1.0 TITLE PAGE

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DAXAS® (roflumilast) in Chronic Obstructive Pulmonary Disease

NDA 22-522

FDA Advisory Committee Briefing Document

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2.0 ABBREVIATIONS

ADCP	4-Amino-3,5-dichloropyridine
ADCP N-oxide	4-Amino-3,5-dichloropyridine N-oxide
AE	Adverse event(s)
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
AUC	Area under the plasma concentration-time curve
BMI	body mass index
bpm	beats per minute
cAMP	cyclic adenosine monophosphate
cGMP	Guanosine 3′, 5′-cyclic monophosphate
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CI	Confidence interval
C_{max}	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome P450
ECG	Electrocardiogram
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FFMI	fat-free mass index
FOB	fecal occult blood
FVC	forced vital capacity
GI	Gastrointestinal
γ-GT	gamma-glutamyltranspeptidase

GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	hazard ratio
IC	inspiratory capacity
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IV	*Intra vena*; by intravenous application
IL	Interleukin
ITT	intention-to-treat
L	Liter
LABA	long-acting β2-agonist
LABD	long-acting bronchodilators
LAMA	long-acting muscarinic agonist = long-acting anticholinergic
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of patients or test animals
NDA	New Drug Application
NOAEL	No observable adverse effect level
PDE	phosphodiesterase
p.o.	*Per os*, by oral application
Pre	pre-bronchodilator
Post	post-bronchodilator
pred.	predicted
PT	preferred term
ROW	rest of world
ROF250	roflumilast 250 mcg once daily
ROF500	roflumilast 500 mcg once daily
ROS	reactive oxygen species

SABA	short-acting β2-agonist
SAMA	short-acting muscarinic agonist = short-acting anticholinergic
SD	standard deviation
SEM	Standard error of the mean
SGRQ	Saint George Respiratory Questionnaire
SOBQ	Shortness of Breath Questionnaire
SOC	system organ class
TDI	Transition Dyspnea Index
t_{max}	Time to reach maximum plasma concentration
TNF-α	Tumor necrosis factor alpha
$t_{½}$	Half-life
ULNR	upper limit of the normal range
V_{last}	last post-randomization measurement

3.0 EXECUTIVE SUMMARY

3.1 INTRODUCTION

Roflumilast is a novel phosphodiesterase-4(PDE4) inhibitor developed as an oral once-a-day treatment for Chronic Obstructive Pulmonary Disease (COPD) targeting the underlying inflammatory processes of this condition. In July 2009, a New Drug Application was submitted pursuing the following claim:

> *Roflumilast, at the dose of 500 mcg per day, is indicated as maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.*

The core of the development program of roflumilast in COPD consists of six long-term randomized, placebo-controlled, parallel-group studies in 7,453 COPD patients (M2-111, M2-112, M2-124, M2-125, M2-127 and M2-128). All six studies consistently demonstrated efficacy of 500 mcg roflumilast over placebo in reducing the rate of moderate to severe exacerbations and improving lung function. The reduction in exacerbation rate due to roflumilast was clinically meaningful in its magnitude (common across all six studies) and statistically significant in the two 1-year pivotal trials (M2-124 and M2-125) specifically designed to study patients at higher risk for exacerbations. The safety of roflumilast 500 mcg once daily has been evaluated in 12,054 randomized and treated COPD patients, of whom 5,766 received roflumilast 500 mcg once daily in a total of 14 Phase 2 and Phase 3 long and short-term studies, demonstrating a positive risk-benefit profile.

3.2 REGULATORY HISTORY

The original IND for roflumilast was submitted in 1999 in support of an asthma clinical development program and was later amended to support the development of roflumilast in COPD. During an End of Phase 2 meeting on December 6, 2001 and during a follow-up teleconference on October 3, 2002, the Sponsor received guidance from the FDA that led to the selection of 500 mcg as the maximum dose in subsequent COPD Phase 3 trials.

The core COPD clinical development program was initiated in the United States with Study M2-111, in December 2003, and the core COPD clinical program was subsequently discussed with the FDA at different stages between 2003 and 2008. FDA advice on primary endpoints, including exacerbations and FEV_1, was taken into account for Study M2-111, the pivotal Studies M2-124 and M2-125, as well as Studies M2-127 and M2-128. The NDA for roflumilast in COPD was received by FDA on July 17, 2009, after which the NDA was transferred from Nycomed to the Forest Research Institute. To date, roflumilast is not approved or marketed in any foreign country.

3.3 COPD BACKGROUND

COPD is characterized by a decline in lung function due to small airway fibrosis, mucus hypersecretion and emphysema. The major causative factor is cigarette smoking that drives an inflammatory process resulting in airway fibrosis and loss of alveolar tissue. COPD is complicated by frequent and recurrent acute exacerbations which are associated with significant morbidity, disability, and also mortality. It is predicted to become the third leading cause of disease burden in terms of disability adjusted life-years and the fifth leading cause of death by 2020 (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2009).

The current mainstay of COPD treatment includes bronchodilators (short- and long-acting beta agonists and muscarinic antagonists) which target lung obstruction but also reduce exacerbations. The long-acting muscarinic antagonist, tiotropium, demonstrated reduction in the frequency of exacerbations of 14% -19% in two large trials, UPLIFT and the Veterans Affairs Trial (Tashkin, 2008 and Niewoehner, 2005). These two trials formed the basis of a recent approval for reducing COPD exacerbations, highlighting the importance of reduction of exacerbations in the management of COPD. Because exacerbations are linked to inflammation, inhaled corticosteroids are often added in advanced disease, to improve lung function and lessen the frequency of exacerbations. For example, salmeterol alone versus placebo reduced exacerbations by 15%; adding fluticasone to salmeterol in a fixed combination demonstrated an additional reduction in exacerbations by 12% versus salmeterol alone in TORCH (Calverley, 2007).

With regards to lung function in a COPD patient, the magnitude of effect size by a potential therapeutic agent depends on the underlying severity of disease as assessed by FEV_1. Changes in FEV_1 following pharmacological therapy are less marked in patients with lower baseline lung function (Cazzola, 2008).

Roflumilast was developed as a novel, once-daily oral treatment option for COPD that targets the underlying inflammatory disease processes. Roflumilast exerts its anti-inflammatory activity via selective phosphodiesterase-4 (PDE4) inhibition. Its mechanism of action is different from steroids, and therefore is not associated with their well-known side effects (eg, increased incidence of pneumonia, glaucoma and cataracts, localized infections, immunosuppression, decrease in bone mineral density). Roflumilast is rapidly absorbed after oral administration and the effective half-lives (steady-state) of roflumilast and its active metabolite, roflumilast-N-oxide, are 17 and 30 hours, respectively, supporting once-daily oral dosing.

3.4 CLINICAL DEVELOPMENT PROGRAM AND EFFICACY

Evidence for the anti-inflammatory activity of roflumilast is derived from short- and long-term preclinical studies in animal models of COPD, multiple *in vitro* studies with human cells relevant to COPD pathology, and two clinical studies of 4-week treatment duration.

In Phase 1 and early Phase 2 studies, doses from 100 to 5,000 mcg were evaluated. A maximum tolerated dose of 1,000 mcg was established, while 500 mcg once daily showed good tolerability during repeat dosing. Based on these findings, the doses of 250 and 500 mcg once daily were assessed in a 6-month study, M2-107, in a total of 1,411 COPD patients, resulting in the 500 mcg dose being selected for all subsequent Phase 3 studies.

The core clinical development in COPD began with two 1-year studies, M2-111 with 1,173 patients[1] and M2-112 with 1,513 patients. Because of the clinical importance of exacerbations, especially in severe COPD, both studies were designed to investigate the effect of roflumilast 500 mcg once daily on two co-primary endpoints, rate of exacerbations and change in FEV_1 from baseline, in patients with a post-bronchodilator FEV_1 of less than 50% predicted. Roflumilast treatment significantly improved pre-bronchodilator FEV_1 compared to placebo by 42 mL in Study M2-111 and by 57 mL in Study M2-112. The rate of moderate or severe exacerbations, using definitions and analysis methods as in the pivotal studies, was numerically reduced by 14% ($p = 0.1294$) in Study M2-111 and by 15% ($p = 0.0847$) in Study M2-112, compared to placebo. The rate of moderate or severe exacerbation in the pooled analysis of both studies was reduced by 14.3% ($p = 0.0257$). A post-hoc subgroup analysis of M2-111 and M2-112 indicated that patients with chronic bronchitis achieved the greatest benefit from treatment with roflumilast (26% reduction in acute exacerbations [rate ratio = 0.738, 95% CI = 0.616, 0.885]).

Based on the results of studies M2-111 and M2-112, two new independent, identical, 1-year pivotal trials, M2-124 with 1,523 patients and M2-125 with 1,568 patients, were designed to confirm the effect of roflumilast in reducing exacerbation rates in COPD patients with chronic bronchitis and a history of exacerbations. The COPD patient population enrolled had a post-bronchodilator FEV_1 of less than 50% predicted, chronic bronchitis, and at least one exacerbation within the previous year prior to enrollment. Both studies M2-124 and M2-125 confirmed the earlier results generated in studies M2-111 and M2-112. Treatment with roflumilast 500 mcg once daily significantly reduced the rate of moderate or severe exacerbations by 14.9% ($p = 0.0278$) in study M2-124 and by 18.5% ($p = 0.0035$) in Study M2-125 compared to placebo. Pre-bronchodilator FEV_1 improved compared to placebo by 39 mL ($p = 0.0003$) in Study M2-124 and by 58 mL ($p<0.0001$) in Study M2-125.

[1] Numbers of patients in each study referred to in this briefing book represent total patients randomized and treated, unless stated otherwise.

Two additional supportive studies, M2-127 with 933 patients and M2-128 with 743 patients, evaluated the treatment effects of roflumilast 500 mcg once daily added to salmeterol (M2-127) or tiotropium (M2-128) in a moderate to severe patient population. Both trials were 6-month double-blind studies with lung function (pre-bronchodilator FEV_1) as the primary endpoint. In Study M2-127, roflumilast with salmeterol significantly improved pre-bronchodilator FEV_1 by 49 mL ($p < 0.0001$) compared to salmeterol alone, and in Study M2-128, roflumilast with tiotropium significantly improved pre-bronchodilator FEV_1 by 80 mL ($p < 0.0001$) compared to tiotropium alone.

Although these studies were not powered to test for exacerbations, moderate or severe exacerbations were analyzed (post-hoc in Study M2-127 and as a designated secondary endpoint in Study M2-128) with results consistent with the 1-year pivotal studies. Reduction in the rate of moderate or severe exacerbations was observed in patients treated with roflumilast by 37% ($p = 0.03$) in Study M2-127 and 23% ($p = 0.20$) in Study M2-128.

The results of M2-127 and M2-128 and various subgroup analyses across other studies demonstrated that the beneficial effects of roflumilast were independent of, and additive to, the effects of LABAs, LAMAs, SAMAs, and ICS. The effects of roflumilast were also independent of gender, age, race, and smoking status.

In summary, oral once-daily administration of roflumilast 500 mcg resulted both in a statically significant and clinically meaningful reduction of moderate and severe exacerbations and in an improvement of lung function in moderate as well as in severe COPD patients with chronic bronchitis.

3.5 SAFETY

Safety of roflumilast 500 mcg has been characterized in a large COPD safety pool that includes 14 double-blind, placebo-controlled trials in which 5,766 COPD patients received roflumilast 500 mcg once daily, 797 patients received 250 mcg once daily, and 5,491 received placebo. The median treatment duration with roflumilast 500 mcg once daily was 169 days (24 weeks) with 1,232 patients treated for at least one year.

In the COPD safety pool, adverse events reported more frequently (≥ 2% and twice the placebo rate) in roflumilast-treated patients were diarrhea (10% roflumilast vs. 3% placebo), weight decrease (7% roflumilast vs. 2% placebo), nausea (5% roflumilast vs. 1% placebo) and headache (5% roflumilast vs. 2% placebo). Most adverse events generally occurred within the first weeks of therapy and resolved during continued treatment.

Adverse events resulting in study discontinuation occurred in 824 patients (14.3%) with roflumilast and in 503 patients (9.2%) receiving placebo. The difference in discontinuation rate between roflumilast and placebo was mostly due to gastrointestinal events (nausea, diarrhea). Discontinuation due to all other AEs other than GI related events was similar between roflumilast (9.2%) and placebo (8.4%).

Serious adverse events occurred approximately in equal numbers in patients receiving roflumilast (13.5%) and placebo (14.2%). A total of 177 deaths occurred in the COPD safety pool. Death was reported for 84 patients (1.5%) in the roflumilast 500 mcg group, 7 patients (0.9%) in the roflumilast 250 mcg group, and for 86 patients (1.6%) in the placebo group.

Roflumilast had no clinically relevant effect on laboratory or ECG values or vital sign measures (with the exception of weight) compared to placebo treatment. On average, roflumilast patients experienced a weight decrease of 2 kg by comparison to placebo patients. The weight loss was greatest (in absolute amounts) in patients who were heaviest at baseline and generally plateaued after 6 months of therapy. Very few patients on roflumilast discontinued from study due to weight decrease. Most subjects did not show further weight loss and many regained weight within 3 months from cessation of treatment.

No clinically relevant pharmacokinetic interactions were observed with drugs that could be used in COPD patients including: inhaled salbutamol, formoterol, budesonide, oral theophylline, montelukast, digoxin, warfarin, sildenafil, oral or intravenous midazolam, Maalox®, oral contraceptives containing gestodene and ethinyl estradiol, fluvoxamine, cimetidine, enoxacin, erythromycin and ketoconazole.

3.6 BENEFIT-RISK

COPD is a major, growing health care problem causing significant morbidity and mortality. Treatment of COPD is mostly based on inhaled bronchodilators (long and short acting beta agonists and muscarinic agents) and inhaled corticosteroids with the objective of improving lung function and decreasing exacerbations.

Roflumilast represents a significant addition to the armamentarium of prescribing physicians for the following reasons:

- A demonstrated clinically relevant efficacy in reducing the rate of moderate and severe exacerbations and in improving lung function
- Additive effect on top of background bronchodilator therapy
- A novel mechanism of action that reduces inflammation with a mechanism different from corticosteroids

- An easy oral administration once-a-day with no clinically significant interactions with drugs commonly used by COPD patients

- Acceptable tolerability and safety profile

In summary, roflumilast offers a well-tolerated, effective, safe and simple once-a-day oral therapy that will benefit COPD patients with chronic bronchitis, providing a reduction of moderate to severe exacerbations and an improvement in lung function.

4.0 INTRODUCTION

4.1 COPD BACKGROUND

Chronic obstructive pulmonary disease (COPD) is characterized by a decline in lung function due to small airway fibrosis, mucus hyper-secretion and emphysema. The major causative factor is cigarette smoking that drives an inflammatory process resulting in airway fibrosis and loss of alveolar tissue. COPD is predicted to become the third leading cause of disease burden in terms of disability adjusted life-years and the fifth leading cause of death by 2020 (GOLD, 2009).

4.1.1 COPD Prevalence and Impact

The prevalence of COPD in the US is estimated to be 12-24 million people. A major clinical manifestation of this disease is symptomatic exacerbations. Exacerbations of COPD are estimated to result in approximately 124,000 deaths, more than 660,000 hospitalizations per year, and approximately 2 million emergency room visits, with over $26 billion spent in direct costs annually (Hess, 2010; Heron, 2009) and indirect costs of over $15 billion annually. In addition to the financial burden required to care for these patients, other costs, such as days missed from work and severe limitations in quality of life are important aspects of this condition (Miravitlles, 2002; 2004).

4.1.2 COPD Pathophysiology

COPD is a progressive disease characterized primarily by its pulmonary component but is also associated with significant extra-pulmonary consequences, such as cardiovascular disease, skeletal muscle dysfunction, cachexia, osteoporosis, depression, fatigue, and cancer (Agusti, 2007). The pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to tobacco smoking and rarely other noxious insults (GOLD, 2009). The inflammatory processes in COPD are characterized by an increase in the number or activity of CD8+ T-cells, macrophages, and neutrophils (O'Byrne, 1999). The chronic airflow limitation is caused by a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from patient to patient. The mechanisms underlying the extra-pulmonary symptoms of COPD are still unclear, but systemic inflammation is increasingly recognized as one of the contributing mechanisms (Fabbri, 2007).

4.1.3 COPD Exacerbations

Exacerbations are the periodic increases in symptoms (ie, cough, breathlessness, sputum) over baseline that usually necessitates a change in therapy. Data from the literature suggest acute COPD exacerbations have significant impact on patient health, longevity and decline in lung function. Exacerbations are significant and detrimental clinical events in the natural history of COPD and the frequency of exacerbations depends on the underlying severity of lung disease and history of prior exacerbations (Miravitlles, 2000). Several investigators have suggested that exacerbation frequency increases with disease severity (Burge, 2000; Paggiaro, 1998). Donaldson and colleagues (2002) have demonstrated exacerbation is a significant risk factor leading to hospitalization and is associated with an accelerated rate of lung function decline. Frequent exacerbations (> 2/yr) have been associated with increased dyspnea and reduced exercise capacity (Donaldson, 2002; Hodgev, 2004), greater decline in health status (Spencer, 2001; 2004); greater likelihood of becoming housebound (Donaldson, 2002; 2005), and increased mortality.

Lung function appears to be a significant predictor of exacerbations. Patients with an FEV_1 of more than 60% had a mean (± SD) of 1.6 (± 1.5) exacerbations per year compared with 1.9 (± 1.8) with an FEV1 of 59–40%, and 2.3 (± 1.9) with an FEV_1 of less than 40% (Paggiaro, 1998; Donaldson, 2002). Once the pattern of exacerbations is established, follow-up studies show that patients who suffer a high number of exacerbations during a given period of time will continue to suffer frequent exacerbations in the future (Gompertz, 2001). Therefore, frequency of exacerbations depends on patients' underlying severity of lung disease and number of prior exacerbations.

4.1.4 COPD Exacerbation-related Mortality

Clinical studies have reported a high mortality rate in patients admitted to the hospital with an acute exacerbation of COPD (Connors, 1996; Almagro, 2002; Groenewegen, 2003; Fuso, 1995; Soler-Cataluna, 2005). In-hospital mortality rates of 11–24% (Crooks, 2000) and 22–35.6% after 1 and 2 years, respectively have been observed(Almagro, 2002; Groenewegen, 2003). Soler-Cataluna et al (2005) reported that severe exacerbations of COPD have an independent, negative prognostic impact, with mortality increasing with the frequency of severe exacerbations and those requiring hospitalization. Patients with frequent exacerbations had the highest mortality rate ($p < 0.001$), with a risk of death 4.3 times greater (95% confidence interval [CI], 2.62-7.02) than that for COPD patients requiring no hospital management. Thus, exacerbation itself may be a significant factor associated with increased mortality in COPD.

4.1.5 Current Management of COPD and Limitations of Available Therapies

Despite rising mortality and health care costs, the therapeutic armamentarium for COPD remains limited to a few treatment options. Bronchodilators, which target lung obstruction but also exacerbation, are currently the mainstay of pharmacological therapy in COPD. Short- and long-acting inhaled anticholinergics and beta-agonists are the bronchodilators of choice. Because of the link of exacerbations to inflammation, inhaled corticosteroids (ICS) are often added in advanced disease. Other pharmacological treatment options include theophylline, which is not widely used anymore because of safety concerns.

The salmeterol/fluticasone fixed-dose combination and tiotropium are the most commonly used COPD treatments, with 38% and 28% of the patients receiving them respectively. Twenty-one percent of patients receive short acting beta agonists and anticholinergics, alone or in combination. Monotherapy with ICS or long-acting beta agonists are used in 8% and 5% of patients, respectively (Decision Resources Report, 2009).

The magnitude of treatment effect on exacerbation is comparable for all currently available treatments when used as a monotherapy for comparison purposes. Tiotropium demonstrated in two large trials (UPLIFT, Veterans Affairs Trial) a 14% - 19% reduction in the frequency of exacerbation. Another large trial (TORCH) showed that salmeterol was able to reduce exacerbation by 15% when compared to placebo; adding fluticasone to salmeterol in a fixed combination demonstrated an additional reduction in exacerbation by 12% versus salmeterol alone.

The effect size of current treatments on lung function in COPD shows a wider variation depending on type of treatment, patient baseline disease and study duration. The overall mean improvement in FEV_1 comparing tiotropium against placebo was 94 mL in a large 4 year study (UPLIFT). A 1-year study comparing a fixed-dose combination of salmeterol/fluticasone, fluticasone alone, and salmeterol alone against placebo demonstrated an improvement in FEV_1 in the salmeterol/fluticasone group of 163 mL, in the salmeterol-alone group of 75 mL, and in the fluticasone-alone group of 67 mL (Advair package insert). In a large 3-year study (TORCH), the improvements seen against placebo were: 92 mL in the salmeterol/fluticasone group, 42 mL in the salmeterol-alone group, and 47 mL in the fluticasone-alone group. These studies also clearly demonstrate the additive effect of adding an anti-inflammatory agent to a long-acting beta-agonist.

The main safety concerns with the most commonly used treatments for COPD are:

- Long-acting beta agonists should be used with caution in patients with cardiovascular disorders because of potential cardiovascular effects including ECG changes (Foradil, Serevent package inserts).

- Long-acting anticholinergics are generally well tolerated with dry mouth, worsening of narrow-angle glaucoma, and worsening of urinary retention as the most relevant adverse events (Spiriva package insert).

- Inhaled corticosteroids have been shown to increase the risk for development of cataracts, osteoporosis (Gartlehner, 2006; Suissa, 2007), open-angle glaucoma (Gartlehner, 2006) and pneumonia (Drummond, 2008) as detailed in the Advair package insert.

It is with this background of available treatment options in mind that roflumilast as a new treatment alternative should be evaluated.

4.2 RATIONALE FOR USE OF ROFLUMILAST IN COPD

The FDA states in their 2007 *Draft Guidance for Industry: "Chronic Obstructive Pulmonary Disease: Development of Drugs for Treatment"* that there is a need to develop new drugs for COPD, especially drugs that alter the underlying inflammation of COPD or disease progression.

Phosphodiesterases (PDEs) are a large family of intracellular enzymes that hydrolyze the cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP). PDE4 is the main enzyme in neutrophils, monocytes, lymphocytes and macrophages which inactivates cAMP. Inhibition of PDE4 increases intracellular cAMP, which ultimately results in reduction of cellular inflammatory activities (Brown, 2007).

Selective inhibition of PDE4 has emerged as a target for rational drug development in a variety of inflammatory diseases such as COPD (Spina, 2008).

The anti-inflammatory activity of the selective PDE4 inhibitor roflumilast has been proven *in vitro* and in several animal models of inflammation and includes, among other activities, inhibition of the synthesis of leukotriene B4 and reactive oxygen species in neutrophils, as well as partial inhibition of tumor necrosis factor α (TNF- α) from mononuclear cells. The therapeutic utility of previous PDE4 inhibitors in development was limited due to intolerability and an inadequate demonstration of efficacy in COPD. In contrast, clinical studies have demonstrated higher pharmacologic activity and better tolerability of roflumilast as compared to earlier PDE4-inhibitors in development. Therefore, roflumilast has been developed as an innovative once-daily oral treatment for COPD, targeting the inflammatory processes that are relevant to the disease. Roflumilast is expected to provide more targeted anti-inflammatory activity in COPD than corticosteroids, which do not suppress a predominantly neutrophilic inflammatory response in this patient population (Barnes, 2003).

