CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022522Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA / Serial Number:	NDA 022-522 / 0029 0035
Drug Name:	Roflumilast tablets (N-(3,5-dichloropyrid4-yl)-3-clyclopropylmethoxy-4-difluoromethoxy benzamide)
Proposed Indication(s):	Maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations
Applicant:	Forest Research Institute, Inc.
Date(s):	Received: 08-30-2010
	PDUFA Due Date: 02-28-2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Reviewer:	Robert Abugov, Ph.D
Concurring Reviewers:	Joan Buenconsejo, Ph.D.
Statistics Supervisor:	Thomas Permutt, Ph.D (Division Director)
Medical Division:	Division of Pulmonary and Allergy Products
Clinical Team:	Anthony Durmowicz, M.D. (Medical Team Leader) Badrul A Chowdhury, M.D., Ph.D (Medical Division Director)
Project Manager:	Carol Hill

Keywords: NDA review, Clinical Studies

Biometrics Review

1. Submission History

After evaluation of original submission NDA 22522 / 0000 provided by Forest Research Institute, Inc.,claiming effectiveness of roflumilast tablets 500 mcg once daily for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations, FDA provided a complete response memorandum on 27 May 2010 stating that further evaluations were required before approval could be granted. In particular, applicant needed to further examine risk of suicides, (b) (4) and the possibility, if it is a P-glycoprotein substrate, of interactions with P-glycoprotein inhibitors.

The applicant provided additional information on 30 August 2010, with proposed labeling revisions on 29 October 2010.

2. Biometrics Evaluation

The Medical Review team determined from the applicant's 30 August 2010 submission that there is no substantial evidence associating suicidality and administration of roflumilast (b) (4) After evaluatiing submission NDA 22522 / 0029 provided on 30 August 2010 as well as additional submission NDA 22522 / 0036 provided on 21 December 2010, the Clinical Pharmacology team determined that roflumilast is not a P-glycoprotein substrate.

Biometrics evaluated the proposed label, recommending that the indication be revised to reflect the determination that the applicant provided evidence for efficacy only among patients with severe to very severe COPD. To facilitate physician interpretation of benefits, Biometrics recommended that reduction of exacerbations by roflumilast be provided in absolute rather than relative rates, amd further recommended deletion of (i) results from pooled analyses, (ii) p-values, (b) (4)

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/s/

ROBERT ABUGOV
01/14/2011

JOAN K BUENCONSEJO
01/14/2011
I concur with Dr. Abugov's statistical review of NDA 22-522 SN29 and SN35.

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Drug Name:	Roflumilast tablets (N-(3,5-dichloropyrid4-yl)-3-clyclopropylmethoxy-4-difluoromethoxy benzamide)
Proposed Indication(s):	Maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations
Applicant:	Nycomed
Date(s):	Received: 07-17-2009
	PDUFA Due Date: 05-17-2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Reviewer:	Robert Abugov, Ph.D
Concurring Reviewers:	Joan Buenconsejo, Ph.D.
Statistics Supervisor:	Thomas Permutt, Ph.D (Division Director)
Medical Division:	Division of Pulmonary and Allergy Products
Clinical Team:	Xuemeng Han Sarro, M.D. (Medical Reviewer) Anthony Durmowicz, M.D. (Medical Team Leader) Badrul A Chowdhury, M.D., Ph.D (Medical Division Director)
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Forest Research Institute, Inc. has proposed Daxas®, a film coated tablet of roflumilast, for "the maintenance treatment of chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis in patients at risk of exacerbation." Sixteen randomized, parallel arm, placebo controlled, double blind trials compared the effect of roflumilast 500 µg oral tablet once daily (QD) to placebo in COPD patients.

The primary endpoints and statistical methodologies varied across studies, and the Applicant proposed two particular studies as representing the population for the indicated use. In both studies, the primary endpoints were change from baseline of pre-bronchodilator FEV1 and rate of exacerbations which were moderate (requiring oral or parenteral glucocorticosteroids) or severe (requiring hospitalization or causing death).

Across all sixteen trials, roflumilast provided an increase in pre-bronchodilator FEV1 which ranged from 39 to 159 milliliters. Of those sixteen trials, only one showed an increase over 100 milliliters. Four 52-week studies were conducted examining exacerbation rate as a primary endpoint. Although the first two did not show significant differences between roflumilast and placebo, post-hoc data explorations suggested that greatest improvements in exacerbation rate would be seen in patients with severe or very severe COPD with a history of chronic bronchitis and exacerbations. A second pair of trials was then conducted enrolling patients with these characteristics which showed a significant difference between roflumilast and placebo in rate of moderate or severe exacerbations, with a pooled rate ratio of 0.8, and with an absolute rate reduction of 0.3 moderate or severe exacerbations per patient per year.

The primary analysis employed by the Applicant compared exacerbation rates between treatments averaged over the entire course of the study. The Applicant's analysis did not explicitly examine whether treatment effect changed over time, a potentially important consideration for maintenance therapy intended for long-term administration. Exploratory analyses of the data suggest that the reduction in exacerbation rate by roflumilast compared to placebo appears to attenuate or even disappear eight months after commencement of treatment. However, it is unclear whether the apparent loss of effect is due to attenuation in treated patients or instead reflects patterns of patient withdrawal.

Whether the magnitude of the benefits outweighs the risks associated with administration of this drug is a matter of clinical judgment rather than statistical significance.

To facilitate the determination of approvability, and as a pilot analysis for other submissions, I attempted in this review to quantify benefits and risks of roflumilast administration. Point estimates, from the two 52-week trials which demonstrated efficacy for exacerbations, suggest that each patient, during the year following initial prescription of roflumilast, will on average reduce by 3.1 days the time spent experiencing exacerbations requiring steroids but not

hospitalization, reduce by 1.2 days the time spent experiencing exacerbations requiring hospitalization, and increase by 1.4 days the time spent experiencing gastrointestinal adverse events causing marked or overwhelming discomfort.

1.2 Statistical Issues and Findings

Issues

During my review of the application, I identified one issue warranting further consideration. In particular, because the maintenance therapy indication implies long-term administration, it seems important that benefits remain positive for an extended period of time, at least throughout the duration of the studies conducted. The exacerbation analyses provided by the Applicant did not explicitly examine potential attenuations in treatment effect; of the four statistical models presented, the Poisson and the negative binomial models only assessed roflumilast's effect averaged over the entire course of each study, while the proportional hazards and the log-rank tests only assess times to onset of exacerbations in each study, without including all exacerbation recurrences.

To address this issue, I conducted exploratory analyses which broke studies into time intervals, similar to those used by the Applicant for the FEV1 analyses, and examined for each time interval the mean number of exacerbations per patient year.

Findings

Roflumilast has a statistically significant effect on pre-bronchodilator FEV1 compared to placebo. In the six studies reviewed (Studies 124, 125, 111, 112, 127 and 128), the size of the effect ranged from 39 to 80 ml, with an average of 54 ml.

In the four one-year studies (Studies 124, 125, 111, and 112), roflumilast numerically reduced the average rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate, from Studies 124 and 125 statistically significant and with two of the reductions, from Studies 111, and 112, not statistically significant. With an explicit requirement for recent bronchitis and exacerbations, the entrance criteria for Studies 124 and 125 more closely matched the proposed label indication than the entrance criteria for Studies 111 and 112.

Exploratory analyses on Studies 124 and 125 suggest that the reduction of exacerbation rate by roflumilast compared to placebo may attenuate or even disappear after 8 months. Although his could be problematic for a long term maintenance indication in which benefits are expected to be positive for an extended period of time, it is not clear whether the observed reduction of effect was due to attenuation of roflumilast's effects or was instead associated with patterns of patient withdrawal.

2. INTRODUCTION

2.1 Overview

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

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

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

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

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

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

Of the 11 studies submitted by the Applicant, this statistical review focuses on Studies 124, 125, 111, 112, 127 and 128. Studies 124 and 125 were 52-week, double-blind, placebo-controlled studies evaluating roflumilast 500 μg QD, and were conducted in the US, Europe, South Africa, Australia, New Zealand, Canada, and India. Both studies allowed concomitant treatment with long-acting β2-agonists (LABA), and 50% of the patients in each study took such medication, and prohibited use of inhaled corticosteroids. Studies M2-111 and M2-112 were similar in design to studies 124 and 125, but patients were not required to have a history of exacerbations and chronic bronchitis. Studies 124, 125, 111, and 112 investigated the effect of roflumilast on exacerbations and lung function in patients with severe to very severe COPD. Studies 127 and 128 were 24-week trials designed to evaluate whether roflumilast adds additional benefits for lung function in patients with moderate to severe COPD who are prescribed long-acting bronchodilators (salmeterol in Study 127 or tiotropium in Study 128).

Table 1: Randomized, Double Blind, Placebo Controlled, Parallel Arm Phase 3 Clinical Trials Conducted to Assess the Effect of Roflumilast, in Chronological Order.

