

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022522Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/31/2011</u>
	Study/Trial Completion:	<u>12/31/2014</u>
	Final Report Submission:	<u>05/30/2015</u>
	Other:	<u>NA</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Roflumilast has demonstrated efficacy compared to placebo in a population of patients with severe COPD with chronic bronchitis and a history of COPD exacerbations. This PMC is to acquire important information for physicians regarding the efficacy of roflumilast when used as an add-on therapy to a fixed dose combination of an inhaled long-acting beta agonist and corticosteroid, a standard of care medication for patients with severe COPD.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

As noted above, this PMC will give important information to physicians regarding the efficacy of roflumilast when used as an add-on therapy to a fixed dose combination of an inhaled long-acting beta agonist and corticosteroid, a standard of care medication for patients with severe COPD.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The trial will be a randomized, placebo-controlled study of roflumilast as an add-on therapy to a fixed dose combination inhaled long-acting beta agonist and corticosteroid in patients with severe COPD with chronic bronchitis and a history of COPD exacerbations.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
02/28/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: February 04, 2011

To: Badrul Chowdhury, MD, Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management (DRISK)

Melissa Hulett, MSBA, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management (DRISK)

From: Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): roflumilast Tablets

Application Type/Number: NDA 22-522

Supplement Number: 029

Applicant/sponsor: Forest Research Institute Inc.

OSE RCM #: 2010-1979

1 INTRODUCTION

This review is written in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to provide a review of the Applicant's Medication Guide (MG) of roflumilast tablets.

On April 23, 2010 the Applicant submitted a New Drug Application for roflumilast tablets indicated as a maintenance treatment to reduce the risk of COPD exacerbations in patients with severe COPD.

2 MATERIAL REVIEWED

- Draft roflumilast tablets Prescribing Information (PI) received on April 23, 2010, revised by the reviewing division throughout the reviewing cycle, and received by DRISK on January 25, 2011.
- Draft roflumilast tablets MG received on April 23, 2010 and received by DRISK on January 25, 2011.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information within the MG
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
02/04/2011

LASHAWN M GRIFFITHS
02/04/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 04, 2011

To: Carol Hill, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Robyn Tyler, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Michael Wade, Regulatory Health Project Manager
Olga Salis, Regulatory Health Project Manager
(DDMAC)

Subject: NDA 022522
DDMAC labeling comments for roflumilast tablets, 500 mcg

DDMAC has reviewed the proposed product labeling (PI), proposed Medication Guide, and proposed carton/container labeling for roflumilast tablets, 500 mcg submitted for consult on September 10, 2010. DDMAC's comments are based on the following:

- proposed draft marked-up labeling titled "RofFDA draft label 01-24-12011.doc" that was sent via email from DPARP to DDMAC on January 25, 2011;
- proposed carton and container labeling located in EDR at:
 - <\\cdsesub5\EVSPROD\NDA022522\0037\m1\us\bottle-label-trade-30-tab.pdf>
 - <\\cdsesub5\EVSPROD\NDA022522\0037\m1\us\bottle-label-trade-90-tab.pdf>
 - <\\cdsesub5\EVSPROD\NDA022522\0037\m1\us\sample-7-outer-box.pdf>
 - <\\cdsesub5\EVSPROD\NDA022522\0037\m1\us\sample-7-blister-pack.pdf>
 - <\\cdsesub5\EVSPROD\NDA022522\0037\m1\us\patient-kit-box.pdf>

- <\\cdsesub5\EVSPROD\NDA022522\0037\m1\us\patient-kit-sample-30-tab.pdf>
- <\\cdsesub5\EVSPROD\NDA022522\0037\m1\us\physician-kit-sleeve.pdf>
- <\\cdsesub5\EVSPROD\NDA022522\0037\m1\us\physician-kit-tray.pdf>

DDMAC has reviewed the carton/container labeling pieces and has no comments at this time.

DDMAC's comments on the PI and Medication Guide are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Robyn Tyler at (301) 796-4212 or robyn.tyler@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
02/04/2011

DSI CONSULT: Amended Request for Clinical Inspections

Date: Jan. 12, 2010

To: **Constance Lewin, M.D., M.P.H, Branch Chief, GCP1**
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: **Xuemeng Han Sarro, M.D., Clinical Reviewer, DPAP**
Anthony Durmowicz, M.D., Clinical Team Leader, DPAP
Lydia Gilbert-McClain, M.D., Deputy Director, DPAP

From: **Carol Hill, M.S. , Regulatory Health Project Manager/DPAP**

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22522

Applicant/ Applicant contact information (to include phone/email): Forest Research Institute, Inc.,
Harborside Financial Center, Plaza Five, Suite 1900, Jersey City, NJ 07311

Phone: 201-386-2031, Fax: 201-524-9711

CP: Lisa L. Travis, M.S., RAC, Director, Regulatory Affairs, Email: Lisa.Travis@frx.com

Drug Proprietary Name: Daxas

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): COPD

PDUFA: May 17, 2010

Action Goal Date: May 17, 2010

Inspection Summary Goal Date: May 1, 2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	# of Subjects	Indication
Site ID 7176 (US) PI: Neal Moser, MD Internal Medicine Associates, 2900 Chancellor Drive, Crestview Hills, KY, 41017 Office Phone: 859-341-0288 Fax: 859-341-0203	M2-124 (pivotal)	12	Efficacy concerns (FEV1 outlier)
Site ID 4545 (Hungary) PI: Dr. Beatrix Bálint Csongrád County Municipal Chest Disease Hospital, Deszk, Alkotmány str. 36, Hungary Office Phone: 436-62-571-556 Fax: 436-62-571-551	M2-124	67	Largest enrollment site in pivotal studies
Site ID 4793 (India) PI: Dr. Anthony Mesquita Center Name: TB and Chest Hospital St. Inez, P.O. Caranzalem, 403 002, India Office Phone: 0832-222-5088 Fax: 0832-242-5007	M2-125 (pivotal)	22	Efficacy concerns (may drive the result for rate of exacerbation, one of the two coprimary endpoints)
Site ID 6675 (Poland) PI: Dr. Halina Batura-Gabryel Department of Pulmonary Diseases, Marcinkowski University of Medical Sciences, Poznan, Szamarzewskiego 84 str. Office Phone: +48 61 84 17 061 Fax: +48 61 84 17 061	M2-125	33	Violations of GCP per previous EMEA inspection

III. Site Selection/Rationale

NDA-22522 is for a new drug class, phosphodiesterase 4 inhibitors (PED4). The applicant designated studies M2-124 and M2-125 as the pivotal trials. Both M2-124 and 125 were

multicenter, multinational studies and together they involved 355 sites from 15 countries in Europe, North America, Asia and Africa.

We initially selected 2 candidate sites, one from the United States (M2-124) and one from Poland (M2-125). While other study sites reached statistical significance preFEV1, study site 7176 in the United States was the only domestic site that reached the statistical significance in pre FEV1 and had N of greater than 10. Site 6675 from Poland has been selected for inspection for cause; a previous inspection by the EMEA identified significant violations. After discussion with Dr. Purohit-Sheth from the Division of Scientific Investigations concerning the findings of deficiencies found during inspections of study sites and the Applicant's monitoring of the sites, the Division is amending the original consult request to include 2 additional sites. These additional sites are being added in order to assess if findings found by EMA inspections may be indicative of more widespread deficiencies in the conduct of the pivotal studies.

Site 4793 from India was added in part because the Indian population represents about 11% of the study subjects and is the largest non-white population in the pivotal studies. This site was one of the few sites that demonstrated efficacy for the proposed product, roflumilast.

Site 4545 from Hungary was selected because it was the highest enroller site among several hundred sites from the 2 pivotal studies. It also represents more than a quarter of enrollment from Hungary. Hungary was the number 3 country in terms of number of enrollment (N=282) and only secondary to US (N=772) and India (N=338).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify): see rationale
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
Additional sites are being suggested for inspection based on significant deficiencies found during inspections conducted by the EMA for this application and discussion with the Division of Scientific Investigations in order to assess for more widespread deficiencies in the conduct of the pivotal studies.
- Other: This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites (approximately 75% of subjects enrolled in the clinical program were from foreign sites). Also, a previous inspection by EMEA revealed violations at the Polish site noted above.

IV. Tables of Specific Data to be Verified (if applicable)

NA

Should you require any additional information, please contact *Carol Hill, RPM* at 301-796-1226 or *Xuemeng Han Sarro* at 301-796-XXXX.

Concurrence: (as needed)

Anthony Durmowicz, M.D., Medical Team Leader

Lydia Gilbert-McClain, Deputy Division Director (for foreign inspection requests or requests for 5 or more sites only)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	NYCOMED GMBH	DAXAS(ROFLUMILAST 500 MCG TABLETS

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/s/

CAROL F HILL
01/12/2010

LYDIA I GILBERT MCCLAIN
01/13/2010



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Pulmonary and Allergy Products**

Memorandum of Facsimile Correspondence

Date: January 20, 2011

To: Kevin McDonald, Associate Director, Regulatory Affairs

Company: Forest Research Institute, Inc.