5.0 NONCLINICAL FINDINGS

Roflumilast and its active metabolite, roflumilast N-oxide, are highly selective PDE4 inhibitors. PDE4 represent a family of four isoenzymes (PDE4A, B, C and D) each with multiple splicing variants; of these, PDE4A has been found to be significantly up-regulated in lung macrophages from smokers with COPD when compared to control smokers. Further, PDE4A as well as PDE4B transcripts were detected in higher amounts in peripheral monocytes from smokers when compared to non-smokers (Barber, 2004). Roflumilast's potential therapeutic activity in COPD is supported by its anti-inflammatory activity and *in vivo* efficacy in relevant animal models, as described below.

5.1 PHARMACOLOGY

5.1.1 *In Vitro* Pharmacology

Roflumilast blocks PDE4 isoenzymes (4A, 4B and 4D) activity with an IC_{50} ranging between 0.08-0.36 mcg/L while the IC_{50} for roflumilast-N-oxide range between 0.16-0.85 mcg/L. Both roflumilast and its active metabolite inhibit PDE4C with lower potency (range for roflumilast 1.21-1.73 mcg/L, and for the N-oxide 2.01-3.94 mcg/L). The potency of roflumilast is about 3-fold higher compared to its N-oxide metabolite, while their selectivity against other phosphodiesterases is at least 700-fold.

Roflumilast and roflumilast-N-oxide have a broad functional role in most of the inflammatory and immune cells that are involved in the inflammation and airway remodeling that occurs in COPD. Neutrophils, macrophages and $CD8^+$ lymphocytes are the predominant leukocytes present in the lungs of COPD patients, with eosinophils present in some individuals during exacerbations. The release of cell-specific mediators (eg, leukotrienes), reactive oxygen species (ROS), and various granule constituents (eg, neutrophilic proteases) appear to be involved in the amplification of the inflammatory response, lung damage, and smooth muscle contraction, which ultimately leads to lung function decline and increases risk for exacerbations (O'Byrne, 1999). Roflumilast and roflumilast N-oxide affect cellular functions in neutrophils, eosinophils, monocytes/macrophages and lymphocytes. Both compounds inhibit the formation of inflammatory mediators including, ROS, leukotriene B4 (LTB_4), TNF-α, interleukins IL-2, IL-4, IL-5 and interferon-γ (IFN-γ) by human cells *in vitro* under multiple experimental conditions (Hatzelmann, 2001). As such, roflumilast is expected to reduce the inflammation associated with COPD.

Table 5.1.1–1 summarizes *in vitro* inhibitory effects of roflumilast and roflumilast N-oxide, when tested against different inflammatory cells.

Table 5.1.1–1. Summary of *In Vitro* Inhibitory Effects of Roflumilast, Roflumilast N- Oxide, When Tested Against Different Inflammatory Cells

Cells	***Stimulus***	***Parameter***	***IC (mcg/L)***	***Roflumilast***	***Roflumilast N-oxide***
Neutrophils	fMLP	ROS	IC_{35}	~1.1	2.5
		LTB_4	IC_{50}	0.5	2.1
Eosinophils	fMLP	ROS	IC_{35}	2.8	8
	C5a	ROS	IC_{35}[a]	4	17
Monocytes	LPS	TNF-α	IC_{40}	8	8
Dendritic cells[b]	LPS	TNF-α	IC_{20}	1.6	1.3
Macrophages[b]	LPS	TNF-α	IC_{35}[c]	5	5
$CD4^+$ T-cells	anti-CD3 + anti-CD28 mABs	Proliferation	IC_{30}	2.8	3.8
		IL-2	IC_{20}	0.4	0.4
		IL-4	IC_{25}	2.0	0.8
		IL-5	IC_{25}	~5.2	2.1
		IFN-$_\gamma$	IC_{35}	3.2	1.3
$CD8^+$ T-cells	anti-CD3 + anti-CD28 mABs	IL-2	IC_{50}[d]	3.4	1.2
		Granzyme B	IC_{45}[d]	1.1	1.5
Whole blood	LPS	TNF-α	IC_{30}	20	25
	fMLP	CD11b	IC_{50}	20.5	76

a in presence of salbutamol.
b differentiated from monocytes.
c in presence of PGE2 + motapizone.
d in presence of motapizone.
ROS = reactive oxygen species; fMLP= Formyl Methionyl-Leucyl-Proline; LPS= lipopolysaccharide; mABs=monoclonal antibodies; TNF-α= tumor necrosis factor alpha.

Leukocyte recruitment into the lung is particularly manifested during exacerbations but it is also responsible for the chronic inflammation seen in COPD patients. In preclinical studies, roflumilast and roflumilast N-oxide have been shown to block leukocyte recruitment by inhibiting the expression of adhesion molecules in both leukocytes and endothelial cells (Jones, 2005; Sanz, 2007), resulting in inhibition of leukocyte adherence to endothelial cells and emigration. Roflumilast and its N-oxide also decreased macromolecule permeability of endothelial cell layers and microvascular permeability *in vivo* (Sanz, 2007).

Mucociliary hyperplexia, alveoli destruction and lung fibrosis, grouped under the general term airway remodeling, are features of COPD pathology (Wright, 2005), and are the primary cause for the progression of lung function decline observed in COPD patients. In pharmacology studies roflumilast and roflumilast N-oxide have been shown to stimulate ciliary beating frequency in human nasal epithelial cells (Milara, 2008), activate the CFTR channel (Pedemonte, 2008) and inhibit the expression of the mucus glycoprotein MUC5AC in human airway epithelial cells (Mata, 2005), suggesting a potential effect of roflumilast in improvement of mucus clearance, reducing mucus plaques and airway obstruction. In addition, roflumilast has been shown to mitigate fibroblast differentiation and proliferation in response to different stimuli *in vitro* (Togo, 2009), further supporting its potential role in blocking airway remodeling and lung fibrosis, typical features of disease progression.

5.1.2 *In Vivo* Pharmacology

The efficacy of roflumilast as an anti-inflammatory agent and its beneficial effect on lung inflammation and remodeling was investigated in COPD and lung injury models. Roflumilast's anti-inflammatory activity is supported by its efficacy in acute and chronic models of lung inflammation. Roflumilast dose-dependently blocked neutrophil infiltration to the lung and the release of TNF-α, MCP-1, and MIP-1α into the BALF after an LPS challenge with oral ID_{50} values in the range of 0.09 to 0.8 mg/kg. In a mouse cigarette smoke model, roflumilast prevented the accumulation of inflammatory cells, decreased IL-8 and keratinocyte-derived chemokine and increased the levels of the anti-inflammatory cytokine IL-10 in BALF and lung tissue; roflumilast also decreased matrix degradation and parenchymal destruction induced by exposure to cigarette smoke (Martorana, 2005/2008, Le Quement, 2008). The potential effect of roflumilast on airway remodeling is further supported by its efficacy in experimental models of lung injury, hypoxia and monocrotaline-induced pulmonary hypertension and bleomycin-induced lung fibrosis. In these models, roflumilast inhibited lung fibrosis, vascular remodeling and the expression of biomarkers of inflammation and tissue remodeling (IL-6, MCP-1, transforming growth factor β-1, connective tissue growth factor, α (I)-collagen, endothelin-1 and MUC5AC).

The anti-inflammatory effect of roflumilast was compared to that of corticosteroids in cigarette smoke and lung injury models. In guinea pigs roflumilast substantially inhibited the cigarette smoke-induced accumulation of leukocytes. In contrast, in the same model, methylprednisolone at a pharmacologically relevant dose did not prevent the infiltration of leukocytes except of eosinophils. Protease activity in BAL-fluid was not affected by roflumilast, but increased by methylprednisolone. In bleomycin-induced lung injury in mice, roflumilast upon therapeutic administration reduced the increase in α I (I) collagen, CTGF and TGFβ1 mRNA and lung fibrosis, while dexamethasone was not effective (Cortijo, 2009). Results from these studies demonstrate that roflumilast exhibits a better anti-inflammatory profile than corticosteroids in animal models of COPD.

5.1.3 Receptor Binding and Non-Clinical Safety Pharmacology

The selectivity and safety of roflumilast and roflumilast N-oxide was evaluated against all known human phosphodiesterases (1-11), a standard panel of receptors, enzymes, and *in vivo* safety pharmacology studies. Roflumilast and its N-oxide metabolite are potent and highly selective PDE4 inhibitors and exhibit selectivity greater than 700-fold over other phosphodiesterases. At a concentration of 10 μM, roflumilast and roflumilast N-oxide did not have any significant effect in any of the 68 molecular targets (receptors and enzymes) tested. Similarly, roflumilast did not show any significant signal on the central nervous system (Irwin test), cardiovascular system (dog cardiovascular safety studies, guinea pig Langendorff heart preparations and hERG assay), gastrointestinal and renal systems at pharmacologically relevant doses. Overall, the results of these non-clinical safety pharmacology studies suggest no safety concerns with roflumilast and roflumilast N-oxide at exposures equivalent to the free plasma maximum drug concentration (C_{max}) in humans dosed with 500 mcg once daily.

5.1.4 Conclusions

In conclusion, the anti-inflammatory activity of roflumilast and its mitigation of lung tissue remodeling support its therapeutic potential in the treatment of COPD pathology. Furthermore, preclinical evidence in COPD models suggests that the inflammatory response in these models is less responsive to the anti-inflammatory effect of corticosteroids when compared to treatment with roflumilast.

5.2 ANIMAL SAFETY STUDIES

A comprehensive nonclinical safety program was conducted to support the use of 500 mcg once daily roflumilast orally in adults for chronic treatment including studies of roflumilast, roflumilast N-oxide, and two main animal metabolites, aminodichloropyridine (ADCP) and ADCP N-oxide.

The nonclinical program included:

- single-dose toxicity studies in rats, mice, and dogs
- subchronic and chronic toxicity studies for durations of up to 3 months in hamsters, 26 weeks in mice and rats, 42 weeks in monkeys, and up to 52 weeks in dogs
- evaluation of the mutagenic and clastogenic potential *in vitro* and *in vivo* systems
- carcinogenicity assessments in conventional two-year hamster and mouse bioassays
- reproductive toxicity assessments in male and female rats or mice and female rabbits
- other studies to investigate specific toxicologic issues (eg, nasal olfactory toxicity)

The gastrointestinal tract is the main target organ of toxicity for PDE4 inhibitors. Emesis, gastric erosions and inflammation, inflammation of the mesentery and mesenteric arteritis are commons lesions noted for these compounds (Dietsch, 2006, Zhang, 2002; Zhang, 2008).

Gastrointestinal observations for roflumilast include emesis in dogs and monkeys and gastric erosions and transient mucosal inflammation in rats and monkeys. Emesis occurred at doses ≥ 2 mg/kg in the dog and ≥ 0.7 mg/kg in the monkey. The exposure multiple (compared to the exposure at the clinical dose of 500 mcg once daily) at the No Observed Adverse Effect Level (NOAEL) was 14X and 15X for roflumilast in the dog and monkey, respectively, and 4X for roflumilast N-oxide in the monkey (dogs do not metabolize roflumilast to roflumilast N-oxide in significant amounts). The NOAEL for gastric erosion and transient mucosal inflammation was 1.5 mg/kg/day for the rat and 0.25 mg/kg/day for the monkey (exposure multiples were 1X in the rat and 6X in the monkey for roflumilast and 2X in both species for roflumilast N-oxide).

In rats, mortality occurred at the high dose of 8 mg/kg/day and histopathologic lesions in the small intestines including inflammation of the mesentery and other secondary lesions were observed. At this dose the estimated exposures were 5X and 11X for roflumilast and roflumilast N-oxide, respectively, as compared to the clinical dose of 500 mcg/day. Such lesions were not observed in other species at equal or higher exposures (at exposures ranging from 3X to 170X for roflumilast and 4X to 37X of roflumilast N-oxide in mice, hamsters, dogs and monkeys as compared to the exposure at the human clinical dose).

All exposure multiples are based on total drug levels and are higher by a factor of 2 to 4 when only free drug levels are considered due to higher protein binding in humans than in animals.

In view of the findings seen only in rats at overtly toxic doses, high safety margins present in other animal species, and based on the extensive clinical trial experience, it is concluded that treatment with roflumilast does not present a risk for mesenteric lesions in humans (see Section 8.6.4).

5.2.1 Other Animal Toxicities

Roflumilast caused species-specific effects on the nasal mucosa in rodents, the testes in rats and the heart in dogs. Based on the determined mechanism of toxicity or clinical data, these observations have been found not to be clinically relevant.

Nasal/olfactory lesions (from inflammation to tumors) were seen in mice, rats and/or hamsters. Roflumilast is metabolized to ADCP N-oxide and further metabolized by CYP 2G1 found in rodent nasal mucosa to a reactive compound that is toxic to the mucosa. Humans not only form very little ADCP N-oxide but also do not possess a functional CYP2G1 to form the toxic metabolite of ADCP N-oxide as in rodents. Furthermore, neither the two major human olfactory CYPs (CYP2A6 and 2A13) nor any of the other CYP isoenzymes which are potentially expressed in human nasal mucosa or lung metabolize ADCP N-oxide. Therefore no clinical relevance of the rodent-specific olfactory lesions is assumed for humans.

In view of the testicular findings in rats a 6-month clinical trial with roflumilast (500 mcg once daily), including a 3-month treatment period and a 3-month follow-up repeated analysis of ejaculates, was conducted. There were no effects seen on spermatogenesis in this trial.

In the dog cardiovascular lesions were seen mainly in the right auricle. Dogs are susceptible to cardiac toxicity caused by inotropic and vasodilatory drugs (Dogterom and Zbinden, 1992). The proposed mechanism for these effects is hypotension leading to increased heart rate and ventricular contraction, increased perfusion of the left and right ventricles by the left coronary artery (supplies left ventricle and part of the right ventricle), and finally a shift of coronary flow from right coronary artery to the left coronary artery leading to lesions in the right atrium and/or auricle caused by insufficient perfusion. These lesions occurred in dogs because of their unique anatomicophysiological features and they did not occur in any other species despite much higher drug exposures to roflumilast and roflumilast N-oxide and have no clinical relevance in humans.

Roflumilast has shown tocolytic (delays in delivery) effects in mice. These effects occurred at systemic exposures similar to those in humans. However, the relevance of these findings to humans is unknown. Roflumilast is not recommended for use during labor and delivery in humans.

5.2.2 Conclusion

Overall, the results of the nonclinical safety studies do not suggest any unique safety concerns with administration of a daily clinical dose of roflumilast 500 mcg once daily to COPD patients.

6.0 CLINICAL PHARMACOLOGY

6.1 MAXIMUM TOLERATED DOSE IN PHARMACOKINETIC STUDIES

In Phase 1 studies, single doses ranging between 100 to 5,000 mcg roflumilast were administered and a maximum tolerated dose of 1,000 mcg was established. Above a 1,000 mcg dose, adverse events, including dizziness, headache and diarrhea, occurred in a high number of patients. Repeated dosing over 7 days in healthy subjects demonstrated acceptable tolerability up to a dose of 500 mcg once daily, while a dose of 1,000 mcg was associated with more frequent as well as more pronounced AEs in comparison to the 500 mcg dose. Based on these results, the 500 mcg dose was selected to be further investigated in clinical development.

6.2 TOTAL PDE4 INHIBITORY ACTIVITY

In humans, after oral administration, roflumilast is rapidly absorbed with high absolute bioavailability of 79%. Roflumilast is metabolized to its major active metabolite, roflumilast N-oxide, mainly by the cytochrome P450 isozymes 1A2 and 3A4. Both roflumilast and roflumilast N-oxide are pharmacologically active, with intrinsic potency of roflumilast N-oxide being 3-fold lower than roflumilast. However, the N-oxide metabolite has 10 to 12-fold higher plasma AUC, and a 3-fold higher free fraction in plasma compared to the parent compound. As the N-oxide contributes about 90% of the overall PDE4 inhibitory activity and is the main moiety contributing to the pharmacodynamic activity of roflumilast, pharmacokinetic data were evaluated for both roflumilast and its N-oxide metabolite to assess overall PDE4 inhibitory activity.

6.3 PHARMACOKINETICS

6.3.1 Absorption

Absorption following single oral dosing with 500 mcg roflumilast was rapid with C_{max} occurring typically about 1 hour and 8 hours post-dose for roflumilast and roflumilast N-oxide, respectively. Median C_{max} was 7 and 9 mcg/L for roflumilast and roflumilast N-oxide, respectively. Median AUC was 40 and 415 mcg/h/L for roflumilast and roflumilast N-oxide, respectively. The absolute bioavailability of roflumilast following a single 500 mcg oral dose is approximately 80%.

Following repeated dosing (500 mcg once daily) under fasted conditions, the mean C_{max} of roflumilast and its N-oxide were between five and 10 mcg/L (median 7 mcg/L) and 22 to 43 mcg/L (median: 24 mcg/L), respectively. Steady-state plasma concentrations are reached after approximately four days (83 hours) for roflumilast, and after six days (148 hours) for the N-oxide.

The systemic exposure (AUC) of roflumilast and roflumilast N-oxide increased proportionally after single and repeated roflumilast doses between 250 mcg and 1000 mcg. Dose-proportionality for the same dose range was also held for C_{max}.

Following repeated dosing (500 mcg once daily), median half-life was approximately 17 and 30 hours for roflumilast and roflumilast N-oxide, respectively. The AUC within a dosing interval for roflumilast N-oxide was about 12 times higher than that of roflumilast.

6.3.2 Distribution

The volume of distribution after IV infusion was high, amounting to 2.9 L/kg. Binding of roflumilast and roflumilast N-oxide to human plasma proteins was approximately 99% and 97%, respectively. Protein binding was independent of drug concentrations up to 200 mcg/L (roflumilast) and 100 mcg/L (roflumilast N-oxide) indicating that saturation of protein binding for both compounds occurs only at plasma concentrations substantially above expected plasma levels at therapeutic doses. Studies in rats with radiolabeled roflumilast indicated low penetration across the blood-brain barrier.

6.3.3 Metabolism

Roflumilast is extensively metabolized via Phase 1 (CYP450) and Phase 2 (conjugation) reactions. The major metabolite found in human plasma is roflumilast N-oxide. The formation of the N-oxide is catalyzed mainly by cytochrome CYP450 3A4 and 1A2. The major compounds identified in urine included glucuronides of both the hydroxy-derivatives of roflumilast and its N-oxide metabolite. Roflumilast and roflumilast N-oxide are almost exclusively eliminated by metabolism with less than 1% found unchanged in urine.

6.3.4 Elimination

Excretion in humans after oral or IV administration occurred almost exclusively in the form of roflumilast metabolites and mainly via the kidneys (~70% of the dose). Fecal elimination accounts for approximately 20% of the dose. The total plasma clearance of roflumilast after IV administration was 9.6 L/h for a 70-kg person.

6.4 PHARMACOKINETIC ASSESSMENTS IN SPECIAL POPULATIONS

6.4.1 Age and Gender

In healthy elderly subjects (≥ 65 years of age), roflumilast and roflumilast N-oxide mean AUCs were greater by 27% and 19%, respectively, as compared to healthy young subjects (18-45 years of age). Mean peak concentration (C_{max}) of roflumilast and roflumilast N-oxide was higher in the elderly by 16% and 13%, respectively, compared with the young. For roflumilast and roflumilast N-oxide, in all age groups, higher systemic exposures were noted in females (45% and 43%, respectively), when compared with male subjects. These differences are not considered to be clinically relevant, therefore, no dosage adjustment is recommended in adult patients based on age or gender.

6.4.2 Liver Impairment

In a pharmacokinetic study, roflumilast 250 mcg once daily was administered to subjects with liver impairment as well as healthy subjects. Roflumilast and roflumilast N-oxide exposure increased with the degree of liver impairment. The AUC_{0-24h} of roflumilast was 51% higher in Child-Pugh A and 92% higher in Child-Pugh B patients compared to healthy subjects. Roflumilast N-oxide AUC_{0-24h} was 24% higher in Child-Pugh A and 41% higher in Child-Pugh B patients when compared with healthy subjects. C_{max} of roflumilast was 3% higher in Child-Pugh A and 26% higher in Child-Pugh B patients and that of roflumilast N-oxide were 26% higher in Child-Pugh A and 40% higher in Child-Pugh B patients compared to healthy subjects. Overall, the increase in exposure for mild hepatic impairment is ≤ 50% and not clinically significant, but the increase in exposure for moderate hepatic impairment is about 2-fold and therefore, the use of roflumilast 500 mcg film-coated tablets in patients with moderate and severe hepatic impairment is not recommended.

6.4.3 Renal Impairment

Mean systemic exposure of roflumilast and roflumilast N-oxide was 21% and 7%, respectively, lower in patients with severe renal impairment when compared with healthy subjects. Mean peak concentration of roflumilast was 16% lower in severe renally impaired subjects when compared with healthy subjects. Overall, there is no clinically relevant difference in exposures to roflumilast and roflumilast N-oxide between healthy subjects and patients with any degree of renal impairment (mild, moderate or severe). Roflumilast can be administered in patients with renal impairment with no dose adjustment. Roflumilast has not been studied in subjects with end-stage renal disease requiring hemodialysis.

6.5 DRUG INTERACTIONS

6.5.1 Inhibition and Induction of P450 Enzymes

Based on *in vitro* studies, roflumilast is metabolized mainly by CYP3A4 and 1A2, with minor contribution of CYP 2C19. *In vitro* studies were also conducted to assess the inhibitory potential of roflumilast and its N-oxide on major human liver CYP450 isoenzymes (CYP 1A2, 2A6, 3A4/5, 4A9/11, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1). There was either no inhibition, or inhibition was seen only at concentrations more than 100-times higher than the maximum plasma levels observed at therapeutic doses. These findings suggest that drug interactions due to inhibition of CYP450 isoenzymes is unlikely at clinically relevant plasma concentrations. Strong cytochrome P450 inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) may reduce the therapeutic effect of roflumilast by reducing the exposure to roflumilast and its N-oxide metabolite. The results of human studies to assess potential drug-drug interactions are described below.

6.5.2 Drug Interaction Studies

A comprehensive Phase 1 program was conducted to assess potential pharmacokinetic interactions of roflumilast with frequently used medications, including medications often used in the COPD population or drugs which are inhibitors of various CYP P450 isoenzymes.

No clinically relevant pharmacokinetic interactions were observed in drug interaction studies with drugs that could be used in COPD patients including: inhaled salbutamol, formoterol, budesonide, oral theophylline, montelukast, digoxin, warfarin, sildenafil, oral or intravenous midazolam, Maalox®, oral contraceptives containing gestodene and ethinyl estradiol, cimetidine, enoxacin, erythromycin and ketoconazole.

Coadministration of roflumilast with a strong CYP1A2 inhibitor fluvoxamine increased the exposure of roflumilast by about 150%, and roflumilast N-oxide by about 50%. Therefore, co-administration with a potent CYP1A2 inhibitor should be done carefully and if intolerance develops, treatment with roflumilast should be reassessed.

Co-administration of roflumilast and the cytochrome P450 enzyme inducer rifampicin 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%. Strong cytochrome P450 inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) might reduce efficacy.

