnancy resulted in dose-related increases in stillborns, maternal deaths, and decreases in pup viability in mice. Roflumilast was not teratogenic in rats and rabbits.

Cardiovascular toxicity
Roflumilast adversely 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 153.1, 203.7 and 251.3 μg.h/L in plasma AUCs. These AUC values provided safety margins of at least 5, an acceptable value for drugs like roflumilast.

Gastrointestinal 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 78.7 and 251.3 μg.h/L in plasma AUCs. These AUC values provided safety margins of at least 5, again an acceptable value.

For more detailed information, see the primary nonclinical pharmacology/toxicology review for the initial NDA submission by Luqi Pei, Ph.D.

5. Clinical Pharmacology/Biopharmaceutics

A deficiency noted in the Complete Response letter was the lack of an in vitro evaluation of roflumilast as a substrate for P-gp. This was required because the proposed dose of roflumilast of 500 mcg once daily is close to the maximal tolerated chronic dose of the drug. Because roflumilast has significant dose related side effects, the increased exposure to roflumilast as a result of it being a P-gp substrate, when taken concomitantly with other drugs (e.g., ketoconazole) would be a safety concern.

Initially, the clinical pharmacology team had also recommended the Applicant repeat the thorough QT study for roflumilast due to the positive control (moxifloxacin) lacking adequate assay sensitivity to be able to discriminate small effects (<10 ms) on the QT interval. However, when taken into context that the COPD safety database contains ECG data from approximately 24,000 COPD patients with about half exposed to chronic dosing of up to one year with the 500 mcg dose of roflumilast without any appreciable QT prolongation apparent, the clinical utility of a formal QT study was felt to be negligible and, therefore not required.

In this complete response, the Applicant submitted the results of in vitro assessments of roflumilast and roflumilast N-oxide as potential substrates for P-gp. The determinations of P-gp substrate potential were conducted in cultured cell monolayers at four different concentrations of roflumilast or roflumilast N-oxide: 0.1, 0.5, 2, and 4 μM with appropriate controls. The results demonstrated that neither roflumilast nor roflumilast N-oxide are P-gp substrates.

Given the data presented above, both I and the clinical pharmacology team have concluded that the data submitted by the Applicant to characterize the clinical pharmacology and biopharmaceutics profile of roflumilast is adequate to support its approval from the clinical pharmacology perspective.

Following is a brief summary of the relevant clinical pharmacology data including the effects of roflumilast on the QT interval.

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 with roflumilast N-oxide 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

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 exposure between young (18-45 years old) and middle-aged (45-65 years old) subjects was comparable for both roflumilast and roflumilast N-oxide. 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 with the AUC of roflumilast increased by 40%, 79%, and 28%, respectively, for young, middle-aged, and elderly female subjects compared to male subjects. Similarly, 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. In addition, the C_{max} of roflumilast N-oxide was increased by 30%, 53%, and 47%, respectively, for young, middle-aged, and elderly female subjects.

Race
Compared to Caucasians, 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. Also, African Americans, Hispanics, and Japanese showed a 15%, 31%, and 17% higher C_{max}, respectively, for roflumilast, and 17%, 9%, and 5% higher C_{max}, respectively, for roflumilast N-oxide compared to Caucasians.

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). The exposure of roflumilast in severe renal impairment patients was 21% less for AUC and 19% less for C_{max}, as compared to healthy subjects. The exposure of roflumilast N-oxide in severe renal impairment patients was comparable for AUC as compared to healthy subjects. No dose adjustment is recommended for renal impairment patients.

Hepatic Impairment
When comparing patients with liver cirrhosis to healthy subjects, an increase in exposure was observed in patients with liver cirrhosis (Child-Pugh stage A and B) for both roflumilast and roflumilast N-oxide. 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 recommendation is that roflumilast be contraindicated in patients with moderate and severe hepatic impairment patients and be used with caution in patients with mild hepatic impairment.

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. Therefore, the exposure of roflumilast is expected to increase when inhibitors of CYP3A4 or CYP1A2 are co-administered and decrease when inducers of CYP3A4 or CYP1A2 are co-administered. 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, or montelukast. However, as a result of drug-drug interactions with increased exposure, roflumilast should be used with caution when co-administered with enoxacin, theophylline, cimetidine, fluvoxamine, ketoconazole, erythromycin, smoking, and sildenafil and roflumilast should not be taken with rifampicin or other strong CYP inducers. Co-administration of roflumilast with the following drugs does not need dose adjustment: midazolam (or other CYP3A4 substrates), digoxin (or other P-gp substrates), Maalox, salbutamol, formoterol, budesonide, warfarin, and montelukast does not require dose adjustment.