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

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

2.2 Data Sources

Documents reviewed were accessed from the CDER document room at:

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3. STATISTICAL EVALUATION

3.1 Study Design and Efficacy Endpoints

As mentioned earlier, of the 16 randomized, double blind, placebo controlled studies submitted by the Applicant and summarized in Table 1. This statistical review focuses on Studies 124, 125, 111, 112, 127 and 128.

Studies 124 and 125

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

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

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

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

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

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

All primary analyses were conducted on the intent-to-treat (ITT) population, defined as all randomized patients taking the prescribed treatment at least once, with secondary analyses

conducted on per-protocol (PP) population, consisting of patients without any major protocol violations.

The primary analysis for treatment effect on mean change in pre-bronchodilator FEV1 from baseline to each visit used a repeated measure analysis of covariance (ANCOVA) with baseline pre-bronchodilator FEV1 value, age, sex, smoking status, concomitant treatment with LABA, and country, and with fixed effects time and time-by-treatment interaction. The default analysis above was to employ restricted maximum likelihood (REML) with an unstructured covariance matrix. If the default analyses failed to converge, the sponsor planned to employ, in order, maximum likelihood (ML) rather than REML, a compound symmetry covariance matrix with REML, and a compound symmetry covariance matrix with maximum likelihood. If the above models failed to converge, factors would be excluded individually from the statistical model in the following order: country, concomitant treatment with LABA, smoking status, and sex. Statistical significance was to be declared if the two-sided, unadjusted p-value at the last measurement is less than 0.05. In this analysis, no replacement of missing values was performed.

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

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

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

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

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

log-transformed CRP baseline value. In this analysis, last observed value was carried forward to replace missing values at the end of study visit.

The key-secondary endpoints were tested in a confirmatory manner two-sided at a significance level of 5% if and only if both primary endpoints were statistically significant at the 5% significance level. According to the Applicant, in the case that the test for a key-secondary endpoint could not be performed on a confirmatory basis, because a test with higher priority had failed, this test was performed in an exploratory manner.

Studies 111 and 112

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

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

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

In both studies, a moderate exacerbation was defined as an exacerbation requiring use of oral or parenteral glucocorticosteroids, with Study 112 additionally including an exacerbation requiring antibiotics. In Study 111, a severe exacerbation was defined as an exacerbation which resulted in hospitalization or death, while in Study 112, a severe exacerbation was originally defined as an exacerbation which resulted in hospitalization, with death added post protocol. Unlike Studies 124 and 125, beginning and end time of exacerbations were recorded by use of drugs or hospital admission or death rather than by time of exacerbation as experienced by the patient. In Study 112, exacerbations not separated by one exacerbation free day were merged and counted as a

single exacerbation, and in Study 111, exacerbations not separated by ten exacerbation free days were merged and counted as a single exacerbation.

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

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

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

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

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

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

The secondary variable (1) was analyzed with a repeated measure ANCOVA analogous to the

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

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

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

Studies 127 and 128

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

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

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

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

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

1. mean rate of COPD exacerbations (mild, moderate, or severe) per patient year
2. mean Transition Dyspnea Index (TDI) focal score during the treatment period

3. mean change in the Shortness of Breath Questionnaire (SOBQ) from baseline to each post-randomization visit during the treatment period

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

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

COPD Exacerbation is defined as follows:

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

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

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

3.2 Study Results

3.2.1 Patient Disposition, Demographic and Baseline Characteristics

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

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

Table 2: Summary of Patient Disposition

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

Note: Results from Study Reports

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

Table 3: Summary of Baseline and Demographic Characteristics

	Study 124		Study 125		Study 111		Study 112		Study 127		Study 128	
	Rof	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**	**Rof**	**Pbo**
N	765	758	772	796	567	606	760	753	466	467	371	372
Age [a] [years] (median)	63	63	64	65	65	64	66	65	65	65	65	65
Sex [a,c] [male] %	71	71	79	81	68	66	75	76	68	64	71	72
Race [a,c] [white] %	96	97	72	71	94	93	99	99	95	95	100	100
Height [a] [cm] (mean)	170	169	167	167	170	170			169	168	168	169
Weight [b] [kg] (mean)	76	75	71	71	75	75	72	72	77	76	78	80
BMI [b] [kg/m^2] (mean)	26	26	25	25	26	26						
COPD [a,c] (%)												
Very severe	26	24	34	32	24	27			0	0	1	1
Severe	64	67	59	60	65	65			35	30	34	32
Moderate	11	8	7	7	11	7			65	69	63	65
Mild	0	0	0	0	0	0			0	0	2	3
Smoking [a,c] (%)												
Current	48	48	35	35	42	44	38	35	40	40	40	39
Former	52	52	65	65	58	56	62	65	61	61	60	61
LABA[d] (%)	49	51	48	51					70 [g]	69 [g]		
ICS [e] (%)	44	44	40	41			62[f]	63[f]				
Pre-bron FEV1[b] (mean)	1.1	1.1	1.0	1.0	1.0	0.9	1.0	1.0	1.4	1.4	1.5	1.5
Post-bron FEV1[b] (mean)	1.2	1.2	1.1	1.1	1.1	1.1	1.1	1.1	1.5	1.5	1.5	1.6
Pre-bron FEV1 [b] % predicted (mean)	35	35	31	32	31	31	37	37	52	52	53	53
Post-bron FEV1 [b] % predicted (mean)	38	38	35	35	37	36	41	41	55	55	56	56
SGRQ (mean)					48	49						

Note: Results from study reports.

[a] measurements were taken at V0

[b] measurements were taken at baseline (last measurement prior to randomization)

[c] percentages are based on the number of patients in the respective treatment group

[d] based on whether the patient had used LABA at least once within the time period start of treatment period (including) up to end of treatment period (including)

[e] based on whether the patient had used ICS at least once within visit V0 + 1 day up to the day preceding randomization, i.e. randomization date – 1 day, including both delimiting days

[f] based on whether patient had concomitant use of ICS treatment

[g] based on whether patient had pre-treatment of LABA

The average percentage of compliance to the study treatment was above 90% in all six studies (Table 4) and generally well balanced between roflumilast and placebo groups.

Table 4: Treatment Compliance and Duration of Exposure

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

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

3.2.2 Change in Pre-Bronchodilator FEV1

Unless otherwise stated, all analyses below were conducted on ITT study population.

The primary analysis for treatment effect on mean change in pre-bronchodilator FEV1 from baseline to each visit of used a repeated measure analysis of covariance (ANCOVA). Patients treated with roflumilast have a statistically significant effect on pre-bronchodilator FEV1 compared to placebo. In these studies, the size of the effect ranged from 39 to 80 ml, with an average of 54 ml.

Table 5: Change in Pre-Bronchodilator FEV1 from Baseline to End of Treatment (ITT population)

Study	Weeks	Pre-Bronchodilator FEV1 (ml)				
		R500	Placebo	Diff	P-Value	Pooled Diff
124	52	46 (745)	8 (745)	39	<0.001	48
125	52	33 (730)	-25 (766)	58	<0.001	
111	52	30 (545)	-12 (596)	42	<0.001	51
112	52	49 (737)	-8 (741)	57	<0.001	
127[1]	24	39 (456)	-10 (463)	49	<0.001	
128[2]	24	65 (365)	-16 (364)	80	<0.001	

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

Other studies conducted by the sponsor confirmed the positive effect on pre-bronchodilator FEV1 of roflumilast over placebo (Table 6). Results from the 12 week studies show the effect appears at or before 12 weeks from commencement of treatment.

Table 6: Change in Pre-Bronchodilator FEV1 at Last Measurement, Pre-Planned Analyses on ITT Populations for Supportive Studies.

Study	Weeks	R500	Placebo	Diff	P-Value
FK1101	26	64 (162)	17 (168)	47	0.0776
FK1103	24	38 (192)	-11 (179)	49	0.0162
108[a]	12	60 (34)	-99 (15)	159	0.0135
706	24	14 (171)	-71 (181)	86	<0.0001
107	24	77 (535)	-1 (276)	78	<0.0001
110	24	59 (431)	-27 (425)	86	<0.0001
118	12	56 (118)	-28 (117)	84	0.0037[b]
119	12	54 (189)	-41 (202)	95	<0.0001
121	24	16 (276)	-25 (284)	40	0.0033

a. per-protocol ANCOVA at week 12
b. one sided p-value
Measurements in milliliters
Diff: difference between roflumilast and placebo.
P-Value: p-value for diff with H_0: Diff = 0.
Number of individuals randomized is provided in parentheses.

For studies 124 and 125, the Applicant's repeated measures analysis did not use the time-by-treatment interaction to trace the course of FEV1 for each timepoint during the study. Instead, for any particular timepoint, the Applicant calculated least square means for each treatment by using the treatment categorical variable, after deleting all subsequent points. For example, to calculate the change from baseline at Week 36, records from subsequent visits at Weeks 44 and 52 were deleted, and the remaining data was then analyzed in a repeated measures ANCOVA to calculate an overall treatment effect spanning Week 36 and all previous weeks. This method does not provide an estimate for particular timepoint, and the results should not be represented as such.