7.0 CLINICAL EFFICACY

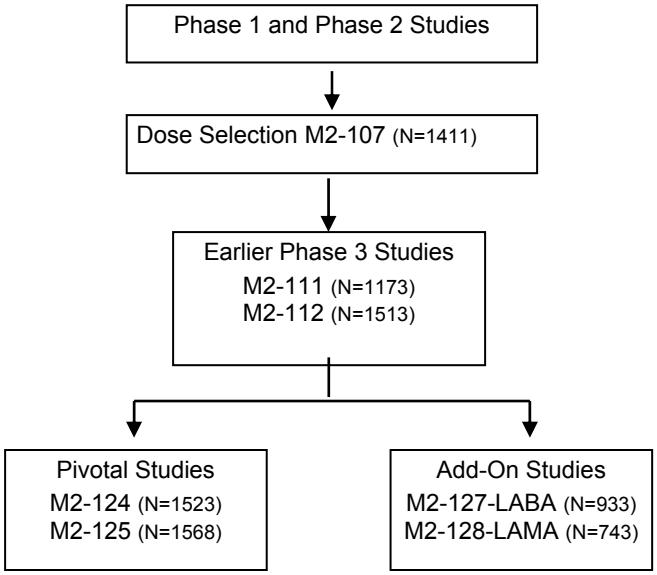
The core of the clinical development program of roflumilast in COPD consists of six large placebo-controlled, parallel group, randomized studies assessing roflumilast 500 mcg using lung function parameters as primary endpoints and rate of exacerbations as co-primary or secondary endpoints, plus one large dose-selection study comparing roflumilast 250 mcg to 500 mcg. The objective of the core program (Figure 7–1) was to assess the following three aspects of efficacy:

- ***Dose selection and identification of the target patient population.*** The selection of dose and identification of a COPD subpopulation that had reduced exacerbations in response to roflumilast were the outcomes of the earlier phase 3 trials including studies M2-107 (N=1411), M2-111 (N=1173) and M2-112 (N=1513). The data of these studies support the 500 mcg once-daily dose and the selection of the COPD population with chronic bronchitis at risk of exacerbations that were tested in the pivotal studies.

- ***Proof of Efficacy.*** This was accomplished in the two pivotal Phase 3 studies M2-124 (N=1523) and M2-125 (N=1568) in a severe to very severely obstructed chronic bronchitis patient population. These two studies demonstrated a statistically and clinically significant effect in improving lung function and decreasing the rate of COPD exacerbations requiring systemic corticosteroids or hospitalizations and/or death (referred to as moderate or severe COPD exacerbations, respectively).

- ***Proof of Additive Efficacy when roflumilast is added on top of background therapy with salmeterol or tiotropium in a moderate to severe COPD patient population.*** This was attained in the two studies M2-127 (N=933) and M2-128 (N=743) respectively.

Figure 7–1. Core Clinical Development Program for Roflumilast in COPD and Key Supporting Studies



7.1 DOSE SELECTION

Doses from 100 to 5,000 mcg were evaluated in Phase 1 and early Phase 2 studies conducted in healthy volunteers and in asthma or COPD patients. A dose of roflumilast 1,000 mcg was established as the maximum tolerated single dose, while the 500 mcg once daily showed acceptable tolerability during repeat dosing. In pharmacokinetic studies in humans, repeated dosing investigations demonstrated that the median half-life of roflumilast and roflumilast N-oxide was approximately 17 and 30 hours respectively supporting once-a-day dosing. Based on these findings, the doses of 250 and 500 mcg once daily were selected for further investigation in Study M2-107.

7.1.1 Study M2-107

Study M2-107 was a randomized, double-blind, 24-week study in 1,411 patients with moderate to severe COPD, comparing roflumilast 250 mcg and 500 mcg once daily with placebo. The primary endpoints were the change from baseline to end of treatment in FEV_1 (post-bronchodilator) and the change from baseline to end of treatment in the SGRQ total score. Secondary endpoints included, among others, number of COPD exacerbations and time to exacerbation. Patients enrolled in the study had a history of moderate to severe chronic obstructive pulmonary disease defined as an FEV_1/FVC ratio (post-bronchodilator) $\leq$ 70% and FEV_1 (post-bronchodilator) 30% to 80% of predicted.

The study demonstrated significant improvements in post-bronchodilator FEV_1 vs. placebo with both roflumilast doses (between-treatment difference: 97 mL for roflumilast 500 mcg, 74 mL for roflumilast 250 mcg, for both p <0.0001) (Table 7.1.1–1).

The SGRQ total score improved with all treatments (placebo: -1.8, Rof250: -3.4, Rof500: -3.5) with the differences vs. placebo approaching statistical significance for the 500 mcg dose (p = 0.0532).

Table 7.1.1–1. Mean Change from Baseline in FEV_1 (mL) and SGRQ (Total Score) at End of Treatment by Roflumilast Dose in Study M2-107 (ITT, LOCF)

	Change from baseline (LSMean)			***Between-treatment difference LSMean (95% CI)***		
	Placebo	*Rof250*	*Rof500*	*Rof250 vs. pbo*	*Rof500 vs. pbo*	*Rof500 vs. R250*
Pre-FEV_1 (mL)						
	-39	24	49	64[a] (28, 100)	88[a] (52, 125)	24 (-5, 54)
Post-FEV_1 (mL)						
	-45	29	51	74[a] (39, 108)	97[a] (62, 131)	23 (-6, 51)
SGRQ (total score)						
	-1.8	-3.4	-3.5	-1.6 (-3.3, 0.2)	-1.7 (-3.5, 0.0)	-0.2 (-1.6, 1.3)

a p <0.05, 2-sided for between-treatment differences.

CI = confidence interval, ITT = intention-to-treat, LOCF = last observation carried forward, LS = least square, N = number of patients, pbo = placebo, pre = pre-bronchodilator, post = post-bronchodilator, Rof250 = roflumilast 250 mcg once daily, Rof500 = roflumilast 500 mcg once daily, SGRQ = St George Respiratory Questionnaire, vs. = versus.

A dose relationship with a higher response for the 500 mcg dose was also seen for the number of mild, moderate, or severe exacerbations per patient in Study M2-107. The mean number of COPD exacerbations (mild, moderate or severe) per patient was 1.13 with placebo, 1.03 in the roflumilast 250 mcg group and 0.75 in the roflumilast 500 mcg group. The observed dose-dependent reduction for exacerbations in the 500 mcg dose was statistically significant (p = 0.0059). Assessment of the time to first mild, moderate or severe exacerbation revealed a statistically significant difference between the two doses in favor of the higher dose (p = 0.0179).

Both doses were well tolerated. The 250 mcg dose showed a lower incidence of single adverse events as compared with the 500 mcg dose, such as diarrhea (4.9% vs. 9.0%), nausea (2.8% vs. 4.9%) and weight decrease (1.0% vs. 2.3%) but the overall number of AEs was similar between the two dose levels (66.3% for 250 mcg and 66.7% for the 500 mcg) and the percentage of patients with serious AEs was also comparable between the two doses (7.1% for the 250 mcg and 9.5% for the 500 mcg).

In conclusion, Study M2-107 showed a consistent dose relationship with a higher response for the 500 mcg dose, as compared to the 250 mcg dose, for the primary endpoint post-bronchodilator FEV_1, number of exacerbations, and time to first exacerbation.

Based on the results of Study M2-107, the 500 mcg dose was selected as the therapeutic dose for the Phase 3 development program because it showed a higher level of efficacy than 250 mcg and an acceptable tolerability and safety profile.

7.2 EARLY PHASE 3 STUDIES M2-111 AND M2-112

7.2.1 Study Design

The early phase 3 clinical development in COPD consisted of two 1-year studies, M2-111 and M2-112 with 1,173 and 1,513 patients with severe and very severe COPD, respectively, to assess the effects of roflumilast 500 mcg once-daily compared to placebo. These earlier 1-year studies were similar in design to the subsequent pivotal studies M2-124 and M2-125. However, in contrast to the pivotal studies, patients in studies M2-111 and M2-112 were not required to have a history of chronic bronchitis or previous exacerbations at inclusion. Concomitant ICSs but no LABAs were allowed in M2-111 and M2-112 (Table 7.2.1–1).

Table 7.2.1–1. Principal Design Features for Studies M2-111 and M2-112

Study	***Design***	***No. of Pats.***	***Duration***	***Eligibility***	***Principal Efficacy Variables***
M2-111	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. ICS allowed.	1,173	52 Weeks	• COPD • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted ≤ 50% and FEV_1/FVC ≤ 70%. • Current or ex-smoker	Primary Endpoint: Pre-bronchodilator FEV_1 Rate of exacerbations requiring oral or parenteral corticosteroid therapy or exacerbations leading to hospitalization and/or death. Pre-Specified Key Secondary Endpoint: Post-bronchodilator FEV_1 Rate of exacerbations in a variety of categories and subpopulations Additional Secondary Endpoints: Frequency of exacerbations SGRQ

Table 7.2.1–1. Principal Design Features for Studies M2-111 and M2-112

Study	*Design*	*No. of Pats.*	*Duration*	*Eligibility*	*Principal Efficacy Variables*
M2-112	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. ICS allowed.	1,513	52 Weeks	• COPD • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted ≤ 50% and FEV_1/FVC ≤ 70%. • Current or ex-smoker • Fixed airway obstruction (FEV_1 increase ≤ 15% and/or 200 mL after inhalation of salbutamol.	Primary Endpoint: Post-bronchodilator FEV_1 Rate of exacerbations requiring oral corticosteroid and/or antibiotic therapy or exacerbations leading to hospitalization Pre-Specified Key Secondary Endpoint: SGRQ Additional Secondary Endpoints: Pre-bronchodilator FEV_1 Rate of exacerbations in a variety of subpopulations; Frequency of exacerbations

LABA = long-acting beta agonist; ICS = inhaled corticosteroids; BID = twice daily; COPD = chronic obstructive pulmonary disease.

7.2.2 Results

Study M2-111 enrolled 1,173 patients (567 receiving roflumilast and 606 placebo) and Study M2-112 enrolled 1,513 patients (760 receiving roflumilast and 753 placebo). Demographic and baseline characteristics were similar between the roflumilast and placebo groups in both studies.

Both studies met their primary endpoint of pre- or post-bronchodilator FEV_1. Consistent with the results of the pivotal trials M2-124 and M2-125, roflumilast 500 mcg daily treatment significantly increased the pre-bronchodilator FEV_1 with a between-treatment difference of 42 mL ($p < 0.0001$) compared to placebo in Study M2-111 and 57 mL ($p < 0.0001$) in Study M2-112 (Table 7.2.2–1). These 42 mL and 57 mL gains in FEV_1 over placebo were observed in patients with advanced obstructive lung disease who had a baseline mean pre-bronchodilator FEV_1 approximately 1 liter.

Table 7.2.2–1. Change From Baseline to End of Treatment in Pre-Bronchodilator FEV_1 (mL) - Supportive 1–Year Studies M2-111 and M2-112 (ITT, Repeated Measures)

Study	*Treatment*	*n*	*Baseline*	*Change from baseline*		*Difference vs. placebo*		
			Mean	*LSMean*	*95% CI*	*LSMean*	*95% CI*	*p-value*[a]
Severe to very severe COPD								
M2-111	Placebo	596	930	-12	-26, 2			
	Rof500	545	963	30	14, 45	42	22, 61	< 0.0001
M2-112	Placebo	741	1055	-8	-25, 10			
	Rof500	737	1041	49	31, 67	57	37, 77	< 0.0001

a 2-sided.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, n = number of patients included in the analysis, LS = least squares, pre = pre-bronchodilator, rep. = repeated, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

Table 7.2.2–2. Change From Baseline to End of Treatment in Post-Bronchodilator FEV_1 (mL) - Supportive 1–Year Studies M2-111 and M2-112 (ITT, Repeated Measures)

Study	*Treatment*	*n*	*Baseline*	*Change from baseline*		*Difference vs. placebo*		
			Mean	*LSMean*	*95% CI*	*LSMean*	*95% CI*	*p-value*[a]
Severe to very severe COPD								
M2-111	Placebo	592	1088	-16	-31, -2			
	Rof500	543	1131	26	10, 42	42	22, 63	< 0.0001
M2-112	Placebo	742	1153	-4	-22, 14			
	Rof500	732	1142	56	38, 75	60	40, 81	< 0.0001

a 2-sided.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, LS = least squares, n = number of patients included in the analysis, post = post-bronchodilator, rep. = repeated, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

In a post-hoc analysis, the rate of moderate or severe exacerbations (using exacerbation definitions, data derivations, and analysis methods of the pivotal studies) was numerically reduced by 14% (p = 0.1294) in Study M2-111 and by 15% (p = 0.0847) in Study M2-112 compared to placebo (Table 7.2.2–3). Importantly, a post-hoc subgroup analysis of M2-111 and M2-112 indicated that patients *with chronic bronchitis* achieved the greatest benefit from treatment with roflumilast (26% reduction in acute exacerbations [rate ratio = 0.738, 95% CI = 0.616, 0.885]).

Table 7.2.2–3. Rate Of Moderate or Severe Exacerbations - Studies M2-111, M2-112, and Their Integrated Analysis (ITT, Poisson Regression)

Exacerbation	***Placebo***		***Rof500***		***Rof500 vs. placebo***			
Study or pool	*N*	*Rate*	*N*	*Rate*	*% Change*	*Rate ratio*	*95% CI*	*p-value*[a]
M2-111	606	0.692	567	0.595	-14.0	0.860	0.708, 1.045	0.1294
M2-112	753	0.537	760	0.455	-15.2	0.848	0.702, 1.023	0.0847
111+112 pool	1359	0.610	1327	0.523	-14.3	0.857	0.748, 0.981	0.0257

a 2-sided.

The table is based on the exacerbation definitions and analysis method used in the two pivotal Studies M2-124 and M2-125 which differed from that used in the original evaluation of Studies M2-111 and M2-112.

COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, CI = confidence interval, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

7.2.3 Conclusions

Roflumilast 500 mcg once daily significantly improved pre-bronchodilator FEV_1 compared to placebo in both studies M2-111 and M2-112. The rates of moderate or severe exacerbations showed numerical improvement in both studies but the difference versus placebo did not reach statistical significance. A post-hoc subgroup analysis of M2-111 and M2-112, which reached statistical significance, revealed that patients *with chronic bronchitis* had the greatest reduction in rate of exacerbations. Based on this analysis a decision was made to confirm the observation that COPD patients with chronic bronchitis benefited most from the treatment with roflumilast in 2 independent large pivotal studies.

7.3 PIVOTAL STUDIES IN COPD: M2-124 AND M2-125

7.3.1 Study Design

Based on the findings in the two previous studies, M2-111 and M2-112, two pivotal studies, M2-124 and M2-125, were designed to further assess the effect of roflumilast on exacerbations and to provide additional confirmation of the drug's effect on pre- and post-bronchodilator FEV_1 values in COPD patients with chronic bronchitis at risk of exacerbations. The designs of the 2 studies were identical (Table 7.3.1–1).

The patients included in these pivotal studies had severe to very severe COPD (post-bronchodilator $FEV_1 \leq 50\%$ predicted) with a history of exacerbations and of chronic bronchitis. Primary endpoints were pre-bronchodilator FEV_1 (other measures of lung function were collected and analyzed as secondary endpoints) and the rate of moderate or severe exacerbations defined as exacerbations requiring oral or parenteral corticosteroid therapy or exacerbations leading to hospitalization and/or death, respectively.

After a 4-week single-blind placebo run-in (baseline) period, patients were randomized (1:1 randomization) to receive either placebo or roflumilast 500 mcg once daily. Treatment duration was 52 weeks. Eight clinic visits were scheduled at regular (4- to 8-week) intervals. Rescue medication (salbutamol or albuterol) was allowed on an as-needed basis during the entire run-in and treatment period. Inhaled corticosteroids could be used during run-in but were to be withdrawn at randomization. Patients were allowed to continue to take long-acting β2-agonists (LABAs) if these had been used prior to study enrollment. Short-acting anticholinergics (SAMAs) were allowed for those patients not taking LABAs (approximately half the patients received concomitant LABA therapy during the trials). Other COPD treatment, including LAMA, had to be withdrawn prior to study start. Systemic glucocorticosteroids for the treatment of exacerbations were allowed during the study.

Table 7.3.1–1. Principal Design Features for Studies M2-124 and M2-125

Studies	***Design***	***No. of Pats.***	***Dur-ation***	***Eligibility***	***Principal Efficacy Variables***
M2-124 M2-125	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. LABA allowed; Use of ICS terminated at randomization.	M2-124: 1523 M2-125: 1568	52 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted ≤ 50% and FEV_1/FVC ≤ 70%. • Chronic bronchitis (chronic productive cough for three months in each of last 2 yrs prior to the study). • History of COPD exacerbations. • Current or ex-smoker • Symptomatic patients: total cough/sputum score ≥ 14 during last week prior to randomization.	Co-Primary Endpoints: Pre-bronchodilator FEV_1 and rate of exacerbations requiring oral or parenteral corticosteroid therapy or exacerbations leading to hospitalization and/or leading to death. Pre-Specified Key Secondary Endpoints: Post-bronchodilator FEV_1 mortality; C-reactive protein; Transition Dyspnea Index Pre-Specified Additional Secondary Endpoints: Time to first exacerbation; Time to second exacerbation; Use of rescue medication

LABA = long-acting beta agonist; ICS = inhaled corticosteroids; BID = twice daily; COPD = chronic obstructive pulmonary disease.

7.3.2 Statistical Methodology

In general, tests with respect to the primary and key-secondary endpoints were done in an *a priori* order to control the overall Type I error, i.e. the second primary endpoint (or first pre-specified key secondary endpoint in instances where a single primary endpoint had been designated) was tested only after a statistically significant finding for the first primary endpoint was concluded. All statistical tests were performed 2-sided at the 5% level.

The sample size was chosen on the basis of the need to be adequately powered for exacerbation. With 750 patients per group, the study was approximately 90% powered to detect a 20% reduction in exacerbation relative to placebo. This same sample size provided 99% power to detect a 46 ml difference in FEV_1.

For the two pivotal studies, M2-124 and M2-125, the order of testing was as follows: the first primary endpoint was mean change from baseline in pre-bronchodilator FEV_1 during the treatment period, followed by the second primary endpoint, mean rate of moderate or severe exacerbations per patient per year. Such ordered testing was also applied to the key-secondary endpoints. In case of no significant finding for a particular endpoint, the tests of all following primary and/or key-secondary endpoints were considered exploratory. The mean rate of exacerbations was evaluated with a Poisson regression model (primary) with treatment group, sex, smoking status, concomitant treatment with LABA, pooled country as factors and the baseline post-bronchodilator FEV_1 % predicted and age as covariates, time to discontinuation was used as an offset variable, and an overdispersion parameter was used to adjust for extra variability in the data. A negative binomial regression was performed on the rate of exacerbations to assess robustness with regard to the distributional assumptions.

Time-to-event analyses were performed with a Cox proportional hazard regression and/or a Kaplan-Meier survival analysis. The mean change from baseline in pre-bronchodilator FEV_1 during the treatment period was analyzed using a repeated measurement analysis of covariance (ANCOVA) which evaluates the difference between active treatment and placebo averaged over the entire treatment period. This model includes all observed measurements from the scheduled visits of the treatment period. The dependent variable was the change from baseline to each scheduled post-randomization visit with the following factors and covariates: treatment group, age, sex, smoking status, concomitant treatment with LABA, pooled country, baseline value, time and treatment by time interaction. For other secondary endpoints, all tests were considered exploratory. All efficacy analyses were based on the ITT analysis set (defined as all patients who received at least one dose of investigational drug).

7.3.3 Demographic Information

M2-124 was conducted at 246 centers in Australia, Austria, France, Germany, Hungary, New Zealand, Romania, Russia, United Kingdom and the United States. M2-125 was conducted at 221 centers in Canada, Germany, India, Italy, Poland, South Africa, Spain and the United States.

In the two studies, the randomized patients ranged in age from 40 to 92 years with a median of 64 years and the majority of patients being male (71 to 81%) and White (≥ 71%). Study M2-125 included 23% Asians. Other races comprised less than 5% of the study population in both studies.

There was a higher proportion of current smokers in Study M2-124 vs. Study M2-125 (48% vs. 35%) however the proportion of current/past smokers were similar in both treatment groups within each study.

Baseline lung function values were similar in both treatment groups across both studies (Table 7.3.3–1). Mean pre-bronchodilator FEV_1 was between 31% and 38% predicted and the corresponding post-bronchodilator values ranged between 35% and 38% predicted, consistent with the American Thoracic Society (ATS)/European Respiratory Society (ERS) definition of severe to very severe COPD. Mean reversibility ranged between 10% and 12% and FEV_1/FVC between 41% and 43%, indicative of fairly pronounced airway obstruction which is not fully reversible. Approximately 50% of patients in both studies received concomitant LABAs.

Table 7.3.3–1. Lung Function at Randomization in Studies M2-124 and M2-125 (ITT)

Study	*Treatment*	*N*	*Pre-FEV_1*		*Post-FEV_1*		*ΔFEV_1*	*FEV_1/FVC*
			[L]	*[% pred.]*	*[L]*	*[% pred.]*	*[%]*	
M2-124	Placebo	758	1.06 ± 0.4	35 ± 10	1.15 ± 0.4	37 ± 10	10 ± 17	43 ± 11
	Rof500	765	1.07 ± 0.4	35 ± 10	1.16 ± 0.4	38 ± 11	10 ± 15	43 ± 12
M2-125	Placebo	796	0.98 ± 0.4	32 ± 11	1.07 ± 0.4	35 ± 11	11 ± 14	41 ± 11
	Rof500	772	0.95 ± 0.3	31 ± 10	1.05 ± 0.4	35 ± 10	12 ± 15	41 ± 11

Means ± SD are shown. Values are rounded.

COPD = chronic obstructive pulmonary disease, DFEV$_1$ = reversibility, ITT = intention to treat analysis set, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, post = post-bronchodilator, pre = pre-bronchodilator, pred. = predicted, Rof500 = 500 mcg roflumilast once daily.

7.3.4 COPD Severity

The distribution of baseline COPD severity reflected the inclusion criteria in the studies (Table 7.3.4–1).

Patients who were enrolled with mild or moderate COPD (about 7% to 11% of the population) were evenly distributed among the placebo and roflumilast treatment arms.

Table 7.3.4–1. COPD Severity at Randomization in Studies M2-124 and M2-125 (ITT)

Study		*N*	*Number (%)[a] of patients*							
			Mild[b]		*Moderate[c]*		*Severe[d]*		*Very Severe[e]*	
M2-124	Placebo	758	3	(< 1)	61	(8)	510	(67)	184	(24)
	Rof500	765	0	(0)	80	(11)	486	(64)	199	(26)
M2-125	Placebo	796	2	(< 1)	59	(7)	479	(60)	256	(32)
	Rof500	772	1	(< 1)	50	(7)	457	(59)	264	(34)

a Percentages are based on the total number of patients in a treatment group.

b Post-$FEV_1 \geq 80\%$ pred.

c Post-$FEV_1 \geq 50\%$ and $< 80\%$ pred.

d Post-$FEV_1 \geq 30\%$ and $< 50\%$ pred.

e Post-$FEV_1 < 30\%$ pred.

COPD = chronic obstructive pulmonary disease, ITT = intention to treat analysis set, pred = predicted
Rof500 = 500 mcg roflumilast once daily.

7.3.5 Previous and Concurrent Diseases

Previous and concurrent diseases were comparable across treatment arms and consistent with recent published epidemiological studies of COPD in the general population (Viegi, 2007; Chatila, 2008; Yawn, 2008). In both pivotal studies, the most commonly reported diseases, besides COPD, included 'essential hypertension' (reported by 40% to 50% of patients), hyperlipidemias, chronic ischemic heart disease, gastro-esophageal reflux disease and depressive disorders.