Thorough QT Study

The thorough QT study conducted for this program was felt to be inconclusive according to the review performed by the IRT because they felt that adequate assay sensitivity could not be

established. This differs from the conclusion of the Applicant that assay sensitivity was demonstrated as the largest mean time-matched change from baseline difference from placebo in the moxifloxacin 400 mg group on Day 1 in QTcF was 6.79 ms and 6.97 ms in QTcP; differences that were statistically significant from zero. However, the IRT statistical reviewer performed an independent analysis and determined that the largest unadjusted 90% lower confidence interval is below 5 ms (4.3 ms), indicating that the assay sensitivity was not established in this study. Thus, without a concurrent positive control, in this case moxifloxacin, the study was not able to exclude small effects (<10 ms) on the QTc interval. The conclusion by the IRT was that the study was therefore not conclusive. As detailed above, the inconclusive nature of the study was superseded by clinical experience in approximately 24,000 COPD patients.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Overview of the clinical program

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, in order to understand the evolution of the roflumilast clinical program over time and understand the totality of the efficacy data for roflumilast, this review focused 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). All the studies were designed such that, if positive, they could potentially serve as pivotal studies to support the safety and efficacy of roflumilast for COPD. The efficacy data will be presented in this section from relevant clinical studies according to endpoint (FEV1, exacerbations, etc.).

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 roflumilast clinical studies had demonstrated 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 in patients with severe COPD 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 with severe COPD (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 in patients with moderate and severe COPD 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).

Design and conduct of the studies

Dose-ranging studies (FK1-101 and M2-107)
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 2/3 trial with 2 week run-in followed by 26 week treatment while study M2-107 was a phase 3 trial with 4 week run-in and 24 week treatment. Patients were randomized 1:1:1 in study FK1-101 (516) and 2:2:1 in study M2-107 (1411) to receive either roflumilast 250 or 500 mcg or placebo once daily. Concomitant uses of systemic or inhaled corticosteroids and long acting beta agonists were not permitted. Stable daily doses 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.

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 the Table 2 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 2 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

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. As such, dose selection appears to have been based on a small nominal separation in FEV1 between the 250 and 500 mcg doses. Doses higher than 500 mg were not evaluated in large efficacy trials due to lack of tolerability.

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.

Efficacy studies

The six Phase 3 studies designed to demonstrate safety and efficacy of roflumilast 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 weeks (M2-127 and M2-128). All studies compared a single dose level of 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 and received placebo, patients were randomized 1:1 to receive either roflumilast 500 mcg or placebo once daily (see table 1 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 active symptoms of chronic bronchitis (cough and sputum production) and COPD exacerbations. Additionally, studies M2-124 and M2-125 allowed concomitant treatment with LABAs (about 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 designs and allowance of different concomitant medications used to treat COPD make inter-study comparisons difficult. In no study was the efficacy of roflumilast evaluated compared to a fixed dose combination of an inhaled LABA and 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 one year-long studies.

Studies M2-127 and M2-128 were 24-week supportive studies that investigated the benefit of roflumilast treatment in generally less ill patient population (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 the single 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

Study Efficacy Findings

The demographics of the overall patient populations are notable for a study population that was predominantly Caucasian (≥ 93% in 5 of the 6 studies) and a preponderance of male patients over females (approximately 70% vs 30%). Within each of the efficacy studies the demographic characteristics were similar with regard to baseline pulmonary function, smoking history, COPD severity, and LABA use (when allowed). Patients with severe COPD who comprised the study populations enrolled in studies M2-111, 112, 124, and 125 had baseline FEV1 values of approximately one liter. Patients with both moderate and severe COPD enrolled in studies M2-127 and M2-128 had higher FEV1 values (approximately 1.5 liters), reflective of an overall population with less severe COPD. These studies also tended to have more current smokers than the other studies (approximately 60% vs 40%).

In the four 52-week studies, approximately two thirds of patients completed the study while in the two 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 was the greater number of patients in the roflumilast groups who discontinued due to adverse events, which was 3-9% higher than for the placebo group. Also of note is the large number of protocol violations across all studies accounting for about 20-30% of the overall study populations.

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. Following are the primary efficacy findings for the applicant-designated 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.

Change in Pre-Bronchodilator FEV1
In the pivotal and supportive studies, patients treated with roflumilast had a statistically significant, albeit 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 approximately 50 mL. This increase in FEV1 resulted in about a 3-5% increase in patient FEV1 (Table 3).

Table 3 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.

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 in patients with severe COPD. 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). 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 (Table 4).