An improved assessment for the course of pre-bronchodilator FEV1 during Studies 124 and 125, whose populations most closely matched the proposed label indication, shows that roflumilast had a significant and positive effect at all timepoints (Table 7). The estimates were obtained by using the time by treatment interaction term in the pre-planned repeated measures analyses to calculated least squares means. There was no clear downward trend in the effect of roflumilast compared to placebo during either study. In Study 125, roflumilast did have the smallest effect at the final timepoint; however the highest effect immediately preceded it. Results from Table 7 are presented graphically in Figure 1 and Figure 2.

Table 7: Time Course of Change in Pre-bronchodilator FEV1, Studies 124 and 125.

Week	Study 124				Study 125			
	Rofl	**Placebo**	**Diff**	**P Value**	**Rofl**	**Placebo**	**Diff**	**P Value**
4	50	5	46	<.001	45	-24	69	<.001
8	53	21	32	0.007	45	-12	58	<.001
12	50	18	33	0.011	40	-12	53	<.001
20	56	21	34	0.009	46	-14	60	<.001
28	53	-2	56	<.001	28	-28	56	<.001
36	44	6	38	0.016	32	-21	52	<.001
44	34	2	32	0.052	33	-40	73	<.001
52	29	-10	39	0.015	-4	-48	44	<.001

adxp, pgm mainline efficacy prefev1 sponsor analysis by week 2010 02 25
Rofl and Placebo: least square mean differences from baseline, in ml
Diff: difference between roflumilast and placebo
P-Value: two-sided probability for H_o: Diff = 0.

Figure 1: Change from Baseline of Pre-bronchodilator FEV1, Study 124

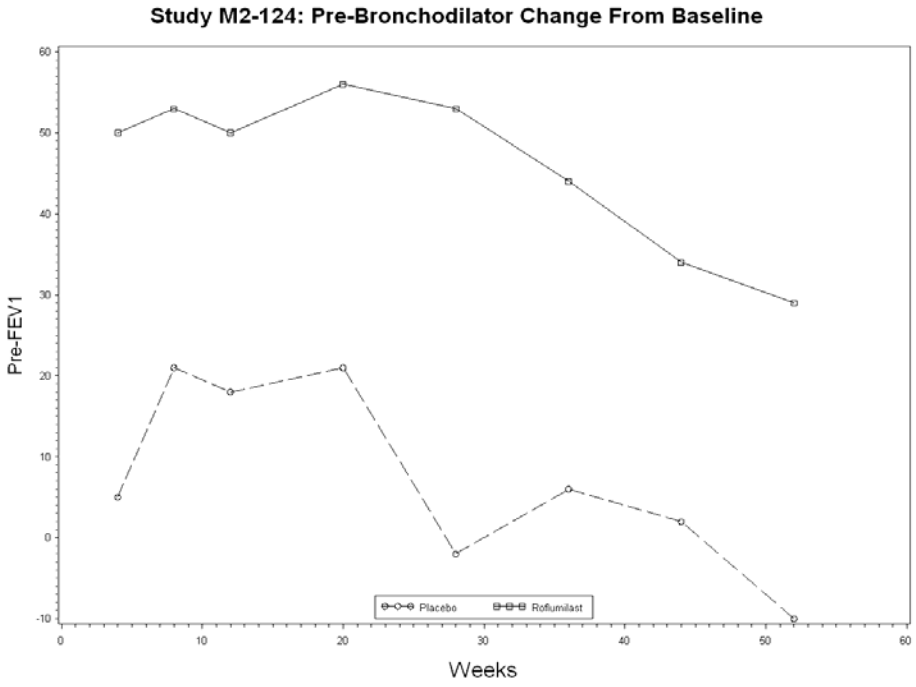
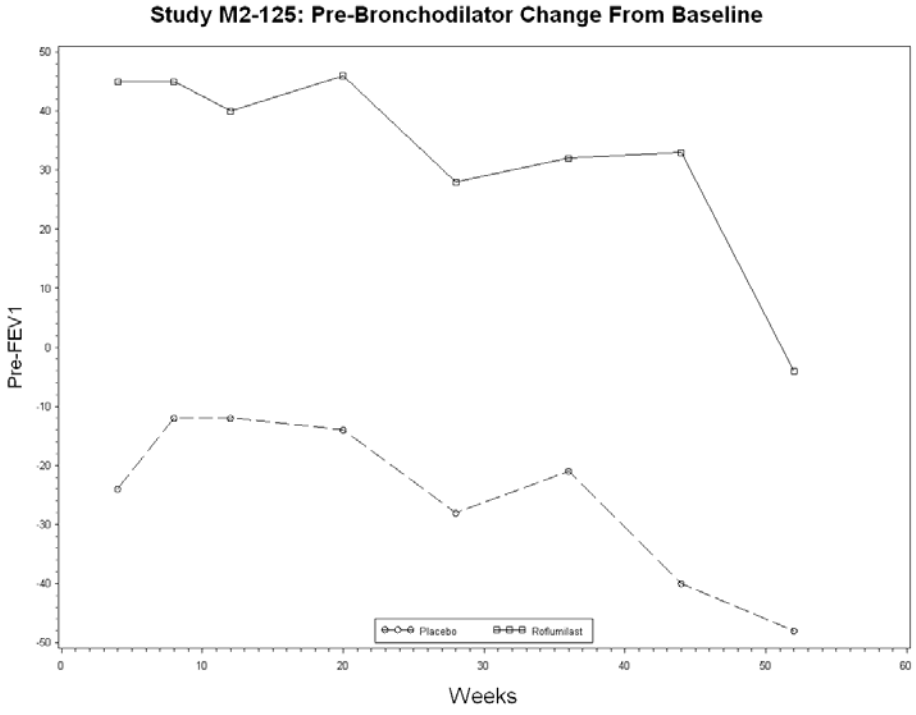


Figure 2: Change from Baseline of Pre-bronchodilator FEV1, Study 125



3.2.3 Rate of Exacerbation

Except in Studies 127 and 128, the mean rate of moderate or severe COPD exacerbations per patient per year is one of the two primary endpoints for Studies 124, 125, 111 and 112. In these four studies, the primary efficacy endpoints were tested in hierarchical manner, with rate of COPD exacerbations tested at the two-sided 0.05 level of significance only if pre-bronchodilator FEV1 was significant at the two-sided 0.05 level. As stated in Section 3.1.1.1, the definition of exacerbation in Study 112 differed slightly with the other studies as it included exacerbations requiring antibiotics treatment (moderate) and exacerbations leading to death were added post-protocol (severe). Also, exacerbations not separated by one exacerbation free day were merged and counted as a single exacerbation.

Roflumilast numerically reduced the annual rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate, from Studies 124 and 125 statistically significant and with two of the reductions, from Studies 111, and 112, not statistically significant (Table 8). To facilitate direct comparison of Studies 111 and 112 with Studies 124 and 125, the definitions of moderate and severe exacerbations were modified post-hoc by the Applicant to match those of 124 and 125. In addition, the analysis method, in particular the covariates included in the model, used in Studies 124 and 125 were applied to Studies 111 and 112 post-hoc. With these post-hoc changes, the rate ratio comparing roflumilast and placebo was still not statistically significant either study.

Table 8: Analyses of Moderate or Severe Exacerbations in Studies 124, 125, 111, and 112 (ITT Population, Pre-Planned Primary Analyses)

Study	Weeks	Poisson Exacerbation Rate					
		R500	Placebo	Rate Ratio	P-Value	Pooled	Rate Ratio
111	52	0.6 (567)	0.7 (606)	0.87	0.129		
112*	52	(760)	(753)		0.451		
124	52	1.1 (765)	1.3 (758)	0.85	0.028		
125	52	1.2 (772)	1.5 (796)	0.82	0.004		0.8

111, 112 from original study reports, T-tables and 15 respectively
Measurements under columns R500 and Placebo provided are the exponentiated mean log of the number of exacerbations per person per year.
* Pre-planned primary analysis was Wilcoxon-Mann-Whitney test, which does not provide an exacerbation rate or rate ratio.

