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APPLICATION NUMBER:

022522Orig1s000

MEDICAL REVIEW(S)

Summary Basis for Regulatory Action

Date	May 17, 2010
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	22-522
Applicant Name	Nycomed/Forest Laboratories
Proprietary / Established (USAN) Names	Daxas roflumilast
Dosage Forms / Strength	Tablet 500 mcg
Proposed Indication(s)	Maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations
Action:	*Complete Response*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding roflumilast and I refer the reader to the reviews in the action package for a more detailed discussion. Roflumilast is a new molecular entity developed for COPD treatment. Ownership of this NDA was transferred from Nycomed to Forest during this review cycle, and the new owners changed the focus from the more general COPD indication listed above, to "maintenance treatment to reduce exacerbations of COPD associated with chronic bronchitis in patents at risk of exacerbations". This was further modified after the AC meeting to delete 'maintenance' to 'once-daily'. While all these changes are subtle, the original indication listed above would require demonstration of clinically meaningful improvements in more than one aspect of COPD, while the new requests are for a more restrictive indication, and would require less investigation limited mainly to one domain, that of exacerbation reduction. The requested change in indication is also in keeping with what other drugs used in this population have received in the past. This change request came around the time that briefing packages were due to the Advisory Committee (AC) staff, and did not allow us an opportunity to modify our review. As such, the original indication was discussed at the Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting, but there was an acknowledgement to the panel members of the new direction the new sponsor was taking and comments were solicited regarding this change.

Roflumilast is not currently market anywhere in the world, but in April the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending granting marketing authorization for roflumilast for the maintenance treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. Positive opinions by the CHMP usually lead to marketing authorization by the European Commission.

Roflumilast inhibits phosphodiesterase-4 (PDE4) and its use in COPD is theorized to be on the basis of anti-inflammatory activity. The mechanism of action is probably very similar to theophylline, which is a more promiscuous PDE inhibitor, having suppressive effects on other subtypes of PDE in addition to PDE4. Current therapies for COPD include inhalation products including beta-agonist bronchodilators (short and long-acting), anti-muscarinic bronchodilator agents (short and long-acting) and long-acting beta agonist (LABA)/corticosteroid combination products. These are approved to treat reversible bronchoconstriction and to reduce exacerbations of COPD in patients with a history of exacerbations. Theophylline, a non-specific PDE inhibitor available as immediate and sustained released formulations, is also indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic lung disease, e.g., emphysema and chronic bronchitis.

The development program for roflumilast is long and complicated as documented in Dr. Durmowicz's review. There have been many changes (evolution) in trial design and endpoints over the years, but ultimately the Phase 3 trials (M2-124, M2-125) to support registration in this package relied upon co-primary endpoints of COPD exacerbation rates and improvement of FEV1. While there is some controversy regarding the definition of COPD exacerbation and minimally important change in FEV1 (discuss further below), for the most part both of these trials were positive. There were serious adverse events (SAE) identified in the database, the most concerning being a suicide imbalance. The sponsor, very late in the game, proposed a REMS to mitigate these safety issues. Their REMS proposals were submited too late in the cycle to afford us adequate review.

While all in DPARP agree that safety needs further evaluation, there is a disagreement within the review division whether substantial efficacy has been demonstrated. Dr. Chowdhury feels that it has whereas Drs. Sarro and Durmowicz feel that it has not. Dr. Durmowicz acknowledges that roflumilast has proven efficacy in the trials above, but feels that its addition as add-on therapy to other active agents needs to be explored before granting approval. Dr. Sarro states that there is insufficient evidence to support the original indication but is silent on the revised indication, although she does comment on whether reduction in moderate or severe COPD exacerbations observed in the pivotal trials were clinically significant.

I will discuss the above further in my review, but for this cycle I agree that safety issues, in particular the suicide signal, need further evaluation and consideration of mitigation that will lead this application to receive a Complete Response (CR) action. I do believe that they have demonstrated that roflumilast does decrease exacerbations of COPD associated with chronic bronchitis in patents at risk of exacerbations. While this in and of itself would fulfill the criteria necessary to demonstrate efficacy, I also think they have demonstrated in trials M2-127 and M2-128 that roflumilast does increase bronchodilation above and beyond LABA and LAMA therapy as add-on therapy. There is also some indication in those trials that roflumilast add-on decreases COPD exacerbation above and beyond LABA and LAMA therapy. While roflumilast may be used as single therapy, and is a convenient form (oral) for those that have trouble taking an inhaled therapy, I do think that for the most part roflumilast probably would be added-on to other therapies. As such, it would be useful for clinicians to know what to expect (noting that trials M2-127, M2-128 do give some indication) if roflumilast were added

to LABA/ICS or to a combination therapy consisting of LABA/ICS & LAMA. Therefore, it would be appropriate to request a trial of add-on therapy to at least bronchodilation/corticosteroid therapy and perhaps even to LABA/ICS & LAMA as a post-marketing commitment. This does not address the issue of safety mentioned above and the possible suicide signal will require further investigation as well as evaluate the sponsor's proposal for a REMS program. As such, I believe their application should receive a CR action.

Efficacy

Please refer to Drs. Durmowicz, Chowdhury, Abugov and Sarro reviews for further details regarding efficacy data evaluation. As discussed by others, in addition to the two pivotal year long trials identified above (M2-124, M2-125), the sponsor had additional trials in COPD. Each of these trials was designed such that they could potentially serve as pivotal trials, and after evaluating each trial (which failed), the sponsor at the time refined the entrance criteria (enriched?) such that it would include the patient population that seemed to respond to roflumilast and exclude patient populations that did not. Ultimately, the sub-group of the general COPD population that seemed to respond was patients with chronic bronchitis (history of cough, sputum production), and recent exacerbations. This group was then used for pivotal trials M2-124 and M2-125 trials. These two trials evaluated the sub-group of patients identified above with severe COPD defined as FEV1 $\leq$ 50% (FEV1 mean approximately 1L) and used co-primary endpoints of rate of COPD exacerbations and FEV1.

Also of note are trials M2-127 and M2-128 which included a broad range of COPD subjects, were 6-months long and involved roflumilast add-on therapy to standard COPD bronchodilator treatments with tiotropium (LAMA, M2-128) and salmeterol (LABA, M2-127). These two trials evaluated if roflumilast added additional benefit on lung function above and beyond a LABA or LAMA. They included patients with moderate as well as severe COPD (FEV1 of 40-70% predicted, FEV1 mean approximately 1.5L). These trials did not require a history of chronic bronchitis with sputum production or COPD exacerbations and evaluated a single primary endpoint of FEV1.

We have not ever standardized a definition of exacerbations. For these trials, a moderate exacerbation was defined as an exacerbation requiring use of oral or parenteral corticosteroids. The decision to add corticosteroids was not based on standard criteria, but was at the discretion of the investigator. Severe exacerbation was defined as an exacerbation which resulted in hospitalization (again without standardized criteria) or death. While not formally endorsed by us, these seem reasonable and randomization should help to limit any bias that may have resulted from individual investigators discretion without standardized criteria.

Below is a revised table from Dr. Durmowicz's review (page 16) demonstrating the results of COPD exacerbation evaluations.

Table 1 Rates of moderate or severe exacerbations in the one year studies (ITT Population)

Trial Number	Duration (Weeks)	Poisson Exacerbation Rate				
		Rof500 mcg	Placebo	Rate Ratio	P-Value	Pooled Rate Ratio

M2-124	52	1.1 (765)	1.3(758)	0.85	0.028	0.83
M2-125	52	1.2 (772)	1.5 (796)	0.82	0.004	

This demonstrates that roflumilast was effective in reducing exacerbation rates as monotherapy.

Trials M2-127 (add-on to LAMA) and 128 (add-on to LABA) also evaluated (as secondary endpoints) the mean rate of COPD exacerbations (mild, moderate or severe). Noted, these trials are about half as large and half as long (less events) as the pivotal trials, and enrolled a broader COPD population (included subjects less likely to respond). The 'mild' category contained subjects using increased rescue medication of three or more puffs/day on at least two consecutive days whereas the moderate and severe categories were the same as in trials M2-124-125. Dr. Abugov has an elegant discussion of the results in his review where he reported the rate of COPD exacerbation (mild, moderate or severe) was lower for roflumilast (1.9) than placebo (2.4) noting that the rate ratio (0.8) comparing roflumilast and placebo was not statistically significant. Post-hoc analysis of moderate or severe COPD exacerbations conducted by the Applicant demonstrated that the rate of COPD exacerbation (moderate or severe) was lower for roflumilast (0.3) than placebo (0.5) and the rate ratio is 0.6. In Study 128, the mean rate of COPD exacerbations (moderate or severe) was slightly lower for roflumilast (0.26) than placebo (0.34). The following table (page 24) comes from Dr. Abugov's review.

Table 1: Poisson rates of Moderate or Severe Exacerbations in Studies 127 and 128 (ITT Population)

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

From datasets dm, xe, ds, dv, see pgm mainline efficacy poisson exacerbation rate 2010 02 09
* Post-hoc analysis (p-value unadjusted)

While these are secondary endpoints, and there was not any correction for multiple statistical evaluations, it is somewhat reassuring that the above data, in trials not powered on exacerbation determinations, give some supportive evidence (viewed cautiously) that roflumilast provides additional decrease in COPD exacerbations above and beyond LABA and LAMA therapy. I do not think this is totally unexpected as it is felt that PDE inhibiting agents would have different mechanism of action and therefore should theoretically have additive effects to LABA or LAMA agents.

The pivotal trials had co-primary endpoints of COPD exacerbations and change FEV1. Below is a revised table from Dr. Durmowicz review (page 16) demonstrating the results of FEV1 evaluation for the pivotal trials as well as M2-127, 128.

Table 2 Change (in mL) from baseline in pre-bronchodilator FEV1* to end of treatment (ITT populations)

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

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

The four trials above demonstrated a statistically significant change in FEV1 improvement with roflumilast. The improvement ranges from 39 ml to 80 ml. It must be kept in mind that this change is in subjects that had baseline 1L to 1.5L FEV1 values. Also, trials M2-127,128 both demonstrate that roflumilast improved FEV1 when added onto two different bronchodilation agents. The additional improvement of FEV1 in trials M2-127,128 was by about the same amount as that seen in the pivotal trials, which may be indicative that roflumilast has a different mechanism of action (MOA) than LAMA or LABA agents. This could give us some evidence that agents with different MOA may have additive effects on bronchodilation.

I do note that there was an exploratory analysis by the FDA statistical team suggesting that the reduction of exacerbation rate by roflumilast compared to placebo may attenuate or disappear after 8 months. This has led Dr. Durmowicz to conclude that this could potentially be problematic for a long term indication in which the benefits are expected to be stable and positive over time. I also note however that Dr. Abugov concluded that it was unclear whether the apparent loss of effect is due to attenuation in treated patients or instead reflects patterns of patient withdrawal. I would agree with this assessment and think that we cannot make definitive conclusions based upon this exploratory analysis.

In summary, roflumilast does provide decreases in exacerbations and improvements in FEV1 in the populations studied in trials M2-124-125. While the changes in FEV1 are not dramatic, if one has an FEV1 of 1L, 50 ml may be important. As such, I do think that roflumilast has demonstrated efficacy in reducing exacerbations in patients with severe COPD associated with chronic bronchitis at risk for exacerbations. Trials M2-127,128 gives evidence supportive of this conclusion and also demonstrates that roflumilast has additive effects to LAMA and LABA agents.

Safety

There are safety concerns associated with roflumilast. I refer the reader to the other reviews for a complete discussion of all safety concerns and will only focus on two, neuropsychiatric events and gastrointestinal events.

Dr. Durmowicz notes that AEs related to the psychiatric system organ class were about twice as common in those receiving the proposed dose of roflumilast compared to lower doses or placebo. This is demonstrated in the table below from his review (page 25).

Table 3 Combined treatment emergent adverse events in the psychiatric SOC reported > once and more in roflumilast treatment groups (COPD safety pool)

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

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

While I would expect that this class of drug would have adverse effects similar to theophylline, so we should expect to see anxiety, nervousness, insomnia and similar types of AEs. However, the imbalance in suicide bears closer inspection. There is also an imbalance in depression above, but some consider suicide attempt and completed suicide to be quite different from depression and the two may not correlate. Therefore, focusing on suicide, there was a total of 5 completed suicides or suicide attempts in the roflumilast group compared to none in the placebo group. None of the three completed suicide cases (all males) had a prior history of depression. In two of the cases the patient had reportedly discontinued roflumilast approximately 20-21 days prior to the suicide event. With regard to the suicide attempts, both females had prior psychiatric histories (depression in one patient and previous suicide attempt in the other). Both patients were receiving roflumilast at the time of the suicide attempt. The sponsor reported at the Pulmonary-Allergy Advisory Committee Meeting (AC) that they had utilized the Columbia classification Algorithm of Suicide Assessment (C-CASA) to assess for additional potential suicide-related cases and did not identify any, but we have not reviewed this data.

One could question whether the roflumilast was involved or not in the two completed suicides in which the drug had been discontinued around three weeks early. From a strict pharmacokinetic standpoint, the drug clearly would have been eliminated from their systems making one skeptical about roflumilast influence. On the other hand, depression and suicide are very complicated, not fully understood by the medical profession, and if drug induced, may involve changes in brain chemistries that perhaps do not resolve immediately with loss of drug. I think it is therefore difficult to ascertain in these two cases if roflumilast is involved. It is also difficult to know if roflumilast played any role in the two suicide attempts as both subjects had previous psychiatric histories. However, this data came from randomized trials and randomization should have given assurance that subjects with similar histories were in the placebo group, and yet there weren't any attempts identified in the placebo group. I believe this signal needs further exploration (review of the C-CASA data), and input from our psychiatric colleagues. If this drug should get approved in the future, this finding should be prominently labeled.

Gastrointestinal adverse events are a known class effect of PDE4 inhibitors. It is therefore not surprising that the most prominent gastrointestinal events associated with roflumilast were weight loss, diarrhea and nausea. Below is a table from Dr. Durmowicz's review summarizing weight loss (page 24).

Table 4 Weight Loss by BMI and COPD Severity (M2-124, M2-125)

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

* Δ Wt kg (%): change in mean body weight from baseline in kilograms (% change in body weight comparing to baseline)
COPD severity: moderate: FEV1 <80% and ≥50%; severe: FEV1<50% and ≥30%; very severe: FEV1 <30%.

It is unclear whether weight loss was from adipose tissue, or muscle mass. While the overall mean weight change is not dramatic, the highest percentage occurred in those that were underweight in the first place and could probably ill-afford to lose any lean body mass. As such, if this is approved in the future, labeling should reflect that careful attention be paid to weight changes in vulnerable populations.

Dr. Durmowicz has summarized the diarrhea and nausea AEs in the table below from his review (page 23).

Table 5 Gastrointestinal Toxicities in patients receiving 250 or 500 mcg of roflumilast

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

I would expect this type of result as this is a class effect and is probably similar to what would be expected with theophylline therapy.

Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held April 7, 2010. There were individual voting questions asking if efficacy (9 yes, 6 no) and safety (9 yes, 6 no) had been demonstrated as well as a question regarding if roflumilast should be approved (5 yes and 10 no). The seemingly contradictory nature of the approval vote is explained that were overlaps in the efficacy/safety no voting such that 10 members total had voted no to one of those initial questions, making the final vote consistent.

Comments were made from the panel members regarding that their 'no' vote on efficacy would have been a 'yes' vote had the sponsor's revised labeling request been voted upon. Regarding safety, and in particular depression and suicide, some members (mostly those voting that safety had been demonstrated) commented that this degree of COPD carries a worse life-expectancy than what most cancer patients would expect and that if this drug provided some symptomatic relief and decreased exacerbations, it would be well a tolerable risk. Others (mostly those voting that safety hadn't been demonstrated) commented that the suicide and weight loss needed further evaluation, while others thought that an adequate REMS would allow approval. Comments were also made regarding the degree of FEV1 change that in someone with a baseline FEV1 of 1L, 50 ml may be important.

2. Conclusions and Recommendations

While all the medical reviewers evaluating the clinical aspect of this application agree that a CR action is appropriate, there is not consensus among the team members regarding what the deficiencies are and therefore what is required for remediation. This application is an example where reasonable people can reasonably come to different conclusions. This is borne out in the divided voting (and disparate comments) from the AC panel members, where some felt this application could be approved in its present state (with the revised indication), some felt that

more efficacy data (add-on to other therapies) was needed, and some felt more safety (or at least a REMS) was needed.

All the clinical reviewers noted the concerning safety signals and seem to agree that further evaluation and potential remediation is necessary. The lack of consensus is concerning the magnitude of the efficacy results, whether there is enough efficacy data and how that impacts the efficacy:safety ratio.

Dr. Sarro states that there is insufficient evidence to support efficacy for the originally proposed indication. While she is silent on the revised indication she notes that the 15-18% reduction in COPD exacerbations composite endpoint were of debatable clinical significance as they were mostly powered by the 'addition of oral corticosteroids' component with minimal contribution of the 'reduction of hospitalization/mortality' component (note the rate ratio reduction for both addition of oral corticosteroids and hospitalization/mortality were about the same in each trial and also between both trials, there was just a higher event rate in the addition of oral corticosteroid group and therefore more events to influence the confidence interval). Dr. Durmowicz's review indicates that the clinical efficacy was modest, but seems to acknowledge that the sponsor has demonstrated that the drug purports to have the effect of the revised indication. He is concerned about the neuropsychiatric findings and indicates they warrant the demonstration of similar efficacy as what has already been demonstrated except that roflumilast should be added onto existing or 'standard of care' therapies which may give an appropriate risk:benefit ratio. To demonstrate the 'marginality' of the efficacy results, either or both state that there were two trials that failed to demonstrate reductions in exacerbations (M2-111,112), there was failure to demonstrate clinically meaningful changes in some of the patient report outcome (PRO) measures, and that FEV1 improvements demonstrated do not reach a mean of 10% change are therefore probably aren't clinically important. Dr. Durmowicz also notes that if one considers the mean reduction of COPD exacerbation rates of 0.24 per patient year, it will take five years of therapy to get benefit. These reasons are given to support their views regarding modest or insufficient efficacy demonstrations. Dr. Durmowicz also notes that the generalizability of the positive COPD exacerbation studies could be questioned as they were conducted in a subset of patients with severe COPD (chronic bronchitis with exacerbations).

Dr. Chowdhury notes the serious safety concerns, but feels none would preclude approval with appropriate mitigation. He discounts the failure of M2-111, 112 to demonstrate efficacy as a reason to question the efficacy of roflumilast as he feels that these studies were part of the evolution of the clinical program over time, informing later trials regarding the appropriate patient population. He feels the later studies (M2-124,125) did demonstrate efficacy in reducing COPD exacerbations and that this conclusion is supported by FEV1 improvements. He feels that roflumilast does not have to prove that efficacy can be generalized to a broad COPD population, as the labeling is restrictive to the population studied in M2-124, 125. Dr. Chowdhury also states that demonstration of benefit over standard of care is not consistent with the current interpretation of efficacy standard (21 CFR 314.125).

COPD, particularly of the severity examined for this application, is a devastating disease. In analyzing this application and what to require of the sponsor, I have taken into consideration

everyone's comments in their reviews, discussions with the team and independent discussions with Dr. Durmowicz and Chowdhury and comments from the advisory committee panel members. I agree with Dr. Chowdhury's assessment concerning efficacy and safety evaluations (with a caveat regarding 'benefit over standard of care' that I will discuss below) and will discuss some of the specific opinions of the reviewers below. I believe however that roflumilast has demonstrated that it decreases exacerbations in patients with COPD associated with chronic bronchitis in patients at risk of exacerbations. While there are other therapies to decrease exacerbations and for symptoms, not all are tolerated by everyone. Roflumilast has proven that it can decrease exacerbations in the population evaluated, and while not compared in trials to theophylline (an approved therapy), I expect that it has a similar risk:benefit profile, although it may be somewhat less demanding to use (compared to theophylline given at labeled doses) as it doesn't require blood levels and only requires once a day dosing.

To comment on some of the observations noted above, I will begin with observations regarding generalizability and roflumilast use in patients with COPD. We recognize in our draft guidance that COPD is a heterogeneous disease encompassing a spectrum of pulmonary processes.[1] The guidance also recognizes that a drug may only be effective for a limited, subset population in this spectrum. While earlier trials may have failed, the sponsor did exactly what we recommend applicants should do, which is to try to identify a patient population that responds and limit their therapy to that population. We should then be able to craft labeling that describes the subset population that could expect to receive benefit. While our guidance does state we like to have data from a broad population (which this program does and can be informative as to who may not receive benefit), it is also flexible in allowing tailored therapy to the group which will get the benefit. To criticize a development program that has done this process is not consistent with our current guidance.

I acknowledge that if one were to look at means of exacerbations, it would take five years to decrease one exacerbation. However, that does not give the complete picture of what might be expect with roflumilast therapy. It is quite common for clinicians to examine the Number Needed to Treat (NNT) as an expression of what effect a drug may have. The NNT for roflumilast effect on decreasing exacerbations is five. Most would consider a single digit NNT impressive, although it should be viewed in the context of what the benefit is and also in comparison to the risk.

Although the health-related quality of life instruments (PRO) did not have 'mean' changes great enough that we would consider any labeling changes, they did for the most part, move in the correct direction. It is actually fairly common that programs where the mean changes with the PRO fail to demonstrate 'clinically important' changes (none of the current agents used for COPD enjoy PRO labeling despite trying), yet experience has taught us that patients do experience symptomatic benefit.

I agree with Dr. Chowdhury that new therapies usually do not necessarily have to be 'better' than existing ones. However, there are some situations where we know that patients most likely will be on a standard therapy, and we require the new drug to be 'added on' to

[1] Guidance for Industry. Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November 2007

demonstrate efficacy, or to 'beat' the standard. This is usually for disease modifying therapies. Examples are oncology drugs, rheumatologic drug or antibiotics. I do not think that is the situation here. Roflumilast could be used as single therapy in some patients, such as those that cannot use an inhaler for whatever reason or those not tolerating inhaled products. However, I believe that roflumilast will be used quite often as add-on therapy to LAMA, LABA or LABA/ICS. I do think that there is supportive evidence that roflumilast does add benefit to LABA and LAMA therapy (as demonstrated in trials M2-127, 128). However, roflumilast will probably also be used in patients taking LABA/ICS either by itself or in combination with LAMA and to help guide physicians optimization of therapy, should roflumilast ever be approved, we should have a Post-Marketing Commitment (PMC) seeking to define the benefit of roflumilast added to LABA/ICS and perhaps also to patients taking LABA/ICS & LAMA. This would be similar to the action that EU is planning.

Dr. Chowdhury's review notes present deficiencies include further evaluation of the neuropsychiatric signal, (b) (4) and a in vitro evaluation of the potential for roflumilast to be a substrate for P-glycoprotein. I agree with these deficiencies and agree with a CR action.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	FOREST RESEARCH INSTITUTE	DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

CURTIS J ROSEBRAUGH
05/17/2010

SUMMARY REVIEW OF REGULATORY ACTION

Date: May 14, 2010

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA

Subject: Division Director Summary Review
NDA Number: 22-522
Applicant Name: Forest Pharmaceuticals, Inc.
Date of Submission: July 15, 2009
PDUFA Goal Date: May 17, 2010
Proprietary Name: Daxas
Established Name: Roflumilast
Dosage form: Film-coated tablets
Strength: 500 mcg
Proposed Indications: Chronic Obstructive Pulmonary Disease
Action: Complete Response

1. Introduction

Forest Pharmaceuticals submitted this 505(b)(1) application for use of Daxas (roflumilast) tablets 500 mcg for once daily treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbation. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies. Major discussion points are the efficacy findings, risk benefit assessment, and a difference in opinion regarding these issues between the clinical review team and this review. The clinical review concludes that the evidence for efficacy is not sufficient to support approval. The CDTL review concludes that the risk benefit assessment does not support approval, and recommends demonstration of efficacy when added to standard of care for COPD as condition for approval. This review disagrees with these recommendations and concludes that substantial efficacy has been demonstrated, and risk benefit assessment based on further analysis of existing safety data and without generation of new efficacy data may support approval.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-2 adrenergic agonists, anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination products containing long-acting beta-2 adrenergic agonists and corticosteroids, and methylxanthines, such as theophylline.

Roflumilast is a new molecular entity that belongs to a new class called phosphodiesterase type-4 (PDE-4) inhibitor. Roflumilast is functionally related to

theophylline, which is a non-specific PDE inhibitor that has broad specificity to different types of PDEs. Although no PDE-4 inhibitor is approved for marketing in the United States, several have been studied for COPD, and one, called cilomilast, was submitted to the FDA for marketing approval for use in COPD patients. The cilomilast application was discussed at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting on September 5, 2003, and not approved because of lack of substantial efficacy (discussed further in this review in section 7 c, under the sub-heading of efficacy findings and conclusions).

The roflumilast NDA was submitted to the FDA by Nycomed. Effective December 4, 2009, the ownership of the NDA was transferred to Forest Pharmaceuticals. The original indication as submitted by Nycomed was for "maintenance treatment of COPD associated with chronic bronchitis in patients with risk of exacerbation." After the change of ownership, Forest Pharmaceuticals revised the indication to "maintenance treatment to reduce exacerbation of COPD associated with chronic bronchitis in patients at risk of exacerbation." The revision is subtle, but is narrower and specific to maintenance treatment to reduce exacerbation. At the same time Forest also pointed out safety concerns with psychiatric adverse reactions and elevated this safety finding to a warning in the proposed product label. Subsequent to the PADAC discussion for roflumilast held on April 7, 2010 (discussed further in this review in section 9), Forest Pharmaceuticals further revised the indication and removed the "maintenance" wording. This review will analyze the efficacy and safety data in the context of the current proposed indication, which is "once daily treatment to reduce exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbation."

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, Daxas (roflumilast) tablets, contains 500 mcg roflumilast and standard compendial excipients. The drug product is proposed to be packaged in HDPE bottles containing 30 tablets or 90 tablets. The active pharmaceutical ingredient will be manufactured at (b) (4) – Nycomed GmbH, Germany, (b) (4) The drug product will be manufactured, packaged, released, and stability tested at Nycomed GmbH, Germany. The drug product will also be packaged at (b) (4). All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate. An expiry of 2 years is proposed and supported by submitted data.

(b) (4)

4. Nonclinical Pharmacology and Toxicology

The Applicant conducted a complete and adequate toxicology program that included general toxicology studies in rodent and non-rodent species, embryofetal development studies, and carcinogenicity studies. In the general toxicology studies, the target organs of toxicity were the cardiovascular system, gastrointestinal system, reproductive system, and the nose. The proposed human dose has adequate safety margins for the animal toxicity findings. The embryofetal studies showed decreased number of live births and reduced pup viability. These findings support pregnancy category C classification for roflumilast. The carcinogenicity study showed increased incidence of nasal tumors in a 2-year hamster study. The carcinogenicity of roflumilast appears to be attributed to a metabolite, ADCP N-oxide that is further converted to a reactive intermediate, ADCP N-oxide epoxide in the nasal tissues. Both steps are catalyzed by cytochrome enzyme P450 CYP 2G1 in rodents. Human nasal tissues appear to lack active enzymes to convert ADCP to ADCP N-oxide, but ADCP N-oxide is found in human plasma and urine. Relevance of the tumor finding to humans is unknown since the tissues and enzymes involved in the production of ADCP N-oxide and its down- stream metabolite are unknown in humans. Nasal tumors with roflumilast do not appear to be a class effect of PDE-4 inhibitors. Of the nine PDE-4 inhibitors for which the Division has nonclinical toxicology data, four have submitted 2-year animal carcinogenicity date, and only one, piclamilast, which also forms the ADCP metabolites, has demonstrated nasal toxicities in rats and mice and nasal tumors in rats.

5. Clinical Pharmacology and Biopharmaceutics

The Applicant submitted a complete and adequate clinical pharmacology program for roflumilast. Roflumilast oral bioavailability is approximately 80% and there is no food effect. Roflumilast is extensively metabolized via cytochrome P450 pathway and by conjugation reactions. Roflumilast N-oxide is the major metabolite observed in human plasma. The plasma AUC of roflumilast N-oxide, on average, is about 10-fold greater than that of roflumilast. *In vitro* metabolism studies using human liver microsomes and *in vivo* drug-drug interaction studies indicated that roflumilast is mainly metabolized by CYP3A4 and CYP1A2 and did not inhibit or induce the activity of the major CYP P450 enzymes. An *in vitro* study showed that roflumilast did not inhibit P-gp transport.

The clinical pharmacology discipline initially recommended four post-marketing studies, one as a PMR and three as PMCs. The PMR study was for quantification data for ADCP N-oxide. The PMC studies were to assess the effect of CYP 2A7, 2F1 and 2C18 on production of ADCP N-oxide; re-evaluation of QT effect of roflumilast; and evaluation of roflumilast as a substrate for P-gp. The two post-marketing studies for further assessment of ADCP N-oxide are not necessary because it is already known that humans produce this carcinogenic metabolite. Furthermore, there are human cancer data available from a safety database of approximately 25,000 patients. Therefore, no additional PMR or PMC studies are necessary. The post-marketing thorough QT study at this late clinical development stage is also not necessary because the Applicant has

already conducted a thorough QT study, albeit with a deficiency that the positive control did not perform as expected. Nevertheless the study was negative. Furthermore, controlled clinical studies involving approximately 25,000 patients, many with COPD, who are elderly with concomitant cardiac disease, did not show any cardiac findings or QT findings on ECGs. Therefore, an additional through QT study is not necessary. The PMC study asking for evaluation of roflumilast as a substrate for P-gp will be of value because roflumilast is proposed to be dosed at the highest tolerated dose. The controlled clinical study excluded many concomitant drugs that may affect P-gp. Elucidating P-gp effect of roflumilast will provide information that will have safety labeling implications. With the above reasoning the clinical pharmacology discipline has revised its position and is recommending one PMC, which is to evaluate roflumilast as a substrate for P-gp. This will be conveyed to the Applicant in this review cycle.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of the review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant COPD clinical studies with roflumilast

ID Year*	**Study type**	**Study duration**	**Patient Age, yr**	**Treatment groups#**	**N (ITT)**	**Primary efficacy variables**	**Countries**
Dose selection studies							
101 2001	Parallel arm	26 week	≥ 40	Rof 250 mcg Rof 500 mcg Placebo	176 169 172	FEV1 + SGRQ	Europe, South Africa
107 2003	Parallel arm	24 week	≥ 40	Rof 250 mcg Rof 500 mcg Placebo	576 555 280	FEV1 + SGRQ	Europe, Canada, Australia, South Africa
Pivotal studies							
111 2005	Parallel arm	52 week	≥ 40	Rof 500 mcg Placebo	567 606	FEV1 + Exacerbation	US, Canada, S Africa, Europe
112 2004	Parallel arm	52 week	≥ 40	Rof 500 mcg Placebo	760 753	FEV1 + Exacerbation	Canada, Europe, S Africa
124 2008	Parallel arm	52 week	≥ 40	Rof 500 mcg Placebo	765 758	FEV1 + Exacerbation	US, Europe, Australia, NZ
125 2008	Parallel arm	52 week	≥ 40	Rof 500 mcg Placebo	772 796	FEV1 + Exacerbation	US, Canada, Europe, India, S Africa
127 2007	Parallel arm	24 week	≥ 40	Rof 500 mcg + salmeterol Placebo +salmeterol	566 467	FEV1	Canada, Europe, S Africa

ID Year*	**Study type**	**Study duration**	**Patient Age, yr**	**Treatment groups#**	**N (ITT)**	**Primary efficacy variables**	**Countries**
128 2008	Parallel arm	24 week	≥ 40	Rof 500 mcg +tiotropium Placebo +tiotoprium	371 372	FEV1	Europe
*Year study subject enrollment ended # Rof = Roflumilast capsules							

b. Design and conduct of the studies

The clinical development program for roflumilast was extensive and evolved over time. Dose ranging exploration was limited to studies 101 and 107. Latter studies apparently carried forward the highest tolerated dose. The once-daily dosing regimen was based on results of pharmacokinetic studies that showed 17 hour and 30 hour half-life for roflumilast and its active metabolite. Although the Applicant has identified studies 124 and 125 as pivotal, all studies shown in Table 1 are relevant and any of the three pairs (101 and 107, 111 and 112, or 124 and 125) with successful outcome could have been adequate to support an NDA. The primary endpoint, patient eligibility criteria, and concomitant medication used during clinical development evolved over time with the Applicant ultimately identifying a narrow COPD population in studies 124 and 125 where efficacy was demonstrated. Studies 127 and 128 were conducted to assess efficacy of roflumilast added to either a long-acting bronchodilator (LABA) or a long-acting anti-cholinergic (LAMA) in a real world like setting. The overall program is acceptable.