Table 4 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

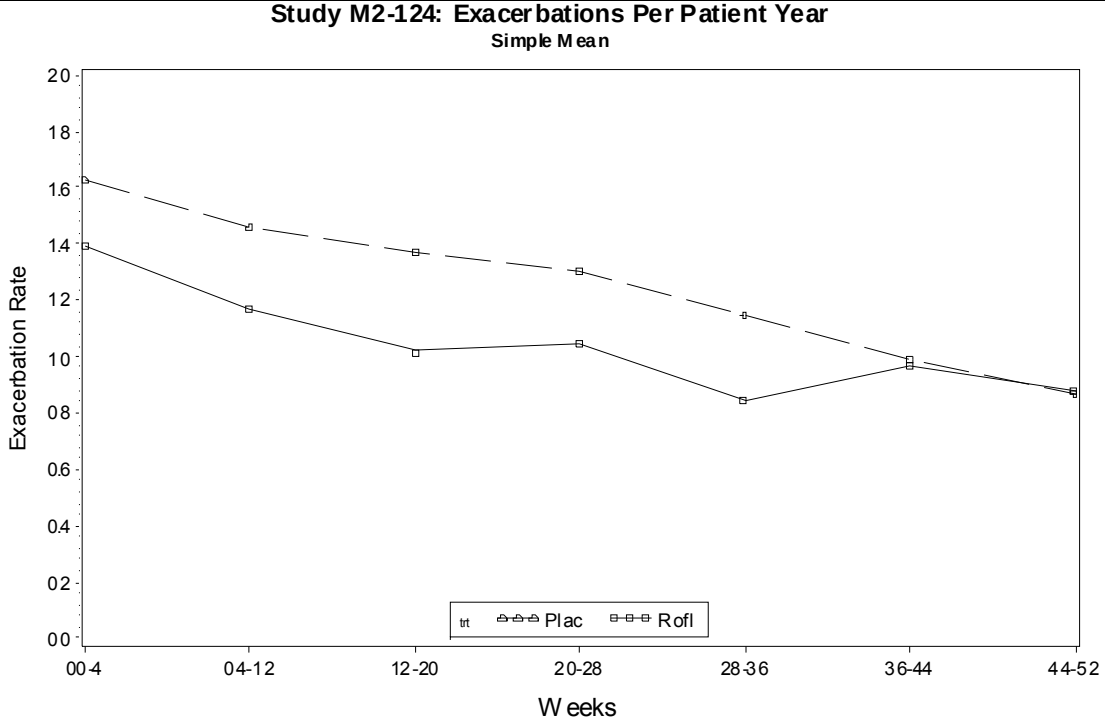
For studies M2-124 and M2-125, the subset of patients who received concomitant long-acting beta agonists or short-acting anti-muscarinics demonstrated a reduction in moderate or severe exacerbations that was similar to that observed for the overall populations of the two trials.

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 Applicant 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.

The time to onset of first moderate or severe COPD exacerbation was also explored in studies M2-124 and 125. In both studies, 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.

Because roflumilast will be marketed as a drug for chronic use, the statistical team conducted exploratory analyses to assess the durability of effect on the rate of COPD exacerbations. These analyses, while difficult to interpret, suggest that the reduction of exacerbation rate by roflumilast compared to placebo may attenuate after 8 months. See the Figure 1 below for study M2-124; the results for study M2-125 are similar.

Figure 1 Study M2-124 Exacerbations per patient year



Source: FDA statistical analyses

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

The SGRQ is commonly used as a patient reported outcome measure to assess for improvements in disease symptoms and quality of life assessment in clinical trials conducted in the COPD population. 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. Of note for the SGRQ is 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 of the studies (Table 5).

Table 5 Change from Baseline in SGRQ total score

Trial Number	Duration	Rof500 mcg	Placebo	Difference	P-Value
FK1-101	26 weeks	-4.7	-4.5	-0.3	0.425
M2-107	24 weeks	-3.5	-1.8	-1.7	0.053
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

Secondary endpoints

Other secondary endpoints evaluated in pivotal 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 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 again driven by a 40% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.

Summary of Efficacy

The proposed indication is for a reduction in COPD exacerbations. In that regard, two of the one-years studies conducted early in a broadly defined population of patients with severe COPD (M2-111 and M2-112) failed to demonstrate efficacy for COPD exacerbations while later studies (M2-124 and M2-125) which targeted a more narrow population of severe COPD patients (those with symptoms of chronic bronchitis and history of exacerbations) did demonstrate a substantial benefit (Table 4).

In addition, patients treated with roflumilast 500 mcg once daily demonstrated a consistent but modest increase in pre-bronchodilator FEV1 compared to placebo of approximately 50 mL or about 3-5% of FEV1 (Table 3).

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.