In Study 127, the mean rate of COPD exacerbations (mild, moderate or severe) per patient year is one of the three the Applicant considered 'key' secondary endpoints and is the second test of the confirmatory testing procedure. The mean rate of moderate or severe COPD exacerbations is one of 'other' secondary endpoints and the Applicant has considered this endpoint 'exploratory'. Based on the analyses by the Applicant, the rate of COPD exacerbation (mild, moderate or severe) was lower for roflumilast (1.9) than placebo (2.4). However, the rate ratio (0.8) comparing roflumilast and placebo was not statistically significant. The confirmatory testing procedure ended with this test. Post-hoc analysis of moderate or severe COPD exacerbations in this study was conducted by the Applicant. The rate of COPD exacerbation (moderate or severe) was lower for roflumilast (0.3) than placebo (0.5) and the rate ratio is 0.6. In Study 128, the mean rate of COPD exacerbations (moderate or severe) per patient year is one of the two the Applicant considered 'key' secondary endpoints and is the second test of the confirmatory testing procedure. Based on the analyses by the Applicant, the rate of COPD exacerbation (moderate or severe) was slightly lower for roflumilast (0.26) than placebo (0.34). However, the rate ratio (0.8) comparing roflumilast and placebo was not statistically significant (Table 9).

Table 9: Poisson rates of Moderate or Severe Exacerbations in Studies 127 and 128 (ITT Population)

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

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

The statistical significance of reductions in exacerbation rate provided by roflumilast compared to placebo in Studies 124 and 125 were re-examined in Table 10 using a negative-binomial distribution (which has more flexibility in handling overdispersion). The rate ratios were nearly the same as in the original Poisson analysis.

Table 10: Negative Binomial Rates of Moderate or Severe Exacerbations (ITT Population)

Study	Weeks	Negative Binomial Exacerbation Rate			
		R500	Placebo	Rate Ratio	P-Value
124	52	1.124 (765)	1.323 (758)	0.85	0.038
125	52	1.268 (772)	1.556 (796)	0.82	0.007

From datasets dm, xe, ds, dv, see pgm mainline efficacy poisson exacerbation rate 2010 02 09
Measurements under columns R500 and Placebo provided are the exponentiated mean log of the number of exacerbations per person per year.

The frequency of moderate or severe exacerbation is presented in Table 11. Overall, a higher proportion of patients in the placebo experienced at least one moderate or severe COPD exacerbation compared to the roflumilast group. The frequency of patients experiencing at least 2 (up to 6 in Study 124 and up to 9 in Study 125) moderate or severe COPD exacerbation was higher in the placebo group compared to the roflumilast group.

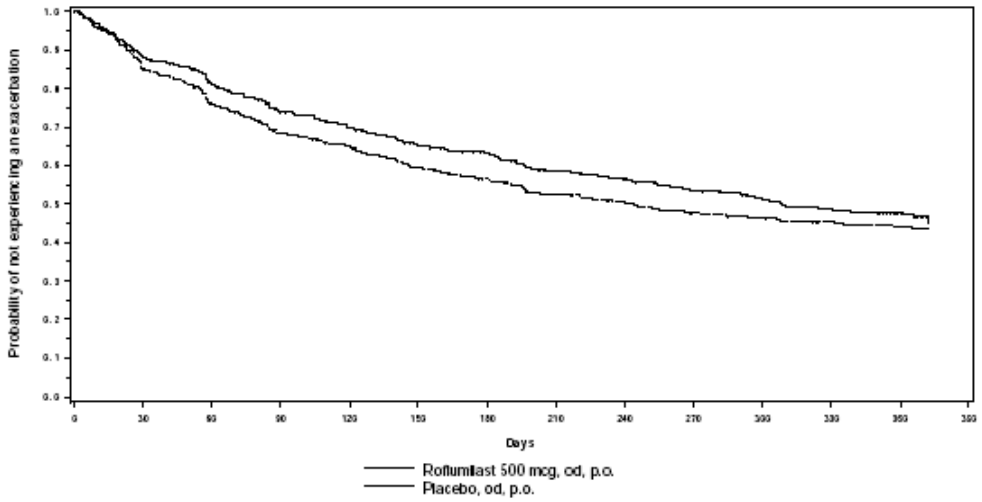
Table 11: Frequency (in %) of Moderate or Severe Exacerbations

	Study 124		**Study 125**	
Frequency	**ITT**		**ITT**	
	Rof	**Pbo**	**Rof**	**Pbo**
N	765	758	772	796
0	**55**	**49**	**52**	**46**
1	25	25	26	25
2	11	13	12	14
3	6	7	6	7
4	2	3	3	4
5	1	2	1	2
6	0.1	1	0.4	1
7	1	0.3	0.1	1
8			0	0.3
9			0	0.3

The time to onset of first moderate or severe COPD exacerbation is explored. In Study 124, median time to first exacerbation (moderate or severe) was 244 days in the placebo group and 309 days in the roflumilast group (Figure 3). Similarly, in Study 125, median time to first exacerbation was 227 days in the placebo group and 290 days in the roflumilast group (Figure 4). This implies a 65-day delay in the time to first COPD exacerbation (moderate or severe) in the roflumilast group compared to placebo.

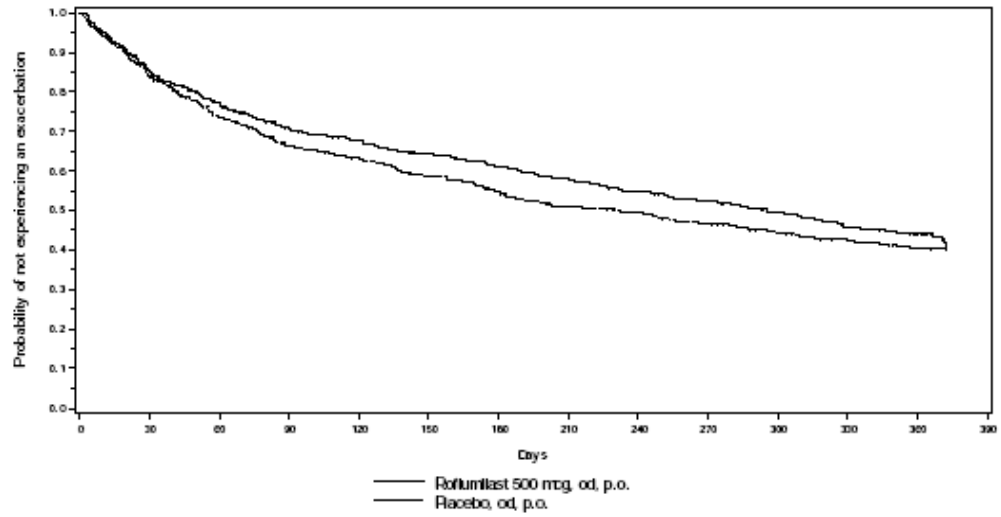
The mean rate of COPD exacerbations per patient year and the time to onset of first COPD exacerbation for different categories of COPD exacerbations are presented in Table 12. In general, the mean rate of COPD exacerbations and the proportion of patients with COPD exacerbations are numerically smaller in the roflumilast group compared to the placebo group for the different categories of COPD exacerbations in both studies. The largest treatment effect appears to be in patients with moderate COPD exacerbation in Study 124, where the 95% confidence limits for rate and hazard ratios do not include one, and in patients with severe COPD exacerbation in Study 125, where the 95% confidence interval for both rate ratio and hazard ratio include one (i.e. the null value), suggesting uncertainty in the difference in risk. In both studies, reduction in exacerbation rates appears to be similar for moderate exacerbations and for exacerbation treated with systemic steroids and/or antibiotics. Meanwhile, the hazard ratios appear to be similar for different categories of COPD exacerbation and numerically favor the roflumilast group.

Figure 3: Time to Onset of First Moderate or Severe COPD Exacerbation (Kaplan-Meier estimates, ITT Population) Study 124



The plots only show events up to Day 372 (52-week study).
Source: Figure 3, Study Report 218/2008

Figure 4: Time to Onset of First Moderate or Severe COPD Exacerbation (Kaplan-Meier estimates, ITT Population) Study 125



The plot only shows events up to Day 372 (52-week study).
Source: Figure 3, Study Report 219/2008

Table 12: Mean Rate of COPD Exacerbation Per Patient Year (Poisson regression) and Time to Onset of First COPD Exacerbation (Cox Proportional Hazards Regression)