Studies 101 and 107:

Studies 101 and 107 were randomized, double-blind, parallel-group, in design, conducted in patients with full range of COPD severity. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, FEV1 30 to 75% predicted (study 101) or 30 to 80% predicted (study 107), FEV1/FVC ≤70%, and be a current or previous smoker with a smoking history of ≥10 pack years. Patients were not required to have a history of COPD exacerbations. Concomitant use of systemic or inhaled corticosteroids and LABAs were not permitted. Stable doses of short-acting anticholinergic were permitted. The studies each had a 2 or 4 week run-in period, followed by a 24 or 26 week double blind treatment period. There were three treatment arms as shown in Table 1. The co-primary efficacy variables were pre-bronchodilator FEV1 and SGRQ in study 101 and post-bronchodilator FEV1 and SGRQ in study 107. Safety assessment included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Studies 111 and 112:

Studies 111 and 112 were randomized, double-blind, parallel-group, in design, conducted in patients with severe COPD. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, FEV1/FVC ≤70%, FEV1 ≤50% predicted, and be a current or previous smoker with a smoking history of ≥10 pack years. Patients were not

required to have a history of exacerbations. Concomitant use of LABAs and LAMAs were not permitted. Stable doses of inhaled corticosteroids were permitted. The studies each had a 4 week run-in period, followed by a 52 week double blind treatment period. There were two treatment arms as shown in Table 1. The co-primary efficacy endpoints were mean change from baseline to the end of treatment in pre- or post-bronchodilator FEV1 (studies 111 and 112 respectively), and the number of moderate or severe COPD exacerbations. In study 111 COPD exacerbation was defined as an event requiring oral or parenteral corticosteroid (moderate exacerbation) or an event resulting in hospitalization or death (severe exacerbation). Exacerbations within 10 days of each other were merged and counted as one exacerbation. In study 112 COPD exacerbation was defined similarly, but also included events requiring antibiotic (moderate exacerbation), and death was added later in the protocol. Exacerbations within 1 day of each other were merged and counted as one exacerbation. Safety assessment included adverse event recording, vital signs, physical examination including body weight measurement, clinical laboratory and hematology measures, ECGs, and 24 hour Holter monitoring at selected sites in study 111.

Studies 124 and 125:

Studies 124 and 125 were randomized, double-blind, parallel-group, in design, conducted in patients with severe COPD associated with chronic bronchitis (cough and sputum production). Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD associated with chronic bronchitis and a history of COPD exacerbation in the recent past, FEV1/FVC <70%, FEV1 ≤50% predicted, and be a current or previous smoker with a smoking history of ≥20 pack years. Concomitant use of inhaled corticosteroids and LAMAs were not permitted. Stable doses of short acting anti-cholinergics, short acting beta-agonists, and LABAs were permitted (LABA were used by about 50% patients). The studies each had a 4 week run-in period, followed by 52 week double blind treatment period. There were two treatment arms as shown in Table 1. The co-primary efficacy endpoints were mean change in pre-bronchodilator FEV1 from baseline to each post-randomization visit, and rate of moderate or severe COPD exacerbations. COPD exacerbation was defined as in study 111 described above. Safety assessment included adverse event recording, vital signs, physical examination including body weight measurement, clinical laboratory and hematology measures, ECGs, and 24 hour Holter monitoring at selected US sites.

Studies 127 and 128:

Studies 127 and 128 were randomized, double-blind, parallel-group, in design, conducted in patients with moderate-to-severe COPD. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD (study 127) or COPD associated with chronic bronchitis (study 128), FEV1/FVC ≤70%, FEV1 ≤40% predicted, and be a current or previous smoker with a smoking history of ≥10 pack years. Concomitant use of inhaled corticosteroids was not permitted. Patients were on stable doses of LABA or LAMA according to the study protocol. The studies each had a 4 week run-in period, followed by a 24 week double blind treatment period. There were two treatment arms as

shown in Table 1. The primary efficacy endpoint was the mean change in pre-bronchodilator FEV1 from baseline to each post-randomization visit during the treatment period. The studies also assessed mild, moderate, or severe COPD exacerbation as a key secondary endpoint. COPD exacerbations were defined as increase in rescue bronchodilator use for 2 consecutive days (mild), event requiring oral or parenteral corticosteroid (moderate exacerbation), event resulting in hospitalization or death (severe exacerbation). Safety assessment included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

c. Efficacy findings and conclusions

The clinical program shows that roflumilast at a dose of 500 mcg once daily reduces exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbation.

There are three components of efficacy that were assessed and relevant to this application. These are COPD exacerbation, airflow or FEV1, and SGRQ. In subsequent sections these three efficacy components are briefly described, followed by a summary. The summary addresses the difference in opinion on efficacy between this review and the clinical review and the CDTL review. The summary also compares this program to a previous PDE-4 inhibitor called cilomilast, which was not approved.

COPD exacerbation

The definition of COPD exacerbation used in various studies was similar with some minor differences noted above where the design and conduct of the studies are described. There is no generally accepted definition of COPD exacerbations, but it usually includes some combination of symptoms and a change of treatment. The roflumilast program defined exacerbation in terms of change of treatment. This definition, though not ideal (because underlying symptoms that led to intervention was not measured), is reasonable and generally follows the definitions used in the literature.[1]

The 52 week studies 111, 112, 124, and 125 were specifically designed to assess the effect of roflumilast on the rate of COPD exacerbations. Studies 111 and 112 did not show statistically significant separation between roflumilast and placebo arms (Table 2). The Applicant conducted further analysis of the data and identified patients who seemed to benefit. Studies 124 and 125 were conducted with modified selection criteria informed by analysis of data from studies 111 and 112. Patients in studies 124 and 125 were COPD patients who had chronic bronchitis (cough and sputum production) with a recent history of COPD exacerbation. In this narrow COPD population there was statistically significant difference between roflumilast and placebo (Table 2). Both moderate and severe COPD exacerbations showed benefit, although most of the events were moderate. Time to first moderate or severe exacerbation also favored roflumilast. Time to first COPD exacerbation was about 65 days longer in patients who received roflumilast

[1] Cazzola M, MacNee W, Martinez FJ, et al. ATS/ERS Task Force Report: Outcomes for COPD pharmacological trials, from lung function to biomarkers. Eur Resp J 2008; 31: 416-468.

compared to placebo. On an exploratory analysis, it appeared that the beneficial effect on COPD exacerbation was attenuated after 8 months. However, such analysis is complicated to interpret because of patient dropouts. Studies 127 and 128 included a broad range of COPD patients and measured COPD exacerbation as a secondary endpoint. One of the two studies showed statistically significant difference between roflumilast and placebo (Table 2).

Table 2. Analysis of moderate or severe exacerbations (ITT population, pre-planned primary analysis)

	Poisson Exacerbation Rate			P-value
	Rof 500 mcg	Placebo	Rate Ratio	
Study 111	0.6	0.7	0.87	0.129
Study 112	0.5	0.5	0.85	0.085
Study 124	1.1	1.3	0.85	0.028
Study 125	1.2	1.5	0.82	0.004
Study 127	0.3	0.5	0.63	0.032
Study 128	0.3	0.3	0.77	0.196

Airflow or FEV1

All studies included FEV1 as a measure of efficacy. Patients on roflumilast had a statistically significant benefit compared to placebo across studies with effect sizes ranging from 39 to 80 ml, with an average of approximately 50 mL. This effect size is generally small compared to drugs such as beta-agonists and anti-cholinergics whose primary mode of action is bronchodilation.

Table 3. Change in pre-bronchodilator FEV1 from baseline to end of treatment (ITT population)

	Pre-bronchodilator FEV1 (mL)			P-value
	Rof 500 mcg	Placebo	Difference	
Study 101	64	17	47	0.0776
Study 107	77	-1	78	<0.001
Study 111	30	-12	42	<0.001
Study 112	49	-8	58	<0.001
Study 124	46	8	39	<0.001
Study 125	33	-25	58	<0.001
Study 127	39	-10	49	<0.001
Study 128	65	-16	80	<0.001

SGRQ

SGRQ was measured in early studies and did not show a statistically significant difference between roflumilast treatment and placebo (Table 3). Later key studies did not use SGRQ as an efficacy endpoint.

Table 4. Change from baseline of SGRQ, total score

	SGRQ			P-value
	Rof 500 mcg	Placebo	Difference	
Study 101	-4.7	-4.5	-0.3	0.425
Study 107	-3.5	-1.8	-1.7	0.053
Study 111	-1.8	-0.3	-1.5	0.016
Study 112	-3.7	-3.2	-0.5	0.268

Summary

The clinical program evolved over time (Table 1), with later studies informed by data from early studies. Early studies 101 and 107 targeted a broad spectrum of COPD patients and aimed to demonstrate broad maintenance treatment benefit by assessing FEV1 and SGRQ. These studies failed to show substantial efficacy, particularly for SGRQ (Table 4). The later studies 111 and 112 targeted more severe COPD patients and aimed to demonstrate broad maintenance treatment benefit by assessing FEV1 and COPD exacerbation. These studies failed to show substantial efficacy for COPD exacerbation (Table 2). The later studies 124 and 125 narrowed the patient population further by including COPD patients with chronic bronchitis and recent history of COPD exacerbation. In this narrowly defined COPD population, benefit was demonstrated for COPD exacerbation. This benefit on COPD exacerbation was supported by FEV1, which is a well accepted efficacy variable in COPD studies. Roflumilast is not claimed or expected to be a bronchodilator, therefore, failure to demonstrate a large numerical improvement typical for bronchodilator is not surprising. The consistent small numerical benefit for FEV1 across studies (Table 3) is supportive of the COPD exacerbation benefit.

The roflumilast clinical program has shown benefit on two aspects of COPD, exacerbation and FEV1. The Applicant is not seeking a broad maintenance treatment of COPD claim, but a restricted claim of COPD exacerbation in a narrow COPD population (chronic bronchitis with history of COPD exacerbation). The submitted data are adequate to support this limited claim in a narrow COPD population that can be clinically identified.

The clinical review concludes that the evidence of efficacy is not sufficient to support approval. The CDTL review states that efficacy has not been demonstrated when roflumilast is added to current standard of care of COPD patients, such as use of combination products containing an inhaled corticosteroid plus an LABA and inhaled LAMA. Considering the safety profile, the CDTL review recommends that prior to approval of roflumilast the Applicant should be required to demonstrate added benefit for roflumilast over concomitant use of combination product containing an inhaled corticosteroid plus a LABA and an inhaled LAMA. The clinical review conclusion and the CDTL review conclusion and recommendation are acknowledged, but requiring an additional clinical study to show benefit over current standard of care is not necessary for approval for various reasons. First, contrary to the clinical review conclusion, replicate studies showing efficacy for COPD exacerbation and FEV improvement has been shown

in the clinical program. Second, demonstration of benefit over standard of care is not consistent with the current interpretation of efficacy standard (21 CFR 314.125). Furthermore, the standard of care is often a moving target. When the roflumilast clinical program was conducted, some of the current standards of care were not available or not approved for use in COPD. Third, roflumilast, being an oral product will provide an alternate to current products approved for COPD exacerbation, which are all inhaled products (a combination product containing an inhaled corticosteroid plus LABA, and an inhaled LAMA product). The CDTL review acknowledges this benefit but concludes that this convenience is not sufficient to support approval. Fourth, although roflumilast has safety findings of concerns (discussed in section 8 below), these are not of a nature that justifies a higher standard of efficacy than what is typical and customary. Fifth, and finally, it is worth noting that the Applicant submitted results of studies 127 and 128 that show some added benefit of roflumilast over LABA and LAMA for COPD exacerbation and FEV1 (Table 2, Table 3). Nevertheless, obtaining data to assess the efficacy of roflumilast when added to current standard of care of COPD patients, such as use of combination product containing an inhaled corticosteroid plus an inhaled LABA and inhaled LAMA, is important and will provide valuable information for the product label and use of roflumilast. Such data will be requested as a PMC study when this product is approved, but not as a condition for approval.

For the sake of maintaining regulatory decision consistency, it is worth noting the difference between the roflumilast clinical program and the cilomilast clinical program. Cilomilast developed by GSK was submitted to the FDA for approval for use in COPD patients. GSK was seeking a maintenance treatment of lung function (FEV1) indication, supported by 4 pivotal studies 24 weeks in duration with co-primary efficacy variables of change from baseline in trough FEV1 and SGRQ. The FEV1 improvement over 24 weeks was demonstrated, but was numerically modest as was for roflumilast. Benefit in SGRQ score was not demonstrated. The cilomilast application was discussed at a PADAC meeting on September 5, 2003. The majority opinion was that efficacy was not demonstrated because the benefit for FEV1 was not demonstrated over a long time period (such as 3 years) for a maintenance treatment of lung function (FEV1) claim, or benefit on two aspects of COPD was not demonstrated. In contrast to the cilomilast clinical program, the roflumilast clinical program has shown benefit on two aspects of COPD, exacerbation and FEV1, and the Applicant for roflumilast is not seeking a broad maintenance treatment of COPD claim, but a restricted claim of COPD exacerbation in a narrow COPD population (chronic bronchitis with history of COPD exacerbation) that can be clinically identified. The Applicant for roflumilast reached this specific narrow COPD population through purposeful sequential studies.

8. Safety

a. Safety database

The safety assessment of roflumilast is based on the COPD studies shown in Table 1, and additional studies conducted for other indications, the largest program being that for asthma. The safety database is large and includes information from approximately

12,000 patients with COPD with approximately half of the patients receiving roflumilast, and additional 12,000 patients from other clinical programs.

b. Safety findings and conclusion

The safety data do not raise safety concerns in the COPD patients that would preclude ultimate approval, but there are various issues that need to be resolved. The unresolved safety issues will preclude approval in this review cycle.

In the COPD safety population of approximately 12,000 patients there were 177 deaths. The large number of deaths is not surprising given the patient population who are elderly with COPD and other concomitant diseases. There was no imbalance on mortality between the groups and there is no signal seen from analysis of the mortality data. Serious adverse events (SAEs) were also common, which is expected for this type of study and the patient population. Analysis of SAEs did not raise a safety signal. Common adverse events included COPD exacerbation, weight loss, diarrhea, nausea, headache, insomnia, and dizziness. Weight loss, diarrhea, and nausea were more common in roflumilast treated patients compared to placebo (discussed further below). Clinical laboratory tests and ECGS did not raise any specific safety concerns.

There are four specific safety issues that are relevant to this application review. These are psychiatric adverse reactions including suicidality, gastrointestinal adverse reactions, weight loss, and cancer. In subsequent sections these four safety issues are briefly described, followed by a summary.

Psychiatric adverse reactions including suicide

Psychiatric adverse reactions were more common in the roflumilast group compared to the placebo in the COPD clinical program. Common adverse reactions of this category were insomnia (3.0% roflumilast 500 mcg vs 1.1% placebo), anxiety (1.4% roflumilast 500 mcg vs 0.8% placebo), and depression (1.4% roflumilast 500 vs 0.8% placebo). Psychiatric adverse reactions were also more common in the roflumilast group compared to the placebo group in other roflumilast programs.

There were 3 completed suicides and 2 suicide attempts reported in the roflumilast COPD safety data base (n = 12054 patients) in roflumilast treated patients compared to none in patients treated with placebo. There was one suicide ideation in a placebo treated patients. Of the three completed suicides none of the patients had a prior history of depression. Two cases of suicides were reported in patients who discontinued roflumilast approximately 20-21 days prior to the suicide event, which makes causal association somewhat distant. With regard to the suicide attempts, both patients had prior psychiatric histories (depression in one patient and previous suicide attempt in the other). Both patients were receiving roflumilast at the time of the suicide attempt. The Applicant had utilized the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to assess for additional potential suicide-related cases in the COPD safety database and presented the finding for the PADAC meeting. But the C-CASA was not discussed with

the Agency and has not been submitted to the NDA for FDA review. The extend and nature of the C-CASA analyses is not clear.

Thorough evaluation of suicidality is necessary before the application can be approved. REMS (possibly limited to a MedGuide) will also be necessary to inform patients and health care providers about the risks for psychiatric events, including suicidality, with use of roflumilast. The Applicant submitted a REMS on April 14, 2010. Lack of comprehensive C-CASA analysis and lack of timely submission of a REMS for Agency review will preclude approval of roflumilast in this review cycle.

Weight loss

Weight loss was a common adverse event reported in roflumilast clinical studies. Patients from all indications studies (including indications other than COPD) were affected, which suggest a drug specific effect. In the studies 124 and 125, where weights were carefully measured, 62.4% patients in the roflumilast group compared to 37.7% patients in the placebo group had measured weight loss below baseline. Weight loss reported as adverse event was more common with roflumilast compared to placebo (10.3% vs 2.8%). Patients who had lower body weight at baseline and most severe COPD lost more weight than others. The Applicant submitted a REMS (MedGuide) to inform patients and health care providers about the risks for weight loss with use of roflumilast. The REMS was submitted on April 14, 2010.

Gastrointestinal adverse reactions

Gastrointestinal adverse reactions were more common in the roflumilast group compared to the placebo group in the COPD clinical program. Common adverse reactions of this category were diarrhea (10.1% roflumilast 500 mcg vs 2.6% placebo), and nausea (5.2% roflumilast 500 mcg vs 1.4% placebo). Diarrhea and nausea were also the most common cause of withdrawal after COPD exacerbation. About 90% of gastrointestinal adverse reactions were mild or moderate in intensity and about 10% met the criteria for severe adverse reactions.

Cancer

Roflumilast was found to cause nasal tumors in rodents. Thus, cancer frequency in humans is a topic of special interest. The overall number of tumors reported as adverse events in the roflumilast group was comparable to that of the placebo group (105 tumors in 6563 roflumilast treated patients vs 80 from 5491 placebo treated patients), but more patients in the roflumilast group compared to the placebo group had lung cancer (29 in 5752 roflumilast treated patients vs 17 in 5505 placebo treated patients), prostate cancer (13 in 5752 roflumilast treated patients vs 5 in 5505 placebo treated patients), and colo-rectal cancer (9 in 5752 roflumilast treated patients vs 2 in 5505 placebo treated patients). Many of these cancers were identified early during treatment suggesting uncovering of existing cancers rather than development of new cancers. Appearance of common cancers more frequently in roflumilast treated patients is difficult to explain. A definite

link between roflumilast and human cancers cannot be proven or excluded. The animal findings provide a biological plausibility, but occurrence of cancers early in treatment with short duration of exposure argues against it. The product label will describe the cancer findings and acknowledge this possible risk.

Summary

The roflumilast clinical program has identified serious safety concerns as noted above, but none rise to the level that would preclude approval or would require demonstration of efficacy above and beyond what is typically expected for a drug for COPD as was recommended in the CDTL review (see discussion in Summary sub-heading under section7c above). The safety findings will be noted in the product label with appropriate level of warning and in the required REMS. The Applicant has proposed a REMS for the risk of psychiatric adverse reactions and suicides, and for weight loss. The REMS was submitted too late in the review cycle for appropriate Agency review and action. Furthermore, as discussed above, the Applicant will need to analyze the total safety database of roflumilast to better understand the risk of suicide, which will also influence the various elements of the REMS. These outstanding safety issues will preclude approval of the application in this review cycle. It is expected that the Applicant will be able to address these deficiencies and respond to them adequately by further analysis of existing data.

c. REMS/RiskMAP

Not relevant because roflumilast will not be approved in this cycle.

9. Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was held on April 7, 2010. Questions were asked about the efficacy, safety, and approvability of roflumilast. The questions were framed against the original broad COPD indication submitted by Nycomed (maintenance treatment of COPD associated with chronic bronchitis in patients with risk of exacerbation), and not the revised more restricted COPD exacerbation indication submitted later by Forest Pharmaceuticals (maintenance treatment to reduce exacerbation of COPD associated with chronic bronchitis in patients at risk of exacerbation). The original indication was used for discussion because the revised indication was submitted late in the review cycle, therefore, there was not sufficient time for review and consideration of potential ramifications of the new proposed indication. Nevertheless, the intention of the Applicant to change the indication was disclosed in the FDA briefing documents and during presentations at the meeting. The committee voted favorably regarding whether there was substantial evidence of efficacy (9 yes, 6 no), and the safety profile of roflumilast (9 yes, 6 no). Regarding the approvability question, which is essentially the sum of demonstration of efficacy and safety, the results were against approval (5 yes, 10 no). During the deliberation, some Committee members expressed that they would be more favorable on efficacy and approvability with the proposed revised and restricted indication. The Applicant did not present a risk-mitigation strategy as part of the NDA and also in the briefing material for the PADAC meeting. Some Committee members felt that a risk mitigation strategy

should be developed for this product and such a plan could have swayed their view on approvability. Some Committee members also had some reservation on the "maintenance treatment" wording in the indication given the possible attenuation of the COPD exacerbation benefit over time and lack of benefit on some other patient reported outcomes, such as SGRQ.

After the PADAC meeting the applicant further modified the indication to remove the "maintenance treatment" wording (the further revised indication reads as: once daily treatment to reduce exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbation), and submitted a REMS limited to a MedGuide to inform patients and health care providers about the potential risks of psychiatric event, including suicidality, and weight loss.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was requested for 4 clinical study sites based on high enrollment and favorable outcome for roflumilast. Final reports of the DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

(b) (4)

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Eight investigators had significant financial interest in the Applicant. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these financial interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name Daxas. The proposed proprietary name was accepted by DMEPA.

b. Physician Labeling

The Applicant submitted a label in the Physician's Labeling Rule format. As noted above in various sections, three versions of label were submitted to the NDA. The original label submitted by Nycomed with the NDA was revised by Forest Pharmaceuticals when it took ownership of this NDA effective December 4, 2009. The indication was revised to make it more limited to a COPD exacerbation claim. At the same time, new warning related to psychiatric adverse reactions and suicides were added. On April 14, 2010, after the PADAC meeting, Forest Pharmaceuticals submitted another version of the label where the indication was revised to delete the "maintenance treatment" wording, and a new MedGuide only REMS was proposed. The label has not been reviewed in this review cycle because the application will not be approved.

c. Carton and Immediate Container Labels

The carton and immediate container labels were not reviewed in detail because the application will not be approved in this review cycle.

d. Patient Labeling and Medication Guide

The patient labeling and medication guide were not reviewed in detail because the application will not be approved in this review cycle.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has not submitted adequate data to support approval of roflumilast tablets 500 mcg for once daily treatment to reduce exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbation. Although substantial efficacy has been demonstrated, there are safety issues as outlined in section 8, and chemistry and manufacturing issues as outlined is sections 3 and 11a that need to be resolved before this application can be approved. The recommended action on this application is a Complete Response.

The comments below are for the Complete Response action letter.

1. The submitted data do not provide substantial evidence of safety to support the use of roflumilast in patients with chronic obstructive pulmonary disease (COPD). Specifically, the safety signal of suicides and the psychiatric adverse reactions with

roflumilast have not been fully assessed to understand the strength of the signal and its impact on the risk-benefit assessment for the treatment of patients with COPD.

To support safety of roflumilast regarding suicides and psychiatric adverse reactions, submit results from comprehensive review of all roflumilast safety data utilizing an acceptable method, such as the Columbia Classification Algorithm of Suicide Assessment (C-CASA). The assessment should include data from all COPD studies, and studies conducted with roflumilast for other indications. Such assessment is necessary to fully assess the safety signal of suicides and the psychiatric adverse reactions and its impact on the risk-benefit assessment.

(b) (4)

The safety findings of suicides, weight loss, and malignancy seen with roflumilast are substantial safety risks and will need to be managed by appropriate safe use strategy. On April 14, 2010, the application submitted a Risk Evaluation and Mitigation Strategy (REMS) to address these safety risks. The REMS was not reviewed because the Applicant will need to analyze the total safety database of roflumilast to better understand the risk of suicide, which will influence the various elements of the REMS. The action letter will acknowledge the receipt of the submission that includes the REMS and state that the submission was not reviewed for this action.

b. Risk Benefit Assessment

A full risk-benefit assessment cannot be made because there are outstanding safety issues that the Applicant will need to address. The major safety issues are suicides, weight loss, malignancy, and gastrointestinal adverse reactions (discussed in section 8 above). These safety issues are not likely to prevent ultimate approval, but the Applicant will need to conduct further analysis of the roflumilast safety data to fully assess the strength of the safety signal of suicide and psychiatric adverse reactions so that its impact on the risk-benefit can be made. The Applicant will also need to develop an acceptable safe use strategy to manage the safety risk of suicides, weight loss, and malignancy. The Applicant has submitted adequate efficacy data to show reduction of exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbation. The safety concerns noted above do not raise to a level that would require a higher level of efficacy such as that recommended in the CDTL review (see discussion in Summary sub-heading under section 7c above).

c. Post-marketing Risk Management Activities

Not relevant because the application will not be approved in this review cycle.

d. Post-marketing Study Commitments

Obtaining data to assess the efficacy of roflumilast when added to current standard of care of COPD patients, such as use of combination products containing an inhaled corticosteroid plus an inhaled LABA and an inhaled LAMA, is important and will provide valuable information for the product label and use of roflumilast. Such data will be requested as a PMC study when this product is approved, but not as a condition for approval as recommended in the CDTL review.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	FOREST RESEARCH INSTITUTE	DAXAS(ROFLUMILAST 500 MCG TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
05/14/2010

Cross-Discipline Team Leader Review

Date	April 28, 2010
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-522
Applicant	Nycomed/Forest Laboratories
Date of Submission	July 15, 2009
PDUFA Goal Date	May 17, 2010
Proprietary Name / Established (USAN) names	Daxas/roflumilast
Dosage forms / Strength	Oral tablet/500 mcg
Proposed Indication(s)	1. …maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations*. * The ownership of the NDA was transferred from Nycomed to Forest Laboratories on December 4, 2009. On January 29, 2010, Forest submitted new labeling with a newly worded indication…"for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease associated with chronic bronchitis in patients at risk of exacerbations".
Recommended:	Complete Response

1. Introduction

Nycomed submitted a 505(b)(1) new drug application (NDA 22-522) on July 15, 2009, for the use of roflumilast at a proposed dose of 500 mcg once daily for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. Of note is that the ownership of the NDA was transferred from Nycomed to Forest Laboratories in the middle of the NDA review period on December 4, 2009. This change in ownership ultimately resulted in submission of a new proposed label on January 29, 2010, that included a change to a more focused proposed product indication than in the original NDA submission, the "maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease associated with chronic bronchitis in patients at risk of exacerbations" and an acknowledgement of a safety concern over increased neuropsychiatric adverse events in patients receiving roflumilast in the clinical trials. The PDUFA due date for this application is May 17, 2010. Roflumilast is not currently marketed anywhere in the world. Although large clinical studies have been performed in patients with asthma, Forest is only seeking approval for roflumilast in COPD patients. This review will provide an overview of the application with a focus on efficacy and safety issues that affect the risk/benefit assessment of roflumilast and, subsequently, the determination of an appropriate COPD patient population in which the potential benefit of the drug may outweigh the risks.

2. Background

Roflumilast is a new molecular entity and a selective phosphodiesterase type 4 (PDE 4) inhibitor. It is purported to act as an anti-inflammatory agent in patients with COPD.

COPD is a chronic progressive disease caused by chronic inflammation and destruction of the airways and lung parenchyma that is characterized by progressive airflow obstruction that is sometimes partially reversible with the administration of a bronchodilator. Current therapies for the treatment of various disease aspects of COPD include bronchodilators (short and long-acting beta agonists such as albuterol, salmeterol, and formoterol as well as anti-muscarinic agents such as ipratropium and tiotropium) that are used to treat reversible bronchoconstriction associated with COPD. Tiotropium (Spiriva) and Advair® 250/50, a salmeterol (50 mcg) and fluticasone propionate (250 mcg) combination product that contains both a long-acting beta agonist (LABA) and inhaled corticosteroid are currently approved to treat both reversible bronchoconstriction and to reduce exacerbations of COPD in patients with a history of exacerbations and have become standard of care therapies for treatment of patients with severe COPD[1], the patient population studies in the applicant's pivotal trials, M2-124 and M2-125. Theophylline, a non-specific member of the phosphodiesterase inhibitor class is available in immediate and sustained released formulations and has been used for many years for the treatment of both COPD and asthma.

Although none have been approved for use, other specific PDE 4 inhibitors have been developed and studied in clinical trials. One, cilomilast, has been studied extensively in patients with COPD. Cilomilast was shown to be a relatively weak bronchodilator as

demonstrated by the 30-40 mL increase from baseline in FEV1 compared to placebo that was observed in cilomilast phase 3 clinical trials. With this data in hand, on September 5, 2003, a Pulmonary and Allergy Advisory Committee voted seven to three that efficacy adequate to support approval had not been demonstrated. Cilomilast and other specific PDE 4 inhibitors have also demonstrated prominent dose-dependent toxicities related to the gastrointestinal system in clinical studies, including nausea, vomiting, diarrhea, anorexia, and weight loss. This adverse event profile of PDE 4 inhibitors has resulted in marginal tolerability at doses felt to be effective and which must be taken into consideration when making a risk-benefit determination.

The regulatory history for roflumilast is quite extensive as the overall clinical development program has been conducted over approximately a fifteen year period and includes a database of more than 15,000 patients with COPD. In addition, the Application has changed ownership multiple times over the course of development. The large clinical program and many phase 3 trials are a reflection that the design, endpoints, and patient populations of the COPD clinical program evolved substantially over time (see table 1). For example, earlier Phase 2/3 dose-ranging and Phase 3 studies (FK1-101 and M2-107 conducted from 1999-2003) focused on a commonly used and accepted patient reported outcome measure used in COPD clinical studies, the St. George Respiratory Questionnaire (SGRQ), as a co-primary endpoint with spirometry measurements (FEV1) as the other co-primary endpoint. However, in later Phase 3 studies (M2-111 and M2-112), exacerbation rates became a co-primary endpoint with spirometry (FEV1) as the other. As there is no consensus definition as to what constitutes a COPD exacerbation, concern was raised to the applicant regarding the definition and determination of exacerbations and criteria used for assessing the severity of an exacerbation. In 2006, protocols for what would be designated as the clinical program's pivotal studies (M2-124 and M2-125) with co-primary endpoints of pre-bronchodilator FEV1 and the rate of exacerbations were submitted to the Division. In a correspondence dated February 7, 2007, regarding M2-124 and M2-125, the Division commented on the following issues:

- That based on evaluation of the data from (earlier) completed studies M2-111 and M2-112, the patient population for studies M2-124 and M2-125 was limited to include only patients with: 1) a defined history of exacerbations, 2) signs of chronic bronchitis at inclusion, and 3) a defined cough/sputum symptom score at randomization.
- That concomitant inhaled corticosteroids (ICS), which were allowed in studies M2-111 and M2-112, and are commonly used in combination with long-acting beta agonists, were prohibited. Additionally, patients were only allowed concomitant medication consisting of long-acting beta agonists plus rescue medication or short acting anticholinergics plus rescue medication.

Despite these restrictions placed on the roflumilast clinical development program population, the Division was asked if it agreed that a general claim for maintenance treatment of COPD could be obtained. The Division responded that the indication that could be claimed would be a review decision. Regarding whether efficacy and safety outcomes from US and non-US patients would allow adequate assessment for approvability, the Division reiterated that this would be a review issue. The Division added that (the endpoint of) COPD exacerbations is a clinical diagnosis and the decision to initiate treatment (with corticosteroids) or hospitalization

is investigator-driven leaving room for variations in the definition of what constitutes an exacerbation and the severity of the exacerbations. It stated that as much as it is feasible the applicant should standardize their definition for a COPD exacerbation as well as the criteria that would prompt the investigator to initiate corticosteroid therapy or hospitalize the patient.

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

As mentioned previously, the proposed indication for roflumilast contained in the original NDA submitted on July 15, 2009, was "for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations". Subsequently, upon transfer of the NDA to Forest, the new applicant submitted new product labeling in a submission dated January 29, 2010, which included a change in the product indication from the original broad indication of "maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations" to the more limited indication of "for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations." It should be noted that from the regulatory perspective, to treat the disease entity, COPD, as a whole (as the original indication states) would require demonstration of clinically meaningful improvements in more than one aspect of the disease which was the reason why co-primary endpoints were chosen for most of the phase 3 roflumilast clinical trials. This is in contrast to the efficacy requirements for the change to the more narrow indication of "reduction in exacerbations of COPD" in which substantial efficacy would need to be demonstrated only for a reduction in the exacerbation endpoint. Because this change in indication was submitted relatively late in the review cycle and close to the time reviews were being finalized for the upcoming roflumilast advisory committee meeting, the Division told the applicant that the presentations for the advisory committee meeting on April 7, 2010, would be based on the original indication submitted with the NDA.

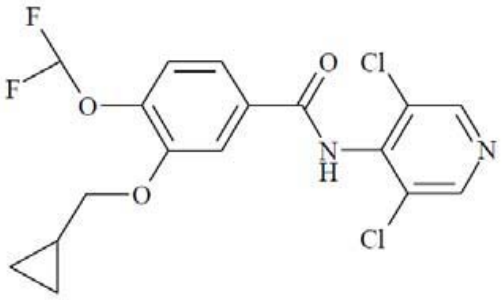
3. CMC/Device

The primary CMC review was conducted by Craig Bertha, Ph.D. His review has concluded that from a CMC perspective, the application is recommended for approval.

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application. In addition, the Applicant has agreed as a post-approval commitment (January 22, 2010 submission) to revisit the drug substance particle size distribution (PSD) acceptance criteria after preparation of multiple (e.g., n = 10) commercial batches that are used to produce drug product and to make adjustments that will reflect the PSD data and taking into consideration the variability in those data.

Following is a brief summary of the chemistry and manufacture of roflumilast.

The drug substance is roflumilast (USAN), a phosphodiesterase type 4 inhibitor. The chemical name is 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4- (difluoromethoxy)benzamide (IUPAC). Roflumilast is achiral and has the following structure, formula, and molecular weight:



Molecular formula:	$C_{17}H_{14}Cl_2F_2N_2O_3$
Relative molecular mass:	403.22

The drug substance is micronized due to its poor water solubility. It has been found in only a single crystalline form (single polymorphic form) and it is characterized as BCS class 2 (poorly soluble, highly permeable) by the applicant. The particle size distribution of the roflumilast is observed to directly correlate with the dissolution or drug release from the dosage form. Roflumilast by itself, and when formulated in the drug product is chemically and physically stable.