8. Safety

Database and Patient Demographics

For the COPD population this safety review focuses primarily on the eight studies which were reviewed in detail and are shown in Table 1. These studies plus additional safety data from placebo-controlled clinical trials of roflumilast in COPD patients comprise the Applicant's COPD safety pool of approximately 12,000 COPD patients of which more than half received roflumilast. In addition to the general safety review, as a result of the nominal difference in suicide-related events and an increase in psychiatric AEs in patients in roflumilast treatment groups that was documented during the first review cycle, as described in the Complete Response letter dated May 17, 2010, for this resubmission the Division required the Applicant to fully evaluate all roflumilast safety data in order to better understand the strength of the suicidality signal for roflumilast and be able to make a better informed risk benefit assessment of roflumilast in the treatment of patients with COPD. The Applicant's response is addressed under the "Specific Safety Issues" heading below.

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 monitoring and bio-impendence. Body weight, occult blood, 24-hour Holter and bio-impendence (assessment for weight loss) were assessed in patients from selected sites in a few studies only.

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.

The demographics of the overall patient populations are notable for a study population that was predominantly Caucasian (88-96%) with a preponderance of male patients over females (approximately 70% vs 30%). The median ages ranged from 63 to 65 years. Within each of the efficacy studies the demographic characteristics were similar with regard to baseline pulmonary function, smoking history, COPD severity, and LABA use (when allowed). Patients with severe COPD who comprised the study populations enrolled in studies M2-111, 112, 124, and 125 had baseline FEV1 values of approximately one liter. Patients with both moderate and severe COPD enrolled in studies M2-127 and M2-128 had higher FEV1 values (approximately 1.5 liters), reflective of an overall population with less severe COPD. These studies tended to have more current smokers than the other studies (approximately 60% vs 40%).

Deaths

There were a total of 177 deaths in the COPD safety population. There were no differences in overall mortality between study groups; 84 in the roflumilast 500 mcg group, 86 in the placebo group, and 7 in the roflumilast 250 mcg group. Cardiac disorders and COPD were the most common AEs reported in patients who died during treatment.

Serious Adverse Events

The general types of SAEs observed reflected the common co-morbidities frequently observed in an older COPD population of patients. For the COPD safety pool, the respective SAE rates were similar; 13.5% and 14.2% for the roflumilast 500 mcg and the placebo groups, respectively. COPD exacerbations and pneumonia were the most frequent SAEs in all treatment groups at 6-7% and about 1%, respectively. The roflumilast 500 mcg group reported more SAEs compared to placebo as a result of atrial fibrillation (24 vs 9 cases), diarrhea (10 vs 1 cases), prostate cancer (12 vs 5 cases) and acute renal failure (6 vs 4 cases). Additionally, 2 patients treated with roflumilast 500 mcg once daily attempted suicide compared to no patients on placebo (see Psychiatric AE section below).

Common Adverse Events

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 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 3 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.

Vital Signs and Clinical Laboratory Assessments

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.

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.

Mesenteric arteritis was seen in rats during pre-clinical studies with another PDE4 inhibitor, cilomilast, and was felt to be a possible class effect of that class of drugs. As a screen for potentially serious GI-related side effects, systematic hemoccult testing was performed in 4 COPD trials and 1 asthma roflumilast trial (M2-124, M2-125, M2-110, M2-111 and M2-023).

More roflumilast treated patients had GI symptoms 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 clinical trial treatment periods. GI workups including colonoscopy were performed on 116 of the 129 patients for positive hemoccult tests, GI bleeds or other reasons. There were no findings that would be consistent with or indicative of ischemic colitis.

There were no differences between the treatments in other hematology parameters and 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).

ECG findings from the 14 trials included in the Applicant's COPD safety pool were analyzed in a meta-analysis with the last visit ECG recordings from all trials compared to those at the baseline. There were 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%). Twenty-four hour Holter ECG monitoring was performed in a subset of 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 results showed no differences in heart rates or occurrence of arrhythmias between the roflumilast and the placebo treated groups.

Specific Safety Issues

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 AEs

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 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. 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 (Table 6).

Table 6 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, approximately 10% were severe and met the criteria for an SAE. Among the 13 cases of diarrhea severe enough to require hospitalization or considered life-threatening 12 occurred in roflumilast treated groups.

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. As weight was regularly and prospectively assessed in studies, M2-124 and M2-125, and because they were long (one year) in duration, the results from these studies the will be discussed here.

Overall, in the pooled data from studies M2-124 and 125, 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) with the reported rates of weight loss as an adverse event being 10.3% and 2.8% for the roflumilast and placebo treated groups, respectively.

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) weight loss. The between treatment differences in absolute and relative weight loss were: 2.01 kg or 4.4% for underweight patients, 1.76 kg or 2.8% for normal weight patients, 2.09 kg for 2.6% for overweight patients and 3.11 kg or 3.2% for obese patients. It is notable that both patient groups that were already underweight or had the most severe COPD lost more weight as a % of body weight than less ill or normal weight patients (Table 7).