Fax: 201-524-9711

Email: kevin.mcdonald@frx.com

Phone: 201-427-8232

From: Carol Hill, MS
Regulatory Health Project Manager
Division of Pulmonary, Allergy and Rheumatology Products

Subject: Clinical and Clinical Pharmacology Labeling Revisions re: NDA 22-522

Pages: 12

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If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.
carol.hill@fda.hhs.gov

NDA 22522
Forest Research Institute, Inc.
Roflumilast

We have begun our review of the label in your October 29, 2010 submission. Per our conversation on December 22, 2010, be advised that additional labeling comments will be forthcoming as we continue to review the labeling. Since we will be providing our revisions and comments to specific sections of the labeling, we do not expect you to provide revised labeling at present. However, if you have questions regarding any of the revised sections, we request that you forward your comments so that we may address any issues you may have. In the attached revised package insert labeling, insertions are underlined and deletions are strike-out.

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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/s/

CAROL F HILL
01/20/2011

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products

Application Number: NDA 22522

Name of Drug: Daxas (roflumilast) Tablets

Applicant: Forest Research Institute

Material Reviewed:

Submission Date(s): July 15, 2009, August 30, 2010, and October 29, 2010

Receipt Date(s): July 17, 2009, August 31, 2010, and October 29, 2010

Submission Date of Structure Product Labeling (SPL): August 30, 2010

Type of Labeling Reviewed: WORD

Background and Summary

On August 30, 2010, Forest Research Institute resubmitted their New Drug Application (NDA) for Daxas (roflumilast) in response to the Agency's Complete Response letter dated, May 17, 2010. The labeling in this submission includes a package insert, medication guide and carton and container labeling. Prior to the complete response letter of May 17, 2010, a discipline review letter dated May 11, 2010, was sent informing Forest that labeling would not be reviewed during the first review cycle of the application. Upon review of the resubmitted application, a CMC Discipline Review letter was sent on September 22, 2010 requesting revision of the DESCRIPTION section to include the pharmacological or therapeutic class of the drug, as per 21 CFR 201.57(c)(12) and to increase the prominence of the established name relative to the proprietary name. Forest responded to this request on October 29, 2010 and submitted updated labeling to the package insert, medication guide and carton and container labeling.

Review

The proposed labeling submitted on October 29, 2010 was reviewed using the SEALD Label Review Tool version, September, 2010. The following deficiencies will be provided with the revisions and comments of the discipline review team and consults.

1. The following comments pertain to the HIGHLIGHTS section of the product label:
 - a. Highlights, excluding the boxed warning, must be limited in length to one-half page.
 - b. Line 12, INDICATIONS AND USAGE section, omit the additional space between the words daily and treatment.
 - c. Line 36, WARNINGS AND PRECAUTIONS section, insert the word with

between treatment and Daxas.

2. The following comments pertain to the FULL PRESCRIBING INFORMATION: CONTENTS (TOC) section of the product label:
 - a. Do not include the medication guide as a subsection heading.
3. The following comments pertain to the FULL PRESCRIBING INFORMATION section of the product label:
 - a. Line 202, ADVERSE REACTIONS section, insert the word “clinical” after the words may not reflect the rates observed in practice.
 - b. Line 857, remove Medication Guide revised XXXXXX.
 - c. Line 861, remove Rx only.

Recommendations

Comments and deficiencies have been identified and will be included in the labeling edits and revisions sent to the sponsor prior to the labeling teleconference on January 19, 2011.

Carol Hill, M.S.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: chill/01Dec10
Revised/Initialed: Barnes/10Dec10
Finalized:chill/13Dec10
Filename: CSO Labeling Review Template (updated 1-16-07).doc

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/s/

CAROL F HILL
12/13/2010

SANDRA L BARNES
12/17/2010

Consultative Review and Evaluation of Clinical Data DPP Consult #11236

Consultant Reviewer: Phillip D. Kronstein, M.D.
Division of Psychiatry Products/OND/CDER

Consultation Requester: Xuemeng Han Sarro, M.D.
Tony Durmowicz, M.D. (TL)
Division of Pulmonary, Allergy, and
Rheumatology Products/OND/CDER

Subject: NDA 22,522: Roflumilast (a PDE 4 inhibitor)

Indication: Maintenance Treatment of Chronic Obstructive
Pulmonary Disease (COPD)

Date Received: October 13, 2010

Requested Completion Date: November 30, 2010

I. Background

Psychiatric adverse events, including suicides and depression, were of particular concern during the original review of NDA 22,522 (Roflumilast in treatment of COPD) by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) in 2009. Among the 7800 COPD patients in placebo-controlled trials who received the active roflumilast treatment, there were 3 completed suicides and 2 suicide attempts (this was based on sponsor adverse event reporting), compared to 1 suicidal ideation in a patient who received placebo. Although there were no completed/attempted suicides or suicidal ideation in other indications (roflumilast clinical trials enrolled over 24,000 subjects in six indications: COPD, asthma, allergic rhinitis, diabetes, rheumatoid and osteoarthritis), there was a 2 to 3 times increase in psychiatric adverse events, such as depression, anxiety, and insomnia, in patients who received roflumilast compared to those who received placebo in clinical trials across all 6 indications.

DPARP felt that the sponsor did not fully assess the safety signal of suicides and psychiatric adverse events in the NDA. In the Complete Response Letter (dated 5/17/2010), the sponsor was told, among other things, that to “understand the signal strength and its impact on the risk benefit assessment,” a comprehensive review and evaluation of the roflumilast program database for suicidality should be performed utilizing an acceptable method, such as the Columbia Classification Algorithm of Suicide Assessment (C-CASA).

The sponsor chose to analyze two pools of patients and provided the results in their NDA resubmission dated 8/30/2010:

- COPD Pool: 16 placebo-controlled, parallel group studies in COPD patients

- Overall Pool: 36 studies, consisting of the COPD pool (16 studies) plus 12 placebo-controlled and 5 active-controlled, parallel group studies in asthma patients, and 3 placebo-controlled, parallel group studies in patients in other indications.

Of note, the 9 placebo-controlled crossover studies were not included in the Overall Pool. In addition, the 5 active-controlled studies were removed for the final statistical analysis.

For each study, a search of the clinical database was conducted on all preferred terms, verbatim terms, and comment fields (if applicable) for all treated patients. The double-blind treatment period was defined as the start of double-blind medication to 1 day after stopping double-blind treatment. The text strings used in the search to indentify possibly suicide-related adverse events (PSRAEs) were:

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

These text strings are almost identical to those used in the classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants, with any differences, in the opinion of this reviewer, being insignificant.

Using the text string search, adverse event listings for each study (with dummy patient numbers and no treatment codes) were generated and reviewed by 3 independent physicians at Forest Research Institute, Inc. These adverse events were classified as "y" for PSRAEs or "n" for obvious false positive events (e.g. included the key words above but were not suicide-related, such as "epigastric pain" indentified in the search for the word "gas"). After this filtering process, for all PSRAEs that were classified as "y," narratives were generated for each patient. The narratives included relevant information such as age, sex, medical history, and previous and concomitant medications; treatment assignment was not included.

The narratives were then forwarded to the (b) (4) for coding under the direction of (b) (4). The complete listing of all possible adverse events indentified in the string search was also forwarded to (b) (4) for an external review to ensure that no cases were overlooked in the internal review by Forest. In addition, to ensure that all potentially suicidal events were indentified, listings of all SAEs/deaths were also forwarded to (b) (4).

Each patient with a narrative and each event in the SAE/death listing were assigned 1 of the 9 possible codes as per the C-CASA methodology. A description of the codes is presented in Table 1. If multiple events were reported

in one patient, warranting assignment of more than 1 code, the more severe code was selected based on the following code order: 1>2>3>4>5>6>9>7 or 8. The coding results for all studies are presented in Table 2.

Table 1 Description of C-CASA Codes

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

C-CASA = Columbia Classification Algorithm of Suicide Assessment

Table 2 Number and Percentage of Patients with Possibly Suicide-Related Adverse Events by C-CASA Code During Double-Blind Treatment Period—COPD and Overall Pools

C-CASA Codes	<i>COPD Pool</i>		<i>OVERALL Pool</i>		
	<i>Pbo</i> (<i>N</i> =5682)	<i>Rof</i> (<i>N</i> =6972)	<i>Pbo</i> (<i>N</i> =8458)	<i>Rof</i> (<i>N</i> =11,848)	<i>Active</i> (<i>N</i> =1317)
	n (%)	n (%)	n (%)	n (%)	n (%)
1 (Completed suicide)	0	1 (0.01)	0	1 (0.01)	0
2 (Suicide attempt)	0	2 (0.03)	0	2 (0.02)	0
3 (Preparatory acts toward imminent suicidal behavior)	0	0	0	0	0
4 (Suicidal ideation)	1 (0.02)	0	1 (0.01)	0	0
5 (Self injurious behavior, intent unknown)	0	0	0	0	0
6 (Not enough information, fatal)	0	0	0	0	0
7 (Self-injurious behavior, no suicidal intent)	0	0	0	0	0
8 (Other; accident, psychiatric, medical)	783 (13.8)	877 (12.6)	860 (10.2)	1024 (8.6)	23 (1.7)
9 (Not enough information, non-fatal)	0	1 (0.01)	0	1 (0.01)	0
Total of all categories	784 (13.8)	881 (12.6)	861 (10.2)	1028 (8.7)	23 (1.7)

The C-CASA data were then statistically analyzed based on the two study populations: the COPD Pool (16 studies) and all placebo-controlled, parallel-group studies in the Overall Pool (31 studies). For the purposes of comparison between roflumilast and placebo, the data for patients in the 5 active-controlled studies was not included in the statistical analysis.