The drug product is Daxas® (roflumilast) tablets and the strength is 500 mcg/tablet. The tablets are yellow, film-coated, "D-shaped," and are embossed on one side with the letter "D." The trade packages consist of a single high-density polyethylene bottle with a child-resistant closure that contains either 30 or 90 tablets. Currently the proposed expiration dating period for the drug product is 24 months. The formulation of the drug product does not contain any novel or noncompendial excipients. No steps have been identified in the manufacturing process that are considered critical in terms of batch reproducibility and product performance,

although, as mentioned above, roflumilast particle size is important to the attainment of the desired release rate as determined by dissolution testing (b) (4)

4. Nonclinical Pharmacology/Toxicology

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

Carcinogenicity
Roflumilast at daily doses of 8 and 16 mg/kg/day for 2 years caused statistically significant increases in the incidence of nasal tumors in hamsters but not in mice. The Agency's Executive Carcinogenicity Assessment Committee (ECAC) reviewed the results and interpretation of the roflumilast carcinogenicity on May 10, 2005. The ECAC concluded that roflumilast was carcinogenic in hamsters and determined that ADCP N-oxide and its metabolite, ADCP N-oxide epoxide, were responsible for these nasal tumors. At that time the nasal findings were deemed not relevant to humans based on the lack of ADCP N-oxide formation in humans. However, human pharmacokinetic data now demonstrates the presence of ADCP N-oxide in human plasma and urine which accounts for 10.5% (urine data) of the roflumilast dose. In light of these new data, the ECAC amended its initial determination on January 19, 2010 and concluded that the ADCP-N-oxide metabolite does not appear to be rodent-specific and the hamster nasal tumor is no longer considered rodent specific. Of the thirteen PDE-4 inhibitors that FDA has nonclinical toxicology data on, one other PDE-4 inhibitor, piclamilist, which also forms the ADCP metabolites, has demonstrated nasal toxicities in rats and mice and nasal tumors in rats.

The exact relevance of the hamster tumor findings to humans is unknown due to differences in tissue ADCP N-oxide concentrations between rodents and humans. In the rodent nasal cavity, cytochrome P450 enzyme CYP2G1 converts ADCP to ADCP N-oxide and then to ADCP N-oxide epoxide intermediate, resulting in very high local exposure to the carcinogens. Human nasal tissues apparently lack active enzymes to convert ADCP to ADCP N-oxide, however, the carcinogen ADCP N-oxide is found in human plasma and urine and accounts for about 10% of the roflumilast dose. Thus, there is systemic exposure of humans to the ADCP N-oxide carcinogen. Whether these findings are related to the increase in some malignancies noted in COPD patients who received 500 mcg of roflumilast daily compared to placebo in clinical trials is unknown.

Fertility

Nonclinical assessments of roflumilast effects on fertility were completed in male and female Wistar rats up to doses of 1.8 mg/kg/day. A statistically significant decrease in male rat fertility rate (64.2% compared to control at 89.2%) was observed at the 1.8 mg/kg/day. The NOAEL for male fertility effects was 0.6 mg/kg. As a result of the fertility studies, the effects of roflumilast on human male fertility were evaluated in a 3-month clinical trial (Report 98/2002). It appears that roflumilast at 500 μg/patient/day had no effects on sperm and fertility parameters evaluated.

Reproductive toxicity

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

Cardiovascular toxicity

Roflumilast adversely affected the cardiovascular system in dogs, mice and monkeys. Dogs treated with >0.6-mg/kg/day roflumilast for 12 months showed cardiac lesions such as focal hemorrhages, hemosiderin deposits and lympho-histiocytic cell infiltration in the right atria/auricles. Male mice treated with ≥12-mg/kg/day roflumilast for 6-months showed moderate peri-arteritis in the heart. Monkeys treated with 0.5-mg/kg/day roflumilast for a month showed myocarditis. The respective NOAELs for cardiac lesions in mice, dogs and monkeys were 153.1, 203.7 and 251.3 μg.h/L in plasma AUCs. These AUC values provided safety margins of at least 5, an acceptable value for drugs like roflumilast.

Gastrointestinal toxicity

Roflumilast treatment-related effects on the gastrointestinal (GI) tract were observed in rats, dogs and monkeys but not in mice and hamsters. Wistar rats treated with 8.0-mg/kg/day roflumilast for 4 weeks showed serositis/inflammation in jejunum, peritonitis, and stomach erosion. No GI findings were observed at roflumilast doses up to 2.5 mg/kg/day in a 6-month rat study. In monkeys, minimal acute inflammation or inflammation foci were noted in the pyloric region of the stomach after roflumilast treatment up to 0.5 mg/kg/day for up to 42 weeks. The respective NOAELs for GI effects of roflumilast in rats and monkeys were 78.7 and 251.3 μg.h/L in plasma AUCs. These AUC values provided safety margins of at least 5, again an acceptable value.

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

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology team has concluded that the data submitted by the applicant to characterize the clinical pharmacology and biopharmaceutics profile of roflumilast is adequate to support its approval from the clinical pharmacology perspective. The team, however, has recommended two post-marketing commitments, an in vitro evaluation of roflumilast as a substrate for P-gp and to repeat the thorough QT study for roflumilast due to the positive control (moxifloxacin) not demonstrating an adequate effect on QT (lack of assay sensitivity, see description of the study below). I agree with the recommendation of the PMC of an in vitro evaluation of the potential of roflumilast as being a substrate for P-gp. The proposed dose of roflumilast of 500 mcg once daily is the maximal tolerated chronic dose of the drug. Because roflumilast has significant dose related side effects, especially potentially severe GI effects, the increased exposure to roflumilast, if it was a P-gp substrate, that would occur when taken concomitantly with other drugs (e.g., ketoconazole) would be a safety concern. With regard to the QT study, a thorough QT study is intended to be conducted early during development in order to help assess the potential effect of a drug on QT and thereby plan for the extent of cardiac monitoring (ECGs) that should be performed in later phase clinical trials. While, according to the IRT team statistician, the submitted thorough QT study lacked adequate assay sensitivity to be able to discriminate small effects (<10 ms) on the QT interval, when taken into context that the COPD safety database contains ECG data from approximately 24,000 COPD patients with about half exposed to chronic dosing of up to one year with the 500 mcg dose of roflumilast without any appreciable QT prolongation apparent, the clinical utility of a formal QT study becomes rather moot. Thus, I do not recommend the need to repeat the study in order to demonstrate better assay sensitivity.

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

Pharmacokinetics in Healthy Subjects

Absorption
The absolute bioavailability of roflumilast following a 500 µg oral dose is 79%. The median time to reach maximum plasma concentrations of roflumilast (t_{max}) is one hour, while t_{max} of roflumilast N-oxide (the major active metabolite of roflumilast) is eight hours in the fasted state. Food intake delays t_{max} of roflumilast by one hour and reduces C_{max} by 40%; however, C_{max} and t_{max} of roflumilast N-oxide are unaffected. The exposure (AUC and Cmax) of roflumilast and roflumilast N-oxide is dose-proportional over the roflumilast dose range of 250 to 1000 µg.

Distribution
Plasma protein binding of roflumilast and its N-oxide metabolite is 99% and 97%, respectively.

Metabolism and Elimination
Roflumilast is extensively metabolized via Phase 1 (cytochrome P450) and Phase II (conjugation) reactions with roflumilast N-oxide the major metabolite observed in human

plasma. The plasma AUC of roflumilast N-oxide, on average, is about 10-fold greater than that of roflumilast. *In vitro* studies and clinical drug-drug interaction studies suggested that the metabolism of roflumilast to roflumilast N-oxide was mediated by CYP1A2 and CYP3A4. Following an oral dose of roflumilast, the median plasma effective half-lives of roflumilast and roflumilast N-oxide were 17 and 30 hours, respectively. Steady state plasma concentrations were reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing of roflumilast. Following once daily oral administration of roflumilast at 500 μg in healthy subjects, the accumulation index was about 1.8 for roflumilast and 2.0 for roflumilast N-oxide. After intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

Pharmacokinetics in COPD Patients

Based on a population PK analysis, COPD patients have a 65% higher AUC for roflumilast and about 8% higher AUC for roflumilast N-oxide compared to healthy subjects.

Pharmacokinetics in Special Populations

Age
The exposure between young (18-45 years old) and middle-aged (45-65 years old) subjects was comparable for both roflumilast and roflumilast N-oxide. However, the exposure in elderly (>65 years old) was 27% higher for AUC and 16% higher for C_{max} for roflumilast and 19% higher for AUC and 13% higher for C_{max} for roflumilast-N-oxide than that in young subjects.

Gender
Women exhibited higher exposures of both roflumilast and roflumilast N-oxide when compared with men with the AUC of roflumilast increased by 40%, 79%, and 28%, respectively, for young, middle-aged, and elderly female subjects compared to male subjects. Similarly, compared to male subjects, the AUC of roflumilast N-oxide was increased by 33%, 52%, and 45%, respectively, for young, middle-aged, and elderly female subjects. In addition, the C_{max} of roflumilast N-oxide was increased by 30%, 53%, and 47%, respectively, for young, middle-aged, and elderly female subjects.

Race
Compared to Caucasians, African Americans, Hispanics, and Japanese showed 25%, 47%, and 15% higher AUC, respectively, for roflumilast, and 69%, 51%, and 16% higher AUC, respectively, for roflumilast N-oxide. Also, African Americans, Hispanics, and Japanese showed a 15%, 31%, and 17% higher C_{max}, respectively, for roflumilast, and 17%, 9%, and 5% higher C_{max}, respectively, for roflumilast N-oxide compared to Caucasians.

Renal Impairment
The effect of renal impairment on the exposure of roflumilast and roflumilast N-oxide was examined after a single dose of 500 μg roflumilast to patients with severe renal impairment as compared to healthy subjects (Study FHP020). The exposure of roflumilast in severe renal impairment patients was 21% less for AUC and 19% less for C_{max}, as compared to healthy subjects. The exposure of roflumilast N-oxide in severe renal impairment patients was

comparable for AUC as compared to healthy subjects. No dose adjustment is recommended for renal impairment patients.

Hepatic Impairment
When comparing patients with liver cirrhosis to healthy subjects, an increase in exposure was observed in patients with liver cirrhosis (Child-Pugh stage A and B) for both roflumilast and roflumilast N-oxide. As compared to healthy subjects, the AUC and C_{max} of roflumilast were 51% and 3% higher for patients with Child-Pugh A, respectively; and 92% and 26% higher for patients with Child-Pugh B, respectively. As compared to healthy subjects, the AUC and C_{max} of roflumilast N-oxide were 24% and 26% higher for patients with Child-Pugh A, respectively; and 42% and 40% higher for patients with Child-Pugh B, respectively. The recommendation is that roflumilast be contraindicated in patients with moderate and severe hepatic impairment patients and be used with caution in patients with mild hepatic impairment.

Drug-Drug Interactions

In vitro metabolism studies using human liver microsomes and *in vivo* drug-drug interaction studies indicated that roflumilast is mainly metabolized by CYP3A4 and CYP1A2. Therefore, the exposure of roflumilast is expected to increase when inhibitors of CYP3A4 or CYP1A2 are co-administered and decrease when inducers of CYP3A4 or CYP1A2 are co-administered. In vitro study showed that roflumilast did not inhibit P-gp transport.

Drug-drug interaction studies were conducted with the following drugs: midazolam, erythromycin, ketoconazole, rifampicin, fluvoxamine, digoxin, Maalox, salbutamol, formoterol, budesonide, theophylline, cimetidine, warfarin, enoxacin, sildenafil, minulet, montelukast. No significant interactions were observed with midazolam, salbutamol, formoterol, budesonide, warfarin, sildenafil, Maalox, digoxin, or montelukast. However, as a result of drug-drug interactions with increased exposure, roflumilast should use with caution when co-administered with enoxacin, theophylline, cimetidine, fluvoxamine, ketoconazole, erythromycin, smoking, and sildenafil and roflumilast should not be taken with rifampicin or other strong CYP inducers. Co-administration of roflumilast with the following drugs does not need dose adjustment: midazolam (or other CYP3A4 substrates), digoxin (or other P-gp substrates), Maalox, salbutamol, formoterol, budesonide, warfarin, and montelukast does not require dose adjustment.

Thorough QT Study

Study CP-069 was a placebo and active controlled QT study in 80 healthy subjects (54 males, 26 females). A single open label 400 mcg dose of moxifloxacin given as positive control or placebo was administered 1 day prior to roflumilast administration. Treatment with roflumilast for 7 or 14 days with doses of 500 and 1000 mcg/day or placebo were tested and QT interval was accessed 1 hour after roflumilast dosing.

The primary comparison for clinical interpretation between active drug and placebo was the largest difference from placebo in time-matched change from baseline in QTcF and QTcP at any nominal time post-dose. The largest mean time-matched change from baseline differences

from placebo for the roflumilast 500 mcg group in QTcF and QTcP were -3.23 and 2.39 ms respectively. These differences were not statistically significant from zero. The largest mean time-matched change from baseline difference from placebo for the roflumilast 1000 mcg group in QTcF was -4.81 ms (placebo higher than roflumilast) and 0.77 ms in QTcP. No QTc change of 30 ms or greater was observed in any subject.

The thorough QT study conducted for this program was felt to be inconclusive according to the review performed by the IRT because adequate assay sensitivity could not be established. This differs from the conclusion of the applicant that assay sensitivity was demonstrated as the largest mean time-matched change from baseline difference from placebo in the moxifloxacin 400 mg group on Day 1 in QTcF was 6.79 ms and 6.97 ms in QTcP; differences that were statistically significant from zero. However, the IRT statistical reviewer performed an independent analysis and determined that the largest unadjusted 90% lower confidence interval is below 5 ms (4.3 ms), indicating that the assay sensitivity was not established in this study. Thus, without a concurrent positive control, in this case moxifloxacin, the study design could not exclude small effects (<10 ms) on the QTc interval. The conclusion by the IRT was that the study was therefore not conclusive.

6. Clinical Microbiology

This section is not applicable as indacaterol is not an antimicrobial product.

7. Clinical/Statistical- Efficacy

Overview of the clinical program

The Applicant has proposed two clinical Phase 3 studies as the "pivotal" studies (M2-125 and M2-125) from which approval of roflumilast should be based. However, the clinical development program for roflumilast is extensive and encompasses 18 late phase clinical studies in COPD patients. Therefore, in order to understand the evolution of the roflumilast clinical program over time and understand the totality of the efficacy data for roflumilast, this review focused primarily on eight studies conducted over the span of the roflumilast COPD development program, 4 one-year studies (Studies M2-111, M2-112, M2-124, and M2-125) which evaluated COPD exacerbations and 4 six-month studies (FK1-101, M2-107, M2-127, and M2-128) (see Table 1). All the studies were designed such that, if positive, they could potentially serve as pivotal studies to support the safety and efficacy of roflumilast for COPD. The efficacy data will be presented in this section from relevant clinical studies according to endpoint (FEV1, exacerbations, etc.).

Table 1 Relevant Clinical Studies for Roflumilast for COPD

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

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

Design and conduct of the studies

Dose-ranging studies (FK1-101 and M2-107)
The dose ranging data for the roflumilast clinical program primarily comes from two studies (studies FK1-101 and M2-107) in which two doses of roflumilast (250 and 500 mcg once daily) were compared against placebo. Both trials were double-blind, placebo-controlled, parallel-group, non-US, multinational studies in patients ≥ 40 years of age with non-reversible airway obstruction across the full range of COPD severity (FEV1 30 to75-80% predicted). Study FK1-101 was a phase 2/3 trial with 2 week run-in followed by 26 week treatment while study M2-107 was a phase 3 trial with 4 week run-in and 24 week treatment. Patients were randomized 1:1:1 in study FK1-101 (516) and 2:2:1 in study M2-107 (1411) to receive either roflumilast 250 or 500 mcg or placebo once daily. It is notable that the 500 mcg once daily dose of roflumilast is regarded as the maximally tolerated dose. Concomitant uses of systemic or inhaled corticosteroids and long acting beta agonists were not permitted. Stable daily dose of short-acting anticholinergics were permitted. Uses of other COPD medications were also restricted except rescue salbutamol, which was provided to all eligible subjects. Co-primary endpoints were pre-bronchodilator FEV1 and the SGRQ in trial FK1-101 and post-bronchodilator FEV1 and SGRQ in trial M2-107. Note that although SGRQ as a primary or key secondary endpoint was the hallmark of earlier COPD trials, it was not evaluated in trials designated as pivotal.

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

Table 2 Pre-bronchodilator FEV1 in studies with 250 and 500 mcg doses of roflumilast

Trial Number	Duration (Weeks)	Rof500 mcg	Rof250 mcg	Placebo	Difference (ml)		P-Value	
					Rof250-P	R500 - R250	R250-P	R500-R250
FK1-101	26	69 (167)	64 (173)	29 (169)	35	5	0.2398	0.8568
M2-107	24	49 (506)	24 (541)	-39(256)	64	24	<0.0006	0.1024

From individual clinical study reports

Regarding the other co-primary endpoint, SGRQ, in both studies there was no significant difference in SGRQ between either the 250 or 500 mcg roflumilast dose group and placebo or between each other. Based on the general lack of separation in efficacy parameters (co-primary endpoints FEV1 and SGRQ) between the 250 and 500 mcg doses, dose selection for the roflumilast program appears to have been arrived at by selection of the maximally tolerated dose.

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

Efficacy studies
The six Phase 3 studies designed to demonstrate safety and efficacy of roflumilast were multicenter, multi-national, randomized, double-blind, placebo controlled parallel group trials which included a 2-4 week run-in period followed by a double blind treatment period of 52 (M2-111, M2-112, M2-124, and M2-125,) or 24 weeks (M2-127 and M2-128). All studies compared a single dose level of roflumilast (500 mcg once daily) to placebo.

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

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

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

included patients with moderate as well as severe COPD (FEV1 of 40-70% predicted) and were not required to have a history of chronic bronchitis with sputum production bronchitis and/or COPD exacerbations

Study efficacy findings

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

In the four 52-week studies, approximately two thirds of patients completed the study while in the two 24-week studies about three quarters of patients completed the studies. Compared to placebo, roflumilast-treated patients had a higher percentage of dropouts in all six studies. The major factor in this difference was the greater number of patients in the roflumilast groups who discontinued due to adverse events, which was 3-9% higher than for the placebo group. Also of note is the large number of protocol violations across all studies accounting for about 20-30% of the overall study populations.

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

Each of the 4 one year studies had co-primary endpoints of lung function (pre-bronchodilator FEV1) and the rate of moderate or severe COPD exacerbations while studies M2-127 and M2-128 had the single primary endpoint of pre-bronchodilator FEV1. The definition of COPD exacerbation was based on the decision to treat a patient with systemic corticosteroids, usually prednisone, or hospitalize a patient, presumably for a worsening of their COPD symptoms. Following are the primary efficacy findings for the applicant-designated pivotal studies M2-124 and M2-125 as well as those for supportive studies. These include pre-bronchodilator FEV1, COPD exacerbations, and in early studies, quality of life as determined by the SGRQ.

Change in Pre-Bronchodilator FEV1
In the pivotal and supportive studies, patients treated with roflumilast had a statistically significant, albeit modest, increase pre-bronchodilator FEV1 compared to placebo. In these studies, the size of the effect ranged from 39 to 80 ml, with an average of approximately 50 mL. This increase in FEV1, although significant statistically, would generally not constitute a clinically meaningful benefit (about 3-5% increase in FEV1).

Table 3 Change (in mL) from baseline in pre-bronchodilator FEV1 to end of treatment (ITT populations)

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

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

Rate of COPD exacerbations

The year-long studies (M2-124, M2-125, M2-111, and M2-112) were specifically designed to assess the effect of roflumilast on the rate of COPD exacerbations. The definition of an exacerbation in Study M2-112 differed slightly from the other 3 studies as it included exacerbations requiring antibiotics treatment (moderate) and exacerbations leading to death were added post-protocol (severe). In these studies, roflumilast numerically reduced the annual rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate (studies M2-124 and M2-125) reaching statistical significance while reduction in exacerbation rates from studies M2-111, and M2-112, were not statistically significant. It is notable that studies M2-111 and M2-112 included a general population of patients with severe COPD while studies M2-124 and M2-125 studied a narrow, more restricted patient population of severe COPD patients who had to have a history of both chronic bronchitis with cough and sputum production and have recent exacerbations of COPD (see table below).

Table 4 Rates of moderate or severe exacerbations in the one year studies* (ITT Population)

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

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

To facilitate direct comparison of studies M2-111 and M2-112 with studies M2-124 and M2-125, the definitions of moderate and severe exacerbations for studies M2-111 and M2-112 were modified post-hoc by the sponsor to match those of M2-124 and M2-125. However, without these post hoc changes, the rate ratio comparing roflumilast and placebo was also not

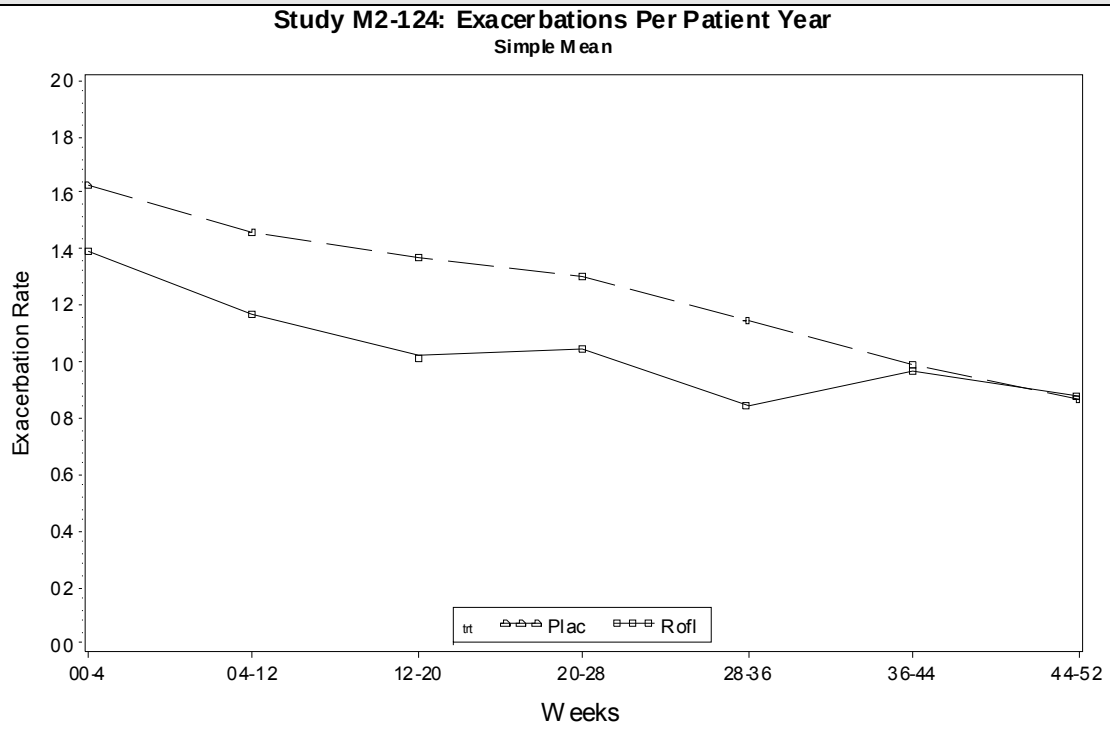
significant in either study. The p-value in Study M2-111 would be 0.218 rather than 0.129 and the p-value in Study M2-112 would be 0.4514 rather than 0.085.

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

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

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

Figure 1 Study M2-124 Exacerbations per patient year



Source: FDA statistical analyses

Change from baseline in St. George Respiratory Questionnaire (SGRQ)
The SGRQ is commonly used as a patient reported outcome measure to assess for improvements in disease symptoms and quality of life assessment in clinical trials conducted

in the COPD population. Results of the SGRQ are reported because it was used as a co-primary endpoint in several of the earlier dose-ranging and Phase 3 studies. Of note for the SGRQ is that a lower number is viewed as an improvement and that the defined difference between measurements that is the minimal clinically meaningful effect is -4.0 units.

Change from baseline in total SGRQ score failed to achieve either statistical or clinical significance in any of the studies.

Table 5 Change from Baseline in SGRQ total score

Trial Number	Duration	Rof500 mcg	Placebo	Difference	P-Value
FK1-101	26 weeks	-4.7	-4.5	-0.3	0.425
M2-107	24 weeks	-3.5	-1.8	-1.7	0.053
M2-111	52 weeks	-1.8	-0.3	-1.5	0.016
M2-112	52 weeks	-3.7	-3.2	-0.5	0.268

Source: individual clinical study reports

Secondary endpoints

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

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

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

Summary of efficacy

Patients treated with roflumilast 500 mcg once daily demonstrated a modest statistically significant but not likely clinically meaningful increase in pre-bronchodilator FEV1 compared to placebo. In six large Phase 3 studies (studies M2-124, M2-125, M2-111, M2-112, M2-127

and M2-128), the size of the effect ranged from 39 to 80 ml, with an average of approximately 50 mL or about 3-5% of FEV1.

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

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

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

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

8. Safety

Data base and patient demographics

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

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

In patients with COPD, safety assessments included adverse events (including COPD exacerbations), clinical laboratories (including hematology, blood chemistry, UA, occult blood and pregnancy), vital signs, physical examinations (including body weight), 12-lead

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

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

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

Deaths

There were a total of 177 deaths in the COPD safety population of approximately 12,000 COPD patients. There were no differences in overall mortality between study groups; 84 in the roflumilast 500 mcg group, 86 in the placebo group, and 7 in the roflumilast 250 mcg group. Cardiac disorders and COPD were the most common AEs reported in patients who died during treatment. The table below lists AEs reported in ≥ 0.2% for patients who died and AEs reported more frequently in roflumilast treated patients who died.

Table 6 Adverse Events Reported at a frequency of ≥ 0.2% in any treatment group for patients who died

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

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

Source: Table 32, pp75, ISS

Although there were no overall difference in mortality between the 500 mcg roflumilast groups and the placebo groups, more roflumilast treated patients, compared to placebo, died as

a result of suicide (3 versus 0). This finding, which is consistent with the overall higher incidence of AEs of anxiety and depression in patients treated with roflumilast compared to placebo, will be further discussed under the heading of "Psychiatric AEs" below.

Serious adverse events

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

Common adverse events

For the COPD safety pool, the most common adverse event for both treatment groups was COPD-related (exacerbations of the underline disease the drug intends to treat). The rate of exacerbations was slightly lower in the roflumilast treated patients compared to placebo treated patients (19.8 versus 21.3%). The most prominent non-COPD related adverse events noted in the controlled studies were weight loss, diarrhea, nausea, headache, insomnia and dizziness. These adverse events were 2 to 4 fold more frequent in the roflumilast treated patients compared to the placebo treated patients. The frequency of these adverse events ranged from 7-10% (weight loss, diarrhea) to 2-5% (headache, insomnia and dizziness) in roflumilast 500 mcg treated patients compared to 2-3% (weight loss, diarrhea) to 1% or less (headache, insomnia and dizziness) in placebo treated patients.

Vital Signs and Clinical Laboratory Assessments

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

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

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

More roflumilast treated patients had GI symptoms and tested positive on hemoccult screening than patients received placebo treatment. A total of 129 patients (of whom 70 received roflumilast 500 mcg, 7 received roflumilast 250 mcg, 52 received placebo) had positive hemoccult tests or other signs of GI bleeding (bloody stool or melena) during the clinical trial treatment periods. GI workups including colonoscopy were performed on 116 of the 129 patients for positive hemoccult tests, GI bleeds or other reasons. There were no findings that would be consistent with or indicative of ischemic colitis.

More patients in the roflumilast 500 mcg treated group had reduction in hemoglobin from within the normal range at the baseline to below the lower limit of the alert range (LLAR), defined as a hemoglobin level of 7.1 mmol/L or lower, compared to those in the placebo and roflumilast 250 mcg treated groups. In the COPD safety pool, 26 patients (0.5%) treated with roflumilast had normal levels of hemoglobin at baseline that shifted to below 7.1 mmol/L, the LLAR. In contrast, 5 patients (0.2%) who had normal hemoglobin levels at baseline shifted to below the LLAR at the end of the study.

There were no differences between the treatments in other hematology parameters including erythrocytes, leukocytes and platelets counts. No patients discontinued from the study or were reported as an AE secondary to a change in a hematology parameter. There were no clinically relevant changes in blood chemistry noted. Less than 1% patients had any abnormality in blood chemistry at the end of the study compared to baseline and more patients in the placebo group had abnormal blood chemistry (predominantly elevated liver enzymes or blood glucose).

ECG findings from the 14 trials included in the COPD safety pool were analyzed in a meta-analysis with the last visit ECG recordings from all trials compared to those at the baseline. There were no differences between treatment groups regarding the percentage of patients who had serious cardiac adverse events (roflumilast 500 mcg 1.8% versus placebo 2.1%), cardiac adverse events leading to death (roflumilast 500 mcg 0.4% versus placebo 0.5%), or cardiac adverse events leading to study discontinuation (roflumilast 500 mcg 0.9% versus placebo 1.0%). Further analysis for cardiac adverse events was performed by categorizing cardiac events of interest (cardiac arrhythmias, coronary artery disorders, heart failures and myocardial disorders). The rates for all cardiac events of interests, except arrhythmia, were marginally higher in the placebo group. The slightly higher incidence of cardiac arrhythmia in the roflumilast treated group was attributed to atrial fibrillation (the incidence of atrial fibrillation was 0.8% for roflumilast 500 mcg versus for 0.6% placebo).

A placebo controlled QT study (thorough QT study) was conducted in 80 healthy subjects (54 males, 26 females). A single 400 mcg dose of moxifloxacin was given as positive control 1 day prior to roflumilast administration followed by 7 or 14 day roflumilast treatment of 500 or 1000 mcg per day. QT interval was assessed 1 hour after roflumilast dosing. While no QTc change of 30 ms or greater was observed in any subject, review of the study by the FDA QT study review group concluded that the study lacked assay sensitivity and therefore was not conclusive. See Section 5, Clinical Pharmacology/Biopharmaceutics for a more complete discussion.

Twenty-four hour Holter ECG monitoring was performed in a subset of patients from trial M2-125 to study the arrhythmogenic potential of roflumilast when used in combination with long-acting beta agonists (LABA) in patients with COPD. The results showed no differences in heart rates or occurrence of arrhythmias between the roflumilast and the placebo treated groups.

Specific safety issues

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

Gastrointestinal AEs
Gastrointestinal adverse events such as diarrhea, nausea, known class effects of PDE4 inhibitors, were the most common adverse events reported from all roflumilast clinical trials and the leading cause for early study termination. The percentage of patients in the COPD safety pool who experienced at least one GI adverse event in the 500 mcg roflumilast treatment groups was 22% compared to 11% for placebo treated patients. Among those in the COPD safety pool who had GI AEs, approximately half experienced diarrhea (10.1%) and 20-25% experienced nausea (5%). Both the frequency and severity of GI AEs appeared to be dose dependent. In the COPD safety pool, which contained 4 independent trials that had a 250 mcg roflumilast treatment arm, the frequency of GI AEs in the 250 mcg groups were about half of what seen in the 500 mcg group but still greater than placebo (see table below).

Table 7 Gastrointestinal Toxicities in patients receiving 250 or 500 mcg of roflumilast

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

While nearly 90% of the GI side effects were mild or moderate in intensity, the remaining 10% were severe and met the criteria for an SAE. The more severe GI side effects were generally related to diarrhea. Though small in number, both occurred almost exclusively in roflumilast treatment groups. Among the 13 cases of diarrhea severe enough to require hospitalization or considered life-threatening (definition of an SAE) all but one case occurred in the roflumilast treated groups. There were two patients who died that had acute pancreatitis listed as an AE around the time of death who were receiving roflumilast 500 mcg at the time of occurrence, however, the overall numbers of patients with pancreatitis listed as an SAE was not different between roflumilast and placebo-treated patients (7 vs 6 patients, respectively).

Weight loss

Weight loss was a common adverse event reported in roflumilast clinical trials. Patients of all indications studied were affected, which suggests that roflumilast related weight loss is a drug specific effect. As weight was regularly assessed in the pivotal studies, M2-124 and M2-125, and because they were long (one year) in duration, the results from these studies the will be discussed here. The results from analyses of other studies were similar.

Overall, in the pooled data from studies M2-124 and 125, 62.4% patients in the roflumilast group and 37.7% patients in the placebo group had measurable weight loss (referred as measured weight loss below baseline). While only a fraction of the measured weight loss was reported as adverse event, the reported rates of weight loss as an adverse event were about 3 times higher in roflumilast treated patients, 10.3 and 2.8% for the roflumilast and placebo treated groups, respectively.

The mean weight change for patients in the roflumilast group was - 2.09 kg, which corresponded to a -2.72% reduction in body weight compared to baseline. For patients who received the placebo, the mean body weight increased slightly by +0.08 kg which equaled to a 0.25% increase in body weight from the baseline. Obese patients had most absolute (kg loss from the baseline) weight loss. The between treatment differences in absolute and relative weight loss were: 2.01 kg or 4.4% for underweight patients, 1.76 kg or 2.8% for normal weight patients, 2.09 kg for 2.6% for overweight patients and 3.11 kg or 3.2% for obese patients. It is notable that both patient groups that were already underweight or had the most severe COPD lost more weight as a % of body weight than less ill or normal weight patients (see table below).