7.3.6 Previous COPD Treatment

There were no major differences in the nature or frequency of previous respiratory medications observed between patients in either treatment group or between studies. The most commonly used previous medications were short-acting β_2-agonists (SABA, documented for 60% to 66% of patients) followed by inhaled combinations of corticosteroids and LABAs (34% to 44% of patients). ICS as single agent or in combination treatments were taken prior to enrollment by about 40% of patients in both studies.

7.3.7 Concomitant COPD Treatment

The nature and frequency of concomitant respiratory medications were similar in both treatment groups as well as in each individual study for both pivotal trials, M2-124 and M2-125, with nearly all patients using inhaled SABAs.

Corticosteroids (other than inhaled or nasal formulations) were reported for about 50% of patients and largely reflected acute courses of oral or parenteral glucocorticoids taken during an exacerbation, which was allowed. LABAs (allowed during the entire treatment period), either taken as single agent or in combination treatment (short courses of LABA/ICS combinations were used in some patients during exacerbation), were also reported by about 50% of patients. SAMAs, which were allowed for those patients not taking LABAs, were used by a higher proportion of patients in Study M2-125 (~40%) compared to Study M2-124 (~30%) without differences between treatment groups (Table 7.3.7–1).

Table 7.3.7–1. Frequently Used Concomitant Respiratory Medication in Studies M2-124 and M2-125 (ITT)

Study	*Treat-ment*	*N*	*Number (%)[a] of patients*											
			SABA		*CS[b]*		*LABA[c]*		*LABA*		*SAMA[d]*		*SAMA*	
			(ih)		**(excl. ih)**		**(incl. comb.)**		**(ih)**		**(incl. comb.)**		**(ih, only)**	
M2-124	Placebo	758	753	(99)	409	(54)	385	(51)	342	(45)	268	(35)	245	(32)
	Rof500	765	761	(> 99)	377	(49)	378	(49)	339	(44)	266	(35)	240	(31)
M2-125	Placebo	796	791	(99)	456	(57)	408	(51)	351	(44)	348	(44)	324	(41)
	Rof500	772	769	(> 99)	404	(52)	371	(48)	329	(43)	322	(42)	297	(39)

Those medications listed were reported by at least 20% of patients in any treatment group.

a Percentages (rounded to the nearest integer) are based on the number of patients in a treatment group.

b Other than inhaled or nasal applications.

c Includes patients who used LABAs only and inhaled combinations of corticosteroids and LABAs.

d Includes patients who used inhaled SAMAs only and combinations of inhaled SAMAs and SABAs.

comb. = combination, CS = corticosteroids, excl. = excluding, ITT = intention to treat analysis set, ih = inhaled, incl. = including, LABA = long-acting β_2-agonist, N = number of patients, Rof500 = 500 mcg roflumilast once daily, SABA = short-acting β_2-agonist, SAMA = short-acting muscarinic agonist = short-acting anticholinergic.

7.3.8 Results for the Pivotal Studies

7.3.8.1 Exacerbations

In each of the pivotal studies, for the primary analysis of exacerbations roflumilast significantly reduced the rate of moderate or severe exacerbations versus placebo by 14.9% (p = 0.0278; Study M2-124) and 18.5% (p = 0.0035; Study M2-125) (Table 7.3.8.1–1). Consistent with this finding, the rate of exacerbations treated with systemic steroids and/or antibiotics was significantly reduced with roflumilast in the two pivotal studies by 15.2% (p = 0.0240; M2-124) and 17.4% (p = 0.0055; M2-125). Moderate exacerbations (ie, exacerbations requiring systemic corticosteroids) were reduced to a comparable extent by 15.7% (p = 0.0325) and 18.0% (p = 0.0075), respectively.

Table 7.3.8.1–1. Rate of Moderate or Severe Exacerbations (Primary Endpoint) in Studies M2-124 and M2-125 (ITT, Poisson Regression)

Exacerbation	***Placebo***		***Rof500***		***Rof500 vs. placebo***			
Study	*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 Rates, 95% CIs, rate ratio, and 2 sided p-values are based on a Poisson regression with factors treatment, baseline post-bronchodilator FEV_1 (%predicted), age, sex, smoking status, concomitant treatment with long-acting β_2-agonists and country pool.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

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

Negative binomial regression analysis was performed as a test for the robustness of the primary Poisson regression analysis. Results from this analysis for each study confirmed the findings of the primary analysis (Table 7.3.8.1–2).

Table 7.3.8.1–2. Rate of Moderate or Severe Exacerbations (Primary Endpoint) in Studies M2-124 and M2-125 (ITT, Negative Binomial Regression)

Exacerbation	***Placebo***		***Rof500***		***Rof500 vs. placebo***			
Study	*N*	*Rate*	*N*	*Rate*	*%Change*	*Rate ratio*	*95% CI*	*p-value*[a]
M2-124	758	1.323	765	1.124	-15.0	0.850	0.729, 0.991	0.0383
M2-125	796	1.556	772	1.268	-18.5	0.815	0.702, 0.946	0.0070

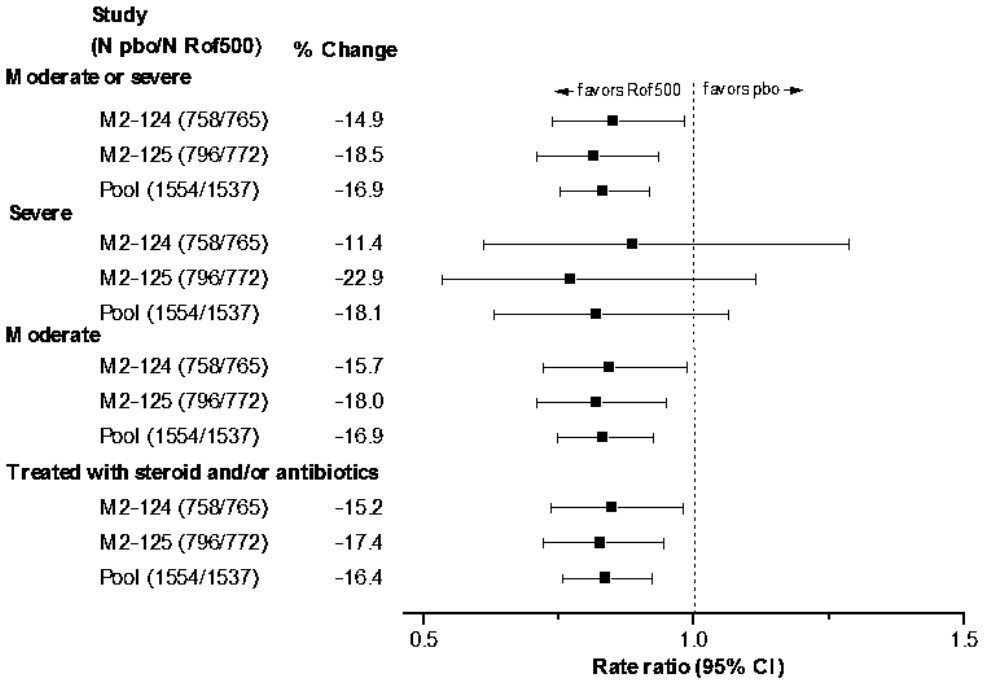
a Rates, 95% CIs, rate ratio, and 2 sided p-values are based on a negative binomial regression with factors treatment, baseline post-bronchodilator FEV_1 (%predicted), age, sex, smoking status, concomitant treatment with long-acting β_2-agonists and country pool.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

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

As shown in Figure 7.3.8.1–1, roflumilast provided a beneficial reduction in exacerbation regardless of the severity and type of exacerbation.

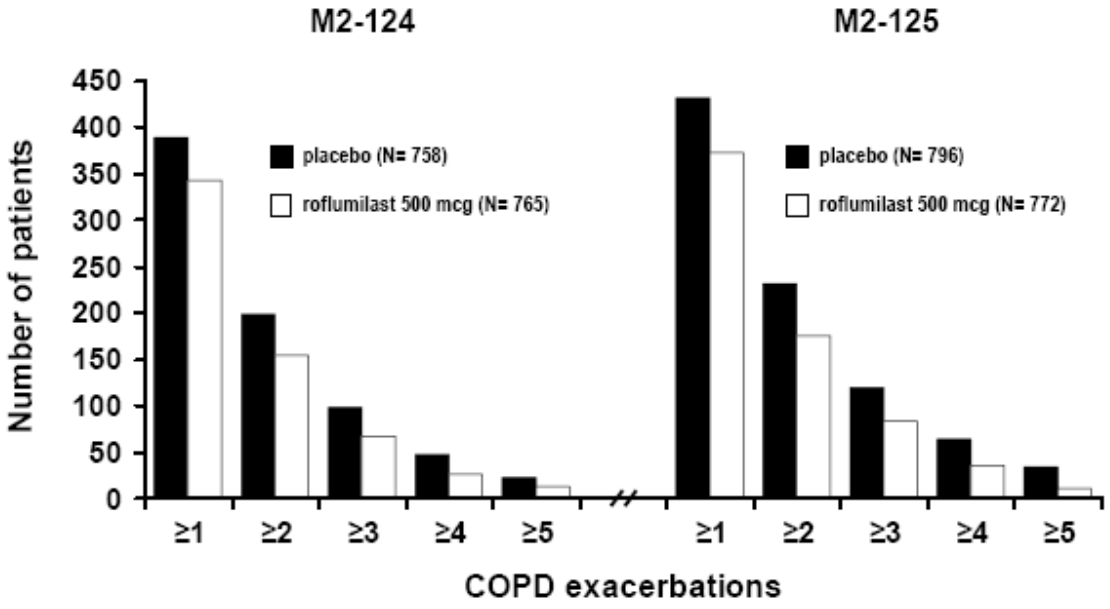
Figure 7.3.8.1–1. Exacerbations - Studies M2-124, M2-125, and Pivotal COPD Studies Pool (ITT, Poisson Regression)



CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, pbo = placebo, Rof500 = 500 mcg roflumilast once daily.

The cumulative number of patients with at least 1 to 5 or more moderate or severe COPD exacerbations is displayed in Figure 7.3.8–2 below. For each study, this figure revealed that there are more patients with each indicated number of exacerbations in the placebo group than in the roflumilast group.

Figure 7.3.8–2. Summary of Moderate or Severe COPD Exacerbations in Studies M2-124 and M2-125 (ITT Population)



A summary of number and percent of patients with exacerbations along with analyses of time from randomization to each of first, second, and third moderate or severe COPD exacerbations during studies M2-124 and M2-125 is presented in Table 7.3.8–3. The hazard ratio (HR) for time to first exacerbation was 0.88 in M2-124 and 0.89 in M2-125, confirming that a moderate or severe exacerbation was likely to occur later in roflumilast-treated than in placebo-treated patients. These reductions did not reach statistical significance. However, the hazard ratio based on time from randomization to second exacerbation was 0.79 in M2-124 and 0.79 in M2-125. These hazard ratios were statistically significant in M2-124 ($p = 0.029$) and in M2-125 ($p = 0.0214$). To assess the robustness of the significance of time to second exacerbation, the time to third exacerbation was performed as a post-hoc analysis. The analysis based on this time to third exacerbation is significant for both M2-124 (HR = 0.71, $p = 0.0296$) and M2-125 (HR = 0.75, $p = 0.0444$) studies. These results were supportive of the primary analysis based on the rate of exacerbations.

An important finding from each study is that the magnitude of the roflumilast treatment effect relative to placebo increases based on the hazard ratios from time to first, to time to second, and time to third exacerbation. These findings suggest that the benefit of roflumilast increases with the propensity for experiencing greater numbers of exacerbations.

Table 7.3.8–3. Summary of Number and Percent of Patients with Exacerbations Along with Analyses of Time From Randomization to Moderate or Severe COPD Exacerbations During Studies M2-124 and M2-125

Study	*Parameter*	*Placebo n, %*		*Rof500 n, %*		*Hazard Ratio[a] (95% CI)*	*p-value[a]*
M2-124		*N=758*		*N=765*			
	Time to 1st exacerbation	389	51%	344	45%	0.88 (0.76, 1.02)	0.0859
	Time to 2nd exacerbation	198	26%	154	20%	0.79 (0.64, 0.98)	0.0290
	Time to 3rd exacerbation	98	13%	68	9%	0.71 (0.52, 0.97)	0.0296
M2-125		*N=796*		*N=772*			
	Time to 1st exacerbation	432	54%	373	48%	0.89 (0.78, 1.03)	0.1132
	Time to 2nd exacerbation	232	29%	175	23%	0.79 (0.65, 0.97)	0.0214
	Time to 3rd exacerbation	120	15%	84	11%	0.75 (0.57, 0.99)	0.0444

a A hazard ratio < 1 means a lower risk for the roflumilast treatment. Hazard ratio, 95% CI, and p-values (2-sided) are based on a Cox proportional hazards model with factors including treatment, age, sex, smoking status, concomitant treatment with long-acting β2-agonists, and country pool for the analysis of time from randomization to each exacerbation.

n and % (rounded to the nearest integer) are the number and observed percentage of patients with the indicated exacerbation in each treatment group.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients in the ITT population, Rof500 = roflumilast 500 mcg.

7.3.9 Pre-Bronchodilator FEV_1

Pre-bronchodilator FEV_1 during treatment was the other primary endpoint in the pivotal studies M2-124 and M2-125. Changes from baseline measures in pre-bronchodilator FEV_1 showed an increase in the roflumilast group (46 mL and 33 mL, respectively), an increase in the placebo group in M2-124 by 8 mL, and a decrease in the placebo group in M2-125 by 25 mL. The between-treatment differences were statistically significant in favor of roflumilast in both studies and were 39 mL ($p = 0.0003$) and 58 mL ($p < 0.0001$), respectively. This improvement was observed in patients with a mean FEV_1 of approximately only one liter at baseline (Table 7.3.9–1).

Table 7.3.9–1. Change From Baseline During Treatment in Pre-Bronchodilator FEV_1 (mL) (Primary Endpoint) in Studies M2-124 and M2-125 (ITT, Repeated Measures)

Study	*Treatment*	*n*	*Baseline*	*Change from baseline*		*Difference vs. placebo*		
			Mean	*LSMean*	*95% CI*	*LSMean*	*95% CI*	*p-value*[a]
M2-124	Placebo	745	1061	8	-8, 23			
	Rof500	745	1071	46	30, 62	39	18, 60	0.0003
M2-125	Placebo	766	985	-25	-39, -11			
	Rof500	730	955	33	19, 48	58	41, 75	<0.0001

a 2-sided.
CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, n = number of patients included in the analysis, LS = least squares, pre = pre-bronchodilator, rep. = repeated, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

Consistent with the prior observation reported in the literature that reversible patients have larger responses to medication (Cazzola, 2008) a corresponding subgroup analysis of the pooled data of the pivotal studies M2-124 and M2-125 demonstrated larger treatment effects in patients with a less fixed airway obstruction (higher reversibility) compared to those with greater fixed airway obstruction (Table 7.3.9–2).

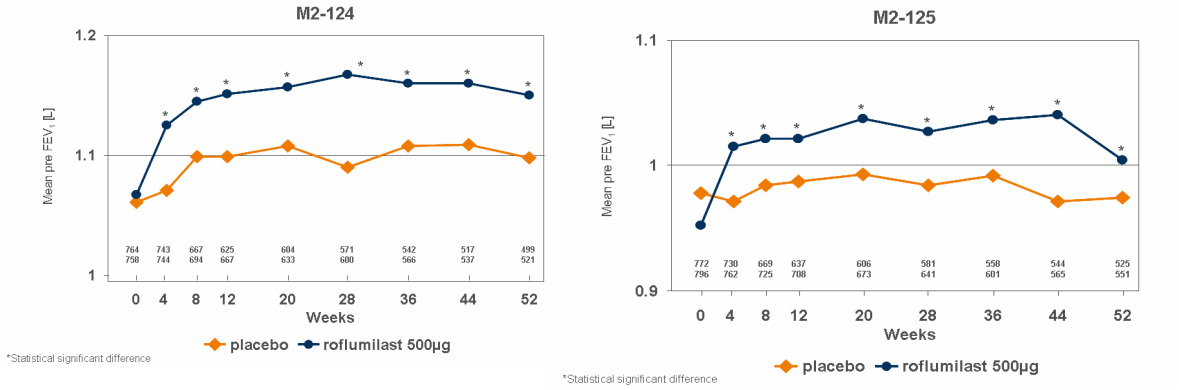
Table 7.3.9–2. Mean Change in Pre-Bronchodilator FEV_1 (mL) at End of Treatment by Reversibility—Pivotal COPD (Studies M2-124 and M2-125) Pooled Analysis (ITT, Repeated Measures)

Reversibility	*Change from Baseline (mL)*				*Difference vs. Placebo*	
	Placebo		*Roflumilast*			
	n	**LSMean**	**n**	**LSMean**	**LSMean**	**95% CI**
≤ 12% or ≤ 200 mL	1251	-20	1231	25	45	30, 59
> 12% and > 200 mL	260	58	244	130	72	34, 110

CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, LS = least squares, n = number of patients included in the analysis, rep. = repeated.

As shown in Figure 7.3.9–1 the effect on lung function occurred early in the study, with separation from placebo by week 4. The separation between roflumilast and placebo remained consistent across the full 1-year duration of the study.

Figure 7.3.9–1. Pre-bronchodilator FEV_1 Over Time in Studies M2-124 and M2-125



7.3.10 Post-Bronchodilator FEV_1

For post-bronchodilator FEV_1, similar results to those found for pre-bronchodilator FEV_1 were seen with statistically significant ($p < 0.0001$) improvements by roflumilast compared to placebo in each of the individual studies. The between-treatment differences were 49 mL for M2-124 and 61 mL for M2-125 (Table 7.3.10–1).

Table 7.3.10–1. Change From Baseline During Treatment in Post-Bronchodilator FEV_1 (mL) in Studies M2-124 and M2-125 (ITT, Repeated Measures)

Study	*Treatment*	*n*	*Baseline*	*Change from baseline*		*Difference Rof500 vs. placebo*		
			Mean	*LSMean*	*95% CI*	*LSMean*	*95% CI*	*p-value*[a]
M2-124	Placebo	736	1155	8	-9, 25			
	Rof500	729	1163	57	40, 73	49	26, 71	< 0.0001
M2-125	Placebo	764	1082	-17	-31, -3			
	Rof500	724	1051	44	30, 59	61	44, 79	< 0.0001

a 2-sided.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, n = number of patients included in the analysis, LS = least squares, post = post-bronchodilator, rep. = repeated, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

7.3.10.1 Use of Rescue Medication and Transition Dyspnea Index

Rescue medication usage in studies M2-124 and M2-125 increased in the placebo group but was reduced in the roflumilast group (mean change from baseline: M2-124: placebo +0.2 puffs/day; roflumilast -0.04 puffs/day; p = 0.1030) or increased to a lesser extent in the roflumilast group than with placebo in the second study (M2-125: placebo +0.6 puffs/day; roflumilast +0.1 puffs/day; p = 0.0003).

The Transition Dyspnea Index (TDI) focal score significantly increased (improved) from baseline to end of treatment in both treatment groups in each of the individual studies (Table 7.3.10.1–1).

Table 7.3.10.1–1. Change From Baseline to End of Treatment in Transition Dyspnea Index (Focal Score) in Studies M2-124 and M2-125 (ITT, Repeated Measures)

Study	*Treatment*	*N*	*Baseline*	*Change from baseline*		*Difference vs. placebo*		
			Mean	*LSMean*	*95% CI*	*LSMean*	*95% CI*	*p-value*[a]
M2-124	Placebo	745	5.858	0.426	0.264, 0.588			
	Rof500	741	5.874	0.658	0.493, 0.823	0.233	0.016, 0.449	0.0356
M2-125	Placebo	769	5.975	0.376	0.211, 0.541			
	Rof500	729	6.026	0.662	0.491, 0.833	0.286	0.082, 0.489	0.0059

a 2-sided.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, LS = least squares, rep. = repeated, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

Between-treatment differences were statistically significant in favor of roflumilast, and were consistent in each study (0.233 in M2-124 and 0.286 in M2-125).

The proportion of patients with an improvement in TDI focal score of ≥ 1 (a value typically considered as a clinically important difference), was numerically greater in the roflumilast vs. placebo group in both studies with a risk ratio of 1.13 in Study M2-124 (p = 0.0617) and 1.09 in Study M2-125 (p = 0.1490), where a risk ratio > 1 indicates effects in favor of roflumilast.

7.4 SUBPOPULATION ANALYSES OF THE PIVOTAL TRIALS M2-124 AND M2-125

Subgroup analyses were performed according to gender, age, race, disease severity, geographic region, smoking status, disease characteristics, concomitant SAMAs, concomitant LABAs, and pre-treatment with ICS.

An overview of subgroup analysis for the pivotal studies pool is graphically depicted in Figure 7.4–1 for moderate or severe exacerbations and in Figure 7.4–2 for pre-bronchodilator FEV_1. The results obtained in a variety of subgroups are highly consistent showing reduced rates of moderate or severe exacerbations and improvements in pre-bronchodilator FEV_1 with roflumilast as compared to placebo across all subgroups.

There were small variations in estimates of treatment effect among subgroups, which in most cases are considered to be of no clinical relevance.

Subgroup analysis with respect to disease severity demonstrated that the positive treatment effects of roflumilast on lung function were independent of COPD severity. For exacerbations, the treatment effects of roflumilast were highly comparable in the subgroups of patients with severe or very severe COPD. The effect was less pronounced in patients who experienced exacerbations less frequently (ie, patients with moderate airway obstruction), although the size of that subgroup was relatively small.