Fisher's exact test was used to compare the risk between treatment groups. The sponsor considered codes 1-4 as a suicidal event, which is consistent with the approach of our Division. The analysis did not take in account which study each of the subjects came from, but due to the small number of suicidal events, this should have little effect on the results.

The results of risk, rate, and the statistical test for between treatment differences are presented in Table 3 for the COPD Pool and Table 4 for all placebo-controlled, parallel group studies in the Overall Pool.

Table 3 Analysis of Possibly Suicide-Related Adverse Events During the Double-Blind Treatment Period—COPD Pool

<i>Treatment Group</i>	<i>Number of Patients With at Least 1 Event</i>	<i>Number of Treated Patients</i>	<i>Patient-Years Exposure, Years</i>	<i>Risk, %</i>	<i>Rate, per 1000 Patient Years</i>	<i>p-Value^a</i>
<i>Completed Suicide, Suicide Attempt, Preparatory Act, or Suicidal Ideation (Codes 1-4)</i>						
Placebo	1	5682	3516	0.018	0.284	0.6327
Roflumilast	3	6972	3781	0.043	0.793	
<i>Completed Suicide, Suicide Attempt, Preparatory Acts, Suicidal Ideation, Self-injurious Behavior, Not Enough Information - Fatal, or Not Enough Information - Non-fatal (Codes 1-6, and 9)</i>						
Placebo	1	5682	3516	0.018	0.284	0.3878
Roflumilast	4	6972	3781	0.057	1.058	

^a The 2-sided p-value for risk difference was based on Fisher's exact test.

COPD Pool (16 studies) includes FK1 101, FK1 103, IN-108, JP-706/708, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127 and M2-128

COPD = chronic obstructive pulmonary disease.

Table 4 Analysis of Possibly Suicide-Related Adverse Events During the Double-Blind Treatment Period—All Placebo-Controlled, Parallel Group Studies

<i>Treatment Group</i>	<i>Number of Patients with at least 1 event</i>	<i>Number of Treated Patients</i>	<i>Patient-years Exposure, Years</i>	<i>Risk %</i>	<i>Rate, per 1000 patient years</i>	<i>p-Value^a</i>
<i>Completed Suicide, Suicide Attempt, Preparatory Act, or Suicidal Ideation (Codes 1-4)</i>						
Placebo	1	8458	4394	0.012	0.228	0.6333
Roflumilast	3	10459	4819	0.029	0.623	
<i>Completed Suicide, Suicide Attempt, Preparatory Acts, Suicidal Ideation, Self-injurious Behavior, Not Enough Information - Fatal, or Not Enough Information - Non-fatal (Codes 1-6, and 9)</i>						
Placebo	1	8458	4394	0.012	0.228	0.3888
Roflumilast	4	10459	4819	0.038	0.830	

a The 2-sided p-value for risk difference was based on Fisher’s exact test.

The patient population for this table excluded 5 active controlled studies from the OVERALL Pool (FK1 005, FK1 008, FK1 009, M2-017, and M2-026). Thus, the statistical analysis was performed on a total of 31 placebo-controlled, parallel-group studies: FHP 031, FKE 001, FKE 002, FK1 003, FK1 004, FK1 011, FK1 020, FK1 021, FK1 101, FK1 103, IN-108, JP-705/707, JP-706/708, M2-012, M2-013, M2-014, M2-023, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128 and M2-401.

As seen in Tables 3 and 4, the risks and rates of suicidal events (codes 1 to 4) for roflumilast-treated patients are slightly higher than the risks and rates of suicidal events for placebo-treated patients, both in the COPD Pool and in all placebo-controlled, parallel group studies in the Overall Pool. However, the differences are not statistically significant based on Fisher’s exact test.

In this NDA resubmission, the sponsor has also provided a table of psychiatric adverse events (by AE preferred term) in the parallel group, placebo-controlled COPD studies (see Appendix 1). The sponsor proposes to include psychiatric adverse events “such as anxiety, depression, and rare instances of suicidal thinking and behavior (including suicide)” in the “Warnings and Precautions” section of their label. They also propose a Med Guide only REMS; the Med Guide, among other things, discusses the possibility of psychiatric adverse events. Finally, the sponsor plans to have expedited reporting and monthly aggregated analysis updates of psychiatric and other adverse events (weight loss and tumors) as part of an enhanced post marketing surveillance program.

II. DPP Response to Division of Pulmonary, Allergy, and Rheumatology Products Questions

Question #1: Please comment on the adequacy of the C-CASA assessment performed by the sponsor. Was the C-CASA properly executed? Do you agree with the sponsor’s conclusion that there was no association between roflumilast treatment and suicide?

The sponsor’s search for possibly suicide-related adverse events (PSRAEs) and their classification using C-CASA by the Columbia group appears to have been

properly executed. The sponsor's statistical analysis of suicidality-related events (codes 1-4) seems reasonable. Normally, the analysis should take into account which study each of the subjects came from, but due to the small number of suicidal events, this should have little effect on the results. Based on these results, there is no statistically significant difference in suicidal events in patients who received roflumilast compared to those who received placebo.

Question #2: Given the C-CASA evaluation was performed adequately, do you feel there is an increased risk for suicidality in patients receiving roflumilast?

Please see answer to Question #1.

Question #3: Does the increased risk (if any) of suicidality in patients receiving roflumilast justify a REMS that includes a Boxed Warning for suicide and increased psychiatric adverse events such as depression, anxiety, and insomnia?

Given that, according to the C-CASA analysis, there is no statistically significant difference in suicidality-related events (codes 1-4) between roflumilast-treated and placebo-treated patients, a REMS that includes a Boxed Warning for suicidal events would not be justified. As for other psychiatric adverse events, examination of the sponsor's table of psychiatric adverse events in COPD patients in parallel group, placebo-controlled studies revealed an at least two to three times increase in anxiety¹, depression², and insomnia³ in patients who received roflumilast compared to those who received placebo, though the total percentage of each in roflumilast-treated patients was less than 5%.

We note that the sponsor has already included psychiatric adverse events in the "Warnings and Precautions" section of their proposed label. However, we would recommend that the sponsor combine the AE terms for anxiety, depression, and insomnia as we have suggested and recalculate the incidence rates of these events. It is also recommended that this information be included in the 2% table under the Adverse Reactions section and the "Warning and Precautions" section (either directly or by referring to the 2% table). For instance, the labeling language under "Warnings and Precautions" might state: "In a pooled analysis of multiple short-term, placebo-controlled studies, xx out of XX roflumilast-treated patients (x%) versus yy out of YY placebo-treated patients (y%) spontaneously reported treatment emergent depressive symptoms, and xx out of XX roflumilast-treated patients (x%) versus yy out of YY placebo-treated patients (y%) spontaneously reported treatment emergent anxiety symptoms."

¹ Combining terms for "anxiety," "anxiety disorder," and "panic attack," and "panic disorder."

² Combining terms for "depressed mood," depression," and "depressive symptoms."

³ Combining terms for "initial insomnia," "insomnia," and "middle insomnia."

Question #4: Do you have any additional comments regarding this NDA resubmission, including, but not limited to, the sponsor's REMS, analysis on suicide, depression, anxiety, insomnia, or other psychiatric adverse events?

We have no additional comments from DPP perspective, but you might consider consulting OSE/DRISK regarding the sponsor's REMS/Med Guide and post marketing surveillance program for further feedback on them.

Phillip D. Kronstein, M.D.
Medical Officer
CDER/DPP

cc: HFD-130/Kronstein
Khin
Laughren
Berman
Hill
Han Sarro
Durmowicz

Appendix 1

Number (%) of COPD Patients with Psychiatric Adverse Events in Parallel Group, Placebo-Controlled Trials

AE Preferred Term	Treatment Group		
	<i>Placebo</i> N=5682	<i>Roflumilast</i> 250 µg N=1002	<i>Roflumilast</i> 500 µg N=5970
Number (%) of Patients with Any psychiatric event	168 (3.0)	31 (3.1)	362 (6.1)
Abnormal dreams	1 (<0.1)	0 (0.0)	0 (0.0)
Acute Psychosis	1 (<0.1)	0 (0.0)	0 (0.0)
Agitation	2 (<0.1)	0 (0.0)	3 (<0.1)
Agoraphobia	1 (<0.1)	0 (0.0)	0 (0.0)
Alcohol Withdrawal Syndrome	1 (<0.1)	0 (0.0)	0 (0.0)
Alcoholic Hangover	0 (0.0)	1 (<0.1)	0 (0.0)
Alcoholism	1 (<0.1)	0 (0.0)	0 (0.0)
Anxiety	43 (0.8)	7 (0.7)	80 (1.3)
Anxiety Disorder	0 (0.0)	2 (0.2)	2 (<0.1)
Apathy	0 (0.0)	0 (0.0)	1 (<0.1)
Attention Deficit/Hyperactivity Disorder	0 (0.0)	0 (0.0)	1 (<0.1)
Bipolar I Disorder	0 (0.0)	0 (0.0)	1 (<0.1)
Bulimia Nervosa	0 (0.0)	0 (0.0)	1 (<0.1)
Completed Suicide	0 (0.0)	1 (0.1)	2 (<0.1)
Confusional State	5 (<0.1)	0 (0.0)	6 (0.1)
Crying	0 (0.0)	0 (0.0)	2 (<0.1)
Delirium	0 (0.0)	0 (0.0)	1 (<0.1)
Depressed Mood	1 (<0.1)	1 (0.1)	4 (<0.1)
Depression	45 (0.8)	3 (0.3)	70 (1.2)
Depressive Symptoms	0 (0.0)	0 (0.0)	1 (<0.1)
Disorientation	0 (0.0)	0 (0.0)	2 (<0.1)
Dysphoria	0 (0.0)	1 (<0.1)	0 (0.0)
Early Morning Awakening	0 (0.0)	0 (0.0)	1 (<0.1)
Eating Disorder	0 (0.0)	0 (0.0)	1 (<0.1)
Emotional Disorder	2 (<0.1)	0 (0.0)	0 (0.0)
Emotional Distress	0 (0.0)	0 (0.0)	1 (<0.1)
Hallucination	0 (0.0)	0 (0.0)	2 (<0.1)
Initial Insomnia	0 (0.0)	0 (0.0)	1 (<0.1)
Insomnia	54 (1.0)	15 (1.5)	165 (2.6)
Listlessness	0 (0.0)	0 (0.0)	1 (<0.1)
Major Depression	0 (0.0)	1 (<0.1)	2 (<0.1)