Table 8 Weight Loss by BMI and COPD Severity (M2-124, M2-125)

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

* Δ Wt kg (%): change in mean body weight from baseline in kilograms (% change in body weight comparing to baseline)
COPD severity: moderate: FEV1 <80% and ≥50%; severe: FEV1<50% and ≥30%; very severe: FEV1 <30%.

Psychiatric AEs including Suicide

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

Table 9 Combined treatment emergent adverse events in the psychiatric SOC reported > once and more in roflumilast treatment groups (COPD safety pool)

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

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

In order to assess whether the incidence of psychiatric AEs was consistent across other disease clinical development programs, psychiatric system organ class AEs were reviewed for COPD studies conducted by a different sponsor in Japan and in asthma and "other" disease indications that roflumilast has been studied (diabetes, allergic rhinitis, rheumatoid arthritis, and osteoarthritis). Review of these data, again, show that the approximately 2-fold increase in psychiatric AEs in patients receiving 500 mcg of roflumilast once daily was persistent across studies in different patient populations and appears to be dose-related (see table 10 below). The types of AEs reported in these studies are consistent with those reported in the COPD population (insomnia, anxiety, depression).

Table 10 Total treatment emergent adverse events in the psychiatric SOC reported across roflumilast clinical programs

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

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

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

Of note is that the applicant's Pulmonary-Allergy Advisory Committee background package dated March 9, 2010, included a paragraph on page 88 of 105 that they had utilized the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to assess for additional potential suicide-related cases in COPD patients and that no other events related to suicidality were found. However, the method of collection of the suicidality data was never discussed with FDA nor has the data ever been submitted to the roflumilast NDA or reviewed by FDA.

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

In the overall roflumilast clinical development program, a total of 218 cancer/tumor events were reported in 208 patients. One hundred thirty one (60%) were in patients in the roflumilast group and 86 (40%) were in patients in the placebo group. The data below show the number and incidences of the most common malignancies/cancer in COPD patients who received the proposed dose of 500 mcg once daily. Note that there were significant increases in lung, prostate, and colo-rectal cancers in the roflumilast treated COPD patients compared to placebo. These differences could not be due to preferential drop-out in the placebo group since more patients receiving roflumilast withdrew from clinical studies prematurely than patients receiving placebo.

Table 11 Malignancy analysis in patients treated with roflumilast 500 mcg compared to placebo (FDA analysis)									
Type	**Roflumilast 500 mcg**				**Placebo**				**P-Value***
	Tumors	N	Prop	Inc**	Tumors	N	Prop	Inc**	
All	93	5752	0.0162	0.0292	73	5505	0.0133	0.0235	**0.058**
All No_Skin	80	5752	0.0139	0.0255	61	5505	0.0111	0.0206	**0.053**
Lung	29	5752	0.005	0.0096	17	5505	0.0031	0.0074	**0.047**
Prostate	13	5752	0.0023	0.0046	5	5505	0.0009	0.0013	**0.045**
Colo-rectal	9	5752	0.0016	0.0027	2	5505	0.0004	0.0004	**0.028**

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

Summary of Safety

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

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was convened on April 7, 2010, to discuss the efficacy and safety data provided to support the approval of roflumilast for the treatment of COPD in the United States. The main issues that the PADAC considered were the evidence for efficacy and safety as well as the overall risk-benefit assessment of roflumilast for the treatment of COPD. The committee also discussed the clinical relevance and generalizability of the magnitude of the effect seen on the efficacy variables and the adequacy of overall safety data base. The committee was asked to deliberate and vote (for questions 3, 4, 5) on following five issues:

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

2. Discuss the overall safety profile of roflumilast.

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

   The vote was Yes: 9, No: 6

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

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

   The vote was Yes: 9, No: 6

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

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

   The vote was Yes 5, No 10

When voting on questions 3 a4, while a majority of the members of the advisory committee felt that roflumilast demonstrated enough efficacy OR had an adequate safety profile for approval, the majority voted that roflumilast did not demonstrate adequate efficacy AND safety to support approval (i.e., the risk/benefit determination was not adequate to support approval). While the committee voted on the original indication submitted by the applicant for a more broad indication rather than the more limited indication of "reduction of COPD exacerbations" now proposed, it is notable that at least 6 members of the panel thought that roflumilast should be required to demonstrate that it gives added benefit when given to patients receiving COPD drugs that are the "standard of care for patients with severe COPD (ICS/LABA combinations and LAMAs) that are more effective and have demonstrated a tolerable safety profile.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

- Financial Disclosure: For the trials designated as pivotal by the applicant (M2-124 and M2-125) no significant equity interest as defined in 21 CFR 54.2(b) were held by the clinical investigators. There were a total of six investigators or subinvestigators involved in either study M2-125 or 125 that had not signed financial disclosure forms. Each of these investigators had left the study practice site prior to completion of the studies and were not able to be located. Based on the large size and number of sites in the trials (approximately 1500 patients and 300 sites for each trial, it is unlikely that any financial interests these investigators would influence the results of these studies.
- DSI audits information: At the request of the Division of Pulmonary and Allergy Products (DPAP), the Division of Scientific Investigations (DSI) audited (b) (4) DSI audits of clinical sites that participated in studies M2-124 and 125 (Beatrix Balint, MD/Site# 4545/Hungary, Neal Moser/Site# 7176/USA, Halina Batura-Gabryel, MD/Site# 6675/Poland, and Anthony Mesquita, MD/Site# 4793/India) have been completed with a preliminary inspection classification of no deviation from regulations/data acceptable (see DSI clinical inspection summary by Anthony Orencia, MD, dated April 30, 2010). The final reports from the field are pending.
- The Division of Medication Error Prevention and Analysis reviewed the proposed proprietary name Daxas from a safety and promotional perspective and judged it acceptable.
- The Division of Risk Management was originally consulted to review proposed patient labeling but since the label has recently changed significantly with the recent submission of a Medication Guide and REMS, comments will not be available until such time as labeling is addressed (see memo from Mary Dempsey, Risk Management Coordinator, dated April 26, 2010).
- The Division of Drug Marketing, Advertising, and Communications (DDMAC) will also defer comments on labeling until such a time as the final labeling will be addressed (see memo from Robyn Tyler, Regulatory Review Officer, DDMAC.

12. Labeling

During the course of the NDA review period, the applicant has submitted three different labels for review, one by Nycomed with the original NDA submission, a second which included a change in the product indication to a more limited "reduction in COPD exacerbations" claim, and a third late in the review period (April 14, 2010) in which the applicant included a Medication Guide as a component of a risk mitigation plan (REMS). Despite the recognition of the need for a Medication Guide to address important safety issues, the recently submitted label tends to overstate the efficacy and minimize the risks associated with treatment with roflumilast. The ultimate label, if the drug is approved, will need to include a Boxed Warning due to the higher rate of psychiatric adverse events, including anxiety, depression, and suicide associated with the use of roflumilast. In addition, the Warnings and Precautions section should include warnings for gastrointestinal side effects and address the increased numbers of patients treated with roflumilast who reported malignancies in the roflumilast clinical program. The Clinical Trials section also needs to be re-written to include efficacy data from individual clinical trials rather than presenting pooled efficacy data which makes the statistical determination of efficacy (p-value) appear more attractive. Substantial revisions are also needed for the Clinical Pharmacology section.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is a Complete Response. The risk benefit assessment for roflumilast does not support its approval as a monotherapy treatment either as a maintenance treatment for COPD as a disease entity or for the newly proposed, more focused indication of maintenance treatment for reduction of exacerbations of COPD. Issues of convenience such as roflumilast being an orally administered once daily treatment do not substantially alter the risk benefit determination.

- Risk Benefit Assessment

Regarding benefit, the clinical efficacy demonstrated for roflumilast was modest; especially so when assessed in the context that common standard of care COPD medications were not allowed to be taken concomitantly in the clinical studies. Studies demonstrated a consistent but modest and likely not clinically relevant improvement of approximately 50 mL in FEV1 (3-5% of FEV1). Additionally, two of four one-year clinical studies specifically designed to assess the effect of roflumilast on the rate of exacerbations of COPD in patients with severe disease demonstrated a statistically significant but again very modest reduction in the rate of moderate or severe exacerbations. The overall rate of moderate or severe exacerbations was reduced by 0.24 per patient year with a reduction of 0.21 for moderate (use of corticosteroids) and 0.03 for severe (hospitalization) exacerbations. Thus for an individual COPD patient treated with roflumilast, it would potentially take five years of therapy to get the benefit of not having to receive one 10-14 day course of corticosteroids, the definition of a moderate exacerbation used

in the clinical trials. Such a patient would not realize a benefit for a reduction in a severe exacerbation. In addition, roflumilast failed to show any additional benefits that are meaningful to patients with COPD. There was no survival benefit nor was their meaningful benefit for any other outcome important to COPD patients such as quality of life, dyspnea, use of rescue medications, COPD symptom scores, or the SGRQ. Finally, the generalizability of the positive COPD exacerbation studies could be questioned as they were conducted in a subset of patients with severe COPD; those who had symptoms consistent with chronic bronchitis (cough and sputum production) and a recent history of COPD exacerbations.

With respect to risk, serious safety issues exist for roflumilast. Patients treated with roflumilast demonstrate a 2-3 times increased occurrence of psychiatric adverse events such as anxiety, depression, and insomnia as well as other adverse events related to the nervous system such as tremor and headache. Five patients in the COPD program have attempted (2) or had completed suicides (3) compared to no subjects who were treated with placebo. These suicide findings are significant especially given the background of the high incidence of anxiety and depression adverse events in patients who were treated with roflumilast, the fact that the psychiatric adverse events are not limited to the roflumilast COPD program but extend to other patient populations who have received roflumilast (diabetes, arthritis, allergic rhinitis), and given the fact that other very large COPD drug trial data bases did not have imbalances in suicides or psychiatric adverse events. Roflumilast also causes significant and at times severe gastrointestinal adverse events (diarrhea, nausea) and weight loss in many, if not most, of the patients who have received it. The gastrointestinal effects are dose-related with greater frequency observed in patients receiving the proposed 500 mcg dose compared to a dose of 250 mcg, a dose not formally assessed for its affect on COPD exacerbations. As for weight loss, it is notable that the patient populations least likely to tolerate weight loss (those either already underweight or those with very severe COPD) lost the most weight as a percentage of their baseline body weight. While this could be viewed as more of a tolerability issue, it is not known if patients who withdrew from the study due to GI effects or weight loss fully recovered. In fact, the effects could be long-lived as data from animal studies demonstrated that GI toxicities of roflumilast had not fully returned to baseline after 4 weeks of recovery after roflumilast administration. Another potential safety issue is the presence in human plasma and urine of a roflumilast metabolite known to be carcinogenic in rodents. While unable to link the presence of the metabolite mechanistically to the development of malignancies in the roflumilast program, it is notable that there was a statistically significant increase in lung, prostate, and colo-rectal cancers in patients who received roflumilast compared to placebo.

These modest benefits and potential risks must be assessed in the context of the current available therapies for COPD. Both the combination of an ICS and LABA (Advair 250/50) and the LAMA, tiotropium, are currently approved both for the treatment of bronchospasm associated with COPD and for the reduction of exacerbations of COPD and have become standard of care therapies for patients with moderate to severe COPD[1]. However, in no study was the efficacy of roflumilast evaluated compared to or in addition to these standard therapies. While the drugs have never been studied head to head in the same clinical trial, the efficacy of these therapies appears to be better than for roflumilast and the safety profile for these drugs is better. Adverse events for tiotropium are tolerable and mostly related to the

physiologic effects of an anti-muscarinic agent (dry mouth, constipation, urinary retention, tachycardia) while FEV1 was increased by 130 mL within 30 minutes of a dose with peak effect of 240 mL improvement (compared to 50 mL for roflumilast). Tiotropium also significantly reduced COPD exacerbations by 14% despite the use of any other respiratory medication including ICS and systemic steroids, LABAs, theophylline, and short-acting beta agonists and anti muscarinic agents[2]. Advair Diskus, a combination of fluticasone propionate and salmeterol xinafoate has increased adverse events of pneumonia, oral candidiasis, and dysphonia compared to placebo while demonstrating a 165 mL increase in pre-dose FEV1 and a 34% and 40% reduction in exacerbations (defined as treatment with oral corticosteroids) in 2 studies designed to assess for reduction in exacerbations[3]. Given the greater clinically meaningful benefits and relatively safe adverse event profile for these therapies compared to roflumilast, the efficacy of roflumilast should be assessed in the context of use of ICS/LABA combination and LAMA therapies and, if additional benefit is observed with roflumilast therapy, it should be considered for approval as an add-on therapy to ICS/LABA combination and LAMA therapies in patients with moderate to severe COPD.

1. Recommendation for Postmarketing Risk Management Activities

If approved, this product will require a REMS with Medication Guide and Boxed Warning to highlight significant safety concerns such as increases in suicide, anxiety, depression, and other neuropsychiatric and gastrointestinal side effects associated with the use of roflumilast.

Additional post-marketing surveillance activities and/or studies should also be performed to monitor for specific adverse reactions associated with the use of roflumilast, including malignancy.

2. Recommendation for other Postmarketing Study Commitments

This product will not be approved during this review cycle. However, in order to assess the potential for increased systemic exposure to roflumilast with subsequent increased safety concerns, the applicant should conduct an in vitro evaluation of the potential of roflumilast as being a substrate for P-gp.

3. Recommended Comments to Applicant

1. You have not adequately demonstrated that the potential benefits of treatment with roflumilast in the reduction of COPD exacerbations in patients with severe COPD and chronic bronchitis at risk for COPD exacerbations outweigh the significant adverse effects associated with the drug. The patients with severe COPD studied in your clinical trials designed to assess for a reduction in COPD exacerbations were not allowed to use concomitant COPD medications that are the standard of care for patients with severe COPD[1] (FEV1$\leq$ 50% predicted) and which, in general, have a more favorable benefit to risk profile than roflumilast has demonstrated.

You will need to conduct a future clinical study(ies) in patients with severe COPD in which standard of care COPD medications (ICS/LABA combination and LAMA treatments) are included as treatments in order to demonstrate the potential benefits of roflumilast in the context of use of these therapies.

2. In the COPD safety population, 5 patients treated with roflumilast either successfully committed suicide (3) or made suicide attempts (2) compared to no patients who received placebo. In addition, the use of roflumilast is associated with an approximately two-fold higher number of psychiatric system associated adverse events such as anxiety, depression, and insomnia. We acknowledge that you have stated that you have utilized the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to assess for additional potential suicide-related cases in COPD patients, however the method of collection of the data was never discussed with FDA nor has the data been submitted to the roflumilast NDA or reviewed by FDA.

To further evaluate the risk of suicidality with roflumilast you should conduct a thorough evaluation of all your controlled clinical trial data. We anticipate a discussion with you in the future in order to determine the specific studies for inclusion in the assessment and the method of conduct of the assessment itself.

(b) (4)

4. The proposed dose of roflumilast of 500 mcg once daily is the maximal tolerated chronic dose of the drug. Because roflumilast has significant dose related side effects, the increased exposure to roflumilast, if it was a P-gp substrate, when taken concomitantly with other drugs that are P-gp inhibitors (e.g., ketoconazole) is a safety concern. Therefore you should conduct an in vitro evaluation of the potential of roflumilast as being a substrate for P-gp.

References

1. Global Initiative for Chronic Obstructive Lung Disease – Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Figure 7, page 11 of the Executive Summary (Updated 2009). Available at http://www.goldcopd.com/

2. Spiriva HandiHaler (tiotropium bromide inhalation powder) prescription labeling.

3. Advai Diskus (250 mcg fluticasone propionate, 50 mcg salmeterol xinafoate) prescription labeling.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	FOREST RESEARCH INSTITUTE	DAXAS(ROFLUMILAST 500 MCG TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY G DURMOWICZ
05/07/2010

CLINICAL REVIEW

Application Type	Original NDA
Application Number(s)	22-522
Priority or Standard	S
Submit Date(s)	July 15, 2009
Received Date(s)	July 15, 2009
PDUFA Goal Date	May 17, 2010
Division / Office	DPAP
Reviewer Name(s)	Xuemeng Han Sarro
Review Completion Date	March 18, 2010
Established Name	Roflumilast
(Proposed) Trade Name	Daxas®
Therapeutic Class	Phosphodiesterase type 4 (PDE4) inhibitors
Applicant	Nycomed (Original applicant) Forest Labs (Current owner)
Formulation(s)	Oral 500 mcg tablet
Dosing Regimen	500 mcg once daily (one tablet)
Indication(s)	Maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations COPD
Intended Population(s)	Patients with COPD

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action is **Complete Response**. The roflumilast clinical development program was substantial and consisted of 114 clinical trials, 18 of which were late phase trials for the proposed COPD indication. The COPD program spans approximately 15 years and underwent series of directional changes. The main body of evidence that supports the efficacy and safety claims for the proposed indication came from 8 COPD trials in the later development phase which are collectively referred as the core COPD program. The core COPD program encompassed 2 six months dose ranging trials, 4 year-long efficacy and safety trials (2 of which were designated as the pivotal trials by the applicant) and 2 additional six months supportive efficacy and safety trials.

The submitted data in the COPD program are not adequate to support the proposed indication of maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. From a clinical perspective, the major deficiencies that preclude approval are as follows:

- There was insufficient evidence to support the efficacy of roflumilast at the proposed 500 mcg daily dose for the proposed indication: maintenance treatment of COPD.

- There are significant safety concerns regarding roflumilast use at the proposed 500 mcg daily dose.

1.2 Risk Benefit Assessment

1.2.1 Potential Benefit

The efficacy of roflumilast at 500 mcg daily dose has not been adequately established for the proposed indication: maintenance treatment of COPD. To treat the disease entity, COPD, as a whole requires demonstration of clinically meaningful improvements in more than one aspect of the disease. Co-primary endpoints were designated for most Phase 3 studies. Although The applicant was able to consistently demonstrate statistically significant improvements in lung function measured by peak (post bronchodilator) or through (pre bronchodilator) FEV1, the improvements were approximately 50(40-80) mL or 2-3% at best, which is less than half of the improvements seen with other COPD medications on the market such as Advair® (165-281mL or 17-27%) or Spiriva®(87-103 mL or 8-9%). Therefore, the clinical significance of FEV1 improvement in roflumilast is questionable.

Change in total SGRQ (St. George Respiratory Questionnaire) score was used in early phase 3 trials as a quality of life measure to demonstrate superiority of roflumilast in managing a

different disease aspect of COPD. It was investigated as co-primary or key secondary endpoint in 4 of 8 core COPD trials and failed to demonstrate any clinically or statistically significant benefit.

Exacerbations are a significant source of mortality and mobility in COPD. Any treatment that could reduce hospitalizations and mortality from COPD exacerbations would offer clinically meaningful benefit. In the 4 more informative year long trials designed to assess for exacerbations, the rates of moderate or severe COPD exacerbations were 15-18% lower in the roflumilast treated groups compared to placebo. However, the differences were not statistically significant in 2 of the 4 trials. While statistic significance was achieved in the pivotal trials, the clinical significance of such a reduction is debatable because the reduction in overall rate of moderate or severe exacerbation was driven by reduction in moderate exacerbations which was defined as use of systemic corticosteroids. Reduction in severe exacerbation defined as requiring hospitalization or leading to death was not significant. Furthermore, there were no statistically significant or clinically meaningful differences in all cause mortality, time to mortality, rescue medication use, symptom score (BDI/TDI, SOBQ) or levels of inflammatory marker (CRP) that would help support the idea that reduction in moderate or severe COPD exacerbation observed in the pivotal trials was clinically significant.

1.2.2 Potential Risk and Safety Concerns

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

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This section is not applicable in the current review cycle as the recommended regulatory action is Complete Response.

1.4 Recommendations for Postmarket Requirements and Commitments

This section is not applicable as the recommended regulatory action is Complete Response.

2 Introduction and Regulatory Background

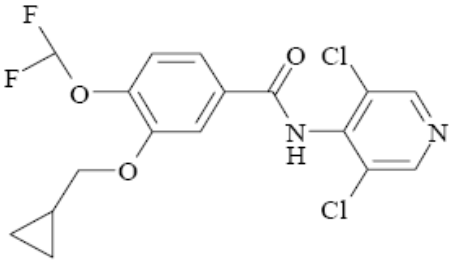
2.1 Product Information

Roflumilast is a selective phosphodiesterase type-4 (PDE4) inhibitor and a new molecular entity. Roflumilast N-oxide is an active metabolite of roflumilast which also has PDE4 inhibitory activity. Daxas® is the proposed trade name for roflumilast. It is supplied as a yellow, film-coated 500 mcg oral tablet. The proposed dosing regimen is 500 mcg once daily.

It's purported to act as an anti-inflammatory agent in patients with COPD. The proposed mechanism of action is to increase cAMP dependent anti inflammatory response through PDE4 inhibition.

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

Trade Name:	Daxas®
US Adopted Name:	Roflumilast
International Non-proprietary Name:	Roflumilast
Molecular Formula:	$C_{17}H_{14}Cl_2F_2N_2O_3$
Molecular Weight:	403.22
Manufacturer:	Nycomed GmbH, Germany



Sponsors:	Current:	Forest Research Laboratories (Since December 4, 2009)
	Previous:	Nycomed Byk-Gulden/Altana

Pharmacia & Upjohn
Pfizer

2.2 Currently Available Treatments for Proposed Indications

Bronchodilators and inhaled corticosteroids (ICS) in combination with a long-acting beta agonist (LABA) are main stays of therapy currently available for the treatment of COPD. Bronchodilators are used to treat the reversible bronchoconstriction associated with COPD. Many types of bronchodilators are available in the US for COPD, either as a single agent or in combination with ICS or a second bronchodilator of different mechanism. Examples of bronchodilators available include the short and the long-acting beta agonists such as albuterol, salmeterol, formoterol and the anti-muscarinic agents such as ipratropium and tiotropium. Advair® 250/50, a salmeterol (50 mcg) and fluticasone propionate (250 mcg) combination product contains both a long-acting beta agonist (LABA) and inhaled corticosteroid and is approved to treat both reversible bronchoconstriction and to reduce exacerbations of COPD in patients with a history of exacerbations.

Theophylline, a non-specific member of the phosphodiesterase inhibitor class is available in immediate and sustained released formulations and has been used for many years for the treatment of both COPD and asthma.

Table 1 Examples of available drugs for the treatment of COPD

Drug Class	Active agent	Brand Name	Dosage forms
Long acting beta agonist	Salmeterol Formoterol	Serevent ® Foradil Aerolizer®	Inhaled aerosol and DPI
Short acting beta agonist	Albuterol	Ventolin® Proventil® Many other generics	inhaled aerosol
Long acting anticholinergics	Tiotropium	Spiriva®	inhaled aerosol
Short acting anticholinergics	Ipratropium	Atrovent®	inhaled aerosol
Combinations	Albuterol & ipratropium Salmeterol & fluticasone Budesonide/formoterol	COMBIVENT® Advair® Symbicort®	Inhaled aerosol and DPI
Other	Theophylline	Many generics	tablet/extended release capsule/oral elixir/oral syrup/injectable

2.3 Availability of Proposed Active Ingredient in the United States

Roflumilast is a new molecular entity and is not commercially available in US or anywhere in the world.

2.4 Important Safety Issues with Consideration to Related Drugs

Theophylline is a non selective phosphodiesterase inhibitor with significant toxicities in the gastrointestinal and neurologic systems (nausea, vomiting, headache, insomnia). It can produce cardiac arrhythmias and seizure activity at high levels of exposure. It has significant drug-drug interaction with commonly prescribed drugs such as H-2 blockers, macrolide antibiotics and benzodiazepines. Therefore, its use generally requires monitoring of blood levels.

In clinical studies, specific PDE4 inhibitors such as roflumilast and cilomilast have also demonstrated prominent dose-dependent toxicities related to the gastrointestinal and neurologic systems. Additionally, prevalent (>60% patients on treatment) and sometime severe weight loss (>10%) were seen in roflumilast trials.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The regulatory history concerning the development of roflumilast was extensive. There are more than 600 documented communications between the division and various sponsors regarding the roflumilast program. The sponsorship for the proposed drug product changed a handful of times, most recently on December 4, 2009, 5 months into the current NDA review cycle.

2.5.1 Pre submission regulatory activity

Both the asthma and the COPD program were developed under a single IND (IND-57883). The original sponsor Altana submitted the initial pre-IND package in October, 2000 for both its asthma and COPD programs. The following is a list of the most clinically pertinent regulatory events and issues regarding the COPD program.

Key Regulatory Events for COPD Program

- Original IND for asthma submitted on 2/16/1999
- Pre IND meeting for COPD program: October 5, 2000
- EOP2 meetings (12/6/2001 by Byk-Gulden/Altana and 3/4/2003, by Pharmacia & Upjohn on behalf of Altana Pharma AG)

- Sponsor submitted Type C meeting request on 11/30/2006 and the request was denied (12/12/2006) by the division considering the previous interactions the division had with the sponsor on its COPD program. The division, however, did agree to respond to sponsor's questions.

- Pre NDA meeting (4/16/2008) discussed preparations for NDA submission.

Key Regulatory Issues and FDA Inputs:

- FEV1 as primary endpoint
    - In response to the proposal of FEV1 as a primary endpoint, the Division indicated that although the change in FEV1 was a reasonable endpoint, because the change seen with roflumilast was very small, supportive evidence would be needed with the secondary endpoints. (March 4, 2003 discussion on study PADEACO-9287-001 with Altana/Pharmacia & Upjohn)

- Pre versus post bronchodilator FEV1
    - DPAP suggested that trough FEV1 (pre bronchodilator FEV1) is a better measurements of pulmonary function for non bronchodilators than post bronchodilator FEV1, which does not allow demonstration of end of dosing interval efficacy needed for once daily regimen. (Clinical review of protocol PDEACO-9287-001 by Dr. Carol Bosken, 2/3/05, comments faxed to the applicant on 2/28/05)

- Clinical relevant outcome measures

    - To use SGRQ to support efficacy claim, a clinically meaningful (at least 4 units) improvement in the mean score of the treated subjects, comparing to placebo, is needed. (Clinical review of protocol PDEACO-9287-001 by Dr. Carol Bosken, 2/3/05, comments faxed to the applicant on 2/28/05)

- Definition of COPD exacerbation and rate of exacerbation as primary endpoint

    - COPD exacerbations is a clinical diagnosis and the decision to initiate treatment (with corticosteroids) or hospitalization is investigator-driven leaving room for variations in the definition of what constitutes an exacerbation and the severity of the exacerbations. "As much as it is feasible you are encouraged to standardize your definitions for a COPD exacerbation as well as the criteria that would prompt the Investigator to initiate corticosteroid therapy or hospitalize the patient." (Division's response to sponsor question submitted on February 27, 2007 after the sponsor's type C meeting request to discuss trial M2-124 and M2-125 on November 30, 2006 were denied)

- In pre NDA meeting with Nycomed on April 16, 2008, the Division acknowledged the Nycomed's definition of exacerbations based solely on the requirement of oral or parental glucocorticoids and/or hospitalization and stated that the acceptability of the definition of exacerbation would be a review issue. The Division explained that there is no consensus definition of a "COPD exacerbation". It acknowledged that the start of the roflumilast program almost 10 years previously pre-dates much of the more recent discussion regarding how to define COPD exacerbations. The Division suggested that it would be in Nycomed's best interest to address these issues prospectively, as they would be likely to come up during an advisory committee discussion regarding their application.

Statistical analysis plan (SAP) (DPAP comments):

The division made multiple SAP related comments through out the development phase. Majority of the comments dealt with issues regarding predetermined data analysis roles, treatment group assignment and pooling of results from different studies. The followings are some of the representative excerpts:

- To preserve the baseline balance between the comparative treatments arms, inclusion of subjects in efficacy analysis should based on randomization, not the actual treatment group received. (Statistical review comments faxed to the applicant on 2/28/05)

- Statistical tests for primary and key secondary end points should follow the standard two sided, 5% test. Testing each efficacy end points at the proposed one-sided 2% level is not appropriate as the direction of the outcome can not be predicted. (Protocol comments for study BY217/M2-112, 2/24/05)

- Predetermined statistical significance criterion and decision role should be use for pooled and subset analysis if the outcome of the analysis is to be included in the labeling. (Protocol comments for study BY217/M2-112, 2/24/05)

- To control the over all rate of type I error, key secondary end points will be tested only if there is a statistically significant outcome for the primary end point. (statistical review, 2/28/05)

- The Division does not generally accept pooled results as substantial evidence of efficacy. (Communication regarding the statistical analyses of the proposed pivotal studies, M2-111 and M2-112, March 13, 2006 with Altana.)

2.5.2 Post submission regulatory activity

The original NDA was submitted on July 15, 2009 by Nycomed for "for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations". On December 4, 2010, the Division was notified of the transfer of ownership of IND# 57883 and NDA 22-522 from Nycomed to Forest Research Institute.

On February 1, 2010, the Division received newly proposed labeling for roflumilast from Forest Research Institute in which the product indication was changed to "for maintenance treatment to reduce exacerbations of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations." Additionally, neuropsychiatric adverse events were added to the Warnings and Precautions section of the label, and other significant changes in were also made to other sections including clinical pharmacology.

Because roflumilast is a new molecular entity, it will be discussed at Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting scheduled for April 7, 2010. During a teleconference held on February 26, 2010, the Applicant (Forest labs) was informed that late changes to proposed indication is not acceptable and that the discussion at the AC will be based on the original application from Nycomed, which seeks an approval for roflumilast 500 mcg to be administered once daily for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations.

2.6 Other Relevant Background Information

In additional to the development program outlined in this review, roflumilast also has been under development by a different sponsor in Japan. To date, the drug is not approved for marketing in any country in the world.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

Nycomed, the original applicant for this NDA submitted financial disclosure information (in accordance with 21 CRF Part 54) for the following covered trials in FDA Disclosure Forms 3455: M2-124, M2-125, M2-127, M2-128, FK1-101, FK1-103, M2-107, M2-110, M2-111, M2-112 and M2-121.

For investigators who reported financial interests or arrangements with the applicant (Nycomed), corresponding background information was provided. Trial M2-110 was conducted by the development partner Pfizer. A list of investigators who disclosed financial interests with Pfizer were also provided.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Roflumilast is a small, synthetic, non-peptide molecule and is a new molecular entity. The proposed commercial drug product for roflumilast is a 500 mcg immediate release film coated tablet. The active pharmaceutical ingredient is a white to off-white powder and is incorporated with the inactive ingredients into the tablet. The product is proposed to be packaged in bottles as well as in blister trays. Refer to section 2.1 Product Information for further details.

From CMC's perspective, the application was considered to be approvable provided that the applicant adequately addresses the following issues including:

- inconsistency regarding to the designation of the starting material for the synthesis

- the system suitability requirements for the drug substance impurity testing
- inconsistency regarding the dissolution acceptance criteria that will be applied at release and during stability testing

Refer to CMC review by Dr. Craig Bertha (12/10/09) for addition details.

4.2 Clinical Microbiology

No significant safety issues related to clinical microbiology have been identified.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical toxicities of roflumilast and/or its metabolites included carcinogenicity, reproductive toxicity, and cardiovascular and GI toxicities. GI toxicities included inflammation and erosion of the mucosa. Cardiac toxicities included cardiac lesions, peri-arteritis, and myocarditis. Roflumilast showed adverse fertility effects in male rats but these effects where not replicated in clinical trials. Structural damage to male reproductive organs was observed in rats, mice and dogs, but not in hamsters and monkeys. Reproductive effects of roflumilast included stillbirths and pup deaths in mice attributed to a tocolytic effect of the drug. Roflumilast metabolite (ADCP N-oxide) induced nasal tumor formation in hamsters. This metabolite has been observed in human plasma and urine; therefore, the metabolite related nasal tumors observed in hamsters may be relevant to humans. Refer to section 7.2.3 of this review and Dr. Luqi Pei's toxicology review for further detail.

4.4 Clinical Pharmacology

This application included over 70 Phase I clinical pharmacology studies. While brief summaries on mechanism of action, PK and PD will be provided below, detailed information can be found in Dr. Ping Ji's clinical pharmacology review.

4.4.1 Mechanism of Action

Roflumilast is a specific inhibitor of phosphodiesterase type 4 (PDE4). The proposed mechanism of action is to increase c-AMP dependent anti inflammatory response through PDE4 inhibition.

4.4.2 Pharmacodynamics

Roflumilast N-oxide is the major roflumilast metabolite observed in human plasma. *In vitro* metabolism studies using human liver microsomes and *in vivo* drug-drug interaction studies indicated that roflumilast is mainly metabolized by CYP3A4 and CYP1A2 and did not inhibit or induce the activity of the major CYP P450 enzymes. Older age (>65 years), female gender and hepatic impairment increase exposure to roflumilast and roflumilast N-oxide. In contrast, renal impairment reduces exposure. No dose adjustment is required for age, gender and renal

impairment. However, roflumilast will be contraindicated in patients with severe hepatic impairment (Child-Pugh C).

4.4.3 Pharmacokinetics

In healthy subjects, the absolute bioavailability of roflumilast following a 500 mcg oral dose is 79%. The median time to reach maximum plasma concentrations of roflumilast (Tmax) is approximately one hour, while Tmax of roflumilast N-oxide is about eight hours in the fasted state. Food intake delays Tmax of roflumilast by one hour and reduces Cmax by approximately 40%, but the Cmax and Tmax of roflumilast N-oxide are not affected. The plasma AUC of roflumilast N-oxide is about 10-fold greater than the plasma AUC of roflumilast. Following an oral dose of roflumilast, the median plasma effective half-lives of roflumilast and roflumilast N-oxide were approximately 17 and 30 hours, respectively. Steady state plasma concentrations were reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing of roflumilast. Based on a population PK analysis, COPD patients have a 65% higher AUC for roflumilast and about 8% higher AUC for roflumilast N-oxide compared to healthy subjects.