Type of Exacerbation	Study 124				Study 125			
	Rof N=765 n (%) rate	**Pbo N=758 n (%) rate**	**Rate Ratio* 95%CI**	**Hazard Ratio** 95%CI**	**Rof N=772 n (%) rate**	**Pbo N=796 n (%) rate**	**Rate Ratio* 95%CI**	**Hazard Ratio** 95%CI**
Moderate	299 (39) 0.9	343 (45) 1.1	0.84 (0.7, 0.99)	0.87 (0.7, 1.0)	325 (44) 1.0	380 (50) 1.3	0.82 (0.7, 0.9)	0.89 (0.8, 1.0)
Severe	69 (9) 0.1	81 (11) 0.1	0.89 (0.6, 1.3)	0.90 (0.7, 1.2)	88 (10) 0.1	117 (12) 0.2	0.77 (0.5, 1.1)	0.85 (0.6, 1.1)
Moderate or Severe	**344 (45) 1.1**	**389 (51) 1.3**	**0.85 (0.7, 0.98)**	**0.88 (0.76, 1.0)**	**373 (50) 1.2**	**432 (56) 1.5**	**0.82 (0.7, 0.9)**	**0.89 (0.8, 1.0)**
Mild, moderate or severe	455 (60) 3.9	508 (67) 4.4	0.89 (0.8, 1.0)	0.89 (0.8, 1.0)	495 (64) 4.3	563 (71) 5.4	0.81 (0.7, 0.9)	0.90 (0.8, 1.1)
Treated with Systemic steroids and/or antibiotics	336 (44) 1.1	382 (50) 1.3	0.85 (0.7, 0.98)	0.87 (0.7, 1.0)	364 (49) 1.2	416 (54) 1.4	0.83 (0.7, 0.9)	0.92 (0.8, 1.1)
Treated with antibiotics only	62 (8) 0.1	73 (10) 0.1	0.95 (0.7, 1.4)	0.87 (0.6, 1.2)	63 (6) 0.1	72 (6) 0.1	0.93 (0.7, 1.3)	0.97 (0.7, 1.4)
Hospitalized	52 (7) 0.2	55 (7) 0.3	0.94 (.6,1.4)	0.82 (0.6,1.2)	59 (8) 0.3	70 (9) 0.3	0.84 (0.5,1.3)	0.86 (0.6,1.2)

pgm mainline efficacy Poisson&Cox exacerbation rate hosp 2010 03 03.sas

* Mean rate of COPD exacerbation: Rate ratio calculated using Poisson regression

** Time to first COPD exacerbation: Hazard ratio calculated using Cox regression mod

The Poisson and negative binomial analyses provided in Table 9 and Table 10 assess the effect of roflumilast on exacerbation rate averaged over the entire course of the study, but do not explicitly examine potential changes in its effect over time. However, the proposed 'maintenance treatment' indication implies that roflumilast will be effective when administered for an extended period, and it therefore seems worthwhile to perform exploratory analyses to assess whether its effect is constant.

For the exploratory analyses, I broke the study into time intervals, similar to those used by the Applicant for the FEV1 analyses, and examined the mean number of exacerbations per patient year. The simple means are presented in Figure 5 and Figure 6.

The reduction of exacerbation rate by roflumilast compared to placebo appears to attenuate or even disappear after 8 months (Table 13, and shown graphically in Figure 5 and Figure 6). This may be problematic for a long term maintenance indication in which the benefits are expected to be stable and positive over time.

Table 13: Number of Exacerbations Per Patient Year, Calculated from Simple Means

Study	Interval	Roflumilast				Placebo				Diff
	(weeks)	N Pat	Exac	PYr	ExPPYr	N Pat	Exac	PYr	ExPPYr	
124	00–04	765	80	57.3	1.4	758	93	57.2	1.6	-0.2
	04–12	732	119	101.7	1.2	736	156	107.0	1.5	-0.3
	12–20	632	96	94.5	1.0	676	136	99.0	1.4	-0.4
	20–28	606	94	90.0	1.0	628	123	94.0	1.3	-0.3
	28–36	575	72	85.1	0.8	600	102	88.7	1.1	-0.3
	36–44	547	78	80.6	1.0	571	83	84.1	1.0	0.0
	44–52	518	68	77.5	0.9	541	71	81.6	0.9	0.0
125	00–04	772	100	57.6	1.7	796	110	59.6	1.8	-0.1
	04–12	731	143	102.5	1.4	763	205	112.6	1.8	-0.4
	12–20	641	100	95.0	1.1	717	141	105.2	1.3	-0.2
	20–28	607	70	90.0	0.8	671	150	99.8	1.5	-0.7
	28–36	578	86	86.6	1.0	640	110	94.0	1.2	-0.2
	36–44	560	90	84.6	1.1	598	98	88.9	1.1	0.0
	44–52	546	85	81.7	1.0	572	90	85.8	1.0	0.0

pgm mainline repeated measures exacerbation 2010 03 01.sas
N_Pat: Number of patients
Exac: Number of exacerbations
PYr: Patient years accumulated during interval
EXPPYr: Number of exacerbations per patient year.

Figure 5: Number of Exacerbations Per Patient Year, Study 124

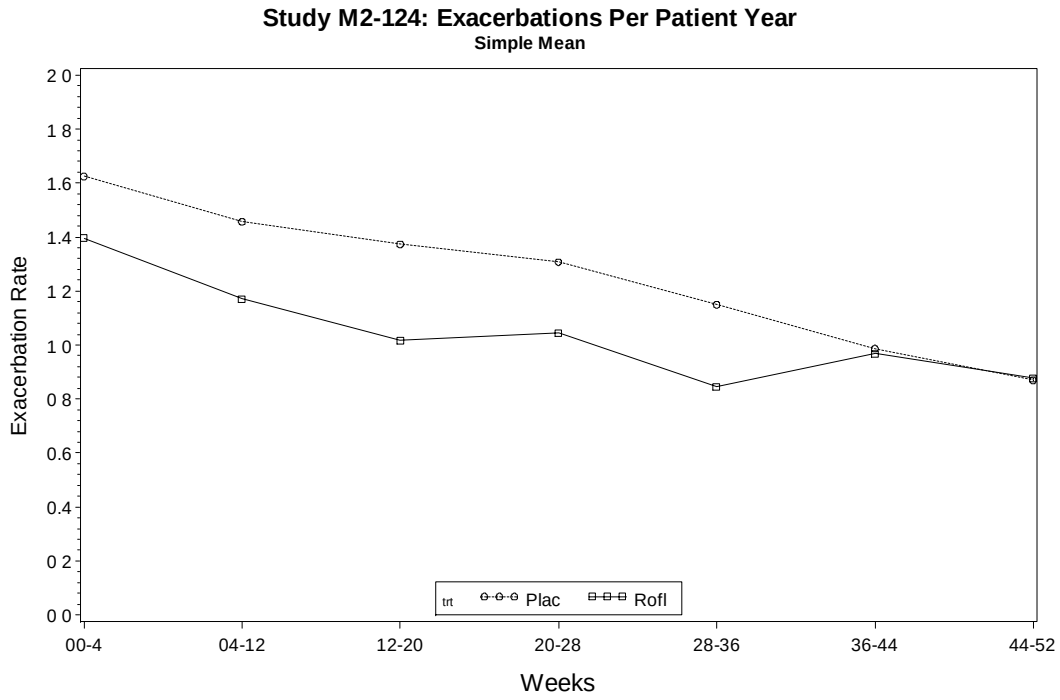
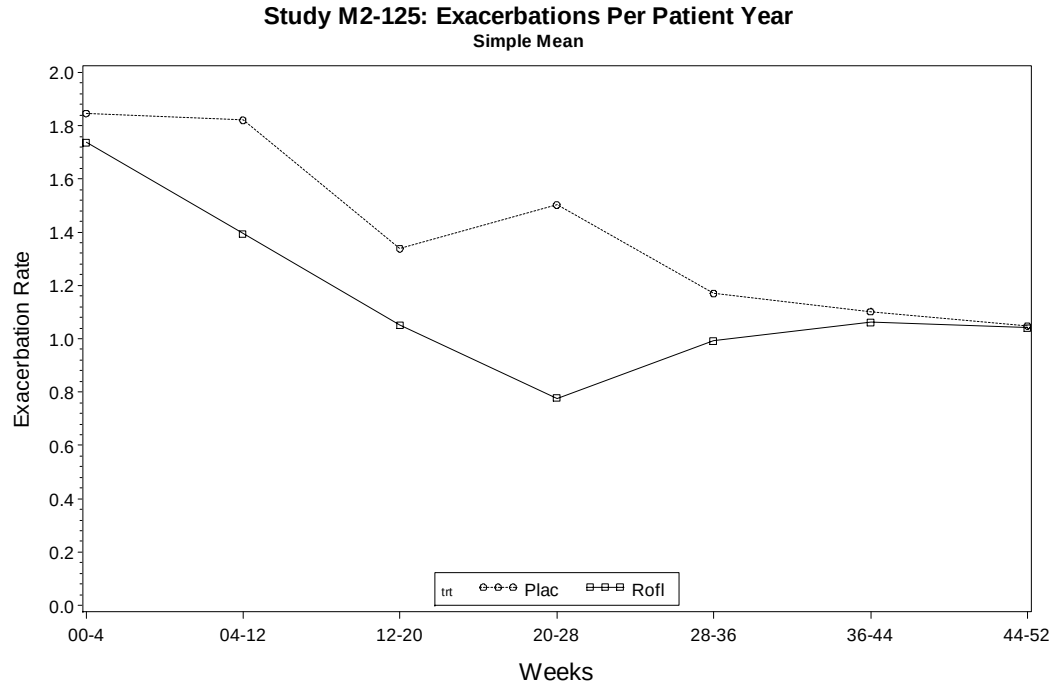


Figure 6: Number of Exacerbations Per Patient Year, Study 125



An integrated analysis for Studies 124 and 125 to examine exacerbations per patient year by time interval is provided in
Table 14 with approximate confidence limits and p-values calculated using a Poisson regression model with explanatory variables pre-bronchodilator FEV1 value, age, sex, smoking status, concomitant treatment with LABA, and country, interval, and interval by treatment interaction. The analyses should be considered only as approximate because, as already noted, exacerbation rates were changing between time periods and would therefore be expected to change within time periods, albeit somewhat less. Estimates of mean exacerbation rates and their differences in Table 14 represent geometric means and so, even without the inclusion of explanatory variables, would be expected to differ somewhat from the simple means given in Table 13 above.