AE Preferred Term	Treatment Group		
	Placebo N=5682	Roflumilast 250 µg N=1002	Roflumilast 500 µg N=5970
Mental Disorder	1 (<0.1)	0 (0.0)	3 (<0.1)
Mental Disorder due to a general medical condition	1 (<0.1)	0 (0.0)	0 (0.0)
Mental Status Changes	0 (0.0)	0 (0.0)	1 (<0.1)
Middle Insomnia	0 (0.0)	0 (0.0)	1 (<0.1)
Mood Altered	0 (0.0)	0 (0.0)	1 (<0.1)
Mood Swings	0 (0.0)	0 (0.0)	1 (<0.1)
Nervousness	3 (<0.1)	0 (0.0)	7 (0.1)
Neurosis	0 (0.0)	0 (0.0)	1 (<0.1)
Nightmare	0 (0.0)	0 (0.0)	1 (<0.1)
Panic Attack	7 (0.1)	0 (0.0)	4 (<0.1)
Panic Disorder	0 (0.0)	0 (0.0)	1 (<0.1)
Psychotic Disorder	1 (<0.1)	0 (0.0)	1 (<0.1)
Restlessness	3 (<0.1)	0 (0.0)	5 (<0.1)
Sleep Disorder	10 (0.2)	1 (0.1)	20 (0.3)
Stress	4 (<0.1)	0 (0.0)	4 (<0.1)
Suicidal Ideation	1 (<0.1)	0 (0.0)	0 (0.0)
Suicide Attempt	0 (0.0)	0 (0.0)	2 (<0.1)
Transient Psychosis	0 (0.0)	0 (0.0)	1 (<0.1)
Withdrawal Syndrome	1 (<0.1)	0 (0.0)	0 (0.0)

COPD Studies: 16 studies (FK1101, FK1103, IN-108, M2-107, M2-110, M2-111, M2-112, M2-118, M2-119, M2-121, M2-124, M2-125, M2-127, M2-128, JP706 & JP 708 (ext of JP 706))

Data Source: Appendix Statistical Table 1.1

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

/s/

PHILLIP D KRONSTEIN
11/15/2010

NI A KHIN
11/16/2010

THOMAS P LAUGHREN
11/16/2010

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

- x There is a lack of domestic data that solely supports approval;

Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **April 17, 2010**. We intend to issue an action letter on this application by **May 17, 2010**.

Should you require any additional information, please contact Carol Hill, Regulatory Health Project Manager, 301-796-1226.

Concurrence: (Optional)

Anthony Durmowicz, Medical Team Leader; Partha Roy, Biopharm Team Leader
Xuemeng Han Sarro, Medical Reviewer; Ping Ji, Biopharm Reviewer

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	NYCOMED GMBH	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/

CAROL F HILL
10/02/2009

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22522 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Daxas Established/Proper Name: roflumilast Dosage Form: Tablet Strengths: 500 mcg		
Applicant: Forest Research Institute, Inc. Agent for Applicant (if applicable):		
Date of Application: July 15, 2009 Date of Receipt: July 17, 2009 Date clock started after UN:		
PDUFA Goal Date: May 17, 2010	Action Goal Date (if different):	
Filing Date: September 15, 2009	Date of Filing Meeting: September 4, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): COPD		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 57883				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.				
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
 <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X																		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>	X			
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			Electronic, but sent anyway.

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Indication is COPD
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	Y			
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>			X	TN granted on 7/23/09
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): December 6, 2001 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 16, 2008 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 4, 2009

BLA/NDA/Supp #: NDA 22522

PROPRIETARY NAME: DAXAS

ESTABLISHED/PROPER NAME: roflumilast

DOSAGE FORM/STRENGTH: tablet/500 mcg

APPLICANT: Nycomed GbmH

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): COPD

BACKGROUND: Sponsor submitted an application on February 12, 1999 for IND 57883/Roflumilast (b)(4) tablets for the treatment of bronchial asthma. On March 18, 1999, the sponsor requested inactivation of the application. A request for reactivation was submitted on July 1, 1999. September 29, 2008, Nycomed proposed the tradename, DAXAS as the proprietary name for NDA submission. The NDA 22522/500 mcg tablet was submitted on July 15, 2009 for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Carol Hill	Y
	CPMS/TL:	Sandra Barnes	N
Cross-Discipline Team Leader (CDTL)	Anthony Durmowicz		Y
Clinical	Reviewer:	Xuemeng Han Sorro	Y
	TL:	Anthony Durmowicz	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ping Ji/Hao Zhu, Arun Agarwal	Y
	TL:	Dakshina Chilukuri	Y
Biostatistics	Reviewer:	Robert Abugov	Y
	TL:	Qian H. Li	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Y
	TL:	Jean Wu	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Craig Bertha	N
	TL/PAL:	Ali Al Hakim/ Prasad Peri	Y/N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees	OSE/DMEPA – Carolyn Volpe, PharmD, RPM Clinical Pharmacology – Arun Agarwal, Ph.D., Reviewer	

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES TBD <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: Date TBD</p> <p>If no, for an original NME or BLA application, include the reason. For example:</p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:

<i>mitigation, treatment or prevention of a disease</i>	
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<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES TBD <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
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<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT

Signatory Authority: ODE II Director

21st Century Review Milestones (see attached) (optional):

GRMP Timeline Milestones:

Filing/Planning Mtg: September 4, 2009

Filing Date: September 15, 2009

74 Day Letter: September 29, 2009

MCR Mtg: December 14, 2009

Full Labeling Mtg: February 15, 2010

WU Mtg: March 13, 2010

Primary Review Due: March 24, 2010

Secondary Review Due: March 31, 2010

Labeling Tcon: April 6, 2010

CDTL Memo: April 7, 2010

Division Director Memo: April 14, 2010

Action Package Readiness: April 16, 2010

Action Package to ODE II IO: April 26, 2010

PDUFA Date: May 17, 2010

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by

	Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/

CAROL F HILL
05/07/2010

SANDRA L BARNES
05/10/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 22522

Name of Drug: Daxas (roflumilast) 500 mcg tablet

Applicant: Nycomed

Material Reviewed:

Submission Date: July 15, 2009

Receipt Date: July 17, 2009

Submission Date of Structure Product Labeling (SPL): July 15, 2009

Type of Labeling Reviewed: WORD/SPL

Background and Summary

Nycomed submitted on July 15, 2009, a original NDA for Daxas (roflumilast) for the indication maintenance treatment of COPD. The submission contained proposed labeling which consists of the PI, carton and container labels.

Review.

The following issues/deficiencies have been identified in the proposed labeling.

Highlights

1. Not limited in length to one half page.
2. Pharmacologic class has been omitted from the statement, “(Drug) is a (name of class) indicated for (indications)” in Indications and Usage section.
3. Manufacturer’s name and phone number omitted from verbatim statement, “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.” of the Adverse Reactions section.

Full Prescribing Information: Contents

4. Two column format not used.

Full Prescribing Information

5. Manufacturer information not included after the Patient Counseling Information section at the end of the labeling.

Recommendations

These labeling deficiencies will be conveyed in the 74 Day letter.

Carol Hill, MS
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: chill/September 24, 2009

Revised/Initialed: Barnes/May 4, 2010

Finalized: chill/May 7, 2010

Filename: NDA 22522 RPM Labeling Review

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/

CAROL F HILL
05/07/2010

SANDRA L BARNES
05/10/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: May 4, 2010

To: Badrul Chowdhury, MD, PhD, Division Director
Division of Pulmonary, Allergy, and Rheumatology Products

Through: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Laura Pincock, PharmD, Acting Team Leader
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Daxas (Roflumilast) Tablets
500 micrograms per Tablet

Application Type/Number: NDA 022522

Applicant/sponsor: Forest Research Institute, Inc.

OSE RCM #: 2009-1448

CONTENTS

1	INTRODUCTION.....	3
2	METHODS AND MATERIALS REVIEWED	3
3	CONCLUSION AND RECOMMENDATIONS	3
3.1	Comments to the Applicant.....	3
	APPENDICES	5

1 INTRODUCTION

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products for medication error assessment of the container labels, carton, and insert labeling for Daxas.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton, and insert labeling submitted on April 23, 2010. See Appendices A-G for images of the proposed container labels and carton labeling.