Figure 7.4–1. Exacerbation Rates for Various Subpopulations in the Pivotal Studies M2-124 and M2-125

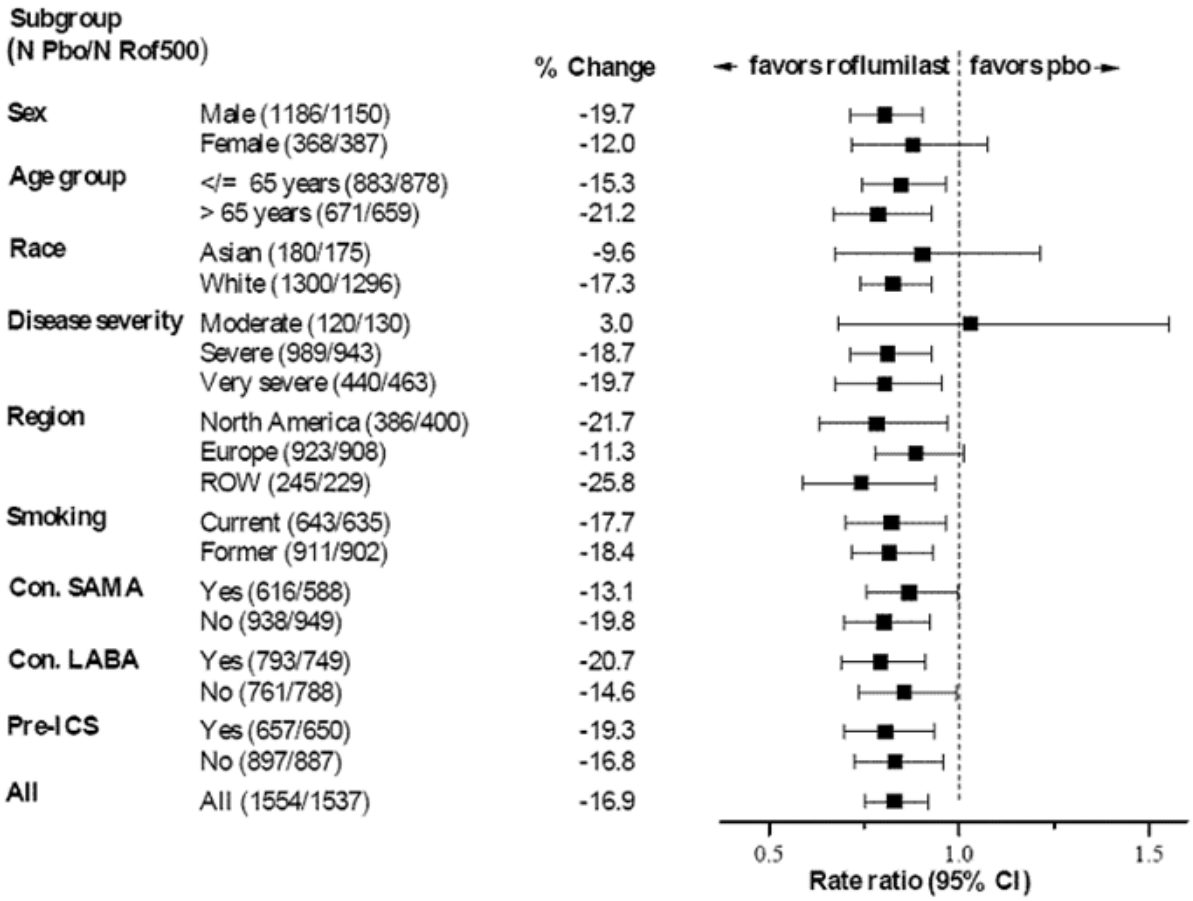
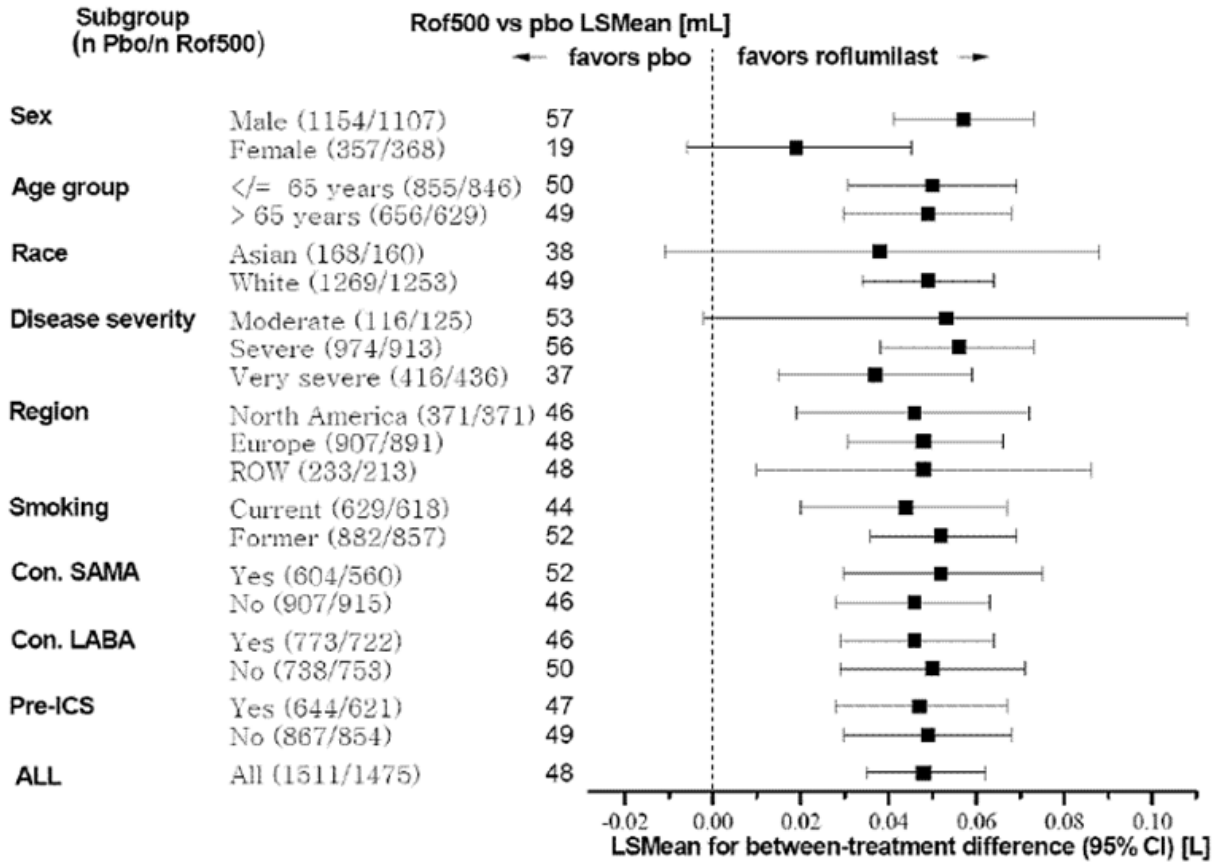


Figure 7.4–2. Pre-Bronchodilator FEV_1 Values During the Study for Various Subpopulations in the Pivotal Studies M2-124 and M2-125



7.5 CONCLUSIONS FROM THE PIVOTAL ROFLUMILAST COPD STUDIES (M2-124 AND M2-125)

Studies M2-124 and M2-125 were conducted to test the effectiveness of roflumilast 500 mcg per day in a defined patient population that was at high risk for exacerbation. Further, the underlying poorly reversible, severe and very severe lung function impairment, and level of bronchitic symptomatology, in this population provided a rigorous test of efficacy. Despite this severity of disease, roflumilast had significant effects on lung function and exacerbation, which were durable over 1 year of treatment:

- Roflumilast reduced the rate of moderate or severe exacerbations in patients with COPD associated with chronic bronchitis and a history of exacerbations and delayed the onset of the first exacerbation.

- Further confirmation of the primary efficacy analysis is supported by reduction in exacerbations treated with systemic steroids and/or antibiotics and the progressive delay in time to first, second and third exacerbations.

- Roflumilast improved lung function (FEV_1) in patients with COPD. These effects were present by 4 weeks and there was no evidence of tolerance over 52 weeks.

- Improvements in the TDI significantly favored roflumilast and were consistent with the overall efficacy trends. Although the mean differences between groups was not of a clinically meaningful magnitude, more patients on roflumilast had clinically meaningful improvements in TDI than did patients randomized to placebo.

- These benefits were independent of concomitant treatment with SAMA or LABA.

- The effect of roflumilast was consistent across subgroups based upon smoking status, age, gender, COPD severity, and region.

7.6 SUPPORTIVE CLINICAL TRIALS IN PATIENTS ON MAINTENANCE THERAPY WITH SALMETEROL (M2-127) OR TIOTROPIUM (M2-128)

7.6.1 Study Design

Studies M2-127 (933 patients) and M2-128 (743 patients) provided further evidence that roflumilast exerts treatment effects in patients with less severe airway obstruction (post-bronchodilator FEV_1 between 40% to 70% of predicted values) and that treatment effects are independent and additive to concomitant long-acting bronchodilator therapy. These studies evaluated the effect of roflumilast in patients concomitantly receiving salmeterol (50 mcg twice daily in Study M2-127) or tiotropium (18 mcg once daily in Study M2-128).

Both studies were 6-month studies with lung function (pre-bronchodilator FEV_1) as the primary endpoint. As such, these supportive studies were not powered to detect an effect on exacerbation. The principal design characteristics are shown Table 7.6.1–1. Aside from use of bronchodilator, the studies differed in that patients recruited to M2-128 were more symptomatic because they had to have chronic cough and sputum production, and frequent use of as needed short acting beta-2 agonists (at least 28 puffs per week prior to randomization). In addition, treatment with tiotropium was required for at least 3 months before enrollment.

Table 7.6.1–1. Principal Design Features for Studies M2-127 and M2-128

Study	*Design*	*No. of Pats.*	*Duration*	*Eligibility*	*Principal Efficacy Variables*
M2-127	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 24 weeks. All patients received salmeterol 50 mcg BID as underlying treatment.	933	24 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted between 40% and 70%. $FEV_1/FVC \leq 70\%$. • Current or ex-smoker • Fixed airway obstruction (defined as an FEV_1 increase ≤ 12% and/or 200 mL after receiving 400 mcg salbutamol).	Primary: pre-bronchodilator FEV_1 Pre-Specified Key Secondary:, rate of exacerbations, TDI focal score, SOBQ Other Secondary: post-bronchodilator FEV_1, other spirometry measures
M2-128	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 24 weeks. All patients received tiotropium 18 mcg once daily as underlying treatment.	743	24 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted between 40% and 70%. $FEV_1/FVC \leq 70\%$. • Chronic bronchitis at enrollment (chronic productive cough for 3 months in each of the last 2 years prior to the study. • Current or former smoker • Fixed airway obstruction (defined as an FEV_1 increase ≤ 12% and/or 200 mL after receiving 400 mcg salbutamol. • Pretreated with tiotropium for at least 3 months before baseline visit. • Use ≥ 28 puffs of rescue medication during week before randomization.	Primary: pre-bronchodilator FEV_1 Pre-Specified Key Secondary: post-bronchodilator FEV_1, rate of exacerbations Other Secondary: other spirometry measures, TDI, SOBQ

LABA = long-acting beta agonist; ICS = inhaled corticosteroids; BID = twice daily; COPD = chronic obstructive pulmonary disease.

7.6.2 Patient Characteristics

Study M2-127 was conducted in 933 patients (466 treated with roflumilast and 467 receiving placebo). Demographic and baseline characteristics were similar between treatment groups with 64-69% being male with an average age of 65 years.

M2-128 was conducted in 743 patients (371 treated with roflumilast and 372 receiving placebo). Demographic and baseline characteristics were similar between treatment groups with 71-72% being male with an average age of 65 years.

In studies M2-127 and M2-128 that enrolled patients with moderate to severe COPD (inclusion criterion post-bronchodilator FEV_1 between 40% and 70% of predicted), baseline pulmonary function tests produced higher values than in studies M2-124 and M2-125.

Table 7.6.2–1. Lung Function at Randomization in Studies M2-127 and M2-128 (ITT)

Study	***Treatment***	***N***	***Pre-FEV_1***		***Post-FEV_1***		***ΔFEV_1***	***FEV_1/FVC***
			[L]	*[% pred.]*	*[L]*	*[% pred.]*	*[%]*	
M2-127	Placebo	467	1.41 ± 0.41	52 ± 10	1.49 ± 0.42	55 ± 9	6 ± 10	50 ± 10
	Rof500	466	1.43 ± 0.40	52 ± 10	1.51 ± 0.39	55 ± 9	6 ± 9	50 ± 9
M2-128	Placebo	372	1.49 ± 0.46	53 ± 12	1.56 ± 0.46	56 ± 12	6 ± 10	52 ± 10
	Rof500	371	1.47 ± 0.45	53 ± 12	1.55 ± 0.45	56 ± 12	6 ± 11	53 ± 10

Means ± SD are shown. Values are rounded.

COPD = chronic obstructive pulmonary disease, DFEV_1 = reversibility, ITT = intention to treat analysis set, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, post = post-bronchodilator, pre = pre-bronchodilator, pred. = predicted, Rof500 = 500 mcg roflumilast once daily.

The distributions of COPD severity reflected the inclusion criteria in that less severe patients were enrolled in M2-127 and M2-128 compared to studies M2-124 and M2-125.

Table 7.6.2–2. COPD Severity at Randomization in Studies M2-127 and M2-128 (ITT)

Study		***N***	***Number (%)[a] of patients***							
			Mild[b]		*Moderate[c]*		*Severe[d]*		*Very severe[e]*	
M2-127	Placebo	467	2	(< 1)	324	(69)	141	(30)	0	(0)
	Rof500	466	1	(< 1)	303	(65)	162	(35)	0	(0)
M2-128	Placebo	372	11	(3)	240	(65)	119	(32)	2	(< 1)
	Rof500	371	8	(2)	235	(63)	125	(34)	3	(< 1)

a Percentages are based on the total number of patients in a treatment group.

b Post-$FEV_1 \geq 80\%$ pred.

c Post-$FEV_1 \geq 50\%$ and $< 80\%$ pred.

d Post-$FEV_1 \geq 30\%$ and $< 50\%$ pred.

e Post-$FEV_1 < 30\%$ pred.

COPD = chronic obstructive pulmonary disease, ITT = intention to treat analysis set, pred = predicted
Rof500 = 500 mcg roflumilast once daily.

7.6.3 Concomitant COPD Treatment

In studies, M2-127 and M2-128, concomitant medication usage primarily consisted of inhaled SABA agents (nearly all patients) and oral or parenteral corticosteroids (14 to 22%) and to a lesser extent, SAMA preparations (< 1 to 3%) (Table 7.6.3–1).

Table 7.6.3–1. Frequently Used Concomitant Respiratory Medication in Studies M2-127 and M2-128 (ITT)

Study	***Treat-ment***	***N***	***Number (%)[a] of patients***							
			SABA		*CS[b]*		*SAMA[c]*		*SAMA*	
			(ih)		**(excl. ih)**		**(incl. comb.)**		**(ih, only)**	
M2-127	Placebo	467	461	(99)	103	(22)	15	(3)	8	(2)
	Rof500	466	461	(99)	77	(17)	13	(3)	7	(2)
M2-128	Placebo	372	368	(99)	70	(19)	6	(2)	3	(< 1)
	Rof500	371	369	(100)	50	(14)	3	(< 1)	2	(< 1)

Those medications listed were reported by at least 20% of patients in any treatment group.

a Percentages (rounded to the nearest integer) are based on the number of patients in a treatment group.

b Other than inhaled or nasal applications.

c Includes patients who used inhaled SAMAs only and combinations of inhaled SAMAs and SABAs.

comb. = combination, CS = corticosteroids, excl. = excluding, ITT = intention to treat analysis set, ih = inhaled, incl. = including, N = number of patients, Rof500 = 500 mcg roflumilast once daily, SABA = short-acting β_2-agonist, SAMA = short-acting muscarinic agonist = short-acting anticholinergic.

7.6.4 Results (M2-127 and M2-128)

7.6.4.1 Primary Endpoints

PRE-BRONCHODILATOR FEV_1

In patients concurrently on long-acting bronchodilator therapy (salmeterol in M2-127 and tiotropium in M2-128), roflumilast increased pre-bronchodilator FEV_1 values by 49 mL over placebo in M2-127 ($p < 0.0001$) and by 80 mL in M2-128 ($p < 0.0001$). The patients in M2-127 and M2-128 had a mean FEV_1 value of 1.4 and 1.5 liters, respectively, at baseline (Table 7.6.4.1–1).

Table 7.6.4.1–1. Change From Baseline During Treatment in Pre-Bronchodilator FEV_1 (mL) (Primary Endpoint) in Studies M2-127 and M2-128 (ITT, Repeated Measures)

Study	*Treatment*	*n*	*Baseline*	*Change from baseline*		*Difference vs. placebo*		
			Mean	*LSMean*	*95% CI*	*LSMean*	*95% CI*	*p-value*[a]
M2-127	Placebo	463	1415	-10	-27, 7			
	Rof500	456	1436	39	21, 56	49	27, 71	< 0.0001
M2-128	Placebo	364	1492	-16	-38, 7			
	Rof500	365	1478	65	41, 88	80	51, 110	< 0.0001

a 2-sided.

b ITT last value analysis.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, ITT = intention-to-treat, n = number of patients included in the analysis, LS = least squares, pre = pre-bronchodilator, rep = repeated, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

For post-bronchodilator FEV_1, similar results to those found for pre-bronchodilator FEV_1 were seen with statistically significant ($p < 0.0001$) improvements by roflumilast compared to placebo. The between-treatment differences were 60 mL for M2-127, and 81 mL for M2-128.

7.6.4.2 Secondary Endpoints

Rate of COPD Exacerbation

Mean rate of moderate or severe exacerbations was assessed as a secondary endpoint in Study M2-128 and as a post-hoc endpoint in Study M2-127 (both studies were 6 months in duration and were not powered to test for exacerbations). The post-hoc analysis showed a significant ($p = 0.0315$) reduction (net difference = 36.8%) in the number of moderate or severe exacerbations in the six-month study, M2-127 (Table 7.6.4.2–1. In M2-128, the number of moderate or severe exacerbations (secondary endpoint) was reduced by 23.2% but the difference was not statistically significant ($p = 0.1957$).

Table 7.6.4.2–1. Rate of Moderate or Severe Exacerbations (Secondary Endpoint) in Studies M2-127 and M2-128 (ITT, Poisson Regression)

Exacerbation	***Placebo***		***Rof500***		***Rof500 vs. placebo***			
Study	*N*	*Rate*	*N*	*Rate*	*%Change*	*Rate ratio*	*95% CI*	*p-value*[a]
M2-127	467	0.5	466	0.3	-36.8	0.63	0.42, 0.96	0.0315
M2-128	372	0.342	371	0.262	-23.2	0.768	0.515, 1.146	0.1957

a 2-sided.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, ITT = intention-to-treat, N = number of patients, Rof500 = 500 mcg roflumilast once daily, vs. = versus.

Patient Questionnaires/Reported Symptom Measures

Transition Dyspnea Index

In Study M2-128, the TDI focal score rose by 1.4 in the roflumilast group and by 0.9 in the placebo group. The difference in TDI focal score for the roflumilast group versus placebo in M2-128 was 0.4 (p = 0.0032). The TDI assessments performed in Study M2-127 showed a small numerical difference (not significant) between roflumilast and placebo.

Shortness of Breath Questionnaire

The Shortness of Breath Questionnaire assessments performed in Study M2-127 did not demonstrate any difference (between roflumilast and placebo). However M2-128 showed a -2.6 difference in favor of roflumilast versus placebo that was statistically significant (p = 0.0051).

Use of Rescue Medication

The rescue medication assessments performed in Study M2-127 did not demonstrate any difference (between roflumilast and placebo). However, roflumilast showed superiority over placebo for the between-treatment differences in rescue medication intake during the 24-week treatment period (roflumilast versus placebo at week 24: LS Mean:-0.512, 95% CI:-0.795,-0.229, p-value: 0.0004).

7.6.5 Conclusions: M2-127 and M2-128

In these two six-month studies in moderate to severe patients on long-acting bronchodilators, M2-127 and M2-128, the net difference in pre-FEV_1 between roflumilast and placebo, 60 mL and 81 mL, respectively, ($p < 0.0001$) added further support to the results observed in the pivotal trials. Although these studies were not designed to demonstrate statistically significant changes in exacerbation rates, the observed reductions in exacerbations were consistent with the observations made in M2-124 and M2-125. In Study M2-128, the inclusion criteria also required a higher level of background symptoms and use of rescue medications. The TDI, SOBQ and use of rescue medications were all improved with roflumilast.

7.7 DISCUSSION OF CLINICAL MEANINGFULNESS OF EFFECT SIZE

When discussing the meaningfulness of the size of clinical effects observed in the roflumilast studies, a comparison to existing treatment options is required. However, caution must be applied when comparing the results obtained in the roflumilast studies with those reported in the literature. Most studies reported in the literature were different from roflumilast studies in study design, co-medications, as well as patient population in terms of reversibility and/or COPD severity. As many studies report the results of combination therapies, a comparison with roflumilast must be based on the effects of the contributing individual components like LABA or ICS as roflumilast will be used in practice also in combination with other COPD treatments. It is important to remember here that the clinical improvements demonstrated in the roflumilast studies were largely achieved as add-on-treatments to standard COPD therapies. To fully account for the differences in baseline COPD severity and reversibility as well as for the differences in background treatments, it is helpful to review also outcomes of sub-group analyses.

7.7.1 Exacerbation

The magnitude of treatment effect on exacerbation is comparable for all currently available COPD treatments when using similar definitions of exacerbation. The reported reduction in rate of exacerbations in three of the largest COPD trials conducted to date ranged from 14% (tiotropium in UPLIFT) to 20% (salmeterol in TRISTAN) and from 5% to 18% (fluticasone in TRISTAN and TORCH) for single agents and up to 25% for combination products (fluticasone/salmeterol in TRISTAN and TORCH). In comparison, the effect size of roflumilast, as a single agent, in the pivotal studies was 15% to 19%.

Table 7.7.1–1 summarizes the treatment effects of roflumilast and currently available COPD treatments. To best characterize the improvements seen with roflumilast, the effect size should not be compared to the -25% a fixed combination of LABA-ICS achieved in comparison to placebo, but rather to what is achieved when adding an ICS to a LABA. For example, salmeterol alone improved the exacerbation rate in the TRISTAN study by 20% compared to placebo. Adding an ICS increased the effect size by just 5% resulting in a total of 25% reduction in exacerbation for the fixed combination of fluticasone and salmeterol compared to placebo. Another large trial, TORCH, showed that salmeterol versus placebo reduced exacerbation by 15% when compared to placebo; adding fluticasone to salmeterol in a fixed combination demonstrated an additional reduction in exacerbation by 12% versus salmeterol alone.

In contrast, a sub-analysis of the pivotal roflumilast studies showed that the effect of adding roflumilast to a LABA background treatment improved the exacerbation rate by 21% ($p = 0.001$) an effect that compares favorably to that of an ICS added to LABA treatment.

Though not powered to test for exacerbations, studies M2-127 and M2-128 indicated as well that roflumilast may substantially reduce exacerbations in patients taking salmeterol or tiotropium in a moderate to severe COPD population by 37% ($p = 0.0315$, post-hoc analysis) or 23% ($p = 0.1957$).

Table 7.7.1–1. Reduction in Exacerbation Frequencies in Studies With Roflumilast and With Currently Available Treatments

Reference	***Dur-ation***	***Concomitant medication***	***Post-FEV_1*** *%pred. at enroll*	***Treatment***	***% change versus placebo*** *Exacerbations defined as*				***Mth***
					Antib. a/o sCS tr.	**sCS tr. a/o hosp. a/o death**	**sCS tr.[c]**	**Hosp. a/o death**	
Roflumilast studies									
M2-124	1 y	SAMA, LABA	≤ 50	Rof500	-15	-15	-16	-11	P
M2-125	1 y	SAMA, LABA	≤ 50	Rof500	-17	-19	-18	-23	P
111+112 pool (CB[a])	1 y	SAMA, ICS	≤ 50	Rof500	-	-26	-	-	P
1-year pool (CB[a])	1 y	SAMA,ICS,LABA	≤ 50	Rof500	-	-20	-	-	P
Effects of roflumilast in patients on LABDs									
Pivotal studies pool[b]	1 y		≤ 50	R+LABA	-	-21	-	-	P
M2-127	24 w		30-80	R+Sal	-	-37[d]	-36[d]	-45[d]	P
M2-128	24 w		30-80	R+Tio	-	-23	-22	-35	P
Literature data (study short name)					**Antib. a/o sCS tr.**	**Antib. a/o sCS tr. a/o hosp.**	**sCS tr.[c]**	**Hosp.**	
Taskin, 2008 *(UPLIFT)*	4 y	no antichol.	≤ 70	Tio	-14	-	-	-	P
Calverley, 2007 *(TORCH)*	3 y	no ICS, no LABA	< 60	Advair[e]	-	-25	-43	-17	NB
				FP	-	-18	-35	-12	
				Sal	-	-15	-20	-18	
Burge 2000 *(ISOLDE)*	3 y	no restrictions	< 85	FP	-25				WRT
Calverley, 2003 *(TRISTAN)*	1 y	no ICS, no LABA	25-70	Advair[e]	-	-25	-39	-	P
				FP	-	-19	-34	-	

Table 7.7.1–1. Reduction in Exacerbation Frequencies in Studies With Roflumilast and With Currently Available Treatments

Reference	*Dur-ation*	*Concomitant medication*	*Post-FEV_1*	*Treatment*	*% change versus placebo*				*Mth*
					Exacerbations defined as				
			%pred. at enroll		**Antib. a/o sCS tr.**	**sCS tr. a/o hosp. a/o death**	**sCS tr.[c]**	**Hosp. a/o death**	
				Sal	-	-20	-29	-	
Calverley, 2003	1 y	terbutaline	≤ 50	Symb[f]	-	-24	-45	-	P
Szafranski, 2003	1 y	terbutaline	≤ 50	Symb[f]	-	-24	-31	-	P
				BUD	-	-15	-29	-	
				FF	-	-2	-3	-	
Casaburi, 2002	1 y	theophylline, ICS, oral predn.	≤ 65	Tio	-20[g]	-	-	-47	LR

a only subset of patients with chronic bronchitis (with or without emphysema).

b Subset analysis in patients with concomitant LABAs.

c Corresponds to moderate exacerbations in roflumilast studies.

d Post-hoc analysis.

e Salmeterol/fluticasone propionate 50/500 mcg BID.

f Budesonide/formoterol 160/4.5 mcg two inhalations BID.

g Treatments with antibiotics and/or steroids were not required but generally treated with such medication.