Like the results from individual studies, the integrated analysis suggests that roflumilast reduced exacerbation rates relative to placebo between weeks 4 to 28, with the effect attenuating during the interval of weeks 28 and 36 (or around month 8) and disappearing by week 36.

Table 14: Exacerbation Rates per Patient Year (Integrated Analysis for Studies 124 and 125)

Weeks	Roflumilast	Placebo	Diff
00–04	1.6	1.8	0.2 (-0.1,0.3)
04–12	1.3	1.7	0.4 (0.1,0.4)
12–20	1.1	1.4	0.3 (0.1,0.4)
20–28	1.0	1.5	0.5 (0.2,0.6)
28–36	1.0	1.2	0.2 (0.0,0.4)
36–44	1.1	1.1	0.0 (-0.2,0.2)
44–52	1.0	1.0	0.0 (-0.2,0.2)

pgm mainline exacerbation by period with cl 2010 03 03.sas
Diff: difference between placebo and roflumilast
Lower and upper confidence 95% bounds in parentheses

3.2.4 SGRQ

Seven studies in the submission conducted earlier in the development program examined changes from baseline of the St. George's Respiratory Questionnaire (SGRQ) as a primary or secondary effectiveness variable. None of these studies showed a difference between roflumilast and placebo which exceeded 1.7 (Table 15). In one of the seven studies, 111, the difference in mean SGRQ between patients in the roflumilast and placebo arms (Table 15) was statistically significant.

Table 15: Changes from Baseline of the Saint George's Respiratory Questionnaire, Total Score.

Study	Roflumilast	Placebo	Diff	P-Value
101	-4.7	-4.5	-0.3	0.425
103	-2.6	-2.9	0.3	0.842
107	-3.5	-1.8	-1.7	0.053
110	-1.2	-1.6	0.47	0.473
111	-1.8	-0.3	-1.5	0.016
112	-3.7	-3.2	-0.5	0.268
706	0.31	-1.04	1.35	0.211

Lower scores indicate better patient-perceived health status.

3.2.5 Mortality

No statistically significant differences in mortality rates were seen between roflumilast and placebo in Studies 111, 112, 124, 125, 127, and 128 (Table 16). The hazard ratios and p-values of Table 16 were obtained from a proportional hazards model with independent variables age, sex, and smoking status, stratified by country. The analysis for Study 111 also included as an independent variable the pretreatment use of ICS, and the analyses for Studies 124 and 125 included concomitant LABA usage. In the Applicant's study report for Study 112, among roflumilast treated patients there were 12 deaths, however the dataset provided by the Applicant enumerated only 11 deaths.

Table 16: Hazard Ratio Analyses for Mortality, Studies 111, 112, 124, 125, 127, and 128.

Study	Roflumilast		Placebo			
	Deaths	N	Deaths	N	Hazard Ratio 95% CI	P-Value
111	11	567	12	606	1.48 (0.63, 3.45)	0.365
112	11	749	20	755	0.59 (0.28, 1.24)	0.165
124	17	765	17	758	1.04 (0.53, 2.03)	0.921
125	25	772	25	796	1.21 (0.69, 2.14)	0.503
127	5	466	4	467	1.22 (.33, 4.56)	0.769
128	2	374	0	369	N/A	N/A

pgm mainline cox mortality 2010 03 03.sas. Analysis of 111 from Table 15.2.19.21 of study report.
Est: Point estimate
Lower and upper 95% confidence bounds in parentheses ( ).
N/A: not applicable since point estimate of hazard rate for placebo is 0.

3.3 Benefits and Risks Associated with Roflumilast

3.3.1 Introduction

The medical officer for this submission, Xeumeng Han Sarro, will detail most of the safety findings, including the concern over suicidality. However, as an exploratory analysis to facilitate comparison of the benefits and risks of roflumilast administration, I attempt to quantify them by comparing efficacy for reduction of exacerbation to potential risks of nausea, diarrhea, and gastrointestinal adverse events. I did not explore the potential risk of suicide in this review. The methodology differs somewhat from analysis tools we usually use in medical statistics, which typically focus on determining statistical significance of treatment effect. For example, the Poisson analysis of exacerbation rate, provided in Table 8, correctly calculates statistical significance if the assumptions of the model are met, but it provides least mean square mean exacerbation rates which are actually geometric means calculated between patients. Such geometric means will not necessarily reflect the actual number of exacerbations per year we expect patients to experience; it is a simple fact that different metrics and different models may be needed to quantify the patient experience.

The analyses strictly avoid assigning utilities to weigh the benefits and risks. Instead, the focus is on presenting risks and benefits in the same units, to facilitate determination of overall utility by those requesting the consulting review.

Studies 124 and 125 were chosen for the analyses provided below because they most closely represent the population in the proposed label indication.

3.3.2 Definitions and Metrics

An adverse event (AE) assessed as being mild was hardly noticeable, with negligible impairment of well-being. An AE assessed as being moderate involved marked discomfort and, although tolerable, without immediate relief. An AE assessed as being serious involved overwhelming discomfort, calling for immediate relief.

Numerous metrics can be calculated to reflect the risks and benefits associated with administration of roflumilast. For example, in studies 124 and 125, physicians planned to administer roflumilast to each patient for a year. Let d_i be the number of days a patient spends experiencing an event before withdrawal from the study, and let N be the total number of patients randomized. Then the mean number of days each randomized patient spends experiencing an event per planned prescription year can be calculated simply as

$$EventDaysPer\,\mathrm{Pr}escribedYear = \frac{\sum_i d_i}{N}$$

Another metric, denoted as 'event days per forced administration year,' treats patients who withdrew as if they remained to complete the study with proportion of events days unchanged. For example, let us say a patient withdraws from the study after only ten days because she experienced an adverse event for nine of the ten days. Making the assumption that, if she had been forced to continue, she would have continued experiencing that adverse event at the same rate as before she withdrew, we infer she would have experienced adverse events for 0.9 x 365.25 days of the study. Letting t_i represent the number of days patient i is in the study, the mean event days per year of forced administration can be calculated as.

$$EventDaysPerForcedAdmistrationYear = \frac{365.25}{N} * \sum_i \left(\frac{d_i}{t_i} \right)$$

Yet another metric, the number of event days per treated year weights each patient's event days by the time during which that patient was treated. For example, if a patient withdrew from a planned 365 day study after 36.5 days, we could acknowledge that the patient was only in the study for 10% of the planned time and downweight that patient's experience accordingly. The resulting metric may be calculated as

$$EventDaysPerTreatmentYear = 365.25 * \sum_i \left(\frac{d_i}{t_i} \right) \left(\frac{t_i}{\sum_i t_i} \right)$$

The calculations for event days per treatment year are simplified by noting that $t_i / t_i = 1$ and that $\sum_i t_i$ is a constant with respect to the left hand summation

$$EventDaysPerTreatmentYear = 365.25 * \frac{\sum_i d_i}{\sum_i t_i}$$

Event days per treatment year quantifies patient experience while taking the medication, but patients withdrawing early because of adverse effects or non-effectiveness of treatment will receive less weight than patients who complete the trial.

If the patient withdrawal rate is low, concern over which metric to use should be minimal, because all will yield the exactly same result, a fact that can readily be seen for the present one year studies by setting all t_i in the above equations to 365.25.

One may be tempted to compare studies of different lengths by simple or complex renormalization techniques to a common length of time. However, one should resist the temptation to do so unless there is good evidence that event rates do not change during the course of the study or changes over time are well characterized and incorporated into the renormalization..

Three further notes, applicable to all of the metrics above should be acknowledged. First, if a patient withdraws from the study, events continuing or beginning beyond withdrawal may not be recorded, causing a downward bias in mean event days. Second, even if a patient completes the study, events continuing or beginning beyond the termination of the study may not be recorded, causing a downward bias in mean event days. Third, the frequency distributions of events in this study were extremely complex, ranging from bimodal, e.g., for weight loss, to poisson for exacerbation events, and so analyses of these metrics taking into account relevant covariates were not performed

Event days per prescribed year was chosen for the analyses presented below, with comparison to event days per treatment year to assess whether patient withdrawal in each treatment was greatly affected by days spent experiencing adverse events. The following considerations affected which analysis was employed. First, event days per forced treatment year, while perhaps relevant to a phase 1 safety study, would probably not reflect the patient benefits and risks physicians may expect when prescribing the drug. Event days per treatment year quantifies patient experience while taking the medication, but patients withdrawing early because of adverse effects or non-effectiveness of treatment will receive less weight than patients who complete the trial. In comparison to event days per treatment year, event days per prescribed year will also be sensitive to patient withdrawal, but arguably less so than event days per treatment year, because it does not have a factor which explicitly put more weight to patients who remain in the study.