- Container Labels (30 count and 90 count)
- Professional Sample Container Label (30 count)
- Patient Sample Kit Carton Labeling (30 count)
- Physician Sample Kit Tray Labeling (5 kits of 30 tablets)
- Physician Sample Kit Sleeve Carton Labeling (5 kits of 30 tablets)
- Professional Sample Blister Pack Label (7 count)
- Professional Sample Pack Carton Labeling (7 count)
- Package Insert Labeling (no image)

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the container labels and carton labeling in Section 2.1, *Comments to the Applicant*. DMEPA has no comments on the insert labeling at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Carolyn Volpe at 301-796-5204.

3.1 COMMENTS TO THE APPLICANT

A. General Comments for All Labels and Labeling

1. We remind the Applicant of their requirement to comply with 21 CFR 208.24. We acknowledge the use of a Medication Guide statement. Please ensure that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:
 - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
 - 2. As currently presented, the established name still does not appear to be one half the size of the proprietary name. Ensure the prominence of the established name is in accordance with 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
 - 3. Delete or minimize the triangular graphic design from the position following the proprietary name because it is as prominent as the proprietary name, established name, and strength. The proprietary name, established name, and strength should be the most prominent information communicated on the principal display panel.
- B. Container Labels (30 count and 90 count) and Professional Sample Container Label (30 count)
- Relocate the net quantity statement (30 tablets or 90 tablets) away from the product strength to improve readability and decrease the potential for confusion with the product strength (500 micrograms). We suggest moving the net quantity statement to the bottom of the principal display panel.
- C. Physician Sample Kit Tray Labeling (5 kits of 30 tablets each) and Physician Sample Kit Sleeve Carton Labeling (5 kits of 30 tablets each)
- Revise the Daxas carton labeling to include the product strength (500 micrograms per tablet). The product strength should be prominently displayed in conjunction with the proprietary and established names on all carton labeling for Daxas.
- D. Professional Sample Blister Pack Label (7 count)
- 1. The printed information on the blister pack label that communicates the proprietary name, established name, strength, and manufacturer is off-set to the side so that the perforated tear lines of the blister pack intersect this important information. This is error-prone, because if a patient cuts the card down the tear line, the information will be cut in half and difficult to read. We recommend that this important information be placed in the center of each blister, so that if the card is cut or a tablet is removed, the information remains intact and readable.
 - 2. The lot number and expiration date should appear on the back of every blister that contains a tablet, so that the information is immediately available if the card is cut to separate a dose from the rest of the blister pack.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

LAURA L PINCOCK
05/04/2010

DENISE P TOYER
05/05/2010

CAROL A HOLQUIST
05/05/2010

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: April 30, 2010

TO: Carol Hill, M.S., Regulatory Project Manager
Xuement Han Sarro, M.D., Medical Officer
Anthony Durmowicz, M.D., Medical Officer
Division of Pulmonary, Allergy and Rheumatologic Products

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Anthony Orenca, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-522

APPLICANT: Forest Research Institute, Inc.

DRUG: roflumilast (Daxas)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: chronic obstructive pulmonary disease (COPD)

CONSULTATION REQUEST DATE: January 12, 2010

DIVISION ACTION GOAL DATE: May 17, 2010

PDUFA DATE: May 17, 2010

I. BACKGROUND:

COPD (chronic obstructive pulmonary disease) is a leading cause of morbidity and mortality in the adult population worldwide. While COPD is a collection of conditions, these share a common physiologic abnormality which is the limitation of expiratory airflow. Inflammatory and structural changes occur in the airways in COPD. Roflumilast is a potent and selective PDE-4 (phosphodiesterase-4) inhibitor with multiple anti-inflammatory activities. Clinical studies have shown that oral roflumilast may be potentially efficacious in COPD.

Protocol BY217/M2-124 (AURA):

Protocol BY217/M2-124 was a randomized, double-blind, parallel-group study with two treatment arms (roflumilast 500 mcg or placebo). The objectives of this study were: (a) to investigate the effect of roflumilast 500 mcg once daily on exacerbation rate, lung function, COPD symptoms, dyspnea, health related quality of life and health care resource use, and (b) to investigate the safety and tolerability of roflumilast. The study consisted of a 4-week baseline period (V0, V1, V2), followed by a 52-week treatment period, and an additional safety follow-up, if necessary. The two primary endpoints were mean change from baseline in FEV₁ ((forced expiratory volume in first second) and mean rate of COPD exacerbations requiring oral or parenteral corticosteroids, or requiring hospitalization, or leading to death per patient per year. These endpoints were tested in a hierarchical manner.

In Protocol BY217/M2-124, there were 293 clinical investigators in 246 study centers in Australia, Austria, France, Germany, Hungary, New Zealand, Romania, Russia, United Kingdom and USA. The ITT analysis group (aka full analysis set (n=1523)) comprised 765 subjects on 500 mcg daily drug and 758 subjects on placebo. The per-protocol analysis group (aka “valid cases set” (n=1102)) comprised 553 subjects on 500 mcg daily drug and 549 subjects on placebo. The study was started on February 27, 2006 and was completed on July 7, 2008.

Protocol BY217/M2-125 (HERMES):

Protocol BY217/M2-125 was a randomized, double-blind, parallel-group study with two treatment arms (roflumilast 500 mcg or placebo). The objectives of this study were (a) to investigate the effect of roflumilast 500 mcg once daily on exacerbation rate, lung function, COPD symptoms, dyspnea, health related quality of life and health care resource use, and (b) to investigate the safety and tolerability of roflumilast. As in the AURA study, the primary efficacy endpoints in HERMES were the mean change from baseline (V2) during the treatment period in pre-bronchodilator FEV₁ [L], and the mean rate of COPD exacerbations requiring oral or parenteral corticosteroids, or requiring hospitalization, or leading to death per patient per year. The analyses were conducted in a similar fashion as in the AURA study.

In Protocol BY217/M2-125, there were 280 clinical investigators in 221 sites located in Canada, Germany, India, Italy, Poland, South Africa, Spain and USA. The ITT analysis group (aka full analysis set (n=1568)) comprised 772 subjects on 500 mcg daily drug and 796 subjects on placebo. The per-protocol analysis group (aka “valid cases set”

(n=1093)) comprised 528 subjects on 500 mcg daily drug and 565 subjects on placebo. The study was started on March 2, 2006 and was completed on April 29, 2008.

Three foreign sites and a domestic site were selected for inspection. Further the spirometry site and the data repository sites for the sponsor were inspected in Germany. The investigative drug in this application is a new molecular entity (NME) for the COPD indication. Of note, potential concerns with the conduct and monitoring of adequate and well-controlled studies submitted in support of this NDA have been recently identified during inspections conducted by the European Medicines Agency (EMA, previously EMEA) and the EMA findings have been shared with CDER. For example, at Site #6675 (Poland), the EMA identified violations including GCP violations, issues with missing documentation, and adequacy of site monitoring. FDA conducted its independent evaluation as well of the clinical site. Site #4545 (Hungary) was selected because it was the highest enrolling clinical site in either protocols M2-124 or M2-125, or both. Finally, Site #4793 (India) was selected because a significant percentage of data in “pivotal” studies was generated by sites in India (approximately 11% of study subjects), and also one of the few sites that demonstrated efficacy of the listed study.

II. RESULTS (by protocol/site):

Name of CI/Sponsor and site #, if known	City, State	Protocol	Inspection Date	EIR* Received Date	Final Classification
Beatrix Balint, MD /Site #4545	Deszk, Hungary	Study M2-124	March 29-April 2, 2010	Pending	Pending Preliminary field classification: NAI
Neal Moser/Site 7176	Crestview Hills, Kentucky	Study M2-124	Completion date: April 13, 2010	Pending	Pending Preliminary field classification: NAI
Halina Batura-Gabryel, M.D./Site 6675	Poznan, Poland	Study M2-125	April 5-9, 2010	Pending	Pending Preliminary field classification: VAI
Anthony Mesquita, MD/Site 4793	Caranzalem, India	Study M2-125	April 12-16, 2010	Pending	Pending Preliminary

					field classification: NAI
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(b) (4)



Nycomed, GmbH archive (for Forest Research Institute, Inc.)	Konstanz, Germany	Sponsor Data Archive	April 13-17	Pending	Pending Preliminary field classification: pending
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Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Pending= The EIR has not been received and findings are based on preliminary communication with the field.