Antib. = antibiotic, antichol. = anticholinergics, a/o = and/or, BID = twice daily, BUD = budesonide (2x200 µg BID), enroll = enrollment, FEV_1 = forced expiratory volume in 1 second, FF = formoterol (2x4.5 mcg BID), FP = fluticasone propionate (500 mcg BID), hosp. = hospitalization, LABA = long-acting β_2-agonist, LABD = long-acting bronchodilators, ICS = inhaled corticosteroid, LR = logistic regression, mth = (analysis) method, m = month, NB = negative binominal regression, P= Poisson regression, post. = post-bronchodilator, pred. = predicted, predn. = prednisolone, QD = once daily, Ref. = reference, R or Rof500 = roflumilast 500 mcg once daily, SAMA = short-acting anticholinergics, sCS = systemic corticosteroid, Sal = salmeterol (50 mcg BID), Symb = Symbicort, Tio = tiotropium (18 mcg QD), tr. = treated, WRT = Wilcoxon rank sum test, y = year.

In conclusion, roflumilast consistently demonstrated a clinically meaningful reduction in exacerbations in a severely ill COPD patient population. The effect size is in the same range as other currently available COPD treatments.

7.7.2 Lung Function (FEV_1)

The pivotal roflumilast studies enrolled a severe to very severe patient population with a mean pre-bronchodilator FEV_1 of about 1 liter and low mean reversibility of 10% to 12%. The lung function effect size achievable in this population is reportedly very limited. For comparison, a Cochrane review (Appleton, 2006) showed that even bronchodilators like formoterol and salmeterol increased FEV_1 by an average of only 51 mL in patients with poorly reversible COPD. In comparison, the pivotal roflumilast study pool demonstrated a mean FEV_1 improvement of 48 mL in a similar population. In all the studies discussed above, roflumilast produced an improvement in FEV_1 values from baseline, whereas, placebo treatment led to no change or a decrease from baseline in FEV_1 values. The importance of reversibility on treatment related FEV_1 improvement was demonstrated in a corresponding subgroup analysis of the pooled data of studies M2-124 and M2-125 where larger treatment effects (72 mL) were seen in severe to very severe COPD patients with less fixed airway obstruction (higher reversibility) compared to those with fixed airway obstruction (Table 7.3.9–2).

Roflumilast exerts its effects in addition to the treatment effects of long-acting bronchodilators employed. In particular, improvements in pre-bronchodilator FEV_1 with roflumilast on top of concomitant LABA or SAMA treatment in patients with severe to very severe COPD were 46 mL and 58 mL in the pivotal studies M2-124 and M2-125, respectively. The effect on lung function on top of salmeterol or tiotropium treatment in patients with moderate to severe COPD was 49 mL and 80 mL (M2-127 and M2-128, respectively).

It is important to realize in this context that roflumilast is not a bronchodilator but achieves its effect through an anti-inflammatory action. The effect size of roflumilast on lung function is similar to what is achieved by inhaled corticosteroids alone or when added to a LABA treatment. In a large 3-year study [TORCH], fluticasone alone improved lung function by 47 mL over placebo, salmeterol alone by 42 mL, and a fixed combination of salmeterol/fluticasone improved lung function by 92 mL.

In conclusion, the effect size measured with roflumilast on lung function was in a severe, poorly reversible COPD population similar to what is achieved with LABAs in similar populations and also comparable to the effect size of inhaled corticosteroids, which are currently the only available anti-inflammatory treatments for COPD.

7.8 EFFICACY CONCLUSIONS

Roflumilast has been developed as a novel once-daily, oral treatment option for COPD, targeting the underlying inflammatory processes.

The core clinical program included two pivotal studies (Studies M2-124 and M2-125), and two studies evaluating roflumilast in patients concurrently on long-acting bronchodilator therapy (Studies M2-127 and M2-128), as well as two earlier supportive studies (M2-111 and M2-112). All six studies were conducted as multicenter randomized, placebo-controlled, parallel-group studies.

In pivotal studies M2-124 and M2-125, roflumilast significantly reduced the rate of moderate or severe exacerbations versus placebo by 14.9% ($p = 0.0278$; Study M2-124) and 18.5% ($p = 0.0035$; Study M2-125). Further analyses based on the number of patients experiencing an exacerbation and time to exacerbation supported the superior control of exacerbations by roflumilast over placebo.

Improvement in lung function with roflumilast over placebo for pre-bronchodilator FEV_1 was demonstrated in both pivotal studies with between-treatment differences of 39 mL ($p = 0.0003$) in M2-124 and 58 mL ($p < 0.0001$) in M2-125. Mean absolute improvements in FEV_1 versus placebo were apparent after 4 weeks and sustained throughout the entire 1-year treatment period in all four 1-year studies.

About 50% of patients in the pivotal studies were on concomitant LABA treatment. The rest of the patients were mostly using SAMAs and SABAs. A subgroup analysis of patients on LABA demonstrated that roflumilast exerted a strong and clinically meaningful effect on top of the LABA treatment. The effect size was similar to the effect seen with add-on ICS in fixed combinations with LABAs in literature studies.

Studies M2-127 (933 patients) and M2-128 (743 patients) provided further evidence that roflumilast exerts treatment effects in patients with less severe airway obstruction (post-bronchodilator FEV_1 between 40% to 70% of predicted values) and that treatment effects are independent of concomitant long-acting bronchodilator therapy (salmeterol M2-127or tiotropium M2-128). The additional benefits of roflumilast treatment on pre-bronchodilator FEV_1 were 49 mL in salmeterol- and 80 mL in tiotropium-treated patients ($p < 0.0001$ in each study). In addition, roflumilast demonstrated a 36.8% reduction ($p = 0.0315$) in the rate of moderate or severe COPD exacerbations in M2-127 (post-hoc analysis) and a 23% reduction ($p = 0.1957$) in M2-128. It should be noted that these studies were not powered to test for exacerbation.

Further supportive evidence is provided by the earlier two 1-year studies (M2-111 and M2-112) which evaluated treatment effects on lung function and rate of exacerbations. For pre-bronchodilator FEV_1, studies M2-111 and M2-112 provided comparable between-treatment differences of 42 mL (M2-111) and 57mL (M2-112). Roflumilast reduced the annual rate of moderate or severe exacerbations, using the definitions employed by the two pivotal studies, by 14.0% (M2-111) and 15.2% (M2-112). Statistical significance was not reached individually in these studies, but in the combined analysis of Studies M2-111 and M2-112, a reduction of 14.3% (p = 0.0257) was shown.

The clinical program demonstrated consistency of the treatment effect size across all these six large studies in terms of reduction of moderate and severe exacerbations (Figure 7.8–1) and improvement in lung function (Figure 7.8–2).

Figure 7.8–1. Roflumilast's Effect on Exacerbations Relative to Placebo as the Rate Ratio and 95% Confidence Interval, in Studies M2-111, M2-112, M2-124, M2-125, M2-127 and M2-128

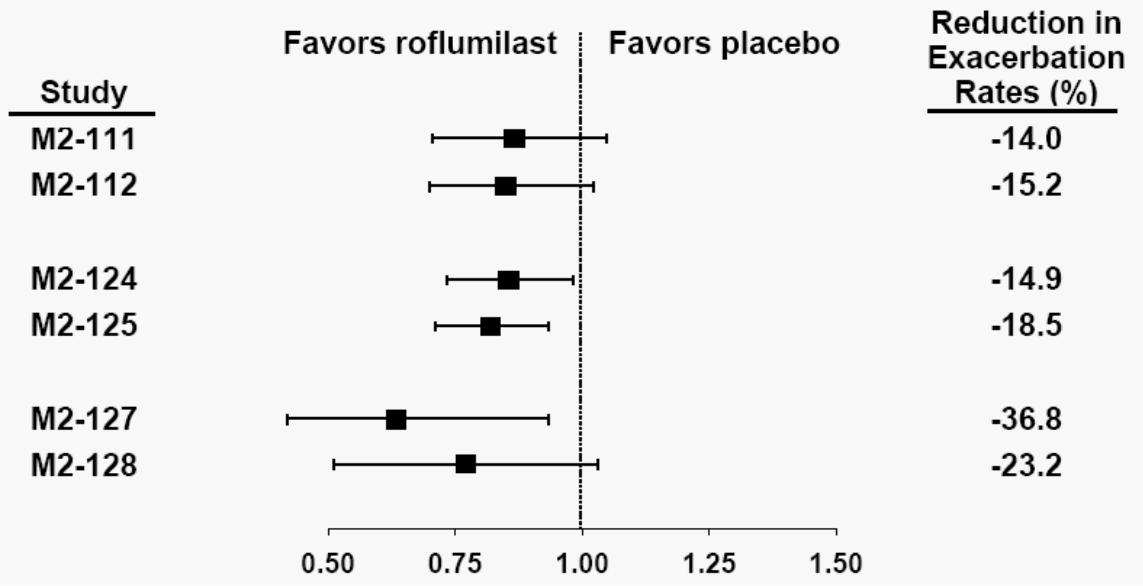
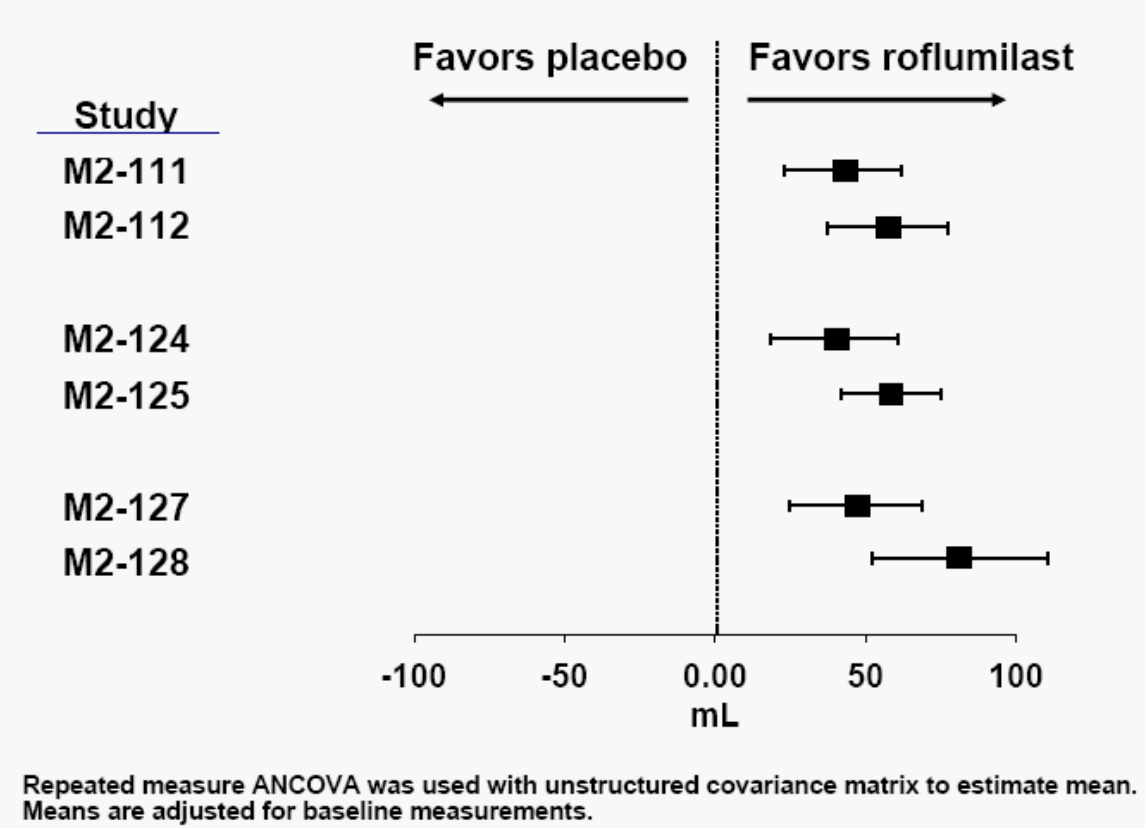


Figure 7.8–2. Roflumilast's Effect on FEV_1 as the Mean Difference from Placebo with 95% Confidence Intervals in Studies M2-111, M2-112, M2-124, M2-125, M2-127 and M2-128



In conclusion, roflumilast offers a new anti-inflammatory treatment option for patients with moderate to severe COPD and signs of chronic bronchitis, who are at risk of exacerbations. It has been shown that roflumilast achieves its beneficial effects independent of other COPD treatments and can be used safely in addition to other COPD medication.

In summary,

- Roflumilast consistently reduced the rate of moderate or severe exacerbations in patients with COPD associated with chronic bronchitis.
- Roflumilast provided improved lung function in patients with COPD.
- The observed effect sizes reflected the underlying patient populations studied, were clinically meaningful and compared favorably with currently available treatments.
- Roflumilast's effects were seen regardless of the type of background therapy and in a variety of patient subgroups.

8.0 SAFETY RESULTS

8.1 INTRODUCTION

The COPD safety pool, defined as a pool of 14 randomized placebo-controlled, double-blind, Phase 2 and Phase 3 trials in COPD patients, includes 12,054 COPD patients (5,766 treated with roflumilast 500 mcg, 5,491 with placebo and 797 with roflumilast 250 mcg). The analysis of roflumilast safety data in this briefing book focuses on the 500 mcg dose as this was the selected dose for the Phase 3 development program. Safety variables studied included AEs, laboratories, physical examination, vital signs, body weight, ECG and 24 hour Holter monitoring of a subpopulation of patients in Study M2-111 and Study M2-125. Fecal occult blood testing was performed in select studies.

8.2 PATIENT DEMOGRAPHICS AND BACKGROUND INFORMATION

Both the roflumilast 500 mcg once daily and placebo treatment groups had comparable demographics and baseline characteristics in the COPD safety pool. Across the COPD safety pool, the median age was 64 years, with 45% of the patients being older than 65 years. The majority of patients were male (72%) and white (88%), and 42% of the patients were current smokers. Approximately 56 % of the patients had severe COPD (Table 8.2–1).

Table 8.2–1. Demographics and Baseline Characteristics—COPD Safety Pool

	Placebo (N=5491)	***Rof500 (N=5766)***
Age, median (range) years	64 (40-92)	64 (25-93)
Age groups		
≤ 65 years, n (%)	3023 (55.1)	3173 (55.0)
> 65 years, n (%)	2468 (44.9)	2593 (45.0)
Male, n (%)	3979 (72.5)	4158 (72.1)
Female, n (%)	1512 (27.5)	1608 (27.9)
Smoker, n (%)		
Never	18 (0.3)	11 (0.2)
Current	2279 (41.5)	2420 (42.0)
Former	3194 (58.2)	3335 (57.8)

Table 8.2–1. Demographics and Baseline Characteristics—COPD Safety Pool

	Placebo (N=5491)	***Rof500 (N=5766)***
Race, n (%)		
White	4851 (88.3)	5128 (88.9)
Asian	402 (7.3)	400 (6.9)
Black or African American	73 (1.3)	67 (1.2)
Other	154 (2.8)	161 (2.8)
Missing	11 (0.2)	10 (0.2)
BMI (kg/m^2)		
mean ± SD	26.01 ± 5.5	25.98 ± 5.4
COPD severity, n (%)		
Very severe (FEV_1 % pred < 30%)	883 (16.1)	930 (16.1)
Severe (FEV_1 % pred ≥ 30% to < 50%)	3117 (56.8)	3201 (55.5)
Moderate (FEV_1 % pred ≥ 50% to < 80%)	1474 (26.8)	1619 (28.1)
Mild (FEV_1 % pred ≥ 80%)	16 (0.3)	14 (0.2)
Missing	1 (< 0.1)	2 (< 0.1)

COPD = chronic obstructive pulmonary disease, N = number of patients in treatment group, n = number of patients with data available, Rof500 = 500 mcg roflumilast once daily, FEV_1 = forced expiratory volume in 1 second, FEV_1 % pred = post-bronchodilator FEV_1 % predicted at baseline, BMI = body mass index.

Patients with asthma and/or other relevant lung diseases, chronic gastrointestinal disorders associated with a history of recurrent gastrointestinal bleeding within the last 12 months, cancer, or clinically significant active or uncontrolled cardiopulmonary disease or ECG abnormalities were excluded from participation in all studies.

Previous and Concomitant COPD Treatment

As shown in Table 8.2–2, the use of concomitant COPD medications during the treatment period was comparable for the roflumilast 500 mcg and placebo groups in the COPD Safety Pool. Most patients in both treatment groups used at least one concomitant COPD medication. Inhaled SABAs, which were allowed as rescue medication, were used by two thirds of patients in both the roflumilast 500 mcg and placebo treatment groups. Other frequent COPD medications in both groups were SAMAs, corticosteroids, and LABAs.

Table 8.2–2. Concomitant COPD Medications—COPD Safety Pool

Concomitant medication[a] (Extended ATC codes)	***Placebo (N=5491)***	***Rof500 (N=5766)***
	n (%)[b]	*n (%)[b]*
At least one COPD medication	4767 (86.8)	4919 (85.3)
Inhaled SABA	3713 (67.6)	3694 (64.1)
Inhaled SAMA	1988 (36.2)	2075 (36.0)
Corticosteroids (excl. inhaled and nasal applications)	1840 (33.5)	1686 (29.2)
Inhaled corticosteroids	1196 (21.8)	1234 (21.4)
Inhaled LABA	771 (14.0)	758 (13.1)
Inhaled combination of corticosteroids and LABA	339 (6.2)	307 (5.3)
Xanthines	234 (4.3)	231 (4.0)
Inhaled combination β_2-agonists and SA anticholinergics	228 (4.2)	232 (4.0)
Inhaled LAMA	175 (3.2)	175 (3.0)

Note: this table presents concomitant COPD medications that potentially were taken during the entire treatment period together with medications that were taken only once or twice, eg, for the treatment of a COPD exacerbation.

a Asthma and allergic rhinitis related treatments may be included.

b Percentages are based on N.

ATC = Anatomical Therapeutic Chemical, COPD = chronic obstructive pulmonary disease, excl. = excluding, IV = intravenously, LA = long-acting, LABA = long-acting β-agonist, N = number of patients in treatment group, n = number of patients with data available, Rof500 = 500 mcg roflumilast once daily, SA = short acting, SABA = short-acting β_2-agonist, SAMA = short acting muscarinic antagonists, LAMA = long-acting muscarinic antagonist.

In conclusion, there were no notable imbalances between the treatment groups with regard to demographics, concomitant medications and COPD severity.

8.3 EXTENT OF EXPOSURE

In accordance with ICH Guideline for Industry: *"Extent of Population Exposure to Assess Clinical Safety"* (dated March 1995) and in accordance with the FDA *Draft Guidance for Industry: "Chronic Obstructive Pulmonary Disease: Development of Drugs for Treatment"* (dated November 2007), most patients were treated with drug for 6 months to 1 year.

More than 2,300 patients were treated for at least 6 months with roflumilast, of these more than 1,200 patients received roflumilast treatment for at least one year. Exposure time was defined as the number of days from the day of first to the day of last intake of double-blind study medication.

The total exposure time for patients in the COPD safety pool was 3,261 patient years for roflumilast and 3,405 for placebo. Patient drug exposure was generally comparable for the roflumilast 500 mcg once daily group and the placebo group. The difference in exposure is a result of a higher number of early terminations in the roflumilast group. Roflumilast treated patients who discontinued did so early, primarily as a result of gastrointestinal system AEs. Discontinuations due to respiratory related AEs were greater in the placebo group and tended to be consistent throughout the study period. Table 8.3–1 summarizes patient drug exposure for the COPD safety pool.

Table 8.3–1. Patient Drug Exposure—COPD Safety Pool

Exposure to study drug	***COPD Safety Pool***[a]	
	Placebo (N=5491)	*Rof500 (N=5766)*
	n (%)[b]	**n (%)**[b]
< 13 weeks	925 (16.8)	1372 (23.8)
≥ 13 weeks to < 26 weeks	2045 (37.2)	2081 (36.1)
≥ 26 weeks to < 52 weeks	1167 (21.3)	1081 (18.7)
≥ 52 weeks	1354 (24.7)	1232 (21.4)
Mean ET per patient (days) [mean ± SD]	226.5 ± 119.0	206.6 ± 125.8
Total ET (patient years)	3405	3261

a 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, M2-128.

b 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, Rof500 = 500 mcg roflumilast once daily.

8.4 ADVERSE EVENTS

8.4.1 Frequently Occurring Adverse Events

Adverse events which occurred in ≥ 2% of patients at the preferred term (PT) level in any treatment group are summarized by System Organ Class (SOC) and PT in Table 8.4.1–1. As shown, 67.2% of patients in the roflumilast group and 62.8% of patients in the placebo group reported AEs.

Most AEs, by preferred term, were balanced between the groups. Diarrhea, nausea, decreased appetite, headaches, dizziness, insomnia and weight decrease were observed more frequently (ie, > 1% difference between groups) in the roflumilast arm compared to the placebo arm. The highest difference between the 2 groups was noted for diarrhea where 10.1% of all roflumilast treated patients reported this AE compared to 2.6% in patients on placebo. By contrast, COPD exacerbations were more frequently reported in placebo treated patients (19.8% on roflumilast versus 23.1 % on placebo). The incidence of pneumonia was balanced between the two treatment arms (1.8% vs. 2.0% in the roflumilast and placebo arms, respectively).

Most adverse events generally occurred within the first weeks of therapy and resolved during continued treatment**.** The duration of most AEs in both treatment groups was less than four weeks. This suggests that most patients who reported AEs discontinued early or developed tolerance to roflumilast with continued dosing.

In the COPD Safety Pool, 32.9% of roflumilast patients and 37.3% placebo patients did not report any AEs while mild adverse events were reported by 16.3% of roflumilast 500 mcg patients vs. 15.4% of placebo patients, moderate events by 36.2 % vs. 33.4% and, severe events by 14.6% vs. 13.9%, respectively.