Table 7 Weight Loss by BMI and COPD Severity (M2-124, M2-125)

Baseline Characteristics	Rof 500 mcg N=1498		Placebo N=1510		
	mean Wt (kg)	Δ Wt kg (%)	mean Wt (kg)	Δ Wt kg (%)	*Δ Treatment (rof–placebo) kg (%)
All	73.7	-2.09 (2.8)	73.3	0.08 (1.1)	- 2.17 (2.9)
Baseline BMI category					
Underweight	**45.6**	**-.073 (1.6)**	**45.8**	**1.28 (2.8)**	**-2.01 (4.4)**
Normal weight	62.7	-1.64 (2.6)	62.4	0.12 (0.19)	-1.76 (2.8)
Over weight	79.0	-2.02 (2.6)	79.0	0.07 (0.09)	-2.09 (2.6)
Obese	97.2	-3.57 (3.7)	96.7	-0.46 (0.48)	-3.11 (3.2)
COPD severity					
Moderate	77.6	-1.90 (2.4)	74.6	0.06 (0.08)	-1.84 (2.4)
Severe	74.7	-2.06 (2.7)	74.8	0.10 (0.13)	-1.96 (2.6)
Very severe	**70.5**	**-2.19 (3.1)**	**69.4**	**0.00**	**-2.19 (3.1)**

* 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%.

Psychiatric AEs including Suicide

Adverse events related to the psychiatric system organ class were about twice as 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 (Table 8). In addition to the increase in psychiatric adverse events, there were also 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 8 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, again, show that the approximately 2-fold increase in psychiatric AEs in patients receiving 500 mcg of roflumilast once daily was persistent across studies in different patient populations and appeared to be dose-related (Table 9). The types of AEs reported in these studies are consistent with those reported in the COPD population (insomnia, anxiety, depression).

Table 9 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 suicide-related events (completed suicides, suicide attempts, or suicidal ideation) reported in the COPD safety data base (N=12,054 patients) for patients in roflumilast treatment groups compared to one in patients treated in the placebo groups. However, for two

of the cases in the roflumilast group, the patients had discontinued roflumilast approximately 3 weeks 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). See the clinical review of the original NDA submission by the Applicant by Xuemeng Han Sarro, M.D., Ph.D. for brief narratives of the completed and attempted suicides.

As a result of the nominal difference in suicide-related events and the increase in psychiatric AEs in patients in roflumilast treatment groups in clinical studies, as described in the Complete Response letter dated May 17, 2010, the Division required the Applicant to fully evaluate all roflumilast safety data in order to better understand the strength of the suicidality signal for roflumilast and thereby be better able assess the impact of any signal on the risk benefit assessment of roflumilast in the treatment of patients with COPD. An acceptable method, such as the Columbia Classification Algorithm of Suicide Assessment (C-CASA), which FDA has previously used to assess for suicidality associated with other drugs/drug classes, was to be used to perform the assessment.

In this resubmission the Applicant utilized the C-CASA suicidality assessment method to identify possibly suicide-related adverse events (PSRAEs) in two patient pools, the "COPD Pool" comprised of 12,654 COPD patients (6,972 receiving roflumilast) enrolled in 16 placebo-controlled parallel group studies of up to one year in duration and the "Overall Pool" comprised of 21,623 patients (11,848 receiving roflumilast) enrolled in 36 controlled parallel group studies across indications that included COPD, osteo- and rheumatoid arthritis, diabetes mellitus, and allergic rhinitis. This pool included a total of 1,317 patients in active controlled studies who were not included in the final suicidality analysis.

The C-CASA assessment was performed according to the procedures previously outlined (Posner, et al., (Am J Psychiatry 2007; 164:1035-1043). Briefly, for each study, a search of the clinical database was conducted on all preferred terms, verbatim terms, and comment fields (if applicable) for all treated patients. The double-blind treatment period was defined as the start of double-blind medication to 1 day after stopping double-blind treatment. The text strings used in the search to indentify PSRAEs were:

> accident-, attempt, burn, cut, drown, gas, gun, hang, hung, immolat-, injur-jump, monoxide, mutilat-, overdos-, self damag-, self harm, self inflict, selfinjur-, shoot, slash, suic-, poison, asphyxiation, suffocation, firearm

These text strings are consistent with those used in the classification of suicidal events in the other FDA suicidal risk analyses.

Using the text string search, blinded adverse event listings for each study were generated and reviewed by 3 independent physicians at Forest Research Institute, Inc. and classified as either PSRAEs or not (i.e., obvious false positive events such as events which included the key words above but were not suicide-related, e.g., "epigastric pain" indentified in the search for the word "gas). Narratives (without treatment group assignments) were then generated for all events classified as PSRAEs and forwarded to Columbia University/New York State Psychiatric Institute for coding. The complete listing of all possible adverse events indentified in the string search was also forwarded for an external review to ensure that no cases were

overlooked in the internal review by Forest Laboratories. Listings of all SAEs/deaths were also forwarded to Columbia. The narratives were reviewed and each patient with a narrative and each event in the SAE/death listing were assigned one of the nine possible codes as per the C-CASA methodology. A description of the codes is presented in Table 11. If multiple events were reported in one patient, the more severe code was selected based on the following code order: 1>2>3>4>5>6>9>7 or 8.