*EIR: Establishment Inspection Report

PROTOCOL M2-124 (AURA)

1. Beatrix Balint, MD/ Site #4545

Csongad County Municipal
 Chest Disease Hospital
 Deszk, Alkotmany str. 36
 HUNGARY

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from March 29 to April 2, 2010. There were 100 subjects screened, 72 randomized, and 58 subjects completed the study. A total of 10 study subject records were reviewed in-depth. A 100% review of the FEV₁ data for all randomized was conducted. There was no evidence of under-reporting adverse events. No discrepancies between the source record and the case report form (CRF) were found. Patients were properly consented. Study drug accountability documentation was maintained.

b. Limitations of inspection:

None.

c. General observations/commentary:

This clinical site appeared to adhere to good clinical practice. Current inspection showed no discrepancies with source data. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision:

The data in support of clinical efficacy and safety at this clinical site appear acceptable.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Neal Moser, MD /Site #7176

Internal Medicine Associates
2900 Chancellor Drive
Crestview Hills, KY 41017

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, with inspection completed on April 13, 2010. There were 24 subjects screened and consented, 12 enrolled and randomized, and 6 completed the study. At this site, 6 serious adverse events were reported, all COPD exacerbations. No deaths were reported. A 100% audit was conducted for informed consents. A 100% audit was conducted on the subjects who completed the study, e.g., for adverse event data and reporting and for primary efficacy endpoints.

b. Limitations of inspection:

None.

c. General observations/commentary:

This clinical site appeared to adhere to Good Clinical Practice principles and guidelines. Current inspection showed no discrepancies with source data. Primary efficacy data points reported in the data listings agreed with the data on site. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision:

The data in support of clinical efficacy and safety at this clinical site appear acceptable.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

PROTOCOL M2-125 (HERMES)

1. Halina Batura-Gabryel, M.D./ Site 6675

Department of Pulmonary Diseases

Marcinkowski University of Medical Sciences, Poznan, Szamarzewskiego 84 str.

POLAND

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from April 5 to April 9, 2010. There were 43 subjects screened, 36 subjects were enrolled, 33 randomized, and 12 subjects completed the study. A total of 12 study subject records were reviewed. A 100% review of the FEV₁ data was conducted. There was no evidence of under-reporting adverse events. No discrepancies between the source record and the case report form (CRF) were found. Patients were properly consented. Study drug accountability documentation was maintained.

b. Limitations of inspection:

None.

c. General observations/commentary:

ORA field office classified this clinical site inspection as VAI, and a three-observation Form FDA 483 was issued, for deficiencies in preparing or maintaining accurate case histories with respect to observations pertinent to the investigation, and in conducting a clinical investigation in accordance with the investigational plan. According to the ORA field investigator, the clinical site team was cooperative and addressed any questions about source documentation and clinical data, e.g., COPD exacerbations. A Polish physician-translator was on-site and translated any materials that were requested.

Examples of inspectional findings include the following observations:

- ECG's were not always conducted at a speed of 25 mm/s for Subjects #94161 at Visit 7, #94164 at Visit 0, and #94170 at Visit 0, respectively
- Digoxin, a concomitant medication for Subject #394149 listed in the source document, was not reported in the CRF
- Study records document the review of chest x-rays and other radiologic procedures, but radiologic reports were not available to verify compliance.
- Dispensing log shows Subject #94145 lost 6 tablets at Visit 3 and lost 30 tablets at Visit 9

d. Data acceptability/reliability for consideration in the NDA review decision:

While minor deficiencies in adherence to protocol and conduct of investigation according to plan were observed for M2-125, these observations do not appear to have a substantive impact on data integrity and patient safety, and appear to be isolated occurrences. The data in support of clinical efficacy and safety from this clinical site appear acceptable.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Anthony Mesquita, M.D./Site 4793

TB and Chest Hospital
St. Inez, P.O. Caranzalem 403 002
INDIA

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from April 12 to 16, 2010.

A total of 25 subjects were screened at this clinical site; 23 subjects were enrolled 22 were randomized, and 13 subjects completed the study. There were four SAEs and no deaths in the study. Subject records were inspected for informed consent, primary efficacy endpoint data, and for other potential discrepancies between source documents and CRFs. No evidence of under-reporting of adverse events was noted.

b. Limitations of inspection:

None.

c. General observations/commentary:

This clinical site appeared to adhere to Good Clinical Practice principles and guidelines. Current inspection showed no discrepancies with source data. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision:

The data in support of clinical efficacy and safety from this clinical site appear acceptable.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

SPONSOR AND CRO FOR SPIROMETRY DATA

(b) (4)

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810 from April 12 to 26, 2010. The inspection concentrated on the evaluation of pulmonary function test (PFT) findings, especially in cases where the CRO overrode clinical investigator's best PFT choice, or in cases where the Clinical Investigator recommended other best PFT choices. Respiratory flow-volume loop

documents were also collected for Site #6675 (Poland) and Site #4545 (Hungary), and may be shared with DPARP, upon request for further review.

b. Limitations of inspection:

None.

c. General observations/commentary:

No Form FDA 483 was issued at the end of the inspection, per verbal communication with the ORA field investigator on April 20, 2010.

According to the amended study protocols, Amendment No. 6 (January 10, 2007) acceptability (e.g., no cough or false starts) and reproducibility criteria, as defined in the ATS/ERS consensus guideline on standardization of spirometry, was further reviewed by a “central overreader.” Per study protocol, this “central overreader” checked quality assurance, and whether effort as “best FEV₁” was acceptable. The value chosen by the overreader as the new “best FEV₁” was utilized for analyses. Further, ORA field investigator at the Hoechberg, Germany site also mentioned in a teleconference on April 13-14, that the Germany CRO site had three additional U.S.-based expert pulmonologist-readers to assess spirometry test results. As discussed also below during the sponsor inspection at Konstanz, Germany, sponsor revisions to values in the PFT predicted data were based upon the principal site investigator-approved revisions.

In prior inspections conducted by the EMA (European Medicines Agency, formerly EMEA), the EMA had concerns regarding PFT over-reads, potential systematic errors in the handling and transfer of PFT data, as well as potential problems with clinical site source data. However, in FDA’s independent inspection audit at the [REDACTED] (b) (4) site, these overreads were conducted according to study protocol. Further, appropriate PFT data revisions at the clinical site were made, upon additional quality control/assurance work by sponsor’s CRO, [REDACTED] (b) (4) (Note: It is extant that demographic variables such as age, sex, and height, and other ATS Task Force Standardization criteria, may alter the PFT values). Any revisions or overreads at the clinical site that were approved by the principal investigator were later incorporated into the sponsor’s database.

d. Data acceptability/reliability for consideration in the NDA review decision:

The data in support of clinical efficacy and safety at this clinical site appear acceptable.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Nycomed GmbH archive/Sponsor Data Archive

Byk-Gulden Str.2, 78467
Konstanz, Germany

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810 from April 12-17, 2010 at the Konstanz, Germany sponsor data repository site. The inspection evaluated the following documents: structural organization, clinical study sites, selection of clinical investigators (i.e., only pulmonologists participated as clinical investigators), and master services agreements. Clinical trial monitoring included the following: project management, site protocol compliance, review of case report forms and informed consent forms, drug accountability, adequate reporting assessment of adverse events, and review of source data.

b. Limitations of inspection:

None.

c. General observations/commentary:

A one-observation Form FDA 483 was issued on April 17, 2010 at the end of the inspection for failure to conduct the investigation according to the general investigation plan and protocol, summarized by the following:

- (a) Sponsor did not promptly conduct an adequate investigation and to document results, following potential unblinding incident that could have affected all 9 members of the sponsor's Clinical Study Team.

Specifically, On June 1, 2006, unblinded information for M2-124 and M2-125 was included as an attachment to an e-mail sent from CRO (b) (4) to sponsor's Clinical Study Team common mailbox. The e-mail was opened by at least one member of this team, and was forwarded to an unblinded Clinical Supplies Coordinator for further examination. The e-mail was confirmed to contain unblinded information for both studies, and reportedly deleted from the Clinical Study Team mailbox on the date it was received, and prior to the incident having been elevated to the sponsor's Quality Assurance Department or senior management. The sponsor's investigation did not include obtaining and reviewing the e-mail and the attachment, or determining and documenting whether this was a singular incident, whereby CRO sent unblinded information to a member of the Clinical Study Team. The Sponsor did not document the sponsor management team's decision not to disqualify potentially unblinded Clinical Study Team members. Per ORA investigator, the Clinical Study Team members were not all disqualified, as this may have led to the decimation of the entire group that conducted oversight on the clinical trials conducted internationally in several continents.

- (b) Sponsor did not have procedures in place to address accidental unblinding of study personnel.

- (c) Sponsor did not notify the Principal Investigators of the revised PFT percent predicted values. The sponsor revisions to the PFT values were based on the principal investigator-approved revisions to factors that affect PFT, such as patient's height, which were used to recalculate percent predicted values. After sponsor made changes to the PFT values, this was not communicated to the Principal Investigator at their respective clinical sites.