Table 8.4.1–1. Patients with Frequent Adverse Events by System Organ Class and Preferred Term (Frequency ≥ 2% of Patients with Regard to Preferred Term in any Treatment Group)—COPD Safety Pool

System Organ Class *Preferred Term (MedDRA)*	***Placebo (N=5491)***	***Rof500 (N=5766)***
	n (%)[a]	*n (%)*[a]
All AEs	**3447 (62.8)**	**3873 (67.2)**
Infections and infestations	**1508 (27.5)**	**1492 (25.9)**
Nasopharyngitis	346 (6.3)	364 (6.3)
Bronchitis	192 (3.5)	177 (3.1)
Upper respiratory tract infection	234 (4.3)	219 (3.8)
Pneumonia	110 (2.0)	104 (1.8)
Influenza	132 (2.4)	145 (2.5)
Respiratory, thoracic and mediastinal disorders	**1607 (29.3)**	**1476 (25.6)**
COPD[b]	1271 (23.1)	1142 (19.8)
Dyspnea	120 (2.2)	84 (1.5)
Gastrointestinal disorders	**587 (10.7)**	**1271 (22.0)**
Diarrhea	143 (2.6)	585 (10.1)
Nausea	79 (1.4)	297 (5.2)
Investigations	**584 (10.6)**	**811 (14.1)**
Weight decreased	101 (1.8)	394 (6.8)

Table 8.4.1–1. Patients with Frequent Adverse Events by System Organ Class and Preferred Term (Frequency ≥ 2% of Patients with Regard to Preferred Term in any Treatment Group)—COPD Safety Pool

System Organ Class *Preferred Term* *(MedDRA)*	***Placebo*** ***(N=5491)***	***Rof500*** ***(N=5766)***
	n (%)[a]	*n (%)*[a]
Nervous system disorders	**304 (5.5)**	**615 (10.7)**
Headache	110 (2.0)	266 (4.6)
Dizziness	65 (1.2)	139 (2.4)
Musculoskeletal and connective tissue disorders	**445 (8.1)**	**590 (10.2)**
Back pain	117 (2.1)	176 (3.1)
Metabolism and nutrition disorders	**186 (3.4)**	**311 (5.4)**
Decreased appetite	22 (0.4)	125 (2.2)
Psychiatric disorders	**164 (3.0)**	**344 (6.0)**
Insomnia	50 (0.9)	148 (2.6)
Vascular disorders	**229 (4.2)**	**196 (3.4)**
Hypertension	136 (2.5)	95 (1.6)

a Percentages of patients with at least one event in the category.

b The preferred term COPD refers to COPD exacerbation.

AE = adverse event, COPD = chronic obstructive pulmonary disease, 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.

8.4.2 Premature Discontinuation Due to Adverse Events

The overall rate of premature withdrawals due to AEs was higher in the roflumilast 500 mcg group than the placebo group (14.3% vs. 9.2%). Table 8.4.2–1 lists the AEs leading to premature discontinuation in more than 0.5% of patients in any treatment group.

Table 8.4.2–1. Patients with Adverse Events Leading to Withdrawal by Preferred Term (Frequency ≥ 0.5% of Patients with Regard to Preferred Term in any Treatment Group)—COPD Safety Pool

Preferred Term (MedDRA)	***Placebo (N=5491) (ET=3405)***	***Rof500 (N=5766) (ET=3261)***
	n (%)[a]	*n (%)*[a]
All AEs	**503 (9.2)**	**824 (14.3)**
COPD[b]	209 (3.8)	187 (3.2)
Diarrhea	5 (<0.1)	145 (2.5)
Nausea	10 (0.2)	91 (1.6)
Headache	4 (<0.1)	45 (0.8)
Weight decreased	2 (<0.1)	30 (0.5)
Decreased appetite	2 (<0.1)	29 (0.5)
Abdominal pain	5 (<0.1)	28 (0.5)
Tremor	2 (<0.1)	28 (0.5)
Dizziness	7 (0.1)	28 (0.5)
Insomnia	3 (<0.1)	27 (0.5)
Dyspnea	31 (0.6)	19 (0.3)
Pneumonia	25 (0.5)	17 (0.3)

a Percentages are based on the total number of patients.

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 data available, PT = preferred term, Resp = respiratory, Rof500 = 500 mcg roflumilast once daily.

The difference between roflumilast and placebo was mostly due to gastrointestinal events and they mostly occurred in the first few weeks of the treatment. This suggests that there are some patients who are sensitive to GI events who may drop out early with the remaining patients tolerating roflumilast as well as patients treated with placebo.

Discontinuation due to all other AEs other than GI related events was similar between roflumilast (9.2%) and placebo (8.4%).

8.4.3 Serious Adverse Events

Serious adverse events (including those leading to death) that occurred in ≥ 0.3% of patients by preferred term in either treatment group are summarized in Table 8.4.3–1.

In patients receiving roflumilast 500 mcg once daily, 781 (13.5%) SAEs were reported, while in patients receiving placebo 782 (14.2%) SAEs were reported. In both treatment groups, COPD exacerbation was the most frequent SAE (5.8% roflumilast vs. 7.1% placebo), followed by pneumonia (1.1% roflumilast vs. 1.1% placebo). The overall rates of cardiac disorders were generally comparable for the two treatment groups. Overall, and by preferred term, the type and incidence of SAEs appeared similar between the roflumilast and placebo treatment groups.

Table 8.4.3–1. Patients with Serious Adverse Events by Preferred Term (Frequency ≥ 0.3% of Patients with Regard to Preferred Term in any Treatment Group)— COPD Safety Pool

Preferred Term (MedDRA)	***COPD safety pool***	
	Placebo (N=5491)	*Rof500 (N=5766)*
	n (%)[a]	**n (%)[a]**
All SAEs	782 (14.2)	781 (13.5)
COPD[b]	389 (7.1)	337 (5.8)
Respiratory failure	20 (0.4)	13 (0.2)
Pneumonia	59 (1.1)	63 (1.1)
Atrial fibrillation	9 (0.2)	24 (0.4)
Myocardial infarction	23 (0.4)	12 (0.2)
Chest pain	17 (0.3)	9 (0.2)

a Percentages of patients with at least one event in the category.

b The preferred term COPD refers to COPD exacerbation.

COPD = chronic obstructive pulmonary disease, 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, Rof500 = 500 mcg roflumilast once daily, SAE = serious adverse event.

8.4.4 Deaths

Adverse Events that led to death that occurred in ≥ 0.1% of patients in either treatment group are summarized in Table 8.4.4–1 by preferred term.

Death was reported for 84 patients (1.5%) in the roflumilast 500 mcg group and for 86 patients (1.6%) in the placebo group. In the roflumilast and placebo groups, most AEs leading to death were related to COPD exacerbation, and were thus most likely complications of the underlying disease. None of the AEs leading to death were considered likely or definitely related to the study medication by either the investigator or the sponsor and there was no clinically relevant imbalance in causes of death between treatment arms.

Table 8.4.4–1. Patients with Adverse Events Leading to Death by Preferred Term (Frequency ≥ 0.1% of Patients in any Treatment Group)—COPD Safety Pool

System Organ Class *Preferred Term* *(MedDRA)*	*Placebo* *(N=5491)*	*Rof500* *(N=5766)*
	n (%)[a]	*n (%)*[a]
All Deaths	86 (1.6)	84 (1.5)
COPD[b]	22 (0.4)	20 (0.3)
Pneumonia	10 (0.2)	9 (0.2)
Cardiac arrest	1 (<0.1)	7 (0.1)
Acute respiratory failure	4 (<0.1)	6 (0.1)
Sudden death	6 (<0.1)	4 (<0.1)

a Percentages are based on the total number of patients.

b The preferred term COPD refers to COPD exacerbation.

AE = adverse event, MedDRA = Medical Dictionary for Regulatory, N = number of patients in treatment group, n = number of patients with data available, Rof500 = 500 mcg roflumilast once daily.

8.5 SUBGROUP ANALYSES

Within the COPD safety pool, AEs were analyzed by age group (≤ 65 years, > 65 years), gender, race, COPD severity (moderate, severe, very severe) and smoking status. There were no noteworthy differences amongst the subgroups in the occurrence of individual AEs with roflumilast treatment as compared to placebo.

8.6 EVENTS OF INTEREST

8.6.1 Weight Change

Weight decrease as an AE was reported more frequently in roflumilast patients in the early Phase 2 and Phase 3 clinical trials. Because of this observation in early studies, the protocols for the pivotal 1-year studies M2-124 and M2-125, and supportive 6-month studies M2-127 and M2-128 included systematic weight measurements at each visit.

Since weight was measured prospectively and systematically for 1-year across the two pivotal trials, this section is focused on the "Pivotal COPD Safety Pool" (ie, the pool of Study M2-124 and M2-125) and not on the full COPD Safety pool. Findings in the two supportive 6-month trials were consistent.

In the pivotal COPD studies pool, the mean baseline BMI of patients was 26 kg/m^2 (ranging from 12.3 kg/m^2 to 55.7 kg/m^2), consistent with a definition of the study population as overweight on average. The baseline population included 9% underweight, 38% normal, 32% overweight and 21% obese patients with the baseline distribution by BMI being similar between treatments Table 8.6.1–1).

Measured weight loss (ie, any measurable decrease in body weight) occurred in about 62% of patients receiving roflumilast and 38% of placebo patients. Table 8.6.1–1 shows the percentage of patients with weight loss was highest in the BMI group defined as "Obese" and lowest in the group defined as "Underweight" on both treatments. Compared to placebo, the number of patients experiencing weight loss was higher in the roflumilast group in all BMI groups.

Table 8.6.1–1. Percentage of Patients with Weight Change from Baseline by Body Mass Index at Baseline—Pivotal COPD Studies Pool

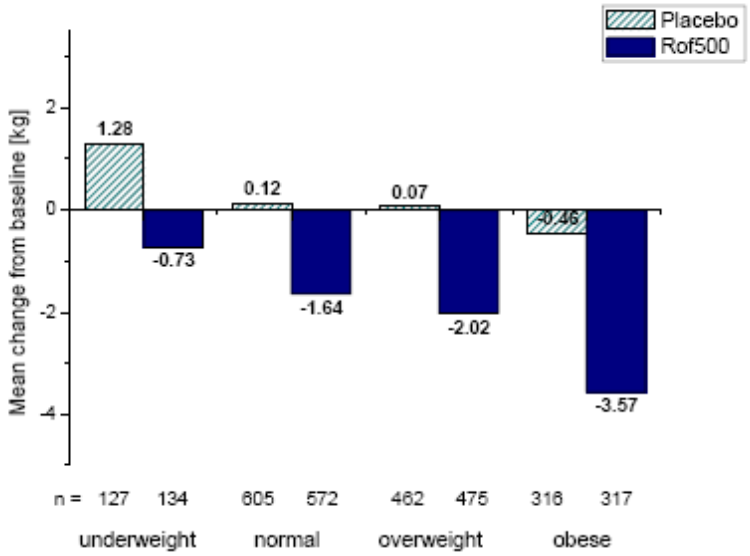
	Placebo		***Rof500***	
		Patients with WD		*Patients with WD*
Number of patients	**n (%)**	**n' (%)**	**n (%)**	**n' (%)**
Total	1510	569 (37.7)	1498	935 (62.4)
By BMI category				
Underweight	127 (8.4)	34 (26.8)	134 (8.9)	64 (47.8)
Normal weight	605 (40.1)	214 (35.4)	572 (38.2)	350 (61.2)
Overweight	462 (30.6)	181 (39.2)	475 (31.7)	298 (62.7)
Obese	316 (20.9)	140 (44.4)	317 (21.2)	223 (70.3)

n = number of patients in treatment group with data available, n' = number of patients in the category; BMI = body mass index, Rof500 = Roflumilast 500 mcg once daily, WD = weight decrease.

The mean weight loss in roflumilast treated patients was 2.09 kg or 2.7%. The obese patient category showed the greatest absolute change in weight, with an average of -3.6 kg with roflumilast compared to -0.5 kg with placebo. The respective results in the BMI category underweight patients indicated an average change of -0.7 kg with roflumilast compared to an increase of +1.3 kg with placebo. The measured weight decrease appears to be proportional to baseline BMI (See Figure 8.6.1–1).

Patients in the "Underweight" category lost an average of about 1.6% weight while patients in the "Obese" category lost on average 3.7%. A total of 8 patients in the underweight category (0.5% of all treated patients) and a total of 32 patients in the obese category (2% of all treated patients) lost more than 10% weight.

Figure 8.6.1–1. Absolute Weight Change from Baseline to End of Treatment by Baseline Body Weight Classification—Pivotal COPD Studies Pool



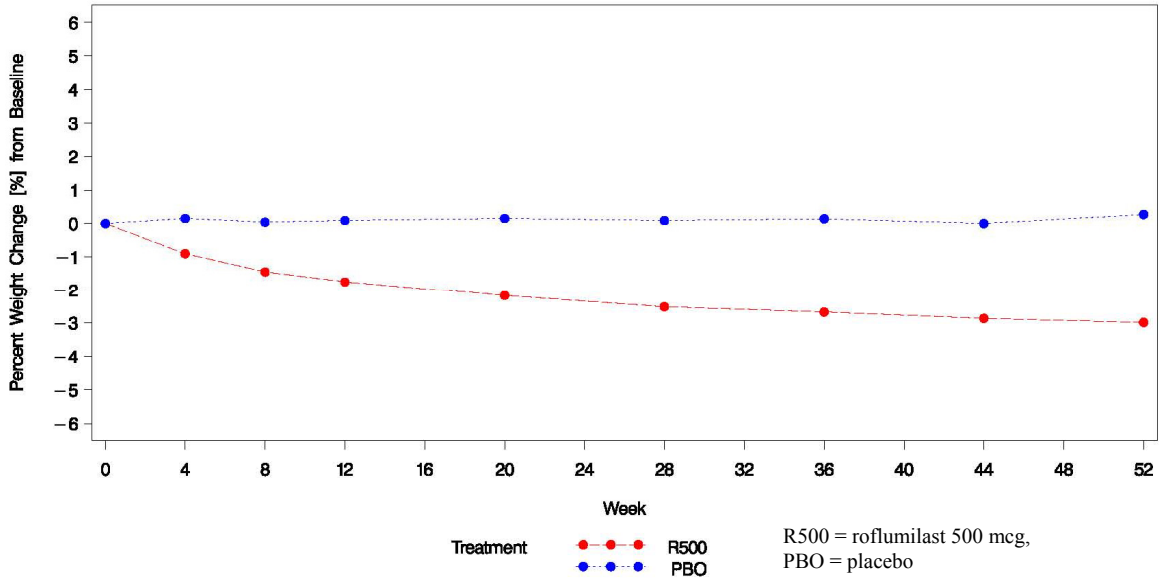
underweight (< 18.5 kg/m^2), normal (≥ 18.5 kg/m^2 to < 25 kg/m^2), overweight (≥ 25 kg/m^2 to < 30 kg/m^2), obese (≥ 30 kg/m^2), n = Number of patients with data available

In summary, measured weight loss occurred most frequently in the obese, who lost proportionately more weight than the non-obese.

There was no apparent effect of COPD severity at baseline on the absolute weight decrease measured in both treatment groups. In the roflumilast group mean changes in body weight ranged from -2.19 kg in patients with very severe COPD to - 1.9 kg in patients with moderate COPD.

The time course of mean body weight percent change from baseline at all study visits during the 52 week treatment period for the pivotal COPD studies pool is illustrated in Figure 8.6.1–2. The loss in body weight was most pronounced during the first 8 weeks of roflumilast treatment and was small from month 6 to the end of treatment (Week 52).

Figure 8.6.1–2. Mean Percent Change from Baseline in Weight (Adjusted LS Means) Over Time by Treatment Group—Pivotal COPD Studies Pool



In a 3 month follow-up of 91 patients taking roflumilast who reported the AE of weight decrease and also had measured weight decrease, more than 95% of these patients had no further weight decease or regained some weight, with approximately 50% of the patients regaining at least one-half of the previous loss. In the pivotal 1-year studies 4 of 1,547 patients (0.3%), and 31 (0.5%) of 6563 in the COPD Safety Pool receiving roflumilast discontinued early from the study due to an AE of weight decrease.

To further characterize weight change, Free Fat Mass Index (FFMI) was measured via bioimpedance in Study M2-128. On average, 67% of the weight decrease appears to be decrease of fat mass. After a decrease within the first month of roflumilast treatment, FFMI remained unchanged over the remainder of the study.

Safety as reflected in adverse events was examined in patients with measured weight loss. While patients with weight loss on roflumilast had a slightly greater AE experience than patients on placebo (72% vs. 68% respectively), this difference was mainly driven by an increased number of GI events in the roflumilast group. Except for GI events, there were no clinically significant differences in reported AEs other than the AE “weight decreased.”

Further post hoc analyses were performed to investigate whether roflumilast associated weight loss predisposed especially vulnerable patients with low baseline BMI (< 18.5 BMI kg/m^2) to increased morbidity such as infections, exacerbations and death as compared to placebo treatment. Patients who met this criterion included 62 subjects receiving roflumilast and 32 receiving placebo. There was a lower incidence of AEs overall in the roflumilast group compared with the placebo group (71.0% roflumilast vs. 75.8% placebo); infections in general (23.7% roflumilast vs. 33.3% placebo), general respiratory AEs (11.3% roflumilast vs. 33.3% placebo) and specifically, COPD exacerbations (8.1% roflumilast vs. 18.2% placebo). Death occurred in 4 "underweight" patients receiving roflumilast (6.5%) and 3 patients receiving placebo (9%).

Thus for patients who had measured weight loss there was no difference in the AE experience between roflumilast or placebo treatments, with the exception of GI events. Most importantly there was no evidence that the underweight group had an increased safety risk when receiving roflumilast compared to placebo.

The mechanism of this weight loss appears to be multifactorial. Patients reporting diarrhea, nausea and/or vomiting as AEs experienced a somewhat greater weight loss than those not reporting those symptoms (2.6 kg vs. 2.0 kg). It is not known whether there was an increase in physical activity in roflumilast treated patients that could also contribute to the weight change. In any case, the data does not suggest that there is an adverse impact due to weight loss on the overall health status of patients treated with roflumilast.

In conclusion, given the results of early clinical trials, weight change was carefully followed in the pivotal trials, Studies M2-124 and M2-125. Most of the weight loss experienced during roflumilast treatment appears to be due to loss of fat mass and the greatest absolute change in weight was observed in patients overweight at baseline. Very few patients discontinued due to weight loss and there appeared to be no greater morbidity in patients who lost weight, including the low BMI category. Thus, no negative consequences of weight loss with respect to the safety of patients treated with roflumilast were observed. Nevertheless, as this is a chronic therapy, the Sponsor recommends the regular monitoring of weight and to take appropriate action if needed.

8.6.2 Cardiac Observations

COPD patients commonly have a concurrent cardiac history. Therefore, potential cardiovascular effects of roflumilast in humans were investigated.

In a "Thorough QT/QTc Study" roflumilast was administered up to 1,000 mcg as the supratherapeutic dose once daily administered for up to 14 days and did not demonstrate a prolongation of the QTc interval. In another study in healthy subjects roflumilast did not show relevant cardiovascular effects as assessed by impedance cardiography, exercise or resting ECGs, blood pressure, and heart rate. Two studies evaluating the potential cardiovascular interaction between roflumilast and sildenafil or inhaled formoterol also indicated that roflumilast had no clinically relevant effects on cardiovascular function.

A comprehensive analysis of cardiac events of interest (comprising the majority of event terms in the SOC Cardiac Disorders, as well as ECGs, including central analysis and 24-Holter ECGs) did not reveal a signal for arrhythmogenic potential of roflumilast administration. The overall proportion of patients with cardiac events of interest was similar in the roflumilast group and the placebo group (5.2% vs. 5.7%). Similarly, this finding was consistently observed for the subcategories of cardiac AEs leading to death (roflumilast, 0.4% vs. placebo, 0.5%), cardiac SAEs (roflumilast, 1.8% vs. placebo, 2.1%), and cardiac AEs leading to study discontinuation (roflumilast, 0.9% vs. placebo, 1.0%).

Within the roflumilast COPD Safety Pool, 177 fatal cases (1.47% of the COPD safety pool) were reported with 84 patients in the roflumilast 500 mcg treatment group, 7 patients in the 250 mcg treatment group (total roflumilast 91), and 86 patients in the placebo treatment group. The percentage of fatal cases was slightly lower in the roflumilast (91 patients, 1.39%) than in the placebo group (86 patients, 1.57%).

As part of the overall investigation of cardiac safety, a blinded post-hoc adjudication by an independent committee of cardiologists was performed of all death cases that occurred during the entire roflumilast development program. This adjudication was performed to establish an unbiased differentiation between *cardiovascular* and *non-cardiovascular* causes of death in the roflumilast and placebo treatment groups and to compare incidence rates in the two treatment groups. The committee's adjudication reported that death as a cardiovascular outcome affected 35 of 91 patients taking roflumilast (0.53%), and 42 of 86 patients taking placebo (0.78%). None of the fatal events was assessed by the investigator or sponsor as "related" to roflumilast.

In the COPD Safety Pool, the number of fatal events adjudicated as having a *cardiovascular* cause was lower in the roflumilast than in the placebo group (35 patients; 0.53% vs. 42 patients; 0.77%). In particular, a balance between the treatment groups was shown for the category, *sudden death due to arrhythmia*, for which a total of 3 cases was established (1 patient in the roflumilast 500 mcg once daily group and 2 in the placebo group). The most frequent primary cause of death was *sudden death, etiology unknown*. In this category there were fewer fatal cases in the roflumilast than in the placebo treatment group (22 patients; 0.34% vs. 26 patients; 0.47%, respectively) (Table 8.6.2–1).

Table 8.6.2–1. Summary of Unblinded Adjudicated Fatal Cases—COPD Safety Pool

Categories Used to Classify Patients' Primary Cause of Death	***Fatal Cases in the COPD Safety Pool***		
	Roflumilast 500 and 250 mcg	*Placebo*	*Relative Risk*
	(N=6563) N'=91	**(N = 5491) N'=86**	**RR (95% CI)[a]**
	n (%)	*n (%)*	
Cardiovascular	35 (0.5)	42 (0.8)	0.70 (0.45, 1.09)
Death Due to Myocardial Infarction	4 (< 0.1)	3 (< 0.1)	
Death Due to Stroke	3 (< 0.1)	4 (< 0.1)	
Sudden Death Due to Arrhythmia	1 (< 0.1)	2 (< 0.1)	
Sudden Death, Etiology Unknown	22 (0.3)	26 (0.5)	
Death Due to Congestive Heart Failure	2 (< 0.1)	4 (< 0.1)	
Other Cardiovascular Deaths	3 (< 0.1)	3 (< 0.1)	
Non-Cardiovascular			
Fatal Non-Cardiovascular Events	52 (0.8)	40 (0.7)	1.09 (0.72, 1.64)
Insufficient Data			
Insufficient Data	4 (< 0.1)	4 (< 0.1)	

a Calculated where number of events was large enough to permit calculation of relative risk.

COPD = chronic obstructive pulmonary disease , N=number of patients in the treatment group; N'= number of patients with fatal events; n=number of patients with that specific fatal event; % percentage of patients based on N.

Note: Unblinding of cases was done by the Sponsor after the adjudication of all cases had been completed.