Table 11 Description of C-CASA Codes

Code	*Description*
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Self-injurious behavior, no suicidal intent
8	Other; accident, psychiatric, medical
9	Not enough information, non-fatal

C-CASA = Columbia Classification Algorithm of Suicide Assessment

Analyses of both the COPD and Overall patient pools failed to indentify any additional PSRAEs that had not been identified during the safety review of the initial NDA submission. For the COPD pool, a total of 3 PSRAEs (2 suicide attempts and 1 completed suicide) were identified for patients who were currently receiving roflumilast (or within one day of discontinuation of treatment) while one PSRAE (suicidal ideation) was identified in the placebo group for a nominal difference of 2 PSRAEs in a pool of 12,654 COPD patients (or 21,623 patients in the larger Overall pool). Of note is that there were 2 additional suicides in COPD patients in the roflumilast group however, in both cases, they occurred 3 weeks after roflumilast had been discontinued and, therefore were excluded from the C-CASA analysis. No additional PSRAEs were identified in the Overall pool that were not already included in the analysis of the COPD pool.

Once the PSRAEs were identified, Fisher's exact test was used to compare the risk between treatment groups. The Applicant considered codes 1-4 as a suicidal event, which is consistent with previous FDA C-CASA analyses. For the COPD pool, the risk and rate (per 1000 patient years) of having a PSRAE were 0.042% and 0.793 per 1000 patient years, respectively, for patients treated with roflumilast and 0.018% and 0.284 per 1000 patient years, respectively for patients treated with placebo. The differences in the occurrence of PSRAEs in patients receiving roflumilast compared to placebo, while nominally higher based on an absolute difference of 2 events, were not statistically significant. The risk and rates for the Overall pool were slightly lower as a result of a greater number of patients being in the pool and no additional PSRAEs.

In addition to the C-CASA analysis described above, , in order to confirm our internal analyses, the Division the Division instructed the Applicant to submit summary data of psychiatric adverse event data in all parallel group, placebo-controlled trials. The results of the analysis were essentially the same as the internal analysis (Table 8).

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. The data below show the number and incidences of the most common malignancies/cancer in COPD patients who received the proposed dose of 500 mcg once daily (Table 12). While the overall incidences were similar, there were increases in lung, prostate, and colo-rectal cancers in the roflumilast treated COPD patients compared to placebo. These differences are difficult to interpret as many of the malignancies were detected relatively early in the clinical trials. Additionally, the trials were at most one year in length which is usually insufficient time for a significant cancer signal to be identified.

Table 12 Malignancy analysis in patients treated with roflumilast 500 mcg compared to placebo (FDA analysis)

Type	**Roflumilast 500 mcg**				**Placebo**				**P-Value***
	Tumors	N	Prop	Inc**	Tumors	N	Prop	Inc**	
All	93	5752	0.0162	0.0292	73	5505	0.0133	0.0235	**0.058**
All No_Skin	80	5752	0.0139	0.0255	61	5505	0.0111	0.0206	**0.053**
Lung	29	5752	0.005	0.0096	17	5505	0.0031	0.0074	**0.047**
Prostate	13	5752	0.0023	0.0046	5	5505	0.0009	0.0013	**0.045**
Colo-rectal	9	5752	0.0016	0.0027	2	5505	0.0004	0.0004	**0.028**

*p-value for difference between rof and placebo (log-rank test)
**Kaplan Meier incidence rate at 365 days

Safety Update

As described at 21 CFR 314.50(d)(5)(vi)(b), the Applicant was required to submit a safety update at the time of NDA resubmission. The Applicant complied with the requirement. Since all roflumilast clinical studies were completed at the time of the 120 Day Safety Update (dated November 17, 2009) during the first review cycle and none have been initiated since, there are no new events from controlled clinical studies.

With regard to post-marketing safety data, a single spontaneous post-marketing serious adverse event report (SAEs) was received by the Applicant since roflumilast was approved in the European Union on July 5, 2010 until the date of this resubmission. This event, which

included the terms dyspnea, ventricular arrhythmia, and respiratory acidosis which occurred 4 days after initiation of roflumilast treatment does not affect the overall safety determination for roflumilast.