5 Sources of Clinical Data

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

The overall roflumilast clinical development program is extensive. This submission contains results from 18 phase II and III COPD trials and information from 29 asthma trials and more than 60 clinical pharmacology studies.

5.1 Tables of Studies/Clinical Trials

Among the 18 phase II and III COPD clinical trials submitted with the application, this review focus on 6 phase III efficacy and safety trials and 2 phase II/III dose ranging trials. Table 2 displays the characteristics of the 6 phase III trails reviewed. Two of the trials are considered as pivotal trials and the other 4 trials are supportive.

Table 2 Six core Phase III Clinical Trial Characteristics

Trail Number, Size, Dates & Participating Countries/Regions	Study Population (COPD related Eligibility & Randomization criteria)	Study Regimens & Permitted Concomitant COPD Treatments	Primary & Key Secondary Endpoints (listed in hierarchy order)

M2-124 (AURA, pivotal) N=1524 22/07/2006 – 07/07/2008 US, Europe, Australia & New Zealand **M2-125** (HERMES, pivotal) N=1571 03/02/2006 – 04/29/2008 US, Canada, Europe, India & South Africa	Eligibility: - Severe COPD (ARS/ERS) with chronic bronchitis - post BD FEV1 ≤ 50%, FEV1/FVC ≤ 70% predicted - ≥ 1 documented COPD exacerbation needed systemic CS or hospitalization < 1 yr before screening - smoking history ≥ 20 pack year RM Criteria: - No moderate or severe exacerbations during run-in - Total cough & sputum score ≥14 the week before RM	Regimen: - 500 mcg roflumilast QD for 52 weeks or - Placebo QD for 52 weeks Permitted during treatment: - LABA or SAMA plus SABA RM Stratification: LABA & smoking	Co primary: - Δ mean pre BD FEV1 - Mean rate of moderate or severe exacerbations per patient per year Key secondary: - Δ mean post BD FEV1 - Time to all cause motility - Δ mean BDI/TDI - Δ mean nature log CRP
M2-127 N=935 04/28/2006 – 07/03/2007 Non US. Canada, Europe & South Africa	Eligibility: - Moderate to severe COPD (ARS/ERS) per criteria - post BD 40% ≤ FEV1 ≤ 70%, FEV1/FVC ≤ 70% predicted - smoking history ≥ 10 pack year RM Criteria: - No moderate or severe exacerbations during run-in	Regimen: - 500 mcg roflumilast QD plus salmeterol (Serevent Diskus 50 mcg) BID for 24 weeks or - Placebo QD plus salmeterol (Serevent Diskus 50 mcg) BID for 24weeks Permitted during treatment: - SABA RM Stratification: smoking	Primary: - Δ mean pre BD FEV1 Key secondary: - Mean rate of all COPD exacerbations (mild, moderate & severe) per patient per year - Δ mean TDI focal score - Δ mean SGRQ
M2-128 N=744 01/05/2007 – 01/31/2008 Non US Europe only	Same as M2-127 plus: Eligibility: - h/o chronic productive cough for 3 month in each of 2 yrs prior to screening, excluding cause other than COPD RM criteria: - rescue SABA use ≥ 28 puffs 1 week before randomization	Regimen: - 500 mcg roflumilast QD plus tiotropium (Spiriva Handihaler, 18 mcg) BID for 24 weeks or - Placebo QD plus tiotropium (Spiriva Handihaler, 18 mcg) BID for 24 weeks Permitted during treatment: - SABA RM Stratification: smoking	Primary: - same as in M2-127 Key secondary: - Δ mean post BD FEV1 - Δ mean rate of moderate or severe exacerbations per patient per year
M2-111 (OPUS) N=1176 12/09/2003-12/02/2005 US, Canada, Europe & South Africa **M2-112** (RATIO) N=1514	Eligibility: - Severe COPD (GOLD) - post BD FEV1 ≤ 50%, FEV1/FVC ≤ 70% predicted - smoking history ≥ 10 pack year - no COPD exacerbations within 4 weeks prior to screening RM Criteria: - No moderate or severe exacerbations during run-in	Regimen: - 500 mcg roflumilast QD for 52 weeks or - Placebo QD for 52 weeks Permitted during treatment: - ICS (≤2000 mcg, ex valve beclomethasone dipropionate or equivalent) plus SABA RM Stratification: smoking	Co primary: - Δ mean pre BD FEV1 - Number of moderate or severe exacerbations per patient per year Key secondary: - Δ mean post BD FEV1 - Number of moderate or severe exacerbations per patient per year in different subgroups (FEV1< 30%, with chronic bronchitis +/- emphysema, cough score ≥ 1 or ≥ 2, h/o moderate or severe COPD exacerbations Co primary: - Rate of moderate or severe exacerbations per patient per year

01/24/2003-10/27/2004 Non US Europe, Canada, Australia & South Africa			- Δ mean post BD FEV1 Key secondary: - Δ SGRQ total score

Δ mean: mean change from baseline (last measurement before randomization) to either each visits during the treatment period (FEV1, TDI and other nominal variables), or to last scheduled visit (nature log transformed CRP).

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

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

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

5.2 Review Strategy

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

lower 250 mcg dose of roflumilast or were designed to evaluate the impact of concomitant treatment with LABA or LAMA on lung function.

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

5.3 Discussion of Individual Studies/Clinical Trials

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

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

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

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

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

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

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

5.3.1 Studies M2-124 and M2-125

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

* N: number randomized

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

Study regimen and restrictions on concomitant COPD medications

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

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

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

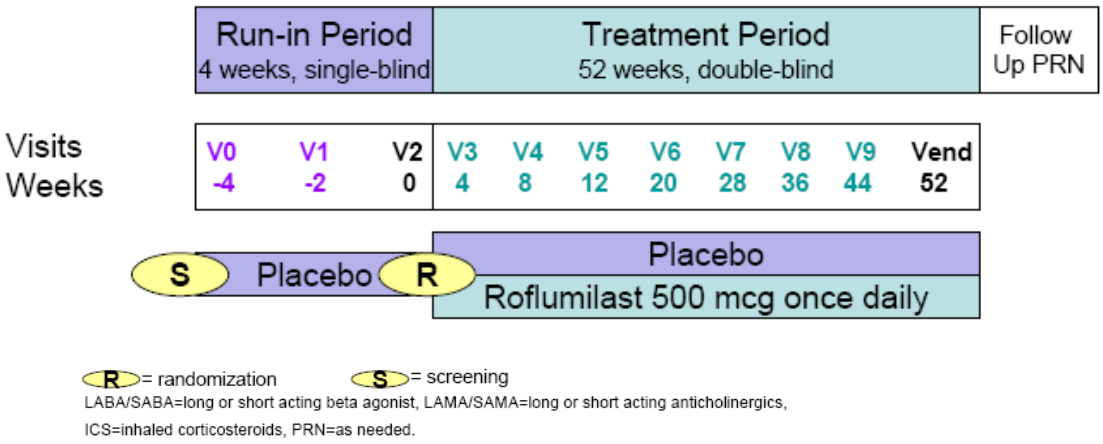


Table 3 Allowed and Disallowed Medications in Trials M2-124 and M2-125

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

Summary:

- PRN SABA allowed for all groups throughout.
- LABA allowed throughout for long term (≥ 12 months) baseline LABA or fixed combination LABA+ICS users.
- Fixed dose SAMA allowed throughout for long term (≥ 12 months) baseline LAMA users; baseline LABA,

LABA+ICS, LAMA users of less than 12 month.; or non-users of baseline long acting bronchodilators.
- ICS disallowed during treatment.
- LAMA disallowed throughout the study.

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

Eligibilities

These pivotal trials had the most selective patient population in the phase 3 roflumilast development program. Although the proposed indication is for COPD associated chronic bronchitis and did not specify disease severity, these trials required patients to have severe to very severe disease with characteristics of chronic bronchitis and recent history of COPD exacerbation to be eligible for enrollment. These trials further restrict the patient population by excluding those enrolled patients who had COPD exacerbation during the run in period or had a cough and sputum score lower than 14.

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

To receive the double blind treatment, eligible patients must enter a 4 week single blind run in period and met the randomization criteria, which included:
- no COPD exacerbation between V0 (baseline) and V2 (randomization)
- total cough and sputum score $\geq$14 during the week before V2
- negative hemoccult test at V0
- medication compliance between 80% and 125% between V0 and V2

The main pertinent criteria for exclusion were**:**
- unstable patients
- not meet randomization criteria
- known history of alpha-1 antitrypsin deficiency or carrying diagnosis of other pulmonary diseases

- recent history (within 12 months of V0) of recurrent GI bleeding secondary to chronic GI disorders
- presence of other concurrent disease(s) or condition(s) that might interfere with study procedure, evaluation or jeopardize patient safety
- unable to give consent or compliant with protocol requirements

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

Study scheme and conduct

The scheme and conduct of both trials were identical and similar to those of other phase 3 trials reviewed here. Both consisted of 3 study periods: baseline or run-in, treatment and follow up. (Figure 1) The 4 week run-in period extends from the initial screening visit (V0) to randomization at visit 2 (V2), during which all eligible subjects received single blind (to patients only) placebo treatment and adjustments of their pre trial COPD medications – withdraw of disallowed medications, mainly corticosteroids and long acting anticholinergics.

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

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

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

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

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

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

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

Patients experienced exacerbations during the treatment period were allowed to remain in the study. However, if a patient experienced a moderate or severe exacerbation during the run-in period, the patient could not be randomized but was allowed to reenroll, only once, in the trial after the exacerbation resolved. Patients who had exacerbation twice during the run-in period were excluded from participating in the trials.

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

Demographics

Both trials were multi national studies. While near 50% study sites were domestic, only 20% population came from US. The number of subjects randomized in trials M2-124 and M2-125 were 1525 and 1571, respectively. Majority of the subjects in both trials were white (>96% in M2-124 and 72 % in M2-125) and significantly more males (70-80%) than females (20-30%). The Asians in trial M2-125 were almost exclusively Indians. There were less than 2% each of blacks and other ethnic minorities in both trials. All demographic characteristics were generally matched between treatment groups within each trial and some were also similar across both trials. There were more current smokers in trial M2-124 than M2-125. Slightly more patients with very severe disease (FEV1< 30% predicted) were in trial M2-125. (Table 4)

Table 4 Demographics and Baseline Characteristics in Studies M2-124 and M2-125

Baseline Characteristics	M2-124 (ITT)		M2-125 (ITT)	
	Rof500 mcg (N=765)	Placebo (N=758)	Rof500 mcg (N=772)	Placebo (N=796)
Age				
median (range) in year	63 (40-89)	63 (40-92)	64 (40-90)	64 (40-90)
Gender				
Male, n (%)	540 (70.6)	538 (71)	610 (79)	648 (81.4)
Female, n (%)	225 (29.4)	220 (29)	162 (21)	148 (18.6)
Race (% randomized)				
White	737 (96.3)	732 (96.6)	559 (72.4)	568 (71.4)
Black	11 (1.4)	15 (2.0)	8 (1)	14 (1.8)
Asian	1 (0.1)	1 (0.1)	174 (22.5)	179 (22.5)
American Indian	0	1 (0.1)	2 (0.3)	1 (0.1)
Other	16 (2.1)	9 (1.2)	29 (3.8)	34 (4.3)
Weight				
mean+/- SD (kg)	76 +/- 17	75 +/- 18	71 +/- 20	71 +/- 19
BMI				
mean+/- SD (kg/m^2)	26.36 +/- 5.5	26.00 +/- 5.5	25.25 +/- 6.2	25.35 +/- 5.9
Smoking Status				
% Current/former	47.7/52.3	47.6/52.4	35/65	35.4/64.6
mean Cigarette pack year +/- SD	48 +/- 24	46 +/- 23	49 +/- 29	64.6
COPD Characteristics*				
Mild, n (%)	0	3 (0.4)	1 (0.1)	2 (0.3)
Moderate, n (%)	80 (10.5)	61 (8)	50 (6.5)	59 (7.4)
Severe, n (%)	486 (63.5)	510 (67.3)	457 (59.2)	479 (60.2)
Very severe, n (%)	199 (26)	184 (24.3)	264 (34.2)	256 (32.2)
PreFEV1				
mean+/- SD (L)	1.07+/-0.4	1.06+/-0.4	0.95+/-0.3	0.98+/-0.4
(mean % predicted+/-SD)	(34.6+/-10.2)	(34.6+/-10.3)	(31.4+/-10.1)	(32.2+/-10.8)
FEV1 reversibility				
mean+/- SD (mL)	88.9+/-150.7	89.9+/-141.7	95.9+/-134.1	94.8+/-131.7

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

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

These trials permitted concomitant LABA and SAMA use. Tables 5 and 6 displayed COPD treatments used by at least 10% of the patients in either treatment groups in at lease one study time period in trials M2-124 and M2-125, respectively. In both trials, nearly all patients (96-100%) used at least one concomitant COPD treatment through out the entire trial period. During the treatment period of both trials, nearly half (42-45%) of the patients used LABA, a third or more (31.4-40.7%) of the patients used SAMA and half or more (49.3-57%) of the patients used corticosteroids. Uses of prohibited concomitant COPD drugs or treatment that could affect outcome, such as supplemental oxygen, were common during the treatment period of both trials. The prevalence of using prohibited COPD treatments were: 9.1-24.2% for ICS, 4.9-6.3% for

LAMA, 4.6-7.7% for LABA/SAMA combinations, 10.8-14.2% for LABA/ICS combinations and 5.1-8.7% for Xanthenes. The prevalence of supplemental oxygen use during treatment period was 10%-13.9%.

Table 5 Concomitant COPD drugs used in trial M2-124

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

Source: Table 8, M2-124 CSR, pp113

Table 6 Concomitant COPD drugs used in trial M2-125

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

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

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

Dispositions

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

Table 7 Patient Dispositions for studies M2-124 and M2-125

Disposition, N (% recruited)	M2-124		M2-125	
Recruited	2238		2277	
Randomized (% recruited)	1525 (68.2)		1571 (69)	
Not randomized (% recruited)	713 (31.8)		706 (31)	
Disposition, N (% randomized)	Rof500 mcg	Placebo	Rof500 mcg	Placebo
Randomized	766	759	773	798

Completed	502 (65.5)	525 (69.2)	527 (68.2)	550 (68.9)
Premature Discontinued	264 (34.5)	234 (30.8)	246 (31.8)	248 (31.1)
Adverse events	119 (15.5)	78 (10.3)	101 (13.1)	83 (10.4)
Withdrew consent	120 (15.7)	100 (13.2)	108 (14)	107 (13.4)
COPD exacerbation	43 (5.6)	69 (9.1)	49 (6.3)	66 (8.3)
Lost to follow up	17 (2.2)	16 (2.1)	22 (2.8)	24 (3)
Met discontinuation criteria	7 (0.9)	4 (0.5)	9 (1.2)	4 (0.5)
Other reasons	29 (3.8)	28 (3.7)	29 (3.8)	30 (3.8)

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

Compliance

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

Table 8 Top Causes of Major Protocol Violations in trials M2-124 and M2-125

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

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

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

Efficacy Results

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

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

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

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

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

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

A. Pre and Post Bronchodilator FEV1

Pre bronchodilator FEV1 (co-primary endpoint)

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

Table 9 Change in pre bronchodilator FEV1 during Treatment from Baseline (M2-124 and M2-125)

M2-124 (Repeated Measurement Analysis)

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

M2-125 (Repeated Measurement Analysis)

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

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

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

Post bronchodilator FEV1 (first rank key secondary endpoint)

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

Table 10 Change in post Bronchodilator FEV1 during Treatment from Baseline (M2-124 &M2-125)

M2-124 (Repeated Measurement Analysis)

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

M2-125 (Repeated Measurement Analysis)

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

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

B. COPD Exacerbations

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

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

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

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

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

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

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

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

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

Table 11 Mean Rates of Moderate or Severe COPD Exacerbations per Patient per Year

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

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

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

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

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

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

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

Table 12 COPD Exacerbations by Severity in studies M2-124 and M2-125

M2-124 (Poisson regression)

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

M2-125 (Poisson regression)

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

Moderate Exacerbations ITT (N = 765)	1.038	1.265	- 18% RR = 0.820 (0.061) 95% CI (0.709, 0.948) P = 0.0075
Severe Exacerbations ITT (N = 765)	0.139	0.180	-22.9% RR = 0.771 (0.145) 95% CI (0.533, 1.114) P = 0.1656
All Exacerbations ITT (N = 765)	4.344	5.396	-19.5% RR = 0.805 (0.059) 95% CI (0.697, 0.930) P = 0.0033

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

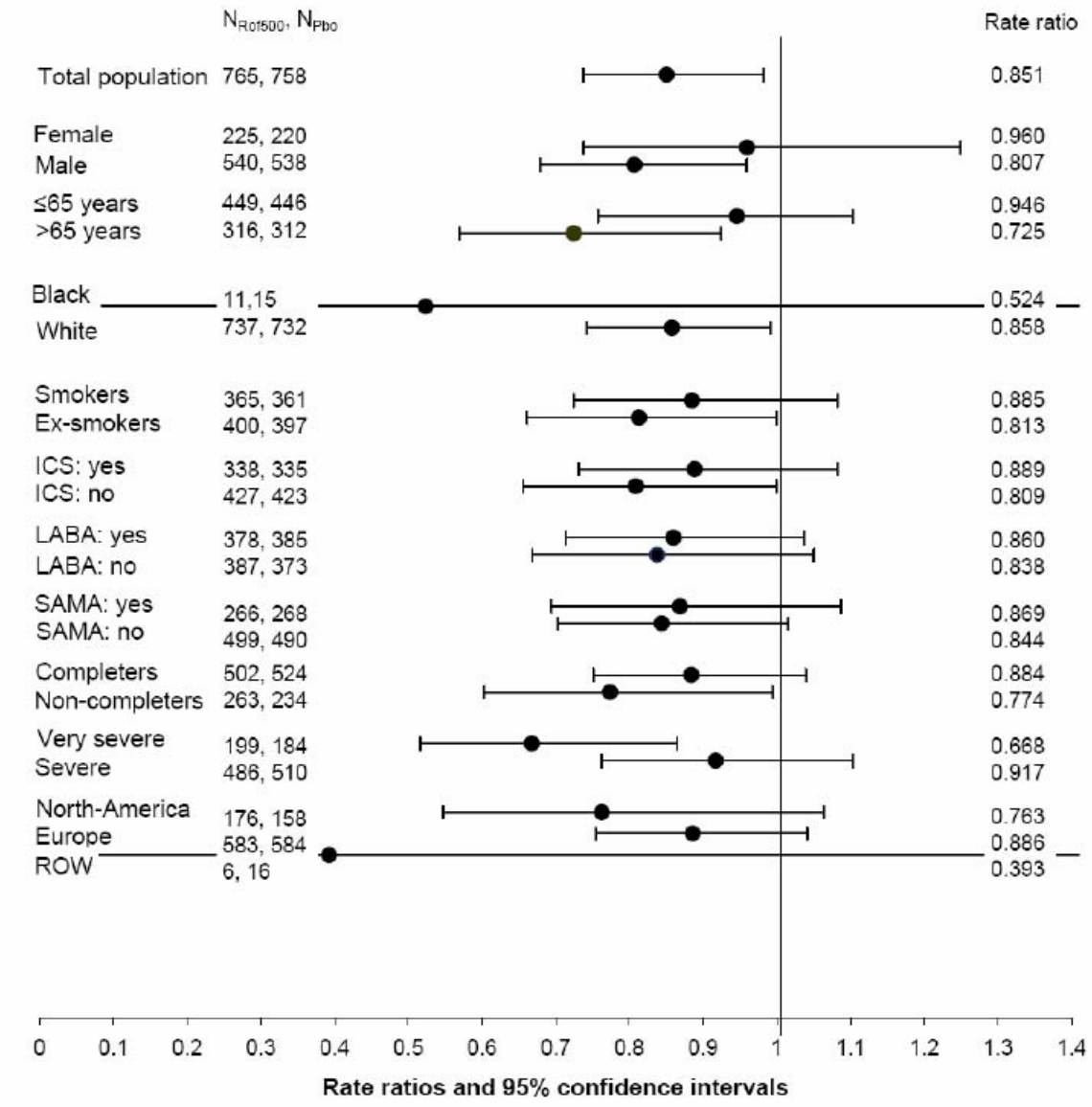
Subgroup analyses on the co primary endpoint (mean rates of moderate or severe COPD exacerbations) according to patient's characteristics were performed using Poisson regression in the ITT population (not in PP) and the results are shown in Figures 2 a and b. The parameters tested included: age ($\leq$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

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

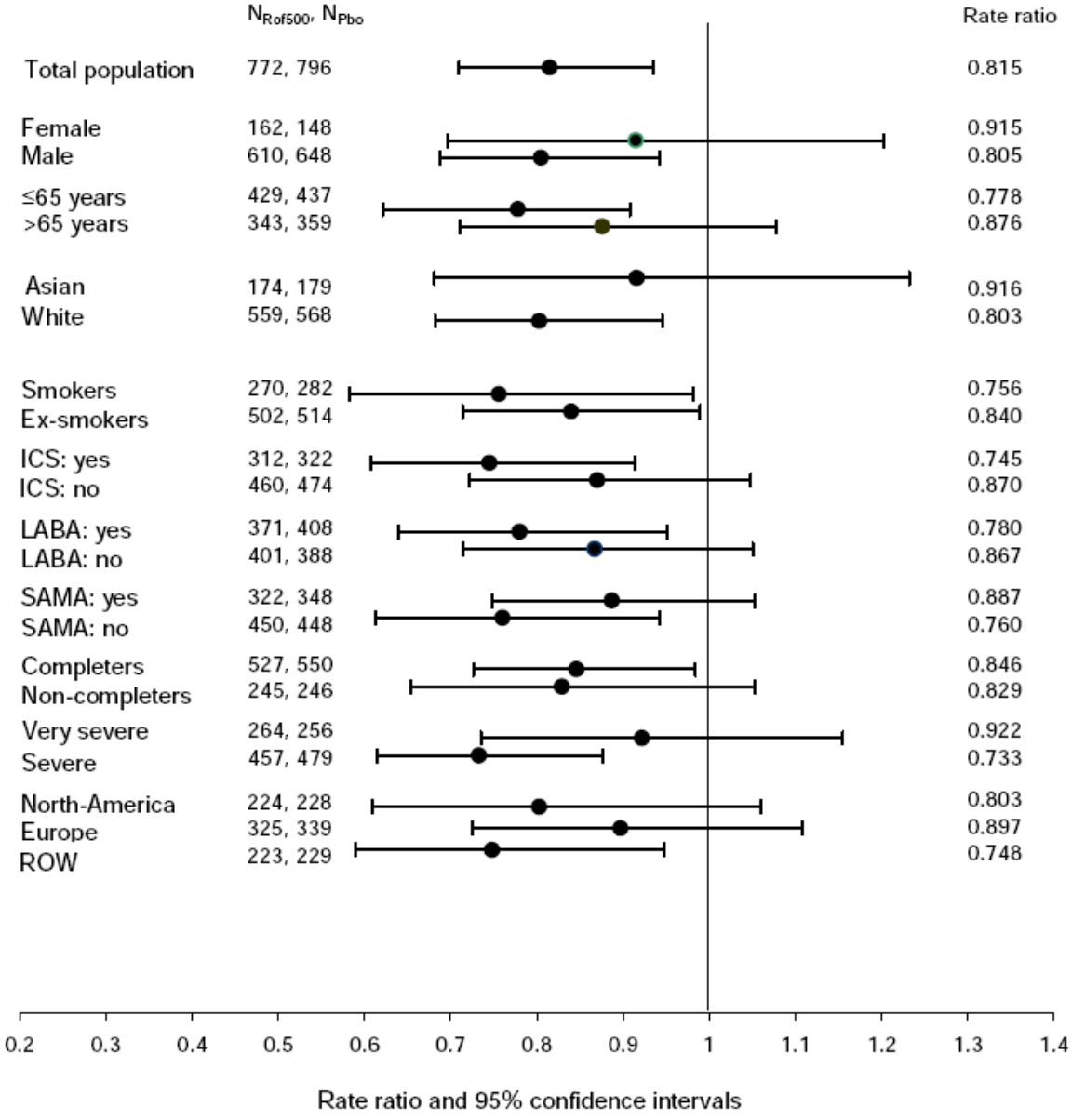
The between treatment differences were statistically significant in trial M2-125 in the following subgroups: males, patients 65 or younger (different from M2-124) and patients older than 65, whites, current (different from M2-124) and ex-smokers, patients with concurrent LABA (different from M2-124),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

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

a) Trial M2-124



b) Trial M2-125



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

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

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

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

Risk of COPD exacerbation (secondary endpoint)

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

Table 13 Risk of COPD Exacerbations in studies M2-125 and M2-125

M2-124 (log binomial regression)

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

M2-125 (log binomial regression)

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

Risk ratio: risk of exacerbation: roflumilast/placebo. SE: standard error
N: number of patients randomized in the respective treatment group.
Risk ratio: roflumilast/placebo
ns: not significant statistically ($p \geq 0.05$)
Sources: CSR M2-124 and CSR M2-125, ITT data from Tables 20 of sections 11.4.2.1 (equivalent of Tables 15.10.1.47), PP data from Table 15.10.1.48 of M2-125 (respective table missing in M2-124) in section 15.10.

Number needed to treat (NNT) (secondary endpoint)

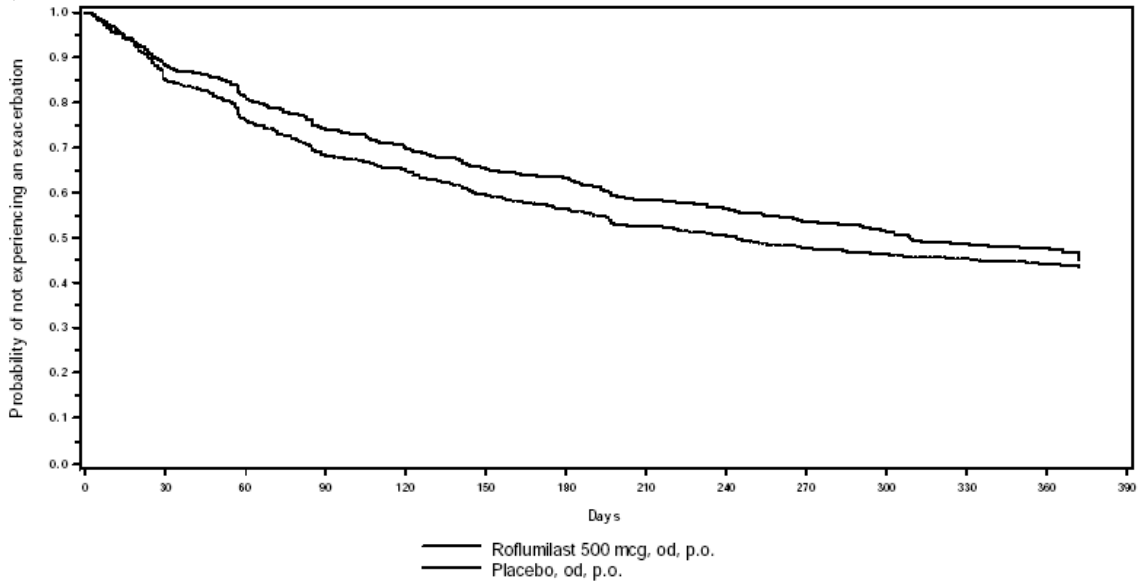
NNT to avoid one moderate or severe COPD exacerbation per patient per year in trials M2-124 and M2-125 were 5.29 and 3.64, respectively for ITT; 11.63 and 3.12, respectively for PP.

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

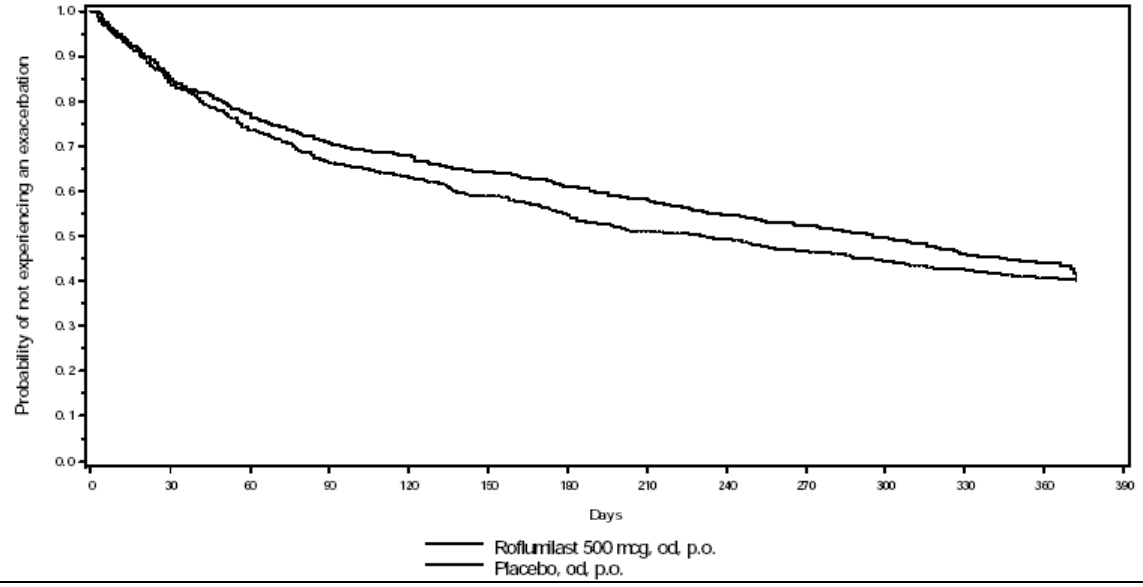
Time to onset of first COPD exacerbation was analyzed with Cox proportional hazards and the results can be found in Tables 21 of CSR in both trials. Results of time to onset of first moderate or severe COPD exacerbation are graphed as survival curve (Kaplan-Meier, ITT) in Table 18 a and b. There were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

Figure 3 Time to onset of first moderate or severe COPD exacerbation (Kaplan-Meier, ITT)

a) Trial M2-124



b) Trial M2-125



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

Number of COPD exacerbation days and duration of COPD

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

Other analyses on COPD exacerbation

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

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

A total of 72 patients died during the double blind treatment period (32 in M2-124 and 50 in M2-125). Two additional deaths from the placebo group in trial M2-124 occurred 2 and 7 months after the trial ended. Results of Cox proportional hazards modeling of time to all cause mortality were equivocal. Comparing to placebo, the mean time to mortality in roflumilast treated group was longer in trial M2-124 (roflumilast: 213.8+/- 118.9 days versus placebo: 207.5+/-108.5 days), but shorter in trial M2-125 (roflumilast: 201+/- 116.9 days versus placebo: 214.6+/-137.3 days). The hazard ratio for trials M2-124 and M2-125 were 1.035 (SE=0.357, p=0.92) and 1.213 (SE=0.35, p=0.5028), respectively.

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

Safety Results

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

5.3.2 Studies M2-111 and M2-112

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

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

contributed to those later amendments to trial M2-111 and the differences in endpoints between these trials.