Additional Comments:

In a teleconference with the ORA field investigator on April 28, 2010, the ORA field investigator underscored that this was a case of potential unblinding, given that no substantive proof or evidence that unblinding truly occurred. At the time the ORA field investigator left Kostanz, Germany, the sponsor revisited this matter. The following were some facts related to this singular 2006 incident:

- (a) the 9 members of the sponsor's Clinical Study Team had signed affidavits stating that they did not open the files containing Lotus spreadsheet attachments with the unblinding kit information,
- (b) one member of the Clinical Study Team, who received the e-mail and confirmed contents of the e-mail attachment after it was received by the sponsor's CST from CRO (b) (4) clinical supplies team with the Lotus document, did not open the enclosed Lotus attachments, when she anticipated that this may contain unblinded data for both Protocols M2-124 and M2-125. This Clinical Study Team employee was not available to provide comments, since she was no longer employed at this sponsor's site,
- (c) the bracket period of time that the e-mail and Lotus spreadsheet attachments resided in the shared Clinical Study Team mailbox was not known,
- (d) the sponsor (Nycomed) performed an audit of CRO (b) (4) that had the clinical data, attributing the incident by the CRO (b) (4) employee as "human error" although the audit did not indicate extent of the "misconduct" on the part of the CRO (b) (4) employee. The CRO (b) (4) employee that sent the e-mail was also not available to provide details, since she was no longer employed at this CRO,
- (e) the sponsor acknowledged this potential unblinding in its original NDA submission Clinical Study Report (e.g., Study Protocol M2-124 Section 9.4.6), For Protocol M2-124 Section 9.4.6, page 51 of the Clinical Study Report in the NDA submission stated: "...An unblinding warehouse report was accidentally sent to the study manager at Nycomed as an email attachment on June 1, 2006. However, none of the Nycomed team members involved in the study read the attachment, and thus, no-one in the team was unblinded....," This incident report was also referenced in the original NDA submission in M2-124 Appendix 16.1.9.13, "Handling of receipt of unblinding warehouse report," and
- (f) no CRO (b) (4) employees (as well as sponsor employee) inadvertently/accidentally were known to have disclosed any blinding information to any clinical investigation sites for Protocols M2-124 and M2-125, respectively.

On April 29, 2010, DSI Reviewer communicated its initial findings of the field inspection, pending receipt of the report (EIR) from the ORA field office. DPARP Medical Officer mentioned that the potential unblinding in Protocols M2-124 and M2-125 was not covered in their clinical team review or during a recent April 7, 2010 Pulmonary-Allergy Drugs Scientific Advisory meeting in Silver Spring, Maryland regarding the roflumilast application approvability. DPARP Medical Officer, however, did not consider this issue to have impacted data integrity.

d. Data acceptability/reliability for consideration in the NDA review decision:

In the absence of substantive proof that the clinical investigation sites, sponsor's quality assurance department, sponsors decision-making and senior management team, had knowledge of the tool kit information containing the blinded identities and listing of patients allocated to roflumilast or placebo, for Protocols M2-124 and M2-125, respectively, it is unlikely that there was an impact on data integrity of this trial. Also, if the Clinical Study Team (on affidavits) and Study Data Manager claiming that the tool kits containing assignment identities were never compromised, were factual, then, the conscientious efforts on sponsor's operations ensured prevention of data unblinding. Further, the sponsor was forthright in documenting this, as part of other operational process, in their original NDA submission Clinical Study Report and Appendix reference.

Based on the inspection at the sponsor site and in conjunction with inspections at the individual clinical investigator sites and the CRO inspection, there is no actual evidence to support that actual unblinding occurred. As such, DSI considers the data reliable. DSI, however, defers to the review division on the impact of this event in their review of the application and the submission of this information under NDA 22-522.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three foreign and one domestic clinical investigator sites, and the sponsor foreign data and spirometry data repository sites were inspected in support of this application for study Protocols M2-124, and M2-125, respectively, in support of roflumilast for the treatment of COPD.

In general, inspection findings documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Although minor regulatory violations were noted for the Polish site, these are not pervasive in nature, and are unlikely to impact data integrity and patient safety. The data generated by these inspected sites appear reliable in support of the application.

For the foreign sponsor data repository site, no substantive evidence would point critically that the potential unblinding to roflumilast or placebo data, due to “human errors” attribution to a CRO Clinical Study Team member actually occurred, and that the kit list numbers that identified roflumilast or placebo randomization became systemically known information throughout the clinical trial operations, such that clinical site investigators, sponsor’s clinical study team, or sponsor’s Quality Assurance Department and senior management unduly influenced the clinical trial outcomes that impacted data integrity.

The data, at the limited number of inspected clinical sites and at the CRO and sponsor’s data repository site, are acceptable and appear reliable in support of the NDA application, with the caveat that the review division should consider the impact of the potential for unblinding discussed above, taking into consideration, that there was no evidence that unblinding actually occurred

Note: Observations noted above, for these three foreign clinical sites (Hungary, Poland and India), one domestic clinical site (California), two sponsor sites (foreign data source and spirometry data in Germany), are based on the Form FDA 483 or preliminary communications from field investigator, an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

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Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/

ANTHONY J ORENCIA
05/03/2010

TEJASHRI S PUROHIT-SHETH
05/03/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

******Pre-decisional Agency Information******

Memorandum

Date: April 23, 2010

To: Carol Hill, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Robyn Tyler, Regulatory Review Officer
Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Sangeeta Vaswani, DTC Group Leader
Lisa Hubbard, Professional Group Leader
DDMAC

Subject: NDA 022522
DDMAC labeling comments for Daxas[®] (roflumilast) tablets

We acknowledge receipt of your August 6, 2009, consult request for the proposed product labeling (Package Insert (PI), Medication Guide, and Carton and Container Labeling) for Daxas[®] (roflumilast) tablets, NDA 022522. DDMAC notes the email from Carol Hill dated April 22, 2010 which stated that DPARP determined that labeling would not be finalized during the current review cycle and that a Complete Response letter would be issued. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle. DDMAC requests that DPARP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the Medication Guide, please contact Robyn Tyler at 301-796-4212 or Robyn.tyler@fda.hhs.gov. If you have any questions regarding the PI or Carton and Container Labeling, please contact Roberta Szydlo at 301-796-5389 or Roberta.szydlo@fda.hhs.gov.

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/

ROBERTA T SZYDLO

04/23/2010

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 22522
Brand Name	Daxas
Generic Name	Roflumilast
Sponsor	Pfizer
Indication	Bronchial asthma and chronic obstructive pulmonary disease (COPD)
Dosage Form	Tablet
Drug Class	Phosphodiesterase 4 (PDE4) inhibitor
Therapeutic Dosing Regimen	500 µg QD
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1000 µg QD
Submission Number and Date	SDN 001, 15 Jul 2009
Review Division	DPAP

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This study is inconclusive because assay sensitivity cannot be established. Without a concurrent positive control, the study design cannot exclude small effects (<10 ms) on the QTc interval.

In this single center, placebo- and active-controlled, blinded (not for moxifloxacin), parallel group study, two cohorts of eighty (80) healthy subjects were enrolled. The two cohorts are dosed more than a month apart. The first forty (40) subjects (Group A) enrolled into the study received placebo on Day 1 and then twenty (20) of them received placebo and the other twenty (20) received roflumilast. The second cohort with forty (40) subjects (Group B) enrolled into the study received moxifloxacin on Day 1 and then twenty (20) of them received placebo and the other twenty (20) received roflumilast. In this design, there was no randomization between moxifloxacin and placebo. In addition, moxifloxacin was not conducted concurrently with investigational drug.

This design is problematic for the following reasons: 1) moxifloxacin was not randomized with other treatment arms; 2) the time between moxifloxacin and its baseline was only one day apart while the time between study drug and its baseline was at least 16 days apart; 3) the mild moxifloxacin-induced QTcP (population corrected QT) effect was not demonstrated in this study since the largest lower 90% confidence bound for $\Delta\Delta\text{QTcP}$ was below 5 ms; and 4) our analysis indicated that data discrepancy for the same treatment arms existed between Group A and Group B (**Table 9**), which makes it

questionable if combining two groups together. We do not believe further analysis of existing data will be meaningful.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- The assay sensitivity was not established.
- There was no randomization between moxifloxacin and other treatment arms.
- Details about ECG interpretation including central read and blinding of readers is unavailable in the study report and the protocol.
- We recommend that the sponsor conducts another TQT study. This can be a PMC from the QT-IRT perspective since there have been no safety signals of concern in the clinical studies, but we defer to the review division.

2 PROPOSED LABEL

Since the study is inconclusive no labeling language is proposed.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Roflumilast is a selective phosphodiesterase-4 (PDE4) inhibitor under clinical development for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations. The recommended dose is one 500-microgram tablet once daily.

3.2 MARKET APPROVAL STATUS

Daxas (roflumilast) is not approved for marketing in any country

3.3 PRECLINICAL INFORMATION

Source: Pharmacology Written Summary- eCTD 2.6.2

“The possible influence of roflumilast and the N-oxide metabolite on cardiac repolarization was tested in in vitro and in vivo pharmacology experiments in addition to ECG monitoring in toxicity studies. Roflumilast had no detectable effect on hERG channel currents in human embryonic kidney cells up to the top test concentration of 24 µg/L, which is more than 300- fold higher than the free plasma C_{max} of roflumilast in humans after 500 µg/day [TS 2.6.3.4, 20/2003]. Roflumilast N-oxide at 251 µg/L reduced the hERG channel current by about 10% without showing any use-dependence; no effect was seen at 84 µg/L, which is about 100-fold the free C_{max} of roflumilast N-oxide in humans [TS 2.6.3.4, 120/2003]. Roflumilast and roflumilast N-oxide did not change the action potential in papillary muscle of guinea pig hearts [TS 2.6.3.4, 222/94, 155/2000]. No ECG changes were observed in dogs when the cardiac performance was investigated by use of echocardiography [TS 2.6.3.4, 142/2001]. Increasing doses of roflumilast and its N-oxide metabolite were infused in anesthetized cats and minipigs with no significant changes in ECG, specifically in QTc-interval [TS 2.6.3.4, 116/95,

144/2001, 118/2006]. No significant QTc changes were observed in short- and long-term toxicity studies in dogs and monkeys [Summary Report 177/2003].”