Summary of Safety

Roflumilast has significant safety issues that need to be weighed against the clinical benefit of a reduction in COPD exacerbations. It causes gastrointestinal disturbances such as diarrhea, nausea, known class effects of PDE4 inhibitors, in about 10% of the patients who take it. Weight loss was also a common event with a mean loss of approximately 2 kg in roflumilast treated COPD patients. In addition to gastrointestinal side effects and weight loss, patients treated with roflumilast demonstrate an approximately 2 times increase in the occurrence of psychiatric adverse events, especially those for anxiety, depression, and insomnia. Because of the increased psychiatric adverse events and the small nominal increase in suicidality identified during the first review cycle, the C-CASA analysis for suicidality described above was conducted and did not identify any additional suicidality-related events. While this is somewhat reassuring and the differences in suicidality are small and not statistically significant, they cannot be completely discounted based on the consistently increased occurrence of psychiatric adverse events such as anxiety and depression in roflumilast treated patients and will need to be continued to be monitored postmarketing.

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was convened during the first review cycle on April 7, 2010, to discuss the efficacy and safety data provided to support the approval of roflumilast for the treatment of COPD in the United States. The main issues that the PADAC considered were the evidence for efficacy and safety as well as the overall risk-benefit assessment of roflumilast for the treatment of COPD. The questions were addressed based on the original broader COPD indication for the "maintenance treatment of COPD associated with chronic bronchitis in patients with risk of exacerbation" rather than the more narrow COPD exacerbation-specific indication of roflumilast as a "maintenance treatment to reduce exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbations" subsequently proposed during the review cycle. The committee also discussed the clinical relevance and generalizability of the magnitude of the effect seen on the efficacy variables and the adequacy of overall safety data base. The committee was asked to deliberate and vote (for questions 3, 4, 5) on following five issues:

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)

The vote was Yes: 9, No: 6

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)

The vote was Yes: 9, No: 6

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)

The vote was Yes 5, No 10

When voting on questions 3 and 4, while a majority of the members of the advisory committee felt that roflumilast demonstrated enough efficacy OR had an adequate safety profile for approval, for question 5 the majority voted that roflumilast did not demonstrate adequate efficacy AND safety to support approval (i.e., the risk/benefit determination was not adequate to support approval).

Comments made by the committee members included that that they would be more favorable on efficacy and approvability with the proposed more restrictive indication and that given its safety profile that a risk mitigation strategy should be developed for roflumilast. Others felt that a study should be conducted to assess whether roflumilast gives added benefit to COPD patients who are already receiving a fixed dose ICS/LABA combination product which are frequently used both to treat reversible bronchoconstriction and to reduce COPD exacerbations.

10. Pediatrics

COPD is an adult disease; therefore, specific pediatric studies are not required nor were conducted.

11. Other Relevant Regulatory Issues

- Financial Disclosure: For the trials designated as pivotal by the applicant (M2-124 and M2-125) no significant equity interest as defined in 21 CFR 54.2(b) were held by the clinical investigators. There were a total of six investigators or subinvestigators involved in either study M2-125 or 125 that had not signed financial disclosure forms. Each of these investigators had left the study practice site prior to completion of the studies and were not able to be located. Based on the large size and number of sites in

the trials (approximately 1500 patients and 300 sites for each trial, it is unlikely that any financial interests these investigators would influence the results of these studies.

(b) (4)

DSI audits of clinical sites that participated in studies M2-124 and 125 (Beatrix Balint, MD/Site# 4545/Hungary, Neal Moser/Site# 7176/USA, Halina Batura-Gabryel, MD/Site# 6675/Poland, and Anthony Mesquita, MD/Site# 4793/India) were also conducted and revealed no irregularities that would impact data integrity.

- The Division of Medication Error Prevention and Analysis reviewed the initially-proposed proprietary name "Daxas" from a safety and promotional perspective and judged it unacceptable based, at least in part, (b) (4)

- The Division of Risk Management and Division of Drug Marketing, Advertising, and Communications were consulted to review proposed patient labeling. Final comments are pending at the time of this review.

12. Labeling

The Applicant submitted a product label in PLR format for review with the resubmission which included reference to a Medication Guide submitted on April 14, 2010, as a component of a risk mitigation plan (REMS).

Despite the recognition of the need for a Medication Guide to fully inform patients of the higher rate of psychiatric adverse and gastrointestinal adverse events and weight loss associated with the use of roflumilast, the label submitted by the Applicant tends to overstate the efficacy and minimize the risks associated with treatment with roflumilast and is being extensively revised to provide fair balance. At the time of this review label discussions with the Applicant are continuing.