Treatment groups and dose regimen

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

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

Eligibilities

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

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

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

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

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

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

Study Scheme and Conduct

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

Demographics

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

Table 14 Demographics and Baseline Characteristics (M2-111 and M2-112)

Baseline Characteristics	M2-111 (ITT)		M2-112 (ITT)	
	Rof500 mcg (N=567)	Placebo (N=606)	Rof500 mcg (N=760)	Placebo (N=753)
Age				
median (range) in year	65 (40-87)	64 (41-86)	66 (40-88)	65 (40-89)
Gender				
Male, n (%)	387 (68.3)	400 (66)	571 (75.1)	574 (76.2)
Female, n (%)	180 (31.7)	206 (34)	189 (24.9)	179 (23.8)
Race (% randomized)				
White	532 (93.8)	564 (93.1)	753 (99.1)	746 (99.1)
Black	20 (3.5)	21 (3.5)	0	0
Asian	3 (0.5)	1 (0.2)	6 (0.8)	7 (0.9)
American Indian	0	1 (0.2)	0	0
Other	12 (2.1)	19 (3.1)	1 (0.1)	0
Weight				
mean+/- SD (kg) –M2-111	75 +/- 18.3	75 +/- 19.1		

or median (range)-M2-112			72 (33-138)	72 (35-150)
BMI				
mean+/- SD (kg/m^2)	26 +/- 5.7	26 +/- 5.7	25 +/- 5	26 +/- 5.1
Smoking Status				
% Current/former	42.3/57.7	43.7/56.3	38/62	34/66
mean Cigarette pack year +/- SD	50 +/- 28.2	51 +/- 26.7	42+/- 22.9	45+/-26.2
COPD Characteristics*				
Mild, n (%)	0	0		
Moderate, n (%)	64 (11.3)	45 (7.3)	N/A	N/A
Severe, n (%)	366 (64.6)	396 (65.3)		
Very severe, n (%)	137 (24.4)	165 (27.2)		
Chronic bronchitis, n, (%)			113 (24.7)	111 (22.4)
Emphysema, n, (%)			124 (27.1)	137 (27.6)
Both, n (%)			221 (48.3)	248 (50)
PreFEV1				
mean+/- SD (L)	0.96+/-0.4	0.93+/-0.3	1.029+/-0.345	1.047+/-0.344
(mean % predicted+/-SD)	(31.3+/-9.9)	(30.8+/-9.1)	(37.2+/-10.4)	(37.4+/-10.4)
FEV1 reversibility				
mean+/- SD (mL)	162.6+/-143.9	157.4+/-155.3	97.7+/-124.1	100.4+/-137.4

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

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

Disposition

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

Table 15 Patient Disposition (Trials M2-111 and M2-112)

Disposition, N (%)	M2-111		M2-112	
Enrolled	1801		1829	
Randomized (% recruited)	1176 (65.3)		1514 (82.8)	
Not randomized (% recruited)	625 (34.7)		315 (17.2)	
Disposition, N (% randomized)	Rof500 mcg	Placebo	Rof500 mcg	Placebo
Randomized	568	608	761	753
Completed	352 (62)	421 (69.2)	544 (71.5)	590 (78.3)
Premature Discontinued	216 (38)	187 (30.8)	217(28.5)	163 (21.7)
Adverse events	113 (19.9)	67(11)	103 (13.5)	56 (7.4)
*Withdrew consent (M2-111)	93 (16.4)	77 (12.7)		
COPD exacerbation	32 (5.6)	26 (4.3)	27 (3.3)	24 (3.2)
*Lost to follow up (M2-111)	11 (1.9)	7 (1.2)		
*Met discontinuation criteria (M2-111)/ Other medical reasons (M2-112)	12 (2.1)	19 (3.1)	13 (1.7)	18 (2.4)
*Other reasons (M2-111)/ Non medical reasons (M2-112)	31 (5.5)	42 (6.9)	74 (9.7)	65 (8.6)

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

Compliance and protocol violations

The overall percentage of patients who had major protocol violations were similar between treatment groups and consistent with those reported from the other two 52 week trials (M2-124 and M2-125). Use of not allowed COPD medications and noncompliance were again the main causes of major protocol violations. In both trials, the rates of noncompliance were significantly higher in the roflumilast treated groups than that of the placebo groups. (Table 16)

Table 16 Top Causes of Major Protocol Violations in Trials M2-111 and M2-112

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

study				
Noncompliance	53 (9.3)	18 (3)	122 (16)	66 (8.8)

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

Efficacy Results

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

M2-111:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pre and post bronchodilator FEV1

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

Table 17 Change in Pre and Post Bronchodilator FEV1 during Treatment from Baseline (M2-111)

M2-111, pre FEV1 (Repeated Measurement Analysis)

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

M2-111, post FEV1 (Repeated Measurement Analysis)

Δ in post FEV1 LS Mean in Lt (SD)	Rof500 mcg	Placebo	Treatment Difference Roflumilast - Placebo
ITT	0.021 (0.008) n = 500	- 0.017 (0.007) n = 534	0.038 (0.010) 95% CI (0.018, 0.058)

	obs = 3020	obs = 3479	P = 0.0002
PP	0.026 (0.009) n = 361 Obs = 2262	- 0.022 (0.008) n = 410 obs =2617	0.048 (0.011) 95% CI (0.026, 0.71) P < 0.0001

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

COPD Exacerbations

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

Table 18 Frequency of Moderate or Severe COPD Exacerbations per Patient per Year (M2-111)

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

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

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

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

The secondary endpoints were to compare the rate of moderate or severe COPD exacerbation in patients with different disease characteristics. Subgroup analyses were stratified on COPD severity, presence of chronic bronchitis, productive cough, h/o COPD exacerbation, concomitant COPD treatments, smoking and study completion status. The results are shown in Table 25. Roflumilast treated patients from certain subgroups did better than their respective subgroup comparator. However, the between treatment differences for these better responder subgroups

were still not statistically significant comparing to their respective placebo group. The subgroups of COPD patients had greater reduction in moderate or severe COPD exacerbation induced:

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

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

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

Table 19 Subgroup analysis according to COPD characteristics (M2-111, Poisson regression, ITT)

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

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

Study M2-112:

The primary endpoints for trial M2-112 were:

- Frequency of moderate or severe exacerbations per patient per year

- Change (endpoint minus baseline value) in post bronchodilator FEV1

Key secondary endpoint for trial M2-112 was:

- change in total score of SGRQ

Other secondary endpoints for trial M2-112 were:

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

Pre and post bronchodilator FEV1

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

Table 20 Change in Pre and Post Bronchodilator FEV1 during Treatment from Baseline (M2-112)

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

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

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

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

Pre FEV1 was secondary endpoint, post FEV1 was primary endpoint. Repeat measurement analysis was not

the primary method of analysis specified by SAP in trial M2-112.
n: number of patients with preFEV1 data available.
obs: number of observations
Sources: Tables 25 (pre FEV1), pp128 and Table 13 (post FEV1), pp117 of CSR M2-112.

COPD Exacerbations:

Mean rate of COPD exacerbations were analyzed primarily with non parametric testing (Wilcox-rank sum). Poisson regression was performed as secondary analysis. To be consistent with other trials reviewed, only results from Poisson regression are presented below in Table 21. Similar with findings from other trials, there was a 13.6% reduction in the rate of moderate or severe COPD exacerbation in the roflumilast treated group, comparing to placebo when the definition for moderate exacerbation was use of systemic corticosteroids. When antibiotics use alone was included as moderate exacerbation in addition to systemic steroids, the rate difference drop to 6.6%. Nevertheless, the differences were not statistically significant regardless the definition used for moderate COPD exacerbation.

Table 21 Frequency of Moderate or Severe COPD Exacerbations per Patient per Year in Study M2-112

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

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

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

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

SGRQ

St. George's respiratory questionnaire (SGRQ) was the primary clinical endpoint chosen to demonstrate roflumilast superiority over placebo in early roflumilast trails. Change in total score of SGRQ (was the sole key secondary endpoint in trial M2-112. The within and between

treatment differences are shown in Table 22. There was no meaningful difference between the roflumilast treated and the placebo treated groups (a clinically meaningful change in SGRQ is a difference of 4 or more units).

Table 22 Change in SGRQ Total Score during Treatment from baseline

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

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

5.3.3 Studies M2-127 and M2-128

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

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

Treatment groups and dose regimen

In trail M2-127, eligible patients were randomized into 2 treatment groups:

- roflumilast 500 mcg once daily (in the morning after breakfast) plus salmeterol (Serevent Diskus) 50 mcg twice daily (in the morning and in the evening)
- placebo once daily plus salmeterol (Serevent Diskus) 50 mcg twice daily

Similarly, in trail M2-128, eligible patients were randomized into 2 treatment groups:

- roflumilast 500 mcg once daily (in the morning after breakfast) plus tiotropium (Spiriva HandiHaler) 18 mcg once daily (in the morning)
- placebo once daily plus tiotropium (Spiriva HandiHaler) 18 mcg once daily

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

Eligibilities

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

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

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

To be eligible for randomization, the patients needed to meet all of the following criteria:
- clinically stable, no moderate or severe COPD exacerbation between V0 (baseline) and V2 (randomization)
- medication compliance of 80% to 125% between V0 and V2

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

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

The main pertinent exclusions were:

- unstable patients
- recent COPD exacerbation required treatment with systemic corticosteroids and/or antibiotics that were not discontinued at least 4 weeks before V0
- recent lower respiratory tract infections not resolved at least 4 weeks before V0
- known history of alpha-1 antitrypsin deficiency or carrying diagnosis of other pulmonary diseases

- presence of other concurrent disease(s) or condition(s) that might interfere with study procedure, evaluation or jeopardize patient safety
- unable to give consent or compliant with protocol requirements

Study Scheme and Conduct

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

Demographics

Both trials were international studies and did not have any US centers. While M2-127 included sites from Canada and South Africa, M2-128 was a pure European study. The number of subjects randomized in trials M2-127 and M2-128 were 935 and 744, respectively. Nearly all subjects in both trials were white (>95% in M2-127 and 100% in M2-128) and significantly more males (65-70%) than female (30-35%). All demographic characteristics were generally similar across treatment groups in both trials (Table 23).

Table 23 Demographics and Baseline Characteristics in Trials M2-127 and M2-128

	M2-127 (ITT)		M2-128 (ITT)	
Baseline Characteristics	Rof500 mcg & salmeterol (N=466)	Placebo & salmeterol (N=467)	Rof500 mcg & tiotropium (N=371)	Placebo & tiotropium (N=372)
Age				
median (range) in year	65 (42-87)	65 (40-89)	65 (40-91)	65 (41-87)
Gender				
Male, n (%)	319 (68.5)	299 (64)	262 (70.6)	267 (71.8)
Female, n (%)	147 (31.5)	168 (36)	109 (29.4)	105 (28.2)
Race (% randomized)				
White	445 (95.5)	444 (95.1)	371 (100)	371 (99.7)
Black	1 (0.2)	2 (0.4)	0	0
Asian	2 (0.4)	2 (0.4)	0	1 (0.3)
Other	18 (3.9)	19 (4.1)	0	0
Weight				
mean +/- SD (kg)	76.9 +/-15.3	76.4+/-17.5	78.4+/-17.7	80.0+/-17.3
Smoking Status				
% Current/former	60.5/39.3	60.6/39.4	60.4/39.6	60.8/39.2
Cigarette pack years	42.5+/-21.9	42.5+/-21.9	42.8+/-22.3	42.1+/-22.0
COPD Characteristics*				

Mild n, (%)	1 (0.2)	2 (0.4)	8 (2.2)	11 (3.0)
Moderate n, (%)	303 (65)	324 (69.4)	235 (63.3)	240 (64.5)
Severe n, (%)	162 (34.8)	141 (30.2)	125 (33.7)	119 (32)
Very severe n, (%)	0	0	3 (0.8)	2 (0.5)
PreFEV1				
mean+/- SD (L)	1.434+/-0.395	1.412+/-0.409	1.5+/-0.5	1.5+/-0.5
(mean % predicted+/-SD)	(51.89+/-9.55)	(52.4+/-9.84)	(53.3+/-11.7)	(53.4+/-11.6)
FEV1 reversibility				
mean+/- SD (mL)	75.24+/-122.32	80.73+/-119.57	75.1+/-128.1	74.0+/-125.3

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

Disposition

These trials had the highest randomization and completion rates among the 6 trials reviewed. Nearly 80% patients enrolled (77-82%) were randomized and similar percentage of patients randomized (77-89%) completed the trial. In both trials, approximately 5% more subjects discontinued from the trial in the roflumilast treated group comparing to placebo. The higher discontinuation rates in the roflumilast treated groups were driven by more adverse events and patient's consent withdrawals. In both trials, slightly more patient withdrawal from the placebo group because of COPD exacerbation or lack of efficacy. Nevertheless, the differences were small and not likely to be significant. Approximately 5% more subjects completed the study in trial M2-128 (83.2% roflumilast plus tiotropium, 89.5% placebo plus tiotropium) than trial M2-127 (77.1% roflumilast plus salmeterol, 82.5% placebo plus salmeterol). Trial M2-128 also had lowest rate of withdraw due to COPD exacerbation for both the roflumilast and the placebo group, 1.1% and 2.2% respectively, comparing to 3.4-5.8% in M2-127, and 5.6-9.1% in the pivotal trials. Refer to Table 24 for disposition data from trials M2-127 and M2-128.

Table 24 Patient Dispositions (Trials M2-127 and M2-128)

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

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

Compliance

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

Table 25 Top Causes of Major Protocol Violations (Trials M2-127 and M2-128)

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

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

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

Efficacy results

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

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

M2-127:

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

M2-128:

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

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

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

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

A. Pre and Post Bronchodilator FEV1

Pre bronchodilator FEV1

Mean change in pre and post bronchodilator FEV1 from baseline to each post randomization visit during the treatment period were analyzed with repeat measurements ANOVA and the results are shown in Tables 26 and 27. Similar to the findings of other roflumilast trials, patients treated with roflumilast and LABA (M2-127) or LAMA (M2-128) had improvements in pre-FEV1 (49-80 mL, ITT). In contrast, pre-FEV1 deteriorated slightly (10-18 mL) in patients who received placebo and LABA or LAMA. The between treatment differences in M2-127 (45 and 49 mL for PP and ITT respectively) were similar to those in the pivotal trials (47-67 mL and 39-58 mL for PP and ITT respectively), but were slightly smaller than that observed in M2-128 (76 and 80 mL for PP and ITT respectively).

Table 26 Mean Change in pre FEV1 during Treatment from Baseline in studies M2-127 and M2-128

M2-127 (Repeated Measurement Analysis)

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

M2-128 (Repeated Measurement Analysis)

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

n: number of patients with preFEV1 data available

obs: number of observations
Sources: Tables 12 of sections 11.4.1.1 in CSR M2-127 and CSR M2-128.

Post bronchodilator FEV1

Similarly, the post bronchodilator FEV1 also improved in roflumilast treated groups and deteriorated in the placebo groups. Again, the treatment differences between roflumilast and placebo were small (60-81 mL, ITT) but statistically significant and consistent with results from other trials (Table 27).

Table 27 Mean Change in post FEV1 during Treatment from Baseline in studies M2-127 and M2-128

M2-127 (Repeated Measurement Analysis)

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

M2-128 (Repeated Measurement Analysis)

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

n: number of patients with preFEV1 data available
obs: number of observations
Sources: Tables 17 of section 11.4.2.2.1 in CSR M2-127 and Table 13, section 11.4.2.1.1 in CSR of M2-128.

B. COPD Exacerbations

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

Mean rate of COPD exacerbations

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

reduction of moderate or severe exacerbation in the test group, driven primarily by moderate exacerbations as those in the pivotal trials.

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

Table 28 Mean rate of COPD exacerbations per patient per year

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

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

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

COPD exacerbation severity	Rof500 mcg plus tiotropium	Placebo plus tiotropium	Rate Difference (% change) Rate Ratio (SE)
Mean Rate of moderate or severe exacerbations per patient per year	0.262 N = 42	0.342 N = 58	- 23.2 % RR = 0.768 (0.157) 95% CI (0.515, 1.146) P = 0.1957

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

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

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

differences in the risk of either moderate or severe exacerbation. The risk ratio for moderate and severe exacerbation were 0.735 (SE=0.135, p=0.1121) and 0.623 (SE=0.453, p=0.5151). (Tables 23, section 11.4.2.2.5, CSR of M2-127 and M2-128)

Time to first COPD exacerbation (Cox proportional hazards)

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

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

Safety Results

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

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

Studies FK1-101 and M2-107 were two of the earlier late Phase 2/3 clinical studies and included a lower dose (250 mcg once daily) of roflumilast than any of the later Phase 3 clinical studies. As such, these two studies represent the roflumilast dose-ranging program. Regarding dosing interval, once daily dosing was used throughout the roflumilast clinical development program based on a single PK study in healthy volunteers, which suggested that roflumilast and its active metabolite (N-oxide) has a respective half lives of 17 and 30 hours. Dosing intervals less than or greater than 24 hours were not evaluated in COPD clinical trials. Highlights of trials FK1-101 and M2-107 are summarized below.

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

Trials M2-107 and FK1-101 had similar designs. Both were double-blind, placebo-controlled, parallel-group multinational studies conducted outside the US. Trial FK1-101 was a phase II/III

trial with 2 week run-in followed by 26 week treatment. Trial M2-107 was a phase III trial with 4 week run-in and 24 week treatment.

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

Treatment groups and dose regimen

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

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

Eligibilities

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

- male or female ages $\geq$ 40 years (also $\leq$ 75 for FK1-101)
- $\geq$12 month history of COPD per GOLD criteria
- Mild, moderate or severe COPD with post bronchodilator FEV1/FVC $\leq$ 70%, FEV1 between 30 and 75% predicted (30-80% for M2-107)
- fixed airflow obstruction (FEV1 increase $\leq$ 12% or $\leq$ 200 mL after receiving 400 mcg salbutamol)
- current or former smoker, with $\geq$ 10 pack-years history
- absence of concurrent disease that might interfere with study procedure or evaluation

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

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

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

Study Scheme and Conduct

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

Demographics

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

Table 29 Demographics and Baseline Characteristics (FK1-101 and M2-107)

	FK1-101 (ITT)			M2-107 (ITT)		
Baseline Characteristics	Roflumilast 500 mcg (N=169)	Roflumilast 250 mcg (N=175)	Placebo (N=172)	Roflumilast 500 mcg (N=555)	Roflumilast 250 mcg (N=578)	Placebo (N=280)
Median Age (range)	61 (42-75)	60 (41-75)	62 (42-75)	64 (42-87)	65 (40-86)	63 (40-82)
Gender, Male, n (%)	122 (72)	121 (69)	129 (43)	410 (73.9)	419 (72.5)	207 (73.9)
Current smoker, n (%) mean pack year +/- SD	88 (52) 36 +/- 18	95 (54) 37 +/- 21	92(53) 38 +/-22	254 (45.8) 41+/- 20.6	267 (46.2) 43+/-24.1	125 (44.6) 43+/-22
preFEV1 mean+/- S(L) (mean % predi+/-SD)	1.53+/-0.43 (52+/-11)	1.55+/-0.42 (52+/-10)	1.48+/-0.40 (51+/-10)	1.41+/-0.49 (51+/-14)	1.40+/-0.47 (50+/-13)	1.45+/-0.48 (51+/-14)
FEV1 reversibility % (SD)	3.2+/-5.9	4.0+/-6.0	3.6+/-5.7	9.1 +/- 13.1	9.6 +/- 12.0	9.6 +/- 13.1

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

Disposition

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

Table 30 Patient Dispositions (Trials FK1-101 and M2-107)

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

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

Compliance

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

Efficacy Results

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

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

Table 31 Primary and Secondary Endpoints in Trials FK1-101 and M2-107

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

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

Pre and post bronchodilator FEV1

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

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

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

Table 32 Between treatment differences in pre or post bronchodilator FEV1 (trials FK1-101 and M2-107, LOCF, ITT)

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

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

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

Source: FK1-101 CSR synopsis, pp5.

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

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

Source: M2-107 CSR synopsis, pp7.

SGRQ total score

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

Table 33 SGRQ total score -- between treatment differences in trial M2-107 (ITT last-value analysis)

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

[a] p-value for between-treatment differences (ANCOVA), two-sided, significance level 5%.
CI = confidence interval, Δ = within-treatment difference, LS = least squares,
n = number of patients with data available at T0 and T_{last}, Rof250, Rof500 = roflumilast 250 µg or 500 µg once daily,
SEM = standard error of the mean, T0 = randomization visit, T_{last} = last visit (ITT endpoint analysis).
Source: M2-107 CSR synopsis, p8.

COPD Exacerbations

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

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

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

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

events in 13 patients, 25 events in 19 patients and 26 events in16 for the roflumilast 500 mcg, 250 mcg and the placebo groups, respectively.

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

Other secondary endpoints

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

Safety Results:

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

6 Review of Efficacy

6.1 Indication

In its original submission in July, 2009 by Nycomed, the proposed drug was indicated for "the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations." However, on December 14, 2009, FDA was notified of a change in ownership of the NDA from Nycomed to Forest Research Institute. Subsequently on January 29, 2010, the new applicant made substantial change to the original proposed drug label and limited the indication to "reduction of exacerbations of COPD" from the original broader indication of "maintenance treatment ..."

Because the regulatory review of an NDA by the FDA is based on the proposed product indication, it should be final at the time of the NDA submission. A change in the indication is therefore not acceptable late in the review cycle regardless of a change in ownership. Thus, this application will be evaluated based on the originally proposed indication "for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations", for the purpose of both this cycle of NDA review and the up coming pulmonary advisory committee meeting scheduled on April 7, 2010. The fact that the NDA will be reviewed according to original submission was communicated to the applicant in a teleconference with Forest lab on Feb 26, 2010.

6.1.1 Methods

The roflumilast COPD program was extensive. This submission encompasses 18 late phase (II/II and III) clinical trials which involved COPD patients spending the entire disease spectrum (mild, moderate and severe, emphysema or chronic bronchitis). The applicant has proposed two clinical Phase III studies as the "pivotal" trials (M2-125 and M2-125) from which approval of roflumilast should be based. However, to understand the evolution of the roflumilast clinical program over time and the totality of the efficacy data for roflumilast, efficacy data will be presented from relevant clinical studies according to endpoints.

The endpoints of roflumilast COPD trials evolved over time with changing of the study focus. Although some of the changes could be attributed to progression of new drug development, frequent change of sponsorship also played a role. The earlier programs focused on quality of life [St. George Respiratory Questionnaire (SGRQ) and others] as a co-primary endpoint with spirometry measurements (pre or post bronchodilator FEV1). This was reflected in 2 phase II/III dose ranging, efficacy and safety trials FK1-101 and M2-107, as well as early phase III trials M2-110 and M2-112. As endpoints based on quality of life measures failed in early phase III trials, the rate of COPD exacerbation became the primary focus. In trial M2-111, COPD exacerbation was the primary endpoint, pre bronchodilator FEV1 was later amended as a co-primary endpoint in late, 2003.

The following discussion will focus on FEV1, exacerbations and SGRQ. COPD exacerbations along with a spirometer measurement (mostly pre bronchodilator FEV1) were the co primary endpoints for the pivotal trials, M2-124 and M2-125 and therefore were most relevant to the current COPD program and this application. SGRQ and selected secondary endpoints will be discussed in the context of demonstrating the totality of the roflumilast COPD program.

The sources of the data presented below were primarily from 8 trials, which were collectively referred as the "core COPD trials". The earliest of the core trials were 2 phase II/III dose ranging trials, FLK1-101 and M2-107, which were the two longer and larger of the four COPD trials that compared the efficacy of 2 roflumilast dosing regimens, 250 and 500 mcg once daily. The data presented for these trials will focus on the treatment differences between the 250 and 500 mcg doses.

Trials M2-111, M2-112, M2-124, and M2-125 were the 4 one-year studies in the program and the main COPD exacerbation studies. Trials M2-127 and M2-128 were 2 supportive six-month studies that evaluated roflumilast treatment in patients on long acting bronchodilator therapy. (Refer to Table of Core clinical Studies in Section 5.1).

All studies were multicenter, multi-national, randomized, double-blind, placebo controlled parallel group trials which included a 2-4 week single blind run-in period followed by a double blind treatment period of 52 (M2-111, M2-112, M2-124, and M2-125,) or 24-26 weeks (FLK1-101, M2-107, M2-127 and M2-128).). After initial screening, eligible patients entered a 2-4 week run-in period, during which they receive daily placebo treatment and were taken off

prohibited concomitant medications. At the end of the run-in period, patients who remained eligible were randomized, usually 1:1 to receive once daily treatment of either 500 mcg of roflumilast 500 or placebo for a trial designated treatment period of 24-52 weeks. In trials FK1-101 and M2-107, patients were randomized to 3 instead of 2 treatment groups and the randomized ratio for roflumilast 500 mcg, 250 mcg and placebo were 2:2:1 for trial FK1-101 and 1:1:1 for trial M2-107.

Despite the similarities in design and conduct, differences existed between the core COPD trials, and most notably in 3 aspects: study endpoints, patient population and concomitant COPD medications permitted during roflumilast treatment.

Lung function measured as pre bronchodilator FEV1 and rate of moderate or severe COPD exacerbation were the co primary endpoints in the 4 year long trials: the pivotal trials M2-124, M2-125 and the original phase 3 trials M2-111 and M2-112 (post bronchodilator FEV1 was used in M2-112). COPD exacerbation was evaluated in other core COPD trials but only as exploratory secondary endpoints or was analyzed post-hoc. Instead, SGRQ was the co primary or a secondary endpoint in earlier 5 of the 8 core COPD trials (FK1-101, M2-10, M2-111, M2-112 and M2-127), but not evaluated in the last 3 trials (M2-124, M2-125 and M2-128).

All 4 year-long trials were conducted in severe COPD patients, 40 year of age or older, with FEV1 equal or less than 50% predicted and non reversible airflow obstruction (FEV1 reversibility $\leq$ 12% or 200 mL. While the entry criteria appeared to be identical, the pivotal trials M2-124 and M2-125 also required patients to have recent histories of chronic bronchitis (cough and sputum production) and COPD exacerbations in the year prior to trial enrollment. However, if an eligible patient had a moderate or severe COPD exacerbation during the run in period, the patient was disqualified and exclude from randomization.

Additionally, trials M2-124 and M2-125 permitted concomitant use of long acting beta agonist (LABA) but not inhaled corticosteroids or long acting anticholinergics (LAMA) during the treatment. As the result, approximately 50% of the patients both trials used LABA. Conversely, trials M2-111 and M2-112 allowed the use of inhaled corticosteroids but prohibited use of either LABA or LAMA.

In contrast, COPD patients of various disease severity (between 30 and 80% FEV1 predicted) were studied in the 4 six month core COPD trials (FK1-101, M2-107, M2-127 and M2-128). Concomitant anticholinergics were permitted in trials FK1-101 and M2-107 (short acting only), required in trial M2-128 (LAMA), prohibited in trial M2-127. Conversely, concomitant long acting beta agonist was required in trial M2-127 but prohibited in the other 3 six-month core trials. Inhaled corticosteroids were not permitted in any of the 6 month core trials.

The difference in study designs and use of concomitant medications used to treat COPD make inter-study comparisons difficult. It should be noted that in no study was the efficacy of roflumilast evaluated compared to what has become standard of care treatment for patients with COPD, concomitant use of a LABA, LAMA, and an inhaled corticosteroid.

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

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

6.1.2 Demographics

A summary of demographic data across studies is presented in the table below. The patient population was predominantly white males. Within each individual study baseline pulmonary function, smoking history, COPD severity, and LABA use (when allowed) were generally balanced. Patients in studies M2-127 and M2-128 overall had less severe COPD, which is reflective in their higher baseline FEV1 values.

Table 34 Summary of Patient Demographics Across Core Phase III Efficacy and Safety Trials

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

ICS (%)*	44	44	40	41			62	63				
Pre-FEV1** (mean, L)	1.1	1.1	1.0	1.0	1.0	0.9	1.0	1.0	1.4	1.4	1.5	1.5
Post-FEV1 (mean, L)	1.2	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.5	1.5	1.5	1.6
Pre-FEV1 (mean % pred)	35	35	31	32	31	31	37	37	52	52	53	53
Post-FEV1 (mean % pred)	38	38	35	35	37	36	41	41	55	55	56	56

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

6.1.3 Subject Disposition

In the 4 year long trials, approximately two-third (65-70%) of the randomized patients completed the trial and the remaining approximately one-third (30% to 35%) dropped out. There were more premature discontinuations in the roflumilast treated groups compared to placebo because of adverse events or withdraw consent. In contrast, more patients withdrew from the placebo group because of COPD exacerbation. Similar trends also applied to the 6 month studies, except the overall drop out rate were lower at 20-30%.

The PDE4 inhibitor class of drugs is known to cause significant GI toxicities. Diarrhea and nausea were one of the most common AEs among patients who received roflumilast or other PDE4 inhibitors, such as cilomilast. The role of GI side effects on patient discontinuation will be discussed in section 7.3.3.

Table 35 Summary of Patient Disposition Across Core Phase III Efficacy and Safety Trials

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

Exacerbation: refer to COPD exacerbation.

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

Table 36 Duration of Drug Exposure Across Core Phase III Efficacy and Safety Trials

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

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

Also of note is the large number of protocol violations across all studies accounting for about 20-30% of the overall study populations. This contributes to the large difference between the ITT and PP study population numbers. Because majority of the protocol violations involved use of not permitted COPD medications, these violations could confound the efficacy results.

Table 37 Compliance Across Core Phase III Efficacy and Safety Trials

	M2-124		M2-125		M2-111		M-112		M-127		M2-128	
	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo	Rof	Pbo
% N	765	758	772	796	567	606	760	753	466	467	371	372
Mean treatment Compliance	94	95	93	96	96	96	99	99	94	96	96	97
Protocol violation	28	28	32	29	27	23	33	29	23	21	18	19

Treatment compliance refers to compliance with trial drug.
Protocol violation included all major violations to the protocol.
%N: as % of randomized in each group.

6.1.7 Analysis of Primary Endpoint(s)

This integrated efficacy review will discuss 3 primary endpoints used over the roflumilast development program: pre bronchodilator FEV1, rate of moderate or severe COPD exacerbations and SGRQ. Pre bronchodilator FEV1 and the rate of moderate or severe COPD exacerbations

were the co primary endpoints in 3 of the 4 year-long trials (M2-111, M2-124 and M2-125) in the core COPD program. The fourth year long trial M2-112 had different co primary endpoints (see below).

Although not included in the scope of the pivotal trials, St. George Respiratory Questionnaire (SGRQ) was the focus and the co primary or key secondary endpoint in several earlier COPD trials including the dose ranging trials FK1-101, M2-107 and the earliest of the year long trial M2-112. SGRQ was accessed as a secondary endpoint in trial M2-111 but not at all in later core COPD trials, including the replicating year long pivotal trials M2-124 and M2-125 and the 6 months add-on trials M2-127 and M2-128.

Long function measured in FEV1 was one of the primary focuses throughout the COPD development program. Post bronchodilator FEV1 was used as primary or co primary endpoint in the earlier trials. In later trials, pre bronchodilator FEV1 became the primary or co primary endpoint and the post bronchodilator FEV1 was investigated as a key secondary endpoint.

As pre bronchodilator FEV1 and rate of moderate or severe exacerbation were the most relevant to the proposed indication, they will be the focus of discussion. SGRQ will be discussed to show the totality of the COPD drug development program. Results for post bronchodilator will be presented as secondary endpoint.

Change from Baseline in Pre bronchodilator FEV1

In the pivotal and supportive studies, patients treated with roflumilast had a statistically significant, though modest, increase in pre-bronchodilator FEV1 compared to placebo. The size of the effect ranged from 39 to 80 ml, which correlated to a 3-5% increase in FEV1 from the baseline. This increase in FEV1, although significant statistically, would not constitute a clinically meaningful benefit.

Table 38 Change (in mL) from baseline in pre-bronchodilator FEV1 to end of treatment (ITT populations)

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

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

Number of individuals randomized is provided in parentheses.
Source: FDA statistics

Rate of Moderate or Severe COPD Exacerbations:

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

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

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

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

To facilitate direct comparison of studies M2-111 and M2-112 with studies M2-124 and M2-125, the definitions of moderate and severe exacerbations for studies M2-111 and M2-112 were modified post-hoc by the sponsor to match those of M2-124 and M2-125. However, without these post hoc changes, the rate ratio comparing roflumilast and placebo was also not significant

in either study. The p-value in Study M2-111 would be 0.218 rather than 0.129 and the p-value in Study M2-112 would be 0.4514 rather than 0.085.

Table 39 Rates of moderate or severe exacerbations in the one year studies* (ITT Population)

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

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

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

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

Table 40 Frequency (%) of Moderate or Severe Exacerbations

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

Source: FDA statistical analysis

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

125, respectively. The mean rate of COPD exacerbations per patient year and the time to onset of first COPD exacerbation for the categories of COPD exacerbations is further described in Section 3.1.2.2 of the statistical briefing document.

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

The SGRQ is one of the most commonly used measures of the quality of life in patients with respiratory disease and is frequently used in clinical trials during drug development programs. It is comprised of 16 questions that assess disease symptoms, disturbances to patients' daily physical activity, and the impact of the disease on the patient. A lower SGRQ score suggests clinical improvement and a clinically meaningful effect requires a minimal of 4.0 unit difference.

SGRQ was used in several earlier COPD trials as either a co-primary, a key secondary or other secondary endpoint. In reviewing the SGRQ data note that Change from baseline in total SGRQ score failed to achieve either statistical or clinical significance in any study in which it was utilized.

Table 41 Change from Baseline in SGRQ total score

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

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

6.1.5 Analysis of Secondary Endpoints(s)

Mortality

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

Additionally, results of Cox proportional hazards modeling of time to all cause mortality were equivocal. Comparing to placebo, the mean time to mortality in roflumilast treated group was longer in trial M2-124 (roflumilast: 213.8+/- 118.9 days versus placebo: 207.5+/-108.5 days), but shorter in trial M2-125 (roflumilast: 201+/- 116.9 days versus placebo: 214.6+/-137.3 days). The

hazard ratio for trials M2-124 and M2-125 were 1.035 (SE=0.357, p=0.92) and 1.213 (SE=0.35, p=0.5028), respectively.

Rate of COPD exacerbations in 6-month supportive studies

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

Table 42 Rates of moderate or severe exacerbations* (ITT Population)

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

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

Change in post-bronchodilator FEV1

Change in post-bronchodilator FEV1 from baseline was assessed in most clinical studies conducted in the roflumilast program both as a co-primary endpoint in earlier studies and as a secondary endpoint in the proposed pivotal studies, M2-124 and M2-125. In general, post-bronchodilator FEV1 demonstrated numerical improvement in most, if not all clinical studies. The effect was very similar to that observed for the co-primary endpoint of pre-bronchodilator FEV1 with a between treatment difference of 50 to 60 mL compared to placebo for the pivotal trials (M2-124 and M2-125).

Change in other spirometry parameters

Changes in other spirometry parameters such as FVC, $FEF_{25-75\%}$, FEV3, FEV6 were also assessed in most clinical studies in the roflumilast COPD program. The results generally followed trends similar to those for pre and post bronchodilator FEV1.

6.1.6 Other Endpoints

Other secondary endpoints evaluated in pivotal studies M2-124 and M2-125 included assessments for dyspnea (BDI/TDI), quality of life measured by the EuroQol (EQ-5), time to

mortality, the use of rescue medication, COPD symptom scores, the inflammatory mediator, C-reactive protein, and time to study withdrawal.