3.3.3 Missing Adverse Event Days

As a clarifying example, study 124 listed 70 moderate or severe weight loss adverse events among 68 patients, 54 treated with roflumilast and 14 treated with placebo. Of these, 50% of the placebo patients and 69% of the roflumilast patients had no recorded number of days for one or more adverse events. Among the 7 placebo subjects with complete data, there were a total of 1364 adverse event days. Since this represents total weight loss days for only 7 of the 14 subjects administered placebo, I added another 1364 events days to represent data from the missing 7 subjects. More generally, then, the method used is to remove subjects missing any adverse event duration data, and represent their total days by the mean total days experienced by others in their treatment group. In practice, the algorithm is to divide days summed over subjects with known adverse event days by the proportion of subjects with complete data. An alternate method, to replace the time for each missing event by the mean number of days per event among others in the same treatment group was rejected because, among individuals with multiple events, the number of adverse event days imputed for an individual could exceed the number of days he or she was observed.

3.3.4. Delineating Adverse Events by Severity

Adverse events such as nausea, diarrhea etc. were recorded individually and graded by severity. Analyzing adverse events by severity alone was complicated by the fact that an individual patient could experience multiple adverse events of the same severity which overlapped in time. The problem of overlapping adverse events was addressed by using the same rule used by the sponsor for exacerbations: merging events not separated by at least ten days. Use of this rule provides consistency between definitions of individual adverse events and exacerbation, desirable when we wish to directly compare roflumilast's effects on exacerbations with roflumilast's effects on adverse events. This procedure can underestimate the cost to patients with overlapping events; alternatively one could for example, count days when two events overlap as two event days. However many of the recorded 'events' seem to be comprised of multiple symptoms stemming from a single underlying event. For example, in study 124, subject 80056 experienced multiple overlapping events during a month of abdominal pain, loss of appetite, overanticoagulation, positive haemoccult test, urinary tract infection, and weight loss. In this case and many others, it seemed possible that apparent multiple events, a mixture of symptoms and possible underlying causes, stemmed from a single underlying event.

3.3.5 Results

Among patients prescribed treatment for a year, roflumilast reduced the average number of moderate or severe exacerbations per prescribed year compared to placebo by 1.7 days, the number of moderate exacerbations by 1.5 days, the number of exacerbations resulting in hospitalization by 1.1 days, and the number of severe exacerbations by 1.0 day (Table 17). The sample sizes *N* provide additional information. For example, *N* for moderate or severe populations in study 124 refers to the fact that there were 624 exacerbations among 347 patients in the full analysis population consisting of 765 individuals. The reduction in the number of exacerbations per treatment year among patients administered roflumilast rather than placebo was comparable to the number of exacerbations per prescribed year. The mean number of exacerbations per treatment year in Table 18 also shows reductions in exacerbation rate by roflumilast.

The statistical significance of differences between studies, treatments, and between days per prescribed year versus days per treatment year has not yet been examined.

Table 17: Mean Exacerbation Days Per Prescribed Year

Severity	**Roflumilast**		**Placebo**		**Diff**	
	N	**Days**	**N**	**Days**	**R – P**	**Mean**
Moderate or Severe						
124	624/347/765	11	774/391/758	14.8	-3.8	-4.1
125	699/381/772	13.1	929/437/796	17.5	-4.4	
Moderate						
124	530/299/765	8.9	663/345/758	12.1	-3.2	-3.1
125	587/328/772	10.5	773/381/796	13.5	-3	
Hospitalization						
124	94/70/765	2	115/84/758	2.9	-0.9	-1.2
125	111/92/772	2.6	156/122/796	4	-1.4	
Severe						
124	94/72/765	2	111/84/758	2.7	-0.7	-1.1
125	112/94/772	2.6	156/123/796	4	-1.4	

data adxe and adsl, pgm mainline exac days per presc year 2010 02 26.sas
N: number of exacerbations/patients with exacerbations/in randomized population
R-P: difference between roflumilast and placebo in days per prescribed year
Mean: value of R-P averaged over studies 124 and 125

Table 18: Mean Exacerbation Days Per Treatment Year

Severity	Roflumilast		Placebo		Diff	
	N	Days	N	Days	R - P	Mean
Moderate or Severe						
124	624/347/765	9.9	774/391/758	11.7	-1.7	-1.6
125	699/381/772	11.4	929/437/796	12.8	-1.4	
Moderate						
124	530/299/765	8.5	663/345/758	10.1	-1.6	-1.3
125	587/328/772	9.6	773/381/796	10.7	-1	
Hospitalization						
124	94/70/765	2.6	115/84/758	3.4	-0.9	-1.2
125	111/92/772	3.3	156/122/796	4.7	-1.4	
Severe						
124	94/70/765	2.6	115/84/758	3.4	-0.9	-1.2
125	111/92/772	3.3	156/122/796	4.7	-1.4	

data adxe and adsl, pgm mainline exac days per trt yr w hosp 2010 02 24.sas
N: number of exacerbations/patients with exacerbations/in randomized population
R-P: difference between roflumilast and placebo in days per prescribed year
Mean: value of R-P averaged over studies 124 and 125

Roflumilast tended to increase the mean number of days during which patients experienced nausea, diarrhea, and gastrointestinal symptoms (Table 19 and Table 20). The term 'Gastrointestinal' comprised of all symptoms associated with gastrointestinal events, including but not limited to, nausea and diarrhea. As seen for moderate exacerbations, absolute event days per treatment year were higher than absolute event days per prescription year, and the difference between treatments tended to be higher for adverse days per treatment year than for adverse event days per prescribed year.

Table 19: Moderate or Severe Adverse Events Per Prescribed Year, by Symptom

Adverse Event	Roflumilast		Placebo		Diff	
	N	Days	N	Days	R - P	Mean
Nausea						
124	21/20/765	0.6	3/2/757	0	0.6	0.4
125	11/10/772	0.2	8/6/796	0	0.2	
Diarrhea						
124	30/29/765	1	14/14/758	0.4	0.6	0.7
125	36/33/771	0.8	10/10/796	0.1	0.7	
Gastrointestinal						
124	106/89/754	3.5	57/48/752	2.1	1.4	1.4
125	86/70/766	3.4	59/43/789	2.1	1.3	

data adae and adsl, pgm mainline ae event days per presc year mean 2010 02 26.sas
N: number of AE/patients with AE/in randomized population
R-P: difference between roflumilast and placebo in days per prescribed year
Mean: value of R-P averaged over studies 124 and 125

Table 20: Moderate or Severe Adverse Events Per Treatment Year, by Symptom

Severity	Roflumilast		Placebo		Diff	
	N	Days	N	Days	R - P	Mean
Nausea						
124	21/20/765	0.8	3/2/757	0.0	0.8	0.6
125	11/10/772	0.3	8/6/796	0.0	0.3	
Diarrhea						
124	30/29/765	1.3	14/14/758	0.4	0.9	0.9
125	36/33/771	1	10/10/796	0.1	0.9	
Gastrointestinal						
124	106/89/754	4.3	57/48/752	2.4	1.9	1.8
125	86/70/766	3.9	59/43/789	2.3	1.6	

data adae and adsl, pgm mainline ae event days per trt yr 2010 02 26.sas
N: number of AE/patients with AE/in randomized population
R-P: difference between roflumilast and placebo in days per prescribed year
Mean: value of R-P averaged over studies 124 and 125

The increases by roflumilast in the rate of moderate or severe exacerbations appear to have been driven by weight loss. After removing weight loss, which was graded by loss of mass rather than by acute distress to the patient, there was no consistent effect of roflumilast compared to placebo on number of moderate or severe adverse event days per prescribed year (Table 21 and Table 22), with roflumilast's effects compared to placebo varying in sign between studies 124 and 125.

Table 21: Moderate or Severe Adverse Event Days Per Prescribed Year, by Symptom, Not Including Weight Loss.

Severity	Roflumilast		Placebo		Diff	
	N	Days	N	Days	R - P	Mean
Moderate or Severe						
124	538/297/675	22.5	526/301/678	23.8	-1.3	-0.6
125	478/310/715	18.1	509/288/719	17.9	0.2	
Moderate						
124	456/253/682	20.9	422/250/687	21.2	-0.3	0.3
125	384/248/723	15.4	387/226/737	14.6	0.8	
Severe						
124	162/127/755	4.5	171/125/744	4.2	0.3	0.1
125	156/125/762	4.2	185/140/775	4.4	-0.2	

data adae and adsl, pgm mainline ae event days per presc year mean 2010 02 26.sas
N: number of AE/patients with AE/in randomized population
R-P: difference between roflumilast and placebo in days per prescribed year
Mean: value of R-P averaged over studies 124 and 125

Table 22: Moderate or Severe Adverse Event Days Per Treatment Year, Not Including Weight Loss.