With regards to nonfatal cardiovascular events, a slightly higher percentage of roflumilast-treated patients with AEs of atrial fibrillation were observed compared to the placebo group (0.8% vs. 0.6%, respectively). Reports of atrial fibrillation were variable between studies in the overall COPD safety pool. Of note, there were very few reported ventricular events (ventricular extrasystoles: 8 [0.1%] on roflumilast and 14 [0.3%] on placebo). Individual ECG readings and individual case reviews did not reveal clinically relevant findings due to administration of roflumilast. For half of the roflumilast-treated patients 'atrial fibrillation' was a non-serious event. The detailed medical review of the individual case records revealed that for more than two thirds of patients the events had a clearly identifiable comorbidity-associated cause.

In summary, roflumilast does not appear to be associated with a risk of cardiac disorders.

8.6.3 Neuropsychiatric Events

In general, depression is common in COPD patients, as evidenced by the results of a large-population-based study conducted by the Pharmacoepidemiology Unit of University Hospital Basel, Switzerland with data from the General Practice Research Database in the UK. In this large epidemiology study, the incidence in the general COPD population is 16.2 per 1000 patient years and only 9.4 per 1000 patient years for patients without COPD, suggesting that COPD patients are twice as likely to experience new onset depression than the non-COPD population (Schneider et. al. 2010).

In the COPD Safety Pool a numerical imbalance of neuropsychiatric events such as anxiety, depression, insomnia, sleep disorders, dizziness, headache, tremor, and rare instances of suicidal thinking and behavior (including suicide) was reported in roflumilast-treated patients compared to placebo treated patients (Table 8.6.3–1).

Table 8.6.3–1. Patients with Psychiatric and Nervous System Disorders AEs—COPD Safety Pool

System Organ Class *Preferred Term (MedDRA)*	***Placebo (N=5491)***	***Rof500 (N=5766)***	***Rof250 (N=797)***
	n (%)	*n (%)*	*n (%)*
Psychiatric disorders	164 (3.0)	344 (6.0)	22 (2.8)
Anxiety/Anxiety disorder	43 (0.8)	81 (1.4)	6 (0.8)
Depression/Depressive[a]	46 (0.8)	78 (1.4)	4 (0.5)
Insomnia[b]/Sleep disorder	60 (1.1)	171 (3.0)	12 (1.5)
Suicidal behaviors[c]	1 (< 0.1)	4 (0.1)	1 (< 0.1)
Nervous system disorders	304 (5.5)	615 (10.7)	45 (5.7)
Headache	110 (2.0)	266 (4.6)	28 (3.5)
Dizziness	65 (1.2)	139 (2.4)	9 (1.1)
Tremor	15 (0.3)	98 (1.7)	1 (0.1)

a Includes MedDRA preferred terms: depressed mood, depression, depressive symptom, and major depression.

b Includes MedDRA preferred term early insomnia.

c Includes MedDRA preferred terms: completed suicide, suicidal attempt, and suicidal ideation.

n = number of patients with the event, Rof250 = roflumilast 250 mcg once daily Rof500 = roflumilast 500 mcg once daily.

However, despite a higher incidence of neuropsychiatric TEAEs, the incidence of SAEs in the psychiatric and the nervous system disorder categories, in roflumilast-treated patients was similar to that in placebo treated patients (Table 8.6.3–2).

Table 8.6.3–2. Patients with Psychiatric and Nervous System Disorders Serious Adverse Events—COPD Safety Pool

System Organ Class *Preferred Term (MedDRA)*	***Placebo (N=5491)***	***Rof500 (N=5766)***	***Rof250 (N=797)***
	n (%)	*n (%)*	*n (%)*
Nervous system disorders	44 (0.8)	37 (0.6)	1 (0.1)
Psychiatric disorders	13 (0.2)	12 (0.2)	1 (0.1)

n = number of patients with the event, Rof250 = roflumilast 250 mcg once daily, Rof500 = roflumilast 500 mcg once daily.

In the COPD safety pool, 78 (1.4%) of patients on roflumilast 500 mcg, and 46 (0.8%) placebo-treated patients reported depression as an AE term. Seven (0.12%) patients on roflumilast 500 mcg and 4 (0.07%) patients on placebo reported depression as a serious AE. Eleven (0.19%) patients treated with roflumilast 500 mcg and six (0.11%) treated with placebo discontinued from study due to depression.

Severe depression is a known risk factor for suicidal ideation which, in turn, may lead to completed suicide. Therefore, a thorough assessment for the risk of suicidality was conducted.

Suicidal ideation/attempt was reported for 2 patients on roflumilast 500 mcg and one on placebo. One of these 2 suicide attempts on roflumilast was reported 11 months after the last administration of roflumilast.

Completed suicide was reported for 2 patients on roflumilast 500 mcg and one patient on roflumilast 250 mcg (Table 8.6.3–3).

Table 8.6.3–3. Patients with Suicidal Behaviors—COPD Safety Pool

	Placebo (N=5491)	***Rof500 (N=5766)***	***Rof250 (N=797)***
	n (%)	*n (%)*	*n (%)*
Suicidal ideation / attempt	1 (0.02)	2 (0.03)	0 (0.0)
Completed suicide			
While on drug	0	1 (0.02)	0
> 3 weeks after discontinuation	0	1 (0.02)	1 (0.13)

n = number of patients with the event, Rof250 = roflumilast 250 mcg once daily, Rof500 = roflumilast 500 mcg once daily.

One patient on roflumilast 500 mcg had discontinued roflumilast for more than 3 weeks when he committed suicide. This patient had also been treated for depression with alprazolam, and, more recently, with venlafaxine, which is associated with an increased risk of suicidality (venlafaxine package insert). For the second patient on roflumilast 500 mcg, it is unknown if this patient had a history of psychiatric disorders. The patient on roflumilast 250 mcg had discontinued roflumilast for more than 3 weeks when he committed suicide. No patients on placebo completed suicide. None of these events were considered by the investigators as likely related to the study drug.

To characterize suicidality observed in the clinical trials, an independent blinded adjudication was performed using the Columbia Classification Algorithm of Suicide Assessment (C-CASA), the methodology that was commissioned by the FDA and developed by Columbia University scientists (lead by Dr. Kelly Posner). The FDA methodology relies on specified word strings to capture verbatim reporting terms and a limited Standard MedDRA query for suicide and related events. The Center for Suicide Risk Assessment at Columbia performed this adjudication for 78 adverse events that were identified using the string search, involving 76 patients from the COPD database of 6,563 patients. Of the 78 adverse events adjudicated, the classification process yielded 3 completed suicides, 2 suicide attempts, and 1 suicidal ideation. Based on this review, no additional cases of suicidality were captured. One suicide attempt by a patient on roflumilast was reported 11 months after the last administration of drug. Of the 3 events of suicidal ideation, and suicide attempt, 2 (suicide attempt) were in the roflumilast group and 1 (suicidal ideation) was in placebo. There did not appear to be an imbalance for these events. While 3 completed suicides were reported in the roflumilast arm, these event rates are too low to be statistically significant. The balance of the (adjudicated) reported events using this methodology did not suggest any other events for suicidality.

In summary, the total number of reported cases and the event rate of suicide and suicide attempts were low and a thorough review of individual case reports does not suggest a causal relationship to roflumilast. However, as an added precaution, the sponsor proposes that patients should be observed for severe neuropsychiatric symptoms and the administration of roflumilast should be stopped if deemed necessary.

8.6.4 Gastrointestinal Events

Mesenteric vasculitis has been a potential safety finding of interest seen with other PDE4 inhibitors. In contrast, nonclinical investigations of roflumilast revealed no evidence of primary vasculitis. Nevertheless, fecal occult blood (FOB) testing and appropriate follow-up was initiated as a further safety precaution in 1-year studies M2-124, M2-125 and M2-111, and 6-month Study M2-110.

Fecal occult blood testing was required for all patients prior to study entry, after 6 months and at end of treatment. In addition, it was required for those patients reporting GI AEs which might be associated with GI bleeding (eg, diarrhea, abdominal pain, loose stool). Patients with positive tests were asked to undergo colonoscopy if the GI bleeding could not be excluded. There were no relevant differences observed in the incidence of positive FOB tests between the treatment groups (see Table 8.6.4–1).

Table 8.6.4–1. Outcomes of Fecal Occult Blood Tests and Colonoscopies

	M2-124		***M2-125***		***M2-110***		***M2-111***	
	Rof500	*Pbo*	*Rof500*	*Pbo*	*Rof500*	*Pbo*	*Rof500*	*Pbo*
	N = 769	**N = 755**	**N = 788**	**N = 790**	**N = 449**	**N = 460**	**N = 567**	**N = 606**
Positive FOB	13 1.7%	6 0.8%	10 1.3%	10 1.3%	2 0.4%	2 0.4%	31 5.5%	23 3.8%
Colonoscopy	15	9	15	9	12	6	15	9
Colonoscopy outcome	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

In the COPD safety pool, 5 patients on roflumilast and 7 taking placebo reported colitis, and no cases of ischemic colitis were observed in either group.

In conclusion, based on data from non-clinical and clinical studies, treatment with roflumilast does not appear to present a risk for ischemic colitis to patients.

8.7 CLINICAL LABORATORY TESTS

8.7.1 Hematology

The frequency of clinically relevant shifts to values outside the alert range was comparable for the roflumilast and placebo groups.

8.7.2 Biochemistry

There was no increase in relevant chemistry measures, including those indicative of liver or renal injury, in roflumilast treated patients compared to placebo treated patients.

8.8 VITAL SIGNS

Blood pressure and pulse rate were comparable between treatment groups and generally stable over time. The frequency of shifts to values outside the alert range was low (< 1% in any treatment group), and no notable differences between the roflumilast and placebo groups were observed.

8.9 SAFETY CONCLUSIONS

The safety of roflumilast 500 mcg daily has been well characterized in a large COPD safety pool that included 14 double-blind, placebo-controlled trials in 12,054 COPD patients with a median treatment duration of 24 weeks and with 1,232 patients treated with roflumilast for at least one year.

Adverse events reported more frequently (≥ 2% and twice the placebo rate) in roflumilast-treated patients were diarrhea (10% roflumilast vs. 3% placebo), weight decrease (7% roflumilast vs. 2% placebo), nausea (5% roflumilast vs. 1% placebo) and headache (5% roflumilast vs. 2% placebo). Most adverse events generally occurred within the first weeks of therapy and resolved during continued treatment.

Adverse events resulting in study discontinuation occurred in 824 patients (14.3%) with roflumilast and in 503 patients (9.2%) receiving placebo. The difference in discontinuation rate between roflumilast and placebo was mostly due to gastrointestinal events (nausea, diarrhea). Discontinuation due to all other AEs other than GI related events was similar between roflumilast (9.2%) and placebo (8.4%).

Serious adverse events occurred approximately in equal numbers in patients receiving roflumilast (13.5%) and placebo (14.2%). A total of 177 deaths occurred in the COPD safety pool. Death was reported for 84 patients (1.5%) in the roflumilast 500 mcg group, 7 patients (0.9%) in the roflumilast 250 mcg group, and for 86 patients (1.6%) in the placebo group.

The data did not show an increased risk for adverse hematological changes, adverse changes in blood chemistry, particularly liver function tests. Vital signs remained stable throughout the trials. There also does not appear to be an increased risk for infection, including pneumonia or ischemic colitis.

An event of interest is weight loss. Measurable weight loss was observed within the first 6 months of roflumilast treatment and showed no significant progression thereafter. Weight loss was not associated with an increase in AEs. Notably there did not appear to be a greater incidence of AEs in the underweight group and no increased morbidity was observed. Since roflumilast is a chronic therapy, monitoring of weight is recommended.

Based on a blinded-adjudication of all-cause mortality, patients on roflumilast do not appear to have increased risk for cardiovascular events.

A slight numerical imbalance of neuropsychiatric events was observed. These included depression, insomnia, anxiety and suicidality. The numbers of events were too small to determine statistical significance. With regard to suicidality behaviors, they were considered unlikely or not related to roflumilast by the investigator and sponsor and they were too few to establish if there is a clear imbalance for these events. However, as an added precaution, the sponsor recommends that patients be monitored for neuropsychiatric events.

In summary, roflumilast 500mcg offers a simple, once-a-day oral therapy that has been shown to be well-tolerated and safe in COPD patients with chronic bronchitis.

9.0 BENEFIT - RISK ASSESSMENT

9.1 MEDICAL NEED

COPD is the fourth leading cause of chronic morbidity and mortality in the United States and, in contrast to many other leading causes of death and disability, COPD prevalence continues to rise. The World Health Organization estimates that by 2020, COPD will be the fifth leading cause of death and the third leading cause of disability in the world. In addition the morbidity and mortality from COPD progresses despite smoking cessation, underscoring the role of chronic inflammation plays in the disease (GOLD, 2009).

Despite rising morbidity for COPD, new therapeutic innovations have been few in recent years. These agents have been limited to enhancing the pharmacologic properties of existing classes of medicines like inhaled beta-agonists, anticholinergics or corticosteroids. Most patients with a more severe disease remain symptomatic and are threatened by frequent exacerbations. The FDA states in their *2007 Draft Guidance for Industry "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment"* that there is a pressing need to develop new drugs for COPD because current treatment options are limited, especially new drugs that alter the underlying inflammation of COPD.

9.2 EFFICACY

Roflumilast was developed as a novel, once-daily oral treatment option for COPD that targets the underlying inflammatory disease processes. Roflumilast exerts its anti-inflammatory activity via selective phosphodiesterase-4 (PDE4) inhibition. Its mechanism of action is different from steroids, and therefore is not associated with their well-known side effects (eg, increased incidence of pneumonia, glaucoma and cataracts, localized infections, immunosuppression, decrease in bone mineral density). Evidence for the anti-inflammatory activity of roflumilast has been derived from short- and long-term preclinical studies in animal models of COPD, multiple *in vitro* studies with human cells relevant to COPD pathology, and two clinical studies of 4-week treatment duration.

The clinical efficacy of roflumilast in COPD has been confirmed in an extensive development program including a core program of six long-term randomized, placebo-controlled, parallel-group studies in 7,453 COPD patients. All six studies consistently demonstrated efficacy of 500 mcg roflumilast over placebo in reducing the rate of moderate to severe exacerbations and improving lung function. The reduction in exacerbation rate due to roflumilast was clinically meaningful in its magnitude (common across all six studies) and statistically significant in the two 1-year pivotal trials (M2-124 and M2-125) specifically designed to study patients at higher risk for exacerbations. The magnitude of the reduction in exacerbation rate was in the same range as seen with other currently available COPD treatments. The effect size of roflumilast on lung function was similar to what has been achieved with long-acting inhaled beta-agonists or muscarinic antagonists in similar populations of severe, poorly reversible COPD patients. Importantly, roflumilast exerted its effects as an add-on treatment to other COPD medications like long-acting bronchodilators or also inhaled corticosteroids.

9.3 SAFETY

Roflumilast belongs to a new generation of PDE4 inhibitors characterized by its high specificity and selectivity. Clinical safety data did not reveal any particular safety risk except weight decrease. Non-clinical findings of species-specific toxicities did not translate into clinical findings. In studies in COPD patients, weight decreased, diarrhea, nausea, headache, and decreased appetite were the most frequently reported AEs and considered associated with intake of roflumilast. These frequently reported AEs were mostly mild to moderate in severity and their incidence decreased with treatment duration.

No safety risks by roflumilast were detectable based on the analysis of deaths and SAEs. Furthermore, a detailed analysis of the clinical data with respect to cardiovascular disorders and mesenteric vasculitis did not reveal any particular risk.

Although higher incidence of weight loss was associated with roflumilast, it was observed in the first few months of treatment without further substantial progression and it resolved in most patients after discontinuation of treatment. Weight loss is a condition that can be readily monitored in clinical practice. With regard to neuropsychiatric events, a higher numerical incidence of events was observed in roflumilast treated patients. However, this higher incidence of neuropsychiatric AEs (eg, depression) did not translate in a higher incidence of serious adverse events in this category, nor was there any evidence of an imbalance in events of suicidality when assessed by a more specific and standardized analysis of individual cases.

In conclusion, no major safety concerns were observed in the roflumilast COPD clinical program on the review of adverse events, serious adverse events, deaths, laboratory examinations or vital signs. Most AEs reported by patients receiving roflumilast were of mild or moderate intensity and occurred early in the trials.

9.4 BENEFIT-RISK RATIO

Roflumilast is a unique anti-inflammatory agent that has been shown to provide safe and effective treatment in COPD associated with chronic bronchitis in patients at risk of exacerbations. The Phase 3 registration program demonstrated that these benefits were independent of other concomitant COPD treatments. When administered at a dose of 500 mcg once daily to COPD patients, beneficial effects of roflumilast with respect to lung function and exacerbation frequency were statistically significant and clinically relevant. These improvements were accompanied by improvements in breathlessness and reductions in rescue medication. While some patients may experience gastrointestinal complaints or headache upon initiation of treatment, there is no evidence to suggest that roflumilast is associated with an increased risk of serious sequelae. Weight decrease has not been associated with increased morbidity and can be easily monitored by both patient and physician.

Roflumilast offers a safe, simple, and effective once-a-day oral therapy that complements treatment with both long and short acting bronchodilators. In patients with chronic bronchitis, roflumilast, taken as a 500 mcg tablet once daily, is expected to improve and support patient treatment compliance in patients already challenged by concomitant diseases, and multiple inhalation delivery devices.

9.5 CONCLUSION

Roflumilast is a selective PDE-4 inhibitor with unique anti-inflammatory effects on a variety of cells and mediators and therefore distinguishes itself from currently marketed treatments for which lung function improvements are mainly based on bronchodilator activity. Roflumilast represents a significant addition to the armamentarium of prescribing physicians for the following reasons:

- Demonstrated efficacy in reducing the rate of moderate and severe exacerbations and in improving lung function
- Additive effect on top of background bronchodilator therapy
- A novel mechanism of action that reduces inflammation with a mechanism different from corticosteroids
- An easy oral administration once-a-day with no clinically significant interactions with drugs commonly used by COPD patients
- Acceptable tolerability and safety profile

In summary, efficacy and safety data support that roflumilast is beneficial as maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

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11.0 APPENDIX

11.1 SUPPORTIVE TABLES

Table 11.1–1. Principal Design Features for Each Major Study

Study	*Type*	*Design*	*No. of Pats.*	*Treatment Duration*	*Eligibility*
M2-111	Earlier Phase 3	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. ICS allowed.	1173	52 Weeks	• COPD • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted ≤ 50% and FEV_1/FVC ≤ 70%. • Current or ex-smoker
M2-112	Earlier Phase 3	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. ICS allowed.	1513	52 Weeks	• COPD • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted ≤ 50% and FEV_1/FVC ≤ 70%. • Current or ex-smoker • Fixed airway obstruction (FEV_1 increase ≤ 15% and/or 200 mL after inhalation of salbutamol.
M2-124	Pivotal	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. LABA allowed; Use of ICS terminated at randomization.	1523	52 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted ≤ 50% and FEV_1/FVC ≤ 70%. • Chronic bronchitis (chronic productive cough for three months in each of last 2 yrs prior to the study. • History of COPD exacerbations. • Current or ex-smoker • Symptomatic patients: total cough/sputum score ≥ 14 during last week prior to randomization.

Table 11.1–1. Principal Design Features for Each Major Study

Study	*Type*	*Design*	*No. of Pats.*	*Treatment Duration*	*Eligibility*
M2-125	Pivotal	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 52 weeks. LABA allowed; Use of ICS terminated at randomization.	1568	52 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted ≤ 50% and FEV_1/FVC ≤ 70%. • Chronic bronchitis (chronic productive cough for three months in each of last 2 yrs prior to the study. • History of COPD exacerbations. • Current or ex-smoker • Symptomatic patients: total cough/sputum score ≥ 14 during last week prior to randomization.
M2-127	Supportive	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 24 weeks. All patients received salmeterol 50 mcg BID as underlying treatment.	933	24 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted between 40% and 70% and FEV_1/FVC ≤ 70%. • Current or ex-smoker • Fixed airway obstruction (defined as an FEV_1 increase ≤ 12% and/or 200 mL after receiving 400 mcg salbutamol).
M2-128	Supportive	Double-blind, randomized, placebo-controlled, parallel group (roflumilast 500 mcg once daily); four-week single-blind placebo run-in followed by a treatment period of 24 weeks. All patients received tiotropium 18 mcg once daily as underlying treatment.	743	24 Weeks	• COPD for at least 12 months. • Age ≥ 40 years. • Post-bronchodilator FEV_1 % predicted between 40% and 70% and FEV_1/FVC ≤ 70%. • Chronic bronchitis at enrollment. • Current or former smoker • Use ≥ 28 puffs of rescue medication during week before randomization. • Fixed airway obstruction (defined as an FEV_1 increase ≤ 12% and/or 200 mL after receiving 400 mcg salbutamol). • Pretreated with tiotropium for at least 3 months before baseline visit.

LABA = long-acting beta agonist; ICS = inhaled corticosteroids; BID = twice daily; COPD = chronic obstructive pulmonary disease.

Table 11.1–2. Overview of Statistical Analysis Procedures Applied to Respective Primary and Key Secondary Variables

Study	*Variable*	*Primary/Secondary*	*Patient Population and Brief Description of Statistical Analysis Model or Procedure Applied*
M2-111	Pre-bronchodilator FEV_1	Primary	ITT, repeated measures analysis
	Rate of COPD exacerbations	Primary	ITT, Poisson regression
	Post-bronchodilator FEV_1	Key Secondary	ITT, repeated measures analysis
	COPD exacerbations	Key Secondary	ITT, Poisson regression
M2-112	Rate of COPD exacerbations	Primary	ITT, Poisson regression
	Post-bronchodilator FEV_1	Primary	ITT, repeated measures analysis
	St. George Respiratory Questionnaire	Key Secondary	ITT, last value analysis
M2-124	Pre-bronchodilator FEV_1	Primary	ITT, repeated measures analysis
	Rate of moderate or severe exacerbations	Primary	ITT, Poisson regression
	Post-bronchodilator FEV_1	Key Secondary	ITT, repeated measures analysis
	Mortality	Key Secondary	ITT, Cox Proportional Hazard Model
	C-reactive protein	Key Secondary	ITT, ANCOVA, log transformed data
	Transition Dyspnea Index	Key Secondary	ITT, repeated measures analysis
M2-125	Pre-bronchodilator FEV_1	Primary	ITT, repeated measures analysis
	Rate of moderate or severe exacerbations	Primary	ITT, Poisson regression
	Post-bronchodilator FEV_1	Key Secondary	ITT, repeated measures analysis
	Mortality	Key Secondary	ITT, Cox Proportional Hazard Model
	C-reactive protein	Key Secondary	ITT, ANCOVA, log transformed data
	Transition Dyspnea Index	Key Secondary	ITT, repeated measures analysis
M2-127	Pre-bronchodilator FEV_1	Primary	ITT, repeated measures analysis
	Rate of COPD exacerbations (mild, moderate or severe)	Key Secondary	ITT, Poisson regression
	Transition Dyspnea Index	Key Secondary	ITT, repeated measures analysis
	Shortness of Breath Questionnaire	Key Secondary	ITT, repeated measures analysis
M2-128	Pre-bronchodilator FEV_1	Primary	ITT, repeated measures analysis
	Post-bronchodilator FEV_1	Key Secondary	ITT, repeated measures analysis
	Rate of COPD exacerbations (moderate or severe)	Key Secondary	ITT, Poisson regression