For both studies M2-124 and M2-125 there were no meaningful differences between roflumilast and placebo for any of the other secondary endpoints listed above. Specifically, in study M2-124, the change from baseline TDI was 0.233 (< the clinically meaningful difference of ≥ 1 unit), the change in use of rescue medication was -0.20 puffs/day driven by increased use in the placebo group, and the time to mortality was 214 and 208 days in the roflumilast and placebo groups, respectively. Time to study withdrawal was 121 and 141 days in the roflumilast and placebo groups, respectively. This difference was driven by a 60% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.
For study M2-125, the change from baseline TDI was 0.286 (< the clinically meaningful difference of ≥ 1 unit), the change in use of rescue medication was -0.43 puffs/day driven by increased use in the placebo group, and the time to mortality was 201 and 215 days in the roflumilast and placebo groups, respectively. Time to study withdrawal was 109 and 146 days in the roflumilast and placebo groups, respectively. This difference was driven by a 40% higher risk of early discontinuation due to an adverse event in the roflumilast group compared to placebo.

6.1.8 Subpopulations

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

While there was no statistically significant difference within each subgroup, the effect size appeared to be numerically smaller in some subgroups comparing to their respective counterparts. The subgroups that had less pre FEV1 improvements in responsive to roflumilast treatment in both trials included: woman, non whites, patients who did not complete the study or with very severe COPD. However, due to the lower N in the inferior responder groups, the subgroup analyses were non conclusive. (Refer to section 5 individual study report for more detail)

Similarly, there was no statistically significant difference in rate of moderate or severe COPD exacerbations among patients of different age, gender, race, geographic location or smoking status. However COPD disease characters appeared to have significant impact on outcome measured by the rate of moderate or severe exacerbations. One of the more informative subgroup analyses was the post-hoc analyses in trial M2-111. Stratification was based on COPD severity, presence of chronic bronchitis, productive cough, h/o COPD exacerbations, concomitant COPD treatments, smoking and study completion status. COPD patients with cough and/or sputum score of 2 or greater, chronic bronchitis, recent history of exacerbation and

on concomitant LAMA treatment did better compared to their respective counter part and had lower rate of moderate or severe COPD exacerbation. Results of this post hoc subgroup analyses was the rational for selection of patients for the pivotal trials. (Refer to section 5 individual study report for more detail)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The primary dosing information was from 2 dose ranging studies FK1-101 and M2-107. Trial FK1-101 was designated as the pivotal dose ranging trial by Nycomed, the original applicant, but later considered to be the supportive dose ranging trial by the current applicant.

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

No clear dose response was shown in the dose ranging trial for pre-bronchodilator FEV1. Treatment with roflumilast 250 mcg once daily resulted in 35 and 64 mL improvements in FEV1 over placebo for studies FK1-101 and M2-107, respectively. The increases in FEV1 for the 500 mcg dose over the 250 mcg dose were 5 and 24 mL for studies FK1-101 and M2-107, respectively. For study M2-107, much of the benefit for roflumilast over placebo is due to a decrease of 39 mL in FEV1 in the placebo group.

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

Trial Number	Duration (Weeks)	Rof500 mcg	Rof250 mcg	Placebo	Difference (ml)		P-Value	
					Rof250-P	R500 - R250	R250-P	R500-R250
FK1-101	26	69 (167)	64 (173)	29 (169)	35	5	0.2398	0.8568
M2-107	24	49 (506)	24 (541)	-39(256)	64	24	<0.0006	0.1024

From individual clinical study reports

Regarding the other co-primary endpoint, SGRQ, in both studies there was no significant difference in SGRQ between either the 250 or 500 mcg roflumilast dose group and placebo or between each other. Based on the general lack of separation in efficacy parameters between the

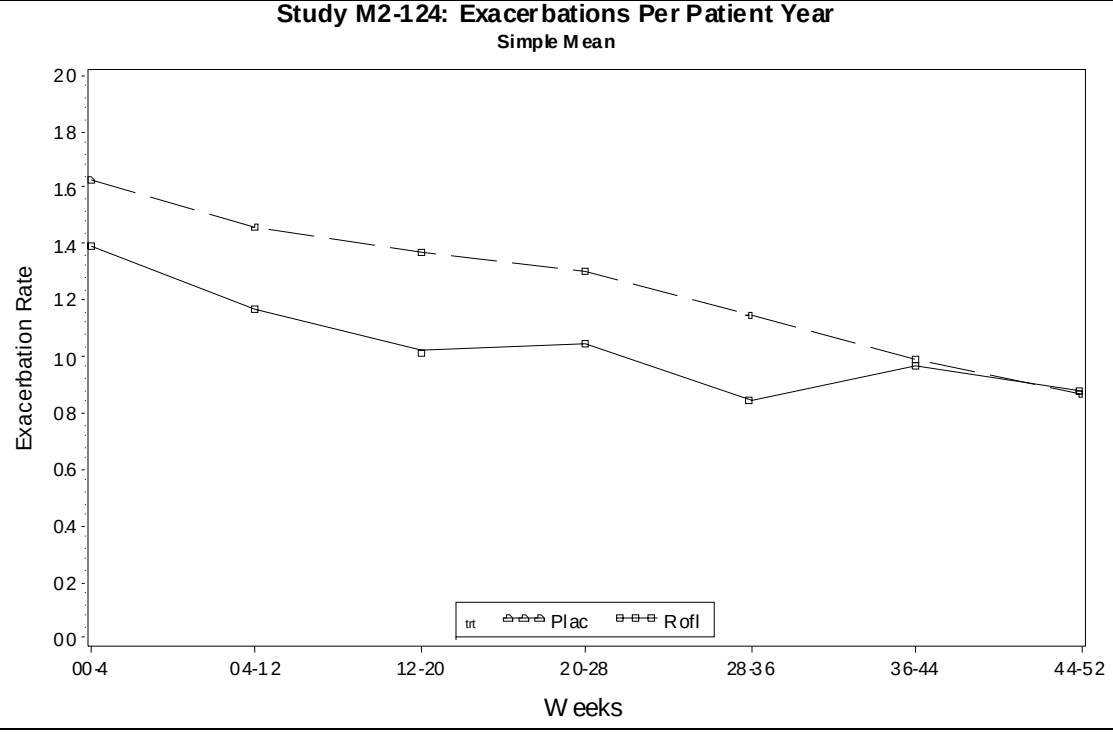
250 and 500 mcg doses, dose selection for the roflumilast program appears to have been arrived at by selection of the maximally tolerated dose.

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

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

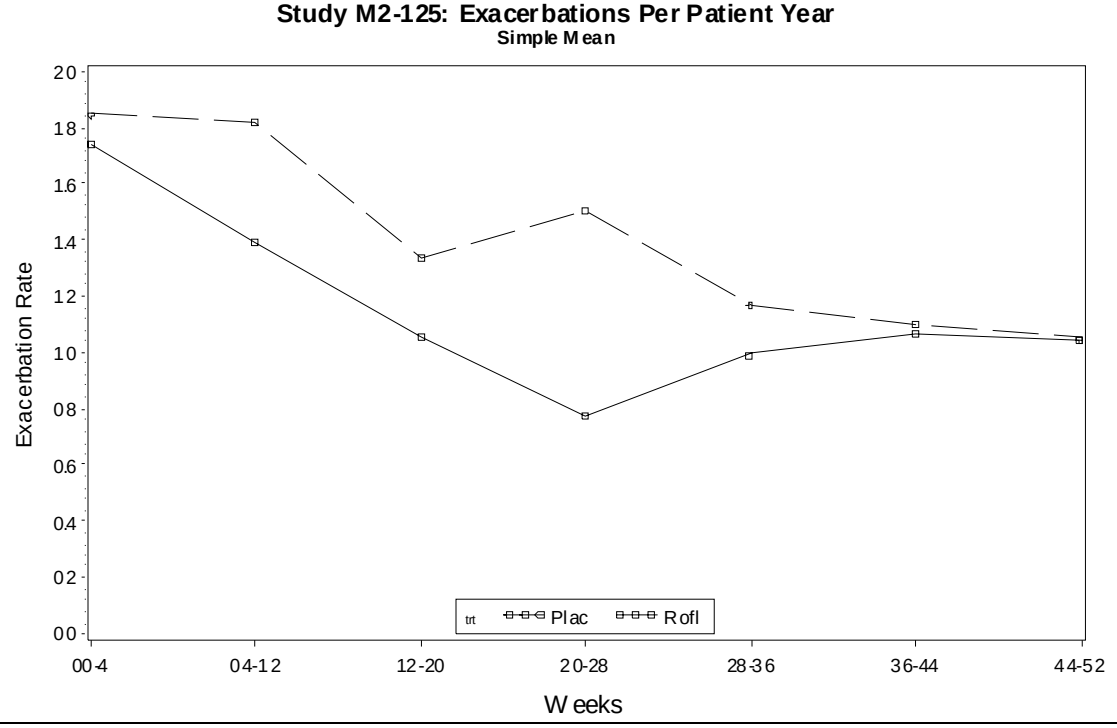
Exploratory analyses by the FDA statistics department evaluated the persistence of efficacy in roflumilast in reducing the rate of COPD exacerbations. Details of the review can be found in Section 3.1.2.2 of the statistical review by Dr. Robert Abugov. These exploratory analyses suggested that the reduction of exacerbation rate by roflumilast compared to placebo may decrease over time.

Figure 4 Exacerbation rate over time (study 124)



Source: FDA statistical analyses

Figure 5 Exacerbation rate over time (study 125)



Source: FDA statistical analyses

7 Review of Safety

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

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

pancreatitis were also reported in the roflumilast group, these rare fatality cases, although small in number are significant.

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

Approximately 2/3 of patients in the COPD safety pool (roflumilast 500 mcg: 67.2%, placebo 62.8%) had at least one treatment emergent adverse event (abbreviated as adverse events or AEs). The AEs reported at a higher frequency in the roflumilast 500 mcg group, in order of descending prevalence, included diarrhea, weight loss, nausea, headache, back pain, insomnia, dizziness decreased appetite, depression and anxiety. AEs that occurred at a higher rate in the placebo group included COPD, URI, and hypertension. Nasopharyngitis were common in both groups at equal rates.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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

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

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

2081 for 3 to less than 6 month and 1370 for less than 3 months. The median duration of exposure with 500 mcg roflumilast was 167 days.

7.1.2 Categorization of Adverse Events

Treatment emergent adverse events (abbreviated as adverse events or AEs) were categorized based on system organ classification (SOC) and preferred terms (PT) according to MedDRA version 11.0. Frequencies of AE were calculated for each treatment group within a safety pool. For all AEs, both intensity and causality were accessed. This review will focus on AE type and intensity, not causality.

The AE intensity was categorized as mild, moderate or severe. A mild AE was hardly noticeable, with negligible impairment of well-being. A moderate AE involved marked discomfort and, although tolerable, without immediate relief. A serious AE involved overwhelming discomfort, calling for immediate relief. Adverse events associated with weight loss were classified as moderate if more than 5% but less than or equal to 10% of body weight was lost from baseline, and were classified as severe if more than 10% of body weight was lost from baseline.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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

For COPD:

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

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

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

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

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

For asthma:

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

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

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

7.2 Adequacy of Safety Assessments

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

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

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

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

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

Over 6500 COPD patients were exposed to roflumilast in 18 phase II and III COPD trials, 5766 of the patients received at least one 500 mcg dose, 797 patients received at least one 250 mcg dose. Among those who received the 500 mcg dose proposed for registration, 1232 patients were treated for 1 year or longer, 1081 for 6 months to less than 1 year, 2081 for 3 to less than 6 month and 1370 for less than 3 months. In the pivotal trials M2-124 and M2-125, 1547 patients were treated with 500 mcg of roflumilast with 721 (46%) of them treated for the full 52 week treatment period. Total human exposure for the roflumilast clinical program (COPD safety pool and pooled data from studies M2-124 and M2-125 pool) is shown in table below.

Table 44 Exposure to roflumilast for COPD population (COPD safety pool and pivotal trials pool)

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

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

It should be noted that the total and mean exposure times were shorter for the roflumilast treated patients than those of placebo treated patients in all pools. This is the result of increased numbers of premature study discontinuations in the roflumilast groups. For the pivotal pool, the respective exposure time for patients received 500 mcg of roflumilast and placebo were: 1186 and 1240 patient years of total exposure time, 280 and 293 of mean exposure time. For the COPD safety pool, the respective exposure time for patients received 500, 250 mcg of roflumilast and placebo were: 3261, 325 and 226 patient years of total exposure time, 207, 149 and 173 days of mean exposure time. For the asthma pool, the respective exposure time for patients received 500, 250, 125 mcg of roflumilast and placebo were: 478, 287, 43 and 738 patient years of total exposure time, 111, 97, 70 and 116 days of mean exposure time.

For the asthma pool, the respective exposure time for patients received 500, 250, 125 mcg of roflumilast and placebo were: 478, 287, 43 and 738 patient years of total exposure time, 111, 97, 70 and 116 days of mean exposure time.

Table 45 Exposure to roflumilast for asthma population

Exposure to study drug	Placebo (N=2318) n (%)[a]	Rof125 (N=221) n (%)[a]	Rof250 (N=1063) n (%)[a]	Rof500 (N=1567) n (%)[a]
<1 week	43 (1.9)	3 (1.4)	35 (3.3)	46 (2.9)
≥1 week to <4 weeks	202 (8.7)	28 (12.7)	119 (11.2)	182 (11.6)
≥4 weeks to <12 weeks	467 (20.1)	62 (28.1)	229 (21.5)	391 (25.0)
≥12 weeks to <24 weeks	675 (29.1)	128 (57.9)	430 (40.5)	317 (20.2)
≥24 weeks	931 (40.2)	0 (0.0)	250 (23.5)	631 (40.3)
Mean ET per person (days) [mean ± SD]	116.3 ± 60.1	70.3 ± 25.5	98.6 ± 55.9	111.3 ± 66.3
Total ET (person years)	738	43	287	478

a Percentage based on N.
ET = exposure time, N = number of patients in treatment group, n = number of patients with data available
Rof125 = 125 mcg roflumilast once daily, Rof250 = 250 mcg roflumilast once daily, Rof500 = 500 mcg roflumilast once daily, SD = standard deviation
Includes studies: FK1-003, FK1-004, FK1-011, FK1-020, FK1-021, FHP-031, M2-012, M2-013, M2-014, M2-023;
Source data: [289/2008, Tables 6.3.1.1, 6.3.1.2]

7.2.2 Explorations for Dose Response

Up to 5000 mcg of roflumilast was tested in phase I trials, single doses above 1000 mcg were poorly tolerated. Repeat doses of between 125 and 500 mcg were studied in phase II and III clinical trials. Only the 250 and the 500 mcg doses were evaluated in COPD trials.

There were 4 COPD trials that had both roflumilast 250 and 500 mcg groups. Trial FK1-101 and M2-107 were 2 independent dose-ranging, efficacy and safety, phase II/III, non US, multinational studies. FK1-101 was a 26 week study and M2-107 was a 24 week study. Two additional phase II studies were conducted in Asia. Trial IN-108 was a 12 week study in India and trial JP-706 was a 24 week study in Japan.

The total number of patients who had AEs was similar between the 2 roflumilast dosing groups and were slightly higher than the placebo group (roflumilast 500 mcg versus 250 mcg versus placebo were 67.4% versus 66% versus 63.9%). However, the number of patients who had SAEs and who withdrawal prematurely because of AEs showed trends of dose response. Roflumilast 500 mcg groups had the highest rate of SAE and AE lead to withdraw and the placebo groups had the lowest rate, except for trial IN-108 which had the smallest sample size and was only 12 weeks long.

Table 46 Patients disposition in dose ranging trials

Category N (%)	Trial number	Roflumilast 500 mcg	Roflumilast 250 mcg	Placebo	Trial subtotal
Patients randomized	FK1-101	169	175	172	516
	M2-107	555	576	280	1411
	JP-106	204	205	191	600
	IN-108	47	46	25	118
	Total	975	1002	668	2645
Patients had at least one AE	FK1-101	82 (49)	85 (49%)	85 (49%)	252 (48.8)
	M2-107	370 (66.7)	382 (66.3)	174 (62.1)	926 (65.6)
	JP-106	187 (91.7)	177 (86.3)	161 (84.3)	525 (87.5)
	IN-108	18 (38.3)	17 (37.0)	7 (28.0)	42 (35.6)
	Total	657 (67.4)	661 (66.0)	427 (63.9)	1745 (66.0)
Patients had at least one SAE	FK1-101	9 (5)	14 (8)	11 (6)	34 (6.6)
	M2-107	53 (9.5)	41 (7.1)	21 (7.5)	115 (8.2)
	JP-106	20 (9.8)	20 (9.8)	12 (6.3)	52 (8.7)
	IN-108	1 (2.1)	2 (4.3)	1 (4.0)	4 (3.4)
	Total	83 (8.5)	77 (7.7)	45 (6.7)	205
Patients withdraw prematurely due to AE	FK1-101	12 (7)	13 (7)	10 (6)	35 (6.8)
	M2-107	82 (14.8)	56 (9.7)	23 (8.2)	161 (11.4)
	JP-106	48 (23.5)	27 (13.2)	12 (6.3)	87 (14.5)
	IN-108	0	2 (4.3)	1 (4.0)	3 (2.5)
	Total	142 (14.6)	98 (9.8)	46 (6.9)	286 (10.8)

Sources:
FK1-101: unnumbered table, pp5, synopsis
M2-107: Table 32, pp135, CSR
JP-706: Table 12.2.1, pp 115, CSR
IN-108:Table 17, pp 94, CSR

Dose response was also evident in roflumilast related AEs such as GI toxicity, weight loss, headache, dizziness and insomnia. For the three 6 month trials (FK1-101, M2-107 and JP-106), the rates of these roflumilast related AEs were roughly doubled in the roflumilast 500 mcg groups compared to the 250 mcg groups. Table 47 lists the incidence of most common roflumilast related AEs. Because the AEs were categorized differently in each trial, the results were listed separately and not pooled together.

Table 47 Most Common TEAEs in dose ranging trials

	Roflumilast 500 mcg	Roflumilast 250 mcg	Placebo
FK1-101 (HARTS terms), N (%)	169	175	172
Diarrhea, nausea, abdominal pain	15 (8.9)	10 (5.7)	5 (3)
Headaches, insomnia	11 (6.5)	5 (3)	5 (3)
Respiratory system (Bronchitis, URI, rhinitis, sinusitis)	40 (24)	52 (30)	53 (31)

M2-107 (PT, MedDRA), N (%)	555	576	280
Diarrhea, nausea, abdominal pain	98 (17.7)	46 (8.0)	10 (3.6)
Weight loss	13 (2.3)	6 (1.0)	0
Headaches, dizziness	42 (7.6)	31(5.4)	16 (5.7)
COPD exacerbation	113 (20.4)	135 (23.4)	65 (23.2)
JP-106 (PT, MedDRA 6.0), N (%)	204	205	191
Diarrhea, nausea, loss stool	72 (35.3)	38 (18.5)	14 (7.3)
Headaches, dizziness, insomnia	36 (17.6)	29 (14.1)	11 (5.7)
IN-108 (PT, MedDRA), N (%)	47	46	25
Diarrhea, abdominal pain, gastritis	3 (6.4)	5 (10.9)	0
Headaches, dizziness, tremor	3 (6.4)	1 (2.2)	0
COPD exacerbation	9 (19.1)	13 (28.3)	6 (24.0)

Sources:
FK1-101: Table, pp125, CSR
M2-107: Table 33, pp136, CSR
JP-706: Table 12.2.2-2, pp 117, CSR
IN-108:Table 18, pp 95, CSR

7.2.3 Special Animal and/or In Vitro Testing

Carcinogenicity

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

Gastrointestinal Tract Toxicity

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

Fertility and Reproductive Toxicity

Effects on male fertility

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

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

Effects on Pregnancy

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

Cardiovascular Toxicity

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

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic clearance, pharmacokinetics, and drug-drug interactions of roflumilast are briefly summarized in section 4.4., 7.54 and 7.55.

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

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

7.3 Major Safety Results

7.3.1 Deaths

Of the approximately 12,000 patients included in the COPD safety pool, there were 177 deaths, 84 in the roflumilast 500 mcg group, 86 in the placebo group, and 7 in the roflumilast 250 mcg group. Nearly half of the mortality (84 of 177) occurred in the 52 week pivotal trials M2-124 and M2-125. The respective mortality in the pivotal pool (studies M2-124 and M2-125 only) was also about equal between roflumilast and placebo groups (2.6 % in the roflumilast 500 mcg group and 2.7% in the placebo group). Cardiac disorders and COPD were the most common AEs reported in patients who died during treatment. The table below lists AEs reported in ≥ 0.2% for patients who died and AEs reported more frequently in roflumilast treated patients who died.

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

Table 48 Adverse Events Reported at a frequency of ≥ 0.2% in any treatment group for patients who died

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

Fatality and Fatality Associated AEs	Pivotal Pool		COPD Safety Pool		
	Rof500 mcg	Placebo	Rof500 mcg	Placebo	Rof250 mcg

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

AEs Reported More Frequently in Roflumilast Treated Fatality Cases

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

Source: Table 32, pp75, ISS

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

Deaths in asthma patients

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

7.3.2 Nonfatal Serious Adverse Events

Table 49 displays the most frequently reported serious adverse events (SAEs) in the pivotal and the COPD safety pools. In general, the overall incidence of SAEs was similar between the roflumilast 500 mcg and the placebo groups and reflected the common co-morbidities frequently observed in an older COPD population of patients. For the COPD safety pool, the respective SAE rates were 13.5 and 14.2% for the roflumilast 500 mcg and the placebo groups. The SAE rates were higher in the pivotal pool (19.5 and 21.7% respectively) likely as a result of the more severe COPD population studied in these trials. COPD exacerbations and pneumonia were the most frequent SAEs in all treatment groups. In both pools, the roflumilast 500 mcg group reported more SAEs as a result of bronchitis, pneumonia, atrial fibrillation, intractable diarrhea, acute pancreatitis, prostate cancer and acute renal failure. In contrast, the placebo group had more COPD related events, cerebrovascular events, and lower respiratory tract infections.

Table 49 Most Frequently Reported Serious Adverse Events (≥0.3% in any group)

	Pivotal Pool	COPD Safety Pool

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

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

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

The more common SAEs observed in the asthma safety pool are shown in table 50 below. Overall, there were numerically more asthma exacerbations, infections, and GI related SAEs in the roflumilast treated patients compared to placebo.

Table 50 Most Frequently Reported Serious Adverse Events (≥0.2% in any group) in asthma trials

	Rof500 mcg	Rof250 mcg	Rof125 mcg	Placebo
Subjects Randomized N	1567	1063	221	2318
Subjects with SAEs, (%N)	48 (3.1)	23 (2.2)	4 (1.4)	48 (2.1)
Asthma exacerbation	12 (0.8)	6 (0.6)	2 (0.9)	11 (0.5)
Infections/infestations	11 (0.7)	2 (0.2)	0	6 (0.3)
Pneumonia	4 (0.3)	2 (0.2)	0	2 (<0.1)
Gastrointestinal disorders	5 (0.3)	2 (0.2)	0	3 (0.1)

Source: Table 65, pp150 of ISS (24/2009).

7.3.3 Dropouts and/or Discontinuations

The overall dropout rate for patients receiving roflumilast was approximately 28% compared to about 23% for patients who received placebo. For nearly all phase II and III trials included in the COPD development program, the roflumilast 500 mcg groups had higher early termination rate than the placebo groups, largely driven by the higher number of adverse events that

ultimately led to early withdrawal. This is in contrary to the findings from most other COPD drug trials, in which the dropout rates were usually higher for the placebo group because of lack of effect from the placebo treatment. Although COPD exacerbation rates were higher in the placebo groups for roflumilast trials, the differences were not large enough to counter balance the effects of high AE rate in the roflumilast group.

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

Table 51 Patients who withdrew early in the pivotal and COPD safety pools

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

Data source: Table 1.3.5, pp 307 and Table 2.3.5, pp 7940 of ISS (289/2008)

7.3.4 Significant Adverse Events

Gastrointestinal adverse reactions

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

Both the frequency and severity of GI AEs appeared to be dose dependent. In the COPD safety pool, which contained 4 independent trials that had a 250 mcg roflumilast treatment arm, the

frequency of GI AEs in the 250 mcg groups were about half of what seen in the 500 mcg group but still greater than placebo (see table 52 below).

Table 52 Gastrointestinal Toxicities in patients receiving 250 or 500 mcg of roflumilast

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

Data source: Tables 20* (pp58), 4** (pp80) and 33 (pp77) in ISS (24/2009)

While nearly 90% of the GI side effects were mild or moderate in intensity, the remaining 10% were severe and met the criteria for an SAE. The more severe GI side effects were intractable diarrhea and pancreatitis. Though small in number, both occurred almost exclusively in roflumilast treatment groups. Among the 13 cases of intractable diarrhea and 7 cases of acute pancreatitis reported in the COPD safety pool, all but one case of each occurred in the roflumilast treated groups. Of the two patients who had acute pancreatitis who died, both were receiving roflumilast 500 mcg at the time of occurrence. Again, occurrence of severe GI side effects appeared to be dose dependent. The risk of developing GI SAEs was low for the roflumilast 250 mcg group, similar to that for the placebo group (see table 53 below).

Table 53 Serious gastrointestinal toxicities (frequency > 0.3% patients in any treatment group)

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

Data source: Table 33 (pp77) in ISS (24/2009)

Roflumilast-related weight loss

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

To better understand how roflumilast associated weight loss affects patients with COPD, a meta analysis was performed using weight measurements collected from trials M2-124, M2-125, M2-

111, M2-112, M2-127 and M2-128. Data were analyzed in several pools depending on the length of the clinical trials. As weight was regularly assessed in the pivotal studies, M2-124 and M2-125, and because they were long (one year) in duration, the results from the pivotal COPD weight pool will be discussed here. The results from analysis of other study pools were similar.

Prevalence and severity of roflumilast related weight loss

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

The mean weight change for patients in the roflumilast group was - 2.09 kg, which corresponded to a -2.72% reduction in body weight compared to baseline. For patients who received the placebo, the mean body weight increased slightly by +0.08 kg which equaled to a 0.25% increase in body weight from the baseline. Obese patients had most absolute (kg loss from the baseline) and relative (% loss from the baseline) weight loss. The between treatment differences in absolute and relative weight loss were: 2.01 kg or % for underweight patients, 1.76 kg or % for normal weight patients, 2.09 kg for % for overweight patients and 3.11 kg or % for obese patients. Subgroup analysis suggested that mild and moderate weight loss affected COPD patients of all disease severity equally. Severe weight loss disproportionally affected more patients with very severe COPD (FEV1 < 30% predicted) than patients with moderate (FEV1 $\geq$ 50%, < 80% predicted) or severe (FEV1 $\geq$ 30%, < 50% predicted) disease (see table 54 below).

Table 54 Analysis of mean weight loss by patient characteristics at baseline (studies M2-124 and M2-125 pooled data)

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

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

Severity of weight loss was categorized as mild, moderate and severe, which were defined respectively as weight loss of 5% or less, more than 5% but equal or less than10% (> 5% and < 10%) and more than 10% of the baseline weight. In the pivotal pool, 35.2% of the patients in the roflumilast group had mild weight loss, 20.1% had moderate weight loss and 7.1% had severe weight loss. In comparison, 27.5, 8.3 and 1.9% of the patients in the placebo group had mild, moderate and severe weight loss (see table 55).

Table 55 Prevalence by severity of weight loss (studies M2-124 and M2-125 pooled data)

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

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

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

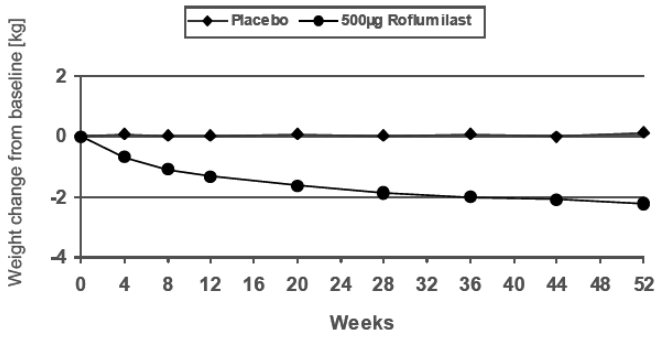
Potential Risk factors for weight loss

Exploratory analysis identified the following pertinent potential risk factors for increased vulnerability to roflumilast related weight loss: age >65, very severe COPD disease (FEV1 < 30% predicted at the baseline), female, on treatment GI, metabolic, nutritional or psychological AE(s) while receiving roflumilast.

Progression of weight loss overtime

Roflumilast related weight loss occurred early in treatment. As shown in Figure 1, body weight decreased most rapidly during the first 4-8 weeks after initiating roflumilast treatment. The decline in body weight persisted through out the entire 52 week trial period at lower but steady rate from around week 12 and onward. In contrast, there was little or no change in body weight for patients who received placebo.

Figure 6 Mean weight change from baseline (Pivotal pool)



Source: Figure 1, pp59 of CSR 348/2008.

Reversibility of roflumilast related weight loss

Roflumilast related weight loss appeared to be partially reversible. A 3 month post treatment follows up of patients who had AE weight loss during trails M2-124 M2-125, M2-127 and M2-128 showed an average regain of 50% the weight lost in the trial.

Psychiatric adverse events including suicide (completed and attempted)

Adverse events related to the psychiatric system organ class were more common in patients who received roflumilast 500 mcg compared to those who received the 250 mcg dose or placebo. There were a total of 403 (7%) psychiatric adverse events reported in patients who received roflumilast 500 mcg once daily compared to 190 (3.5%) total events in the placebo group. There were 2-3 times greater insomnia, anxiety, and depression related adverse events in the 500 mcg roflumilast group compared to placebo (see table 56). In addition to the increase in psychiatric adverse events, of note is that there were more patients treated with roflumilast 500 mcg that had headache, dizziness, and tremor reported as adverse events compared to placebo [266 (4.6%), 139 (2.4%), and 98 (1.7%) compared to 110 (2%), 65 (1.2%), and 15 (0.3%) for headache, dizziness, and tremor in the roflumilast 500 mcg compared to placebo, respectively.

Table 56 Combined treatment emergent adverse events in the psychiatric SOC reported > once and more in roflumilast treatment groups (COPD safety pool)

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

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

In order to assess whether the incidence of psychiatric AEs was consistent across other disease clinical development programs, psychiatric system organ class AEs were reviewed for COPD studies conducted by a different sponsor in Japan and in asthma and "other" disease indications that roflumilast has been studied (diabetes, allergic rhinitis, rheumatoid arthritis, and osteoarthritis). Review of these data show that an approximately 2-fold increase in psychiatric AEs in patients receiving 500 mcg of roflumilast once daily is persistent across studies in different patient populations and appears to be dose-related (see table 67 below). The types of AEs reported in these studies are consistent with those reported in the COPD population (insomnia, anxiety, depression).

Table 57 Total treatment emergent adverse events in the psychiatric SOC reported across roflumilast clinical programs

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

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

In addition to the general 2-3 fold increases insomnia, anxiety, and depression, there were a total of 5 completed suicides or suicide attempts reported in the roflumilast COPD safety data base

(N=12054 patients) in roflumilast treated patients compared to none in patients treated with placebo. In none of the three completed suicide cases (all males) did the patient have a prior history of depression. In two of the cases the patient had reportedly discontinued roflumilast approximately 20-21 days prior to the suicide event. With regard to the suicide attempts, both females had prior psychiatric histories (depression in one patient and previous suicide attempt in the other). Both patients were receiving roflumilast at the time of the suicide attempt. Brief narratives of the completed and attempted suicides follow:

Completed Suicides

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

- Patient 96102 (Study M2-125, Spain): The patient is a 76 year old male enrolled in Study M2-125 who received roflumilast 500 mcg once daily. Medications included ipratropium, salmeterol and salbutamol for COPD. He had no previous history of depression or other emotional problems. Five days after being randomized to the roflumilast 500 mcg once daily treatment group the patient started to complain about insomnia, irritability, and anxiety. The patient decided to withdraw from the study and did so on (b) (6) (11 days post-randomization). Five days after stopping therapy (a total of 9 tablets), he suffered from an anxiety crisis and was treated in an emergency room with intramuscular diazepam and prescribed clorazepate which he took twice over the next 4 days. He was subsequently prescribed alprolazolam by his physician. Eleven days after discontinuing roflumilast he took an overdose of alprazolam (7-9, 0.5mg tablets) and was treated in an emergency room. There he was seen by a psychiatrist who prescribed venlafaxin, 75 mg, in addition to alprazolam. Four days later the patient was seen by a private psychologist who referred him to a psychiatrist because of ongoing anxiety and insomnia. He committed suicide by jumping from the 3rd or 4th floor of an office building on (b) (4) 3 weeks after discontinuing roflumilast.

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

after being treated with roflumilast 250 mcg once daily for approximately 17 weeks. Of note is that upon further investigation the investigator indicated that since the last study visit on (b) (6), the patient had taken 6 tablets of roflumilast (Note: if taken consecutively immediately following that last visit, then the patient committed suicide approximately 20 days after the last dose of roflumilast 250 mcg once daily).

Suicide Attempts

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

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

The Applicant included limited information regarding an independent blinded assessment of a subset of the roflumilast COPD database for suicide and suicide related events using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) on page 88 of the Applicant's (Forest Laboratories) background package for the Pulmonary and Allergy Advisory Committee (PADAC) meeting for roflumilast on April 7, 2010. It should be noted, however, that neither the C-CASA analysis noted above or any other independent analyses of suicide or psychiatric events for roflumilast have been submitted to the roflumilast NDA (22-522) for review by the FDA. In addition, FDA was not involved in the selection of clinical trials or patient populations included in the analysis.