Also of note, is that at the time of this review, there has been no agreement as to the tradename. The original proposed tradename, "Daxas", was viewed as unacceptable by the Division of Medication Error Prevention and Analysis. The alternative name, (b) (4) is currently being reviewed.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for Approval. During the first review cycle, substantial evidence for efficacy was provided for roflumilast to reduce the risk of COPD exacerbations a specific subpopulation of COPD patients, those with severe COPD (post-bronchodilator FEV1 < 50% predicted) associated with chronic bronchitis and a history of exacerbations. In this review cycle, based on a comprehensive assessment of suicidality submitted by the Applicant not finding additional events of suicidality, the risk benefit assessment for roflumilast supports approval in the subpopulation of patients with severe COPD associated with chronic bronchitis and a history of exacerbations for which it demonstrated efficacy in two 1-year clinical trials. The psychiatric and gastrointestinal adverse events and weight loss safety risks will be managed by a Medication Guide-only Risk Evaluation and Mitigation Strategy (REMS) to fully inform patients of the higher rate of psychiatric adverse and gastrointestinal adverse events and weight loss associated with the use of roflumilast. An enhanced pharmacovigilance plan will also be in place in which postmarketing reports of psychiatric adverse reactions related to depression and suicidality will be submitted as expedited reports.

In addition to the safety concerns which precluded approval during the first review cycle, the Applicant has also adequately addressed the two other deficiencies outlined in the May 17, 2010, Complete Response letter, (b) (4) and the determination that roflumilast is not a P-gp substrate.

- Risk Benefit Assessment

In this response to the Complete Response letter dated May 17, 2010, the Applicant has conducted additional analyses of the roflumilast clinical trials database to better assess the degree and extent of a potential suicide and known psychiatric adverse event safety signal. Based on a lack of additional findings of suicidality in the clinical program and the belief that use of a Medication Guide will be able to adequately inform patients of the higher rate of psychiatric and gastrointestinal adverse events and weight loss associated with roflumilast, the use of roflumilast in the subpopulation patients with severe COPD patients associated with chronic bronchitis and a history of COPD exacerbations, a population with few alternative therapies, is acceptable.

1. Recommendation for Postmarketing Risk Management Activities

A Medication Guide-only REMS was proposed by the Applicant on April 14, 2010, and is appropriate to fully inform patients of the potential risks associated with the use of roflumilast and to help ensure that the benefits of roflumilast outweigh those potential risks. Based on the results of the full C-CASA assessment of suicidality submitted in this complete response in which no additional suicidality-related adverse reactions were detected for the entire roflumilast program and the known small nominal increase in suicide-related events in roflumilast treated patients was observed, a Boxed Warning is not felt to be necessary. A Medication Guide-only REMS will be employed to fully inform patients of the potential risks regarding psychiatric adverse events and suicidality. The increase in gastrointestinal system adverse events and weight loss observed in patients treated with roflumilast in clinical trials will also be addressed in the Medication Guide.

An enhanced pharmacovigilance plan will also be in place in which postmarketing reports of psychiatric adverse reactions related to depression and suicidality will be submitted as expedited reports.

2. Recommendation for other Postmarketing Study Commitments

During the course of the first review cycle, there was agreement within the Division that the issue of the efficacy of roflumilast when added to current therapies for COPD patients, such as use of combination products containing an inhaled corticosteroid plus an inhaled LABA, would be important to address in order to make provide useful information for physicians on the use of roflumilast. Additional internal discussion occurred regarding whether this issue should be addressed as a condition for approval or could be handled as a post-marketing commitment. Based on the acknowledgement that roflumilast has demonstrated substantial efficacy in an identifiable subpopulation of patients with severe COPD associated with chronic bronchitis and a history of exacerbations and that no additional suicidality signal was detected in the C-CASA suicidality assessment across all roflumilast clinical programs, a clinical trial to assess the efficacy of roflumilast when added to a fixed-dose LABA/ICS combination drug in the roflumilast indicated population will be performed as a post-marketing commitment. The following postmarketing commitment was discussed with the Applicant by telephone on

January 20, 2011. The Applicant is to submit the dates the final protocol will be submitted, the study will be finished by, and when the final study report will be submitted,

- Conduct a controlled clinical study to evaluate the efficacy of roflumilast as an add-on therapy to a long-acting beta agonist and inhaled corticosteroid fixed dose combination therapy in the population of COPD patients for which roflumilast is indicated [severe COPD (FEV1 < 50% predicted) associated with chronic bronchitis and a history of exacerbations]. The design of the study should be appropriate to demonstrate a clinically relevant beneficial effect of roflumilast as an add-on therapy compared to a long-acting beta agonist and inhaled corticosteroid fixed dose combination treatment.

The following postmarketing CMC Commitment is also recommended:

- Reassess the drug substance particle size distribution (PSD) acceptance criteria after preparation of multiple (e.g., n = 10) commercial batches that are used to produce drug product and to make adjustments that will reflect the PSD data.

3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed to the applicant.

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/s/

ANTHONY G DURMOWICZ
02/07/2011