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Cardiac safety report No-350/2008

“In clinical studies with roflumilast, adverse events were analyzed in patients with COPD, using data from the COPD safety pool, which consists of 14 clinical studies (total N=12,054; roflumilast 500 µg group N=5,766; roflumilast 250 µg group N=797; placebo group N=5,491).

“The grouping ‘cardiac adverse events of interest’ contains the MedDRA High Level Group Terms (HLGTs) ‘cardiac arrhythmias’, ‘coronary artery disorders’, ‘heart failures’, and ‘myocardial disorders’. Examination of the cardiac adverse events of interest at the MedDRA high level group term (HLGT) showed that the proportion of patients with events was lower or similar in the roflumilast vs placebo group for ‘coronary artery disorders’, ‘heart failures’, and ‘myocardial disorders’. The exception was the HLGT ‘cardiac arrhythmias’, in which the proportion of patients with events was slightly higher for roflumilast 500 µg than for the placebo group (3.5% vs 3.1%). Analysis of this imbalance at the MedDRA preferred term (PT) level showed that the event ‘atrial fibrillation’ contained slightly higher proportion of patients in the roflumilast 500 µg vs placebo group (0.8% vs 0.6%). Individual review of all 56 patients with ‘atrial fibrillation’ or ‘atrial flutter’ in the roflumilast treatment group provided a plausible or convincing medical explanation for most of these adverse events. Furthermore, the difference in the proportion of patients with ‘atrial fibrillation’ was not recognized in the ECG recordings that were obtained as part of the cardiac safety surveillance program from all studies with healthy subjects and patients (described below).

T-Table 6: Summary of patients with cardiac adverse events by PT in the HLGT ‘cardiac arrhythmias’ in greater than or equal to 0.1% of patients in any treatment group

High Level Group Term Preferred Term (MedDRA)	Pivotal COPD studies pool		COPD safety pool		
	Rof500 (N=1547)	Pbo (N=1545)	Rof500 (N=5766)	Rof250 (N=797)	Pbo (N=5491)
	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiac events of interest					
Cardiac arrhythmias	65 (4.2)	59 (3.8)	202 (3.5)	12 (1.5)	169 (3.1)
Arrhythmia	2 (0.1)	1 (<0.1)	12 (0.2)	3 (0.4)	3 (<0.1)
Arrhythmia supraventricular [#]	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	4 (<0.1)
Atrial fibrillation	17 (1.1)	7 (0.5)	48 (0.8)	2 (0.3)	31 (0.6)
Atrial flutter	0 (0.0)	1 (<0.1)	8 (0.1)	0 (0.0)	5 (<0.1)
Atrial tachycardia	2 (0.1)	1 (<0.1)	3 (<0.1)	0 (0.0)	1 (<0.1)
Atrioventricular block first degree	1 (<0.1)	1 (<0.1)	8 (0.1)	0 (0.0)	11 (0.2)
Bradycardia	1 (<0.1)	4 (0.3)	3 (<0.1)	0 (0.0)	8 (0.1)
Bundle branch block left	2 (0.1)	2 (0.1)	6 (0.1)	0 (0.0)	5 (<0.1)
Bundle branch block right	1 (<0.1)	0 (0.0)	7 (0.1)	1 (0.1)	5 (<0.1)
Cardiac arrest	3 (0.2)	0 (0.0)	8 (0.1)	0 (0.0)	1 (<0.1)
Cardio-respiratory arrest	2 (0.1)	0 (0.0)	2 (<0.1)	0 (0.0)	0 (0.0)
Sinus bradycardia	0 (0.0)	1 (<0.1)	1 (<0.1)	2 (0.3)	2 (<0.1)
Sinus tachycardia	9 (0.6)	9 (0.6)	21 (0.4)	1 (0.1)	19 (0.3)
Supraventricular tachycardia	1 (<0.1)	1 (<0.1)	6 (0.1)	0 (0.0)	7 (0.1)

High Level Group Term Preferred Term (MedDRA)	Pivotal COPD studies pool		COPD safety pool		
	Rof500 (N=1547)	Pbo (N=1545)	Rof500 (N=5766)	Rof250 (N=797)	Pbo (N=5491)
	n (%)	n (%)	n (%)	n (%)	n (%)
Tachyarrhythmia	0 (0.0)	1 (<0.1)	3 (<0.1)	1 (0.1)	1 (<0.1)
Tachycardia	21 (1.4)	25 (1.6)	54 (0.9)	2 (0.3)	47 (0.9)
Ventricular extrasystoles	4 (0.3)	4 (0.3)	8 (0.1)	0 (0.0)	14 (0.3)
Ventricular tachycardia	1 (<0.1)	1 (<0.1)	7 (0.1)	0 (0.0)	11 (0.2)

N: Number of patients in treatment group MedDRA version 11.0, n: Number of patients with at least one event in the category, %: Percentage of patients with at least one event in the category based on N;

R500: Roflumilast 500 µg, od, p.o.; R250: Roflumilast 250 µg, od, p.o.; PBO: Placebo, od, p.o.;

Arrhythmia supraventricular occurred for ≤0.1% of patients in any of the treatment groups. Despite this low rate of occurrence, the event is included in the table to ease legibility of text that refers in several locations to this event.

Source data: [Tables 1.4.3.1, 1.4.3.2, 2.4.3.1 and 2.4.3.2].

“All death cases, who had at least one cardiac event with the outcome ‘death’ were reviewed by an external Independent Cardiovascular Adjudication Committee. All cardiovascular categories of deaths determined by the Independent Cardiovascular Adjudication Committee were balanced between the roflumilast and placebo treatment groups. This applies specifically also for the category death due to ‘arrhythmia’, for which a total of 3 fatal cases were established (1 patient from the roflumilast 500 µg group and 2 from the placebo group).

T-Table 8B: Overview of results for patients with cardiac adverse events leading to death (Independent Cardiovascular Adjudication Committee)

Categories used to classify patients' the primary cause of 'death'	COPD safety pool		
	Rof500 (N=24) n (%)	Rof250 (N=3) n (%)	Pbo (N=29) n (%)
Insufficient data	0 (0.0%)	0 (0.0%)	3 (5.4%)
Death due to Fatal Myocardial Infarction	3 (5.4%)	1 (1.8%)	3 (5.4%)
Death due to Stroke	0 (0.0%)	0 (0.0%)	1 (1.8%)
Sudden death, due to arrhythmia	1 (1.8%)	0 (0.0%)	2 (3.6%)
Sudden death, etiology unknown	10 (17.9%)	1 (1.8%)	11 (19.6%)
Death due to congestive heart failure	1 (1.8%)	1 (1.8%)	4 (7.1%)
Fatal Non-Cardiovascular Events	9 (16.1%)	0 (0.0%)	5 (8.9%)

N: Number of patients who died in treatment group; %: Percentage of patients with at least one event in the category based on N; R500: Roflumilast 500 µg, od, p.o.; R250: Roflumilast 250 µg, od, p.o.; Pbo: Placebo, od, p.o.;

Note: Unblinding of cases was done by the sponsor *after* the Cardiovascular Adjudication Committee report was received.

Source data: [[Independent Cardiovascular Adjudication Committee Report, Appendix 4](#)]

“In all studies, the ECG recordings at the last visit were compared with those at the baseline visit. The results did not reveal any clinically relevant changes due to administration of roflumilast with time. Furthermore, expert reports from cardiologists based on ECG data from healthy subjects and patients with COPD or asthma receiving roflumilast (more than 4,600) did not reveal any clinically relevant effects of roflumilast on cardiac electrophysiology.

“In the COPD safety pool, the proportion of patients reported with the adverse events ‘ECG QT prolonged’ was equal for the roflumilast 500 µg and the placebo group (0.9% vs 0.9%). None of the adverse events were serious or leading to death. Only in the placebo group two events led to study discontinuation (T-Table 14).

“There was a higher proportion of patients with the event ‘ECG QT prolonged’ assessed as related to study drug for the roflumilast 500 µg compared to the placebo group (0.4% vs 0.2%). However, in the pivotal COPD studies pool this pattern could not be confirmed as in this study pool only one patient with this event occurred (T-Table 14). This different pattern of the distribution of the event ‘ECG QT prolonged’ derives mainly from a single study in which 44 of 567 patients in the roflumilast 500 µg and 39 of 606 patients in the placebo group had this event [Study M2-111].

T-Table 14: Overview of patients with ECG QT prolonged (SOC Investigations)

Preferred Term (MedDRA)	Pivotal COPD studies pool		COPD safety pool		
	Rof500 (N=1547) n (%)	Pbo (N=1545) n (%)	Rof500 (N=5766) n (%)	Rof250 (N=797) n (%)	Pbo (N=5491) n (%)
Adverse event					
ECG Prolonged QT/QTc	1 (<0.1)	1 (<0.1)	51 (0.9)	1 (0.1)	47 (0.9)
AEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
AEs related to study medication	0 (0.0)	0 (0.0)	23 (0.4)	0 (0.0)	12 (0.2)
AEs leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)

N: Number of patients in treatment group MedDRA version 11.0; n: Number of patients with at least one event in the category; %: Percentage of patients with at least one event in the category based on N;
 Rof500: Roflumilast 500 µg, od, p.o.; Rof250: Roflumilast 250 µg, od, p.o.; Pbo: Placebo, od, p.o.;
 Source data: [Report 289/2008, Tables 1.6.1.3, 1.6.2.1, 1.6