7.3.5 Submission Specific Primary Safety Concerns

Submission specific primary safety concerns include GI toxicity, weight loss, psychiatric effects including depression and suicide. These significant adverse events are discussed above in section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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

The most prominent non-COPD related adverse events noted in the controlled studies were weight loss, diarrhea, nausea, headache, insomnia and dizziness. These adverse events were 2 to 4 fold more frequent in the roflumilast treated patients compared to the placebo treated patients. The frequency of these adverse events ranged from 7-10% (weight loss, diarrhea) to 2-5% (headache, insomnia and dizziness) in roflumilast 500 mcg treated patients compared to 2-3% (weight loss, diarrhea) to 1% or less (headache, insomnia and dizziness) in placebo treated patients (see table 58 below).

Table 58 Patients with AEs ≥ 2% by system organ class and preferred term (pivotal COPD study pool and COPD safety pool)

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

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

7.4.2 Laboratory Findings

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

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

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

Table 59 Change in hemoglobin levels from baseline to end of treatment

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

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

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

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

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

7.4.3 Vital Signs

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

7.4.4 Electrocardiograms (ECGs)

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

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

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

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

In addition, 24-hour Holter ECG monitoring was performed in selected patients from trial M2-125 to study the arrhythmogenic potential of roflumilast when used in combination with long-acting beta agonists (LABA) in patients with COPD. The evaluation consisted of a 24-hour Holter ECGs with 3 channels and was performed with 55 US patients (33 in the roflumilast and

22 in the placebo group) receiving LABA as concomitant medication. In addition to the standard 12-lead centralized ECGs, the 24-hour Holter ECGs were performed at baseline, 6 months, and at the last study visit (which was either the scheduled end of the study or an earlier date if the patient discontinued the study). The results of the 24-hour Holter ECGs showed no differences in heart rates or occurrence of arrhythmias between the roflumilast and the placebo treated groups. Furthermore, 3-channel 24 hour Holter was also performed in about 150 patients from US study sites in trial M2-111 and there were no significant findings.

In addition to assessing for cardiac safety in the clinical studies in COPD patients, the effects of roflumilast on cardiovascular function were investigated in healthy volunteers in 4 phase 1 studies. Refer to section 7.4.5 for details.

7.4.5 Special Safety Studies/Clinical Trials

Mesenteric Vasculitis

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

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

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

The search identified two patients with suspected ischemic colitis, one from the roflumilast 500 mcg treated group in trial FK1-007, and the other from the placebo group in trial M2-110. The

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

Cardiac safety

The main sources of roflumilast cardiovascular safety data were: Phase I cardiovascular safety trials in health volunteers and meta analysis of ECG and Holter findings from COPD trials. Four phase I clinical trials were conducted in healthy volunteers to investigate the effects of roflumilast on cardiovascular function.

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

Trial CP-069 was a placebo controlled QT study in 80 healthy subjects (54 males, 26 females). Single 400 mcg dose of moxifloxacin was given as positive control 1 day prior to roflumilast administration. Seven or 14 day roflumilast treatment of up to 1000 mcg per day were tested. OT interval was accessed 1 hour after roflumilast dosing. No QTc change of 30 ms or greater was observed in any subjects.

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

Trial CP-070 was a randomized, double-blind; placebo controlled 4 way crossover, single dose study in 12 healthy males. The subjects received single dose of 500 mcg roflumilast or 100 mcg sildenafil each alone or in combination, or placebo. There was no clinically relevant change in vitals signs, ECG and impendence cardiography. Mean QTc-prolongations of 5 to less than 20 sec were noted for roflumilast and sildenafil and roflumilast alone. However, the clinical implication of such a finding was unclear as single dose study was not designed to detect differences of QT/QTc prolongation between treatments.

Infections

As a PDE4 inhibitor, roflumilast has a wide range of anti inflammatory properties. In non-clinical studies, roflumilast has been shown to be able to partially inhibit the formation and release of pro-inflammatory mediators such as tumor necrosis factor (TNF-α) and reactive oxygen species (ROS), as well as accumulation of neutrophils and macrophages. Therefore, infection was a special topic of interest identified prospectively. Both preclinical and clinical studies were conducted to evaluate the effect of roflumilast on infection.

Several repeat dose toxicity studies were conducted in multiple species (mice, hamster, dog and monkey) and showed no increased risk for infection with roflumilast use.
Treatment emergent infection AEs were analyzed in the pivotal and the COPD safety pool and showed no difference in the overall incidence of infections in the roflumilast 500 mcg treated group compared to the placebo (Pivotal pool: 27.7% verses 27.3%. COPD safety pool: 25.9% versus 27.5%). Additionally, there were no overall difference in infection related death, SAEs or early withdraw. There appeared no increased risks for serious infections known to be associated with TNF-alpha blockade, such as tuberculosis, invasive fungal and opportunistic infections.

7.4.6 Immunogenicity

The proposed drug is a small molecular entity and there is no concerns regarding immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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

7.5.2 Time Dependency for Adverse Events

The pertinent information regarding time dependency for adverse events was discussed throughout this review with individual AEs.

7.5.3 Drug-Demographic Interactions

Drug demographic interactions were examined pharmacologically in phase I PK/PD trials in healthy volunteers and clinically using pooled safety data from COPD trials.

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

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

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

Table 60 Affects of gender, age and COPD severity on adverse events (Studies M2-124 and M2-125 pooled data, ITT)

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

Smoking status							
Current							
Placebo	641	519	386 (60.2)	35 (5.5)	14 (2.2)	120 (18.7)	73 (11.4)
Rof500	638	504	421 (66.0)	88 (13.8)	16 (2.5)	119 (18.7)	83 (13.0)
Former							
Placebo	904	721	577 (63.8)	38 (4.2)	26 (2.9)	216 (23.9)	104 (11.5)
Rof500	909	682	619 (68.1)	137 (15.1)	26 (2.9)	182 (20.0)	136 (15.0)

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

7.5.4 Drug-Disease Interactions

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

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

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

7.5.5 Drug-Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP 3A4 and CYP 1A2. Both roflumilast (the parent drug) and roflumilast N-oxide (the active metabolite) have intrinsic phosphodiesterase 4 (PDE4) inhibitory activities.

Co-administration of theophylline (375 mg twice daily for 10 days) and 500 mcg oral roflumilast did not alter the pharmacokinetics of theophylline, roflumilast or roflumilast N-oxide to a clinically relevant extent.

Drugs that have been shown not to produce any pharmacokinetic or pharmacodynamic interaction with 500 mcg oral roflumilast included albuterol, budesonide, digoxin, formoterol, oral and intravenous midazolam, montelukast, sildenafil, warfarin and antacid such as magnesium aluminum hydroxide.

However, Phase I studies showed higher AE incidences for the combination therapy of roflumilast with ketoconazole, sildenafil, digoxin, and oral contraceptives gestodene and ethinylestradiol in comparison to roflumilast monotherapy. More AEs under combination therapy than under treatment with the reference drug alone were observed for warfarin, erythromycin, sildenafil, and formoterol. Headache was the most frequent reported AE under roflumilast or combination therapy, followed by gastrointestinal symptoms (gastrointestinal irritation, diarrhea, nausea, vomiting) and musculoskeletal symptoms (back pain, myalgia).

Additionally, subgroup analysis of patients in the pivotal pool suggested that patients who were on concomitant LABA or SAMA therapy during roflumilast treatment had higher incidence of AE, SAE and AE leading to study withdrawal or death comparing to patients who were on roflumilast alone.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Pharmacology studies suggested that both roflumilast and its active metabolite, roflumilast N-oxide are weak antagonists (less than 30% inhibition) of tumor necrosis factor alpha (TNF-α). As discussed earlier in section 7.2.3, roflumilast has been demonstrated to be carcinogenic in animal species. As a result, cancer and tumor-related adverse events were identified as a topic of special interest.

In the overall roflumilast clinical development program, a total of 218 tumor events were reported in 208 patients. One hundred thirty one (60%) of the tumors were in patients in the roflumilast group and 86 (40%) of the tumors were in patients in the placebo group. These data are consistent with what was observed in COPD patients where 105 of 185 (57%) and 80 of 185 (43%) of tumors were in the roflumilast and placebo treated groups, respectively. There was more lung and prostate cancer reported for patients treated with roflumilast than those who received placebo (33 and 14 compared to 17 and 7, for lung and prostate cancers in the roflumilast and placebo groups, respectively (see table 61 below).

Table 61 Summary of cancer/tumor types in COPD patients (COPD safety pool)

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

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

7.6.2 Human Reproduction and Pregnancy Data

Male reproduction:

In vivo animal studies showed that high dose of roflumilast caused prostate and testicular atrophy and hypo function of male reproductive organs. Three phase I safety studies on male fertility were conducted to investigate the clinical relevance of toxicology findings.

Trial FHP033 was a double-blind, placebo-controlled, 3-period crossover study on the effect of roflumilast on male endocrine function in 25 healthy male subjects. During the 15-day administration periods, subjects received once daily dose of roflumilast 250 or 500 mcg or placebo. Serum levels of testosterone, FSH, LH, inhibin B, progesterone, aldosterone, adrenocorticotropic hormone (ACTH), sodium and potassium were measured and compared. There was no clinically relevant difference between treatment groups.

Trial FHP035 was a double-blind, placebo-controlled, parallel-group study in 351 healthy men. The study began with a 12 week active treatment period followed by a 12 week, off treatment follow up. The subjects received once daily dosing of roflumilast 500 mcg or placebo for 12 weeks during the active treatment. Sperm concentration, progressive motility and male reproductive hormones (testosterone, FSH, LH, inhibin B) were measured at the baseline as well as during the treatment and follow-up period. Compared to baseline, both the roflumilast 500 mcg and the placebo treated patients had > 50% reduction in sperm counts and sperm motility during the treatment and follow up periods. There were no between treatment differences in male reproductive hormones.

Trial CP-052 was a 48 week no treatment post study observation of 96 subjects (48 received the roflumilast and 48 received the placebo) from trial FHP035. All 96 subjects had greater than 50% reduction from the baseline values in sperm concentration or motility during the treatment or follow-up period in trial FHP035. Several semen samples were collected during the 48 week trial period and no relevant differences were identified between the groups previously treated with roflumilast or placebo for any of the variables tested.

The AE profile reported from above male fertility studies were in line with those reported from other trials in healthy volunteers. Two cases of appendicitis were reported in 2 patients received roflumilast 500 mcg in trial FHP035. One subject in the placebo group died in the observation only trial CP-052. There was no other SAE or early withdrawals reported from any of the 3 male fertility trials.

Pregnancy:

Pregnancy was a criterion of exclusion for participating in roflumilast clinical trials. As of December 9, 2008, a total 47 females became pregnant under the entire clinical development program (all indications) of. Twenty (20) of the 47 pregnancies occurred in patients who were in the roflumilast treatment group (16 in the 500 mcg group, 3 in the 250 mcg group and 1 in the 125 mcg group). The estimated duration of in utero drug exposure was 2 to 65days. The pre pregnancy drug exposure was between 2 days and 5 months.

Of the 20 pregnancies in roflumilast treated woman, 11 resulted in healthy neonates, 2 spontaneously aborted, 3 ended with elective abortion, 2 terminated medically (one due to severe maternal hypertension) and 2 lost to follow up. Six of the healthy neonates were delivered full term vaginally without any complication, four were delivered via uncomplicated caesarean sections (three at term, one pre term at 37 weeks in response to maternal preeclampsia).

Lactation:

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

7.6.3 Pediatrics and Assessment of Effects on Growth

COPD is not a pediatric disease. Therefore effects in pediatric patients and on growth were not evaluated.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

To date, there was no experience with accidental overdose. A single dose of up to 5000 mcg and repeat doses of up to 1000 mcg were administered to healthy volunteers in phase I trials. Single escalating dose of 1000 to 5000 mcg of roflumilast were planned for trials FHP001 and FHP002. However, dose escalation stopped at 2500 mcg in trial FHP001 due to poor tolerability. Trial FHP002 terminated early after only 1 subject received the maximum 5000 mcg dose. The most frequently reported AEs after administration of 2500 mcg dose were headache, gastrointestinal complaints (diarrhea, nausea and lower abdominal pain), dizziness, palpitation and clamminess. Additionally, decreased systolic and diastolic blood pressure were noted in subjects received single 2500 mcg or 5000 mcg dose of roflumilast.

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

No independent study conducted to evaluate any withdrawal or rebound effects after long term roflumilast use. Nevertheless, trial FK1-103 included a roflumilast withdrawal arm, in which 12 weeks of roflumilast treatment was followed by 12 weeks of placebo treatment. Patients in the roflumilast withdrawal arm were compared to patients in the 24 weeks roflumilast or placebo treatment arms for efficacy and tolerability. There was no evidence of any effect on vital signs, ECG, lab values or physical exams from roflumilast withdrawal.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

The Applicant submitted the proposed label in the PLR format. DMEPA has reviewed and found the proprietary name, Daxas, to be acceptable. However, given the deficiencies described in this review and the late proposed change of indication by the new sponsor, Forest labs, this clinical development program will require major revisions to be considered for approval. Therefore, a detailed labeling review was not conducted during this review cycle. The originally planned labeling negotiations with the Applicant have been canceled.

9.3 Advisory Committee Meeting

This NDA application will be discussed in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting scheduled for April 7, 2010. The discussion will be based on the original application from Nycomed, which seeks an approval for roflumilast 500 mcg to be administered once daily for the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbations. A complete briefing package has been sent to all related parties.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	FOREST RESEARCH INSTITUTE	DAXAS(ROFLUMILAST 500 MCG TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XUEMENG HAN SARRO
03/24/2010

ANTHONY G DURMOWICZ
03/24/2010

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:	22-522	**APPLICATION TYPE:**	NDA
SPONS0R:	Nycomed GmbH	**PROPRIETARY NAME:**	Daxas®
INVESTIGATOR:	Multiple	**USAN NAME:**	Roflumilast
CATEGORY:	Anti-inflammatory	**ROUTE:**	oral
MEDICAL OFFICER:	Xuemeng Han Sarro, MD, Ph.D.	**REVIEW DATE:**	2009

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
July 15, 2009	July 15, 2009	Electronic hybrid with Adobe and PDF documents	NDA 22-522

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a clinical NDA filing review of roflumilast (Daxas) oral tablet for COPD. The proposed indication is for "maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations." The proposed regimen is 500 mcg once daily.

Roflumilast belongs to a new drug class: phosphodiesterase type IV (PED4) inhibitors. It has been under development for the treatment of both COPD and asthma by 4 different sponsors for more than a decade. The overall clinical development program has 114 clinical trials.

This submission contains results from 18 phase II and III COPD trials and information from 29 asthma trials and more than 60 clinical pharmacology studies. The submission appears complete enough for a further review, and is therefore considered "fileable."

The Division plans to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee (AC). Audits of clinical study sites will be conducted by the Division of Scientific Investigations.

OUTSTANDING ISSUES:

Potential review issues include:

1. Clinical significance of the statistically significant efficacy claim (AC)
2. Role of Roflumilast in COPD management (AC)
3. Safety

RECOMMENDED REGULATORY ACTION

__X__ **FILEABLE** _____ **NOT FILEABLE**

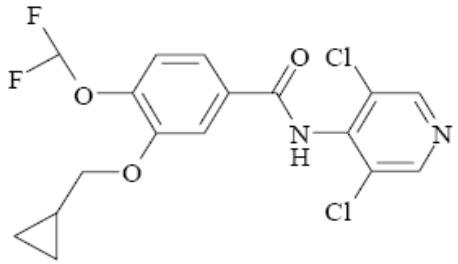
REVIEWERS

Medical Reviewer: Xuemeng Han Sarro, MD, Ph.D.

Clinical Team Leader: Anthony G. Durmowicz, MD

I. General Information

Trade Name:	Daxas®
US Adopted Name:	Roflumilast
International Non-proprietary Name:	Roflumilast
Molecular Formula:	$C_{17}H_{14}Cl_2F_2N_2O_3$
Molecular Weight:	403.22
Manufacturer:	Nycomed GmbH, Germany



Proposed indication:		Maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.
Proposed regimen:		500 mcg tablet, once a day
Proposed Mechanism of Action:		increase cAMP mediated anti-inflammatory response via PDE4 inhibition
Sponsors:	Current:	Nycomed
	Previous:	Byk-Gulden/Altana
		Pharmacia & Upjohn
		Pfizer

II. Regulatory and Foreign Marketing History

A. Regulatory History

The regulatory history concerning the development of roflumilast is extensive. The original sponsor Altana submitted the initial pre-IND package in October, 2000 for both its asthma and COPD programs. To date, there are more than 600 documented communications in the DARRTS system. Both the asthma and the COPD program were developed under a single IND (IND-57883). The following is a list of the most clinically pertinent regulatory events and issues regarding the COPD program.

<u>Key Regulatory Events for COPD Program:</u>

Original IND for asthma submitted on 2/16/1999

Pre IND meeting for COPD program: October 5, 2000

EOP2 meetings (12/6/2001 by Byk-Gulden/Altana and 3/4/2003, by Pharmacia & Upjohn on behalf of Altana Pharma AG)

SPA (4/7/2003) and follow up T-con (6/23/2003) to discuss 2 phase III studies (M2-110 for COPD and M2-023 for asthma).

SPA on 2 COPD protocols: PADEACO-9287-001 (24 week study on PFT and respiratory symptoms; OPUS study (BY217/M2-111, 52 wk study on rate of exacerbation)

Sponsor submitted Type C meeting request on 11/30/2006 and the request was denied (12/12/2006) by the division considering the previous interactions the division had with the sponsor on its COPD program. The division, however, did agree to respond to sponsor's questions.

Pre NDA meeting (416/2008) discussed preparations for NDA submission.

<u>Previous Regulatory Issues and FDA Inputs:</u>

End points selection: (DPAP, recommended or concurred)

- Pre versus post bronchodilator FEV1
    - DPAP suggested that trough FEV1 (pre bronchodilator FEV1) is a better measurements of pulmonary function for non bronchodilators than post bronchodilator FEV1, which does not allow demonstration of end of dosing interval efficacy needed for once daily regimen. (Clinical review of protocol PDEACO-9287-001 by Dr. Carol Bosken, 2/3/05, comments faxed to the applicant on 2/28/05)
- Definition of COPD exacerbation and rate of exacerbation
    - CS use alone not adequate to define severe exacerbation, need add hospitalization with predetermined criteria (OK to define moderate exacerbation)
- Clinical relevant outcome measures
    - Need for "at least one of the clinically related outcome measures", in addition to changes in FEV1 for approval of an anti-inflammatory drug in COPD. Use of any quality of life instrument as outcome measures would "need to be validated in the patient population being studied." (4/10/03, clinical review of SPA for M2-110 by Lydia Gilbert-McClain)
    - To use SGRQ to support efficacy claim, a clinically meaningful (at least 4 units) improvement in the mean score of the treated subjects, comparing to placebo, is needed. (Clinical review of protocol PDEACO-9287-001 by Dr. Carol Bosken, 2/3/05, comments faxed to the applicant on 2/28/05)

Statistical analysis plan (SAP) (DPAP comments):

The division made multiple SAP related comments through out the development phase. Majority of the comments dealt with issues regarding predetermined data analysis roles, treatment group assignment and pooling of results from different studies. The followings are some of the representative excerpts:

- To preserve the baseline balance between the comparative treatment arms, inclusion of subjects in efficacy analysis should based on randomization, not the actual treatment group received. (Statistical review comments faxed to the applicant on 2/28/05)

- Statistical tests for primary and key secondary end points should follow the standard two sided, 5% test. Testing each efficacy end points at the proposed one-sided 2% level is not appropriate as the direction of the outcome can not be predicted. (Protocol comments for study BY217/M2-112, 2/24/05)

- Predetermined statistical significance criterion and decision role should be use for pooled and subset analysis if the outcome of the analysis is to be included in the labeling. (Protocol comments for study BY217/M2-112, 2/24/05)

- To control the over all rate of type I error, key secondary end points will be tested only if there is a statistically significant outcome for the primary end point. (statistical review, 2/28/05)

B. Foreign Marketing History

Not applicable.

III. Clinical Program

The clinical program began in 1996 and contains 114 studies that enrolled 24,000 subjects. More than 14,000 subjects were exposed to roflumilast. The safety and tolerability of roflumilast were studies in healthy volunteers, patients with COPD, asthma, allergic rhinitis, arthritis, psoriasis and diabetes.

- 114 clinical trials for 6 indications
  - 18 COPD, 29 asthma, 4 others (AR,RA,OA, DM)
  - BA,BE, PK, PD studies in healthy volunteers and patients with cirrhosis or RF
    - 2 BA, 5 BE
    - 50 PK, 8 PK/PD or 3 PD (food, Drug-drug interactions, hepatic or renal impairment and the elderly)
- >24,000 enrolled
- > 14,000 subjects exposed to the drug including:

- COPD: >7800
- Asthma: > 5000

The COPD Program included 18 phase II and phase III clinical trials.

- 2 pivotal clinical trials
  - M2-124, M2-125
    - 52 wk, r, pc, p, db, 500 mcg, 3091 Pts, 1475 Rof treated
    - Population: FEV1≤ 50% predicted, allowed baseline LABA (50%) or SAMA. ICS OK during "run in"
    - Primary EPs: preFEV1, rate of exacerbation

- 9 supportive trials

  - M2-111 and M2-112 (concomitant ICS permitted)
    - 52 wk, r, pc, p, db, 500 mcg, 1282 Rof treated
    - Population: FEV1: ≤ 50% predicted, allowed baseline ICS or SAMA
    - Primary EPs: pre or post FEV1, rate of moderate or severe exacerbation

  - M2-127 and M2-128 (as "add-on")
    - 24 wk, r, pc, p, db, 500 mcg, 821 treated
    - Population: FEV1: 40-70 % predicted, mandatory concomitant LABA (salmeterol M2-127) or LAMA (tiotropium, M2-128)
    - Primary EPs: pre FEV1

  - M2-107, M2-110, M2-121, FK1-101 and FK1-103
    - 250 (M2-107 and FK1-101 only), 500 mcg, 1596 Treated
    - 24 wk (26 wk, FK1-101), r, pc, p, db
    - Population:
      - FEV1: 30-80 % (M2-107, M2-110)
      - FEV1: ≤ 65% (M2-121)
    - Co-Primary EPs:
      - post FEV1 (all except FK1-101, preFEV1)
      - post FRC (M2-121)
      - SGRQ (M2-110, FK1-101 and FK1-103)

- 7 other studies (shorter duration, open cross over design, extension of other studies, different end points)

IV. Items Required for Filing and Reviewer Comments

A. Necessary Elements (21 CFR 314.50)

The table below lists the necessary elements for an NDA and their location within the electronic submission.

Necessary Elements

Type	Status	Location (Item #: Folder from Main Table of Contents)
Application Form (FDA 356h):	Present	Module 1.1.2
Debarment Certification:	Present	Module 1.3.3
Financial Disclosure:	Present	Module 1.3.4
Statements of Good Clinical Practice:	Present	Individual study reports
Environmental Assessment:	Present	Module 1.12.14 categorical exclusion under 21CFR25.31(b)
Proposed label:	Present	Module 1.14.1
Integrated Summary of Efficacy	Present	Module 2.7.3
Integrated Summary of Safety:	Present	Module 2.7.4
Integrated Summary of Benefits and Risks:	Present	Module 2.5
Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures:	Present	Individual study reports
Statistical Analyses:	Present	2.7.3.1.2.6 and individual study reports
Pediatric Use Section:	Present	Module 1.9 (waiver request)
Case Report Tabulations:	Present	Module 5.3.7.1

Necessary Elements

Type	Status	Location (Item #: Folder from Main Table of Contents)
Case Report Forms (for patients who died or did not complete study):	Present	Individual studies
Patent Information:	Present	Module 1.3.5.1

B. Decision

The submission appears adequate from a clinical standpoint to allow for further review, and is therefore fileable.

V. Preliminary Review of Package Insert

- Proposed indication
  - "Maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbation"
- Safety
  - Includes AEs >1% from 14 PBO controlled COPD trials
  - D-D interaction
  - Pregnancy category C, labor and delivery, nursing mothers
  - Pediatric (not studied) and geriatric use (no dose adjustment)
  - No dose adjustment in RF or Child-Pugh A & B
  - Contraindicated in Child-Pugh C
- Clinical trials to be included for efficacy
  - Pivotal trials (M2-124 and 125)
  - Supportive LABA/LAMA add on trials (M2-127 and 128, 24 wks, preFEV1 only)
  - Claim " significant" improvement in pre-FEV1

VI. Clinical Studies

The COPD program contains 11 randomized, placebo controlled phase 3 studies (2 pivotal and 9 supportive) with variable end points and eligibility criteria. Two of the studies, M2-124 and M2-125, are considered to be the pivotal trials by the sponsor. However, to obtain a more balanced view of the entire drug development program, this NDA review will focus on the 6 studies that

had primary end points most relevant to the proposed claims of "treatment for COPD associated chronic bronchitis" and "reduction of COPD exacerbation". Four of the six studies (M2-124, 125, 111 and 112) were one year duration in severe COPD patients with pre bronchodilator FEV1 and rate of moderate or severe exacerbation as co primary end points. The other 2 studies (M2-127 and 128) were 6 month studies designed to evaluate the impact of concomitant treatment with LABA or LAMA and had only pre bronchodilator FEV1 as the sole primary end point. Table 1 lists the key design characters and results of the 6 phase III studies.

Table 1 Characteristics of Key Phase III Roflumilast COPD Trials

Roflumilast	Sample Size	Population	Study Groups	PreBD-FEV1 (mL)	PostBD-FEV1 (mL)	Annual rate of moderate or severe exacerbation	Moderate	Severe
M2-124	1524 (52 wks trial)	COPD with Bronchitis, preBD-FEV1 <50% predicted, mean 1.1 L (reversibility 10-12% or 110-132 mL)	Roflumilast 500 versus placebo	39 mL (3.55%)	49 mL (4.05%)	14.9% reduction over placebo	15.7% reduction over placebo	11.4% reduction over placebo (p=0.29)
M2-125	1568 (52 wks trial)	COPD with Bronchitis, preBD-FEV1 <50% predicted, mean 1.0 L (reversibility 10-12% or 100-120 mL)	Roflumilast 500 versus placebo	58 mL (5.8%)	61 mL (5.55%)	18.5% reduction over placebo	18.0% reduction over placebo	22.9% reduction over placebo (p=0.15)
M2-127	933 (24 wks trial)	preBD-FEV1 40-70% predicted, mean1.4 L (reversibility 6% or 84 mL)	Roflumilast 500 +LABA versus placebo	49 mL (3.5%)	60 mL (4.04%)	(not primary EP)		
M2-128	743 (24 wks trial)	preBD-FEV1 40-70% predicted, mean 1.5 L (reversibility 6%, or 90 mL)	Roflumilast 500 +LAMA versus placebo	80 mL (5.33%)	81 mL (5.09%)	(not primary EP)		
M2-111	1173 (52 wks trial)	preBD-FEV1 <50% predicted, mean 0.9-1 L (reversibility 19%)	Roflumilast 500 versus placebo	42 mL	42 mL	14.0% reduction over placebo (p=ns)		
M2-112	1513 (52 wks trial)	preBD-FEV1 <50% predicted, mean 1-1.1 L (reversibility 11%)	Roflumilast 500 versus placebo	57 mL	60 mL	15.2% reduction over placebo (p=ns)		

Efficacy

The applicant claims that there are statistically significant improvements in pre-bronchodilator FEV1 (an increase of 39 mL in M2-124, 58 ml in M2-125) and rate of "moderate or sever" exacerbation (a decrease of 15% in M2-124 and 18.5% in M2-125).

Reviewer's comment: The applicant claimed that their studies have reached the co-primary end points and there are significant improvements in pre-bronchodilator FEV1 and reduction in the rate of moderate or sever exacerbations in the roflumilast treated subjects. However, the magnitude of change is minimal for both primary end points and their clinical significance will be the key review issue for this NDA and topic of discussion for the advisory committee.

Safety

There are no major differences in the overall incidence of AEs, SAEs and all cause mortality in the roflumilast treated group comparing to placebo. However, more roflumilast treated subjects (about twice as many) has GI related AEs and more patients treated with roflumilast withdrew due to treatment related AEs. The most common AEs leading to withdraw in the roflumilast group were GI related symptoms such as diarrhea, nausea, abdominal pain, poor appetite and weight loss; as well as neurological symptoms such as tremor, dizziness and insomnia. (Tables 2 and 3)

Table 2 Overview of adverse events

T-Table 2.5- 10: Overview of adverse events

		Placebo (N = 5491)	Rof500 (N = 5766)
		N (%)[a] of patients	
Number of patients			
with any AE		3447 (62.8)	3873 (67.2)
with related[b] AEs		294 (5.4)	1003 (17.4)
withdrawn due to AEs		503 (9.2)	824 (14.3)
with SAEs		782 (14.2)	781 (13.5)
with AEs leading to death		86 (1.6)	84 (1.5)
with mild AEs		843 (15.4)	941 (16.3)
with moderate AEs		1835 (33.4)	2088 (36.2)
with severe AEs		765 (13.9)	842 (14.6)
		n (%)[a] of events	
Number of AEs		**9884**	**11991**
Outcome[c]	Disappeared	8098 (81.9)	9983 (83.3)
	Still present	1089 (11.0)	1278 (10.7)
	Permanent damage	369 (3.7)	354 (3.0)
	Death	120 (1.2)	122 (1.0)
	unknown	208 (2.1)	254 (2.1)

[a] Percentages are based on the total number of patients or events in the respective treatment group. [b] Likely, probably, or definitely related as assessed by the investigator, or missing assessment. [c] Definition of outcome categories: 'disappeared'= recovered without sequelae, recovered, disappeared; 'permanent damage' = recovered with sequelae, permanent damage; 'still present' = improved, but not yet recovered, still ongoing, not recovered.
AE = adverse event, COPD = chronic obstructive pulmonary disease, N = number of patients, n = number of events, Rof500 = roflumilast 500 µg once daily, SAE = serious adverse events.

Table 3 The Most Commonly Reported Adverse Events

T-Table 2.5- 11: Frequently reported adverse events

	N (%)[a] of patients	
	Placebo (N = 5491)	**Rof500 (N = 5766)**
SOCs (MedDRA)[b]		
Infections and infestations	1508 (27.5)	1492 (25.9)
Respiratory, thoracic and mediastinal disorders	1607 (29.3)	1476 (25.6)
Gastrointestinal disorders	587 (10.7)	1271 (22.0)
Investigations	584 (10.6)	811 (14.1)
Musculoskeletal and connective tissue disorders	445 (8.1)	590 (10.2)
Nervous system disorders	304 (5.5)	615 (10.7)
Preferred Term (MedDRA)[c]		
COPD[d]	1271 (23.1)	1142 (19.8)
Diarrhea	143 (2.6)	585 (10.1)
Weight decreased	101 (1.8)	394 (6.8)
Nasopharyngitis	346 (6.3)	364 (6.3)
Nausea	79 (1.4)	297 (5.2)
Headache	110 (2.0)	266 (4.6)
Upper respiratory tract infection	234 (4.3)	219 (3.8)
Bronchitis	192 (3.5)	177 (3.1)
Back pain	117 (2.1)	176 (3.1)
Insomnia	50 (0.9)	148 (2.6)
Influenza	132 (2.4)	145 (2.5)
Dizziness	65 (1.2)	139 (2.4)
Decreased appetite	22 (0.4)	125 (2.2)
Pneumonia	110 (2.0)	104 (1.8)
Hypertension	136 (2.5)	95 (1.6)
Dyspnea	120 (2.2)	84 (1.5)

[a] Percentages are based on the total number of patients in the respective treatment group. [b] Reported by ≥10% of patients in the roflumilast groups. [c] Reported by ≥2% of patients. [d] 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, Rof500 = roflumilast 500 µg once daily, SOC = system organ class.

VII. DSI Review / Audit

This NDA application requires DSI review and audit. The study sites to be inspected will be determined.

VIII. Summary

This is a clinical NDA filing review of roflumilast (Daxas) oral tablet for COPD. The proposed indication is for "maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations." The proposed regimen is 500 mcg once daily.

Roflumilast belongs to a new drug class: phosphodiesterase type IV (PED4) inhibitors. It has been under development for the treatment of both COPD and asthma by 4 different sponsors for more than a decade. The overall clinical development program has 114 clinical trials.

This submission contains results from 18 phase II and III COPD trials and information from 29 asthma trials and more than 60 clinical pharmacology studies. The submission appears complete enough for a further review, and is therefore considered "fileable."

The Division plans to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee (AC). Audits of clinical study sites will be conducted by the Division of Scientific Investigations.

IX. Timeline for Review

- Filing/Planning Meeting: September 4, 2009
- 74 Day Letter: September 29, 2009
- MCR: December 14, 2009
  - Pivotal/supportive studies reviewed
- Labeling: February 15, 2010
- Schedule AC Meeting Early March
- WU: March 13, 2010
- Primary Review Due: March 24, 2010
- Labeling T-con: April 6, 2010

- PDUFA Date: May 17, 2010

X. Comments for the Applicant

No clinical comments will be conveyed to the Applicant at this time.

Reviewed by:

Xuemeng Han Sarro, MD, Ph.D. Medical Officer, DPAP
Anthony G. Durmowicz, MD Clinical Team leader, DPAP

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/s/

XUEMENG HAN SARRO
09/25/2009

ANTHONY G DURMOWICZ
09/25/2009