Severity	Roflumilast		Placebo		Diff	
	N	Days	N	Days	R - P	Mean
Moderate or Severe						
124	538/297/675	19.7	526/301/678	20.5	-0.8	0.7
125	478/310/715	17.6	509/288/719	15.5	2.1	
Moderate						
124	456/253/682	18.9	422/250/687	19.2	-0.3	0.9
125	384/248/723	15.5	387/226/737	13.4	2.1	
Severe						
124	162/127/755	5.2	171/125/744	4.5	0.7	0.5
125	156/125/762	5	185/140/775	4.7	0.3	

data adae and adsl, pgm mainline ae event days per trt yr 2010 02 26.sas
N: number of AE/patients with AE/in randomized population
R-P: difference between roflumilast and placebo in days per prescribed year
Mean: value of R-P averaged over studies 124 and 125

4. FINDINGS IN SUBGROUPS and SPECIAL POPULATIONS

4.1 Sex, race and age

No gender, race, or age specific differences were apparent in the effect on exacerbation rate of roflumilast compared to placebo (Table 23, Table 24, and Table 25), with confidence limits within each study overlapping between subgroups. The analyses used to generate these tables used the Poisson regression model for exacerbations in Section 3.1 for Studies 124 and 125, with the addition of a subgroup by treatment term from which were derived least square means and confidence limits for differences.

Table 23: Exacerbation Rates by Gender

Study	Sex	Poisson Exacerbation Rate			
		R500	Placebo	Rate Ratio	RR 95% CI
124	M	1.0 (540)	1.3 (538)	0.81	0.68, 0.96
	F	1.1 (225)	1.1 (220)	0.96	0.73, 1.25
125	M	1.0 (610)	1.3 (648)	0.81	0.69, 0.94
	F	1.5 (162)	1.7 (148)	0.91	0.69, 1.20

pgm mainline efficacy Poisson exacerbation rate by subgroup 2010 02 09.sas

Table 24: Exacerbation Rates by Race

Study	Race	Poisson Exacerbation Rate			
		R500	Placebo	Rate Ratio	RR 95% CL
124	W	1.1 (737)	1.3 (732)	0.86	0.74, 0.99
	NW	0.01 (28)	0.02 (26)	0.51	0.14, 1.89
125	W	1.1 (559)	1.4 (568)	0.80	0.68, 0.94
	NW	1.2 (213)	1.4 (228)	0.86	0.65, 1.12

pgm mainline efficacy Poisson exacerbation rate by subgroup 2010 02 09.sas

Table 25: Exacerbation Rates by Age

Study	Age	Poisson Exacerbation Rate			
		R500	Placebo	Rate Ratio	RR 95% CL
124	≤ 65	1.1 (449)	1.1 (446)	0.94	0.79, 1.13
	> 65	1.0 (316)	1.1 (312)	0.72	0.57, 0.92
125	≤ 65	1.1 (429)	1.4 (437)	0.77	0.64, 0.92
	> 65	1.2 (343)	1.3 (359)	0.89	0.71, 1.08

pgm mainline efficacy Poisson exacerbation rate by subgroup 2010 02 09.sas

No gender, race, or age specific differences were apparent in the effect on pre-bronchodilator FEV1 of roflumilast compared to placebo (Table 26, Table 27, and Table 28), with confidence limits within each study overlapping between subgroups. The analyses generating these tables employed the repeated measures model for pre-bronchodilator FEV1 of Table 7, Figure 1, and Figure 2 at Week 52, with the addition of a subgroup by treatment term from which were derived least square means and confidence limits for differences.

Table 26: Change in Prebronchodilator FEV1 by Gender

Study	Sex	Δ Pre-Bronchodilator FEV1 (ml)			
		Rofl	Placebo	Diff	95% CL
124	M	31 (140)	-21 (149)	51	14, 90
	F	37 (359)	36 (372)	0	-52, 52
125	M	-5 (426)	-45 (463)	40	-7, 86
	F	15 (98)	-30 (87)	45	17, -73

pgm mainline efficacy prefev1 sponsor analysis by week 2010 03 03 subgroups.sas

Table 27: Change in Prebronchodilator FEV1 by Race

Study	Race	Δ Pre-Bronchodilator FEV1 (ml)			
		Rofl	Placebo	Diff	95% CL
124	W	28 (481)	-12 (502)	40	8, 71
	NW	-2 (18)	9 (19)	-11	-187, 165
125	W	6 (145)	-45 (161)	51	24, 78
	NW	-36 (379)	-53 (389)	17	-35, 70

pgm mainline efficacy prefev1 sponsor analysis by week 2010 03 03 subgroups.sas

Table 28: Change in Prebronchodilator FEV1 by Age Category

Study	Age	Δ Pre-Bronchodilator FEV1 (ml)			
		Rofl	Placebo	Diff	95% CL
124	≤ 65	22 (314)	-20 (318)	41	0, 82
	> 65	35 (185)	-6 (203)	41	6, 86
125	≤ 65	-42 (296)	-80 (299)	38	2, 73
	> 65	40 (228)	-14 (251)	53	20, 86

pgm mainline efficacy prefev1 sponsor analysis by week 2010 03 03 subgroups.sas

5. SUMMARY AND CONCLUSIONS

5.1 Statistical issues and collective evidence

Issues

During my review of the application, I identified one issue warranting further consideration. In particular, because the maintenance therapy indication implies long-term administration, it seems important that benefits remain positive for an extended period of time, at least throughout the duration of the studies conducted. The exacerbation analyses provided by the Applicant did not explicitly examine potential attenuations in treatment effect; of the four statistical models presented, the Poisson and the negative binomial models only assessed roflumilast's effect averaged over the entire course of each study, while the proportional hazards and the log-rank tests only assess times to onset of exacerbations in each study, without including all exacerbation recurrences.

To address this issue, I conducted exploratory analyses which broke studies into time intervals, similar to those used by the Applicant for the FEV1 analyses, and examined for each time interval the mean number of exacerbations per patient year.

Collective Evidence

Roflumilast has a statistically significant effect on pre-bronchodilator FEV1 compared to placebo. In the six studies reviewed (Studies 124, 125, 111, 112, 127 and 128), the size of the effect ranged from 39 to 80 ml, with an average of 54 ml.

In the four one-year studies (Studies 124, 125, 111, and 112), roflumilast numerically reduced the average rate of moderate or severe exacerbations, with two of the reductions in exacerbation rate, from Studies 124 and 125 statistically significant and with two of the reductions, from Studies 111, and 112, not statistically significant. With an explicit requirement for recent bronchitis and exacerbations, the entrance criteria for Studies 124 and 125 more closely matched the proposed label indication than the entrance criteria for Studies 111 and 112.

Exploratory analyses on Studies 124 and 125 suggest that the reduction of exacerbation rate by roflumilast compared to placebo may attenuate or even disappear after 8 months. Although his could be problematic for a long term maintenance indication in which benefits are expected to be positive for an extended period of time, it is not clear whether the observed reduction of effect was due to attenuation of roflumilast's effects or was instead associated with patterns of patient withdrawal.

5.2 Conclusions and Recommendations

The analyses support a conclusion that treatment with roflumilast increases pre-bronchodilator FEV1 by about 50 ml in one year and reduces rate of moderate or severe exacerbations (absolute rate reduction of 0.3) in patients with severe or very severe COPD with a history of exacerbations and chronic bronchitis. Whether the magnitude of the benefits outweighs the risks associated with administration of this drug is a matter of clinical judgment.

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/

ROBERT ABUGOV
03/31/2010

JOAN K BUENCONSEJO
03/31/2010
I concur with Robert Abugov's statistics review of NDA 22522

THOMAS J PERMUTT
03/31/2010
concur

STATISTICS FILING CHECKLIST 022-518

NDA Number: 022-522 **Applicant: Nycomed** **Stamp Date: 07/17/2009**

Drug Name: Roflumilast **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index sufficient to locate necessary reports, tables, data, etc.	**x**			
2	Original protocols, statistical analysis plans, and subsequent amendments available.	**x**			
3	Safety and efficacy for gender, racial, and geriatric subgroups investigated (if applicable).		**x**		
4	Data sets in EDR available and conform to applicable guidance.	**x**			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Comments for Applicant

Provide all macros and formats required to run submitted statistical programs for each of your phase 3 studies. For example, program t-exa-poisson.sas in study M2-124 will not run without stratspecs.sas, which has not been included, requires calls to macros setup, setupltf, logscan, and countwords, which have not been included, and uses format sev, which has not been included.

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ROBERT ABUGOV
09/29/2009

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09/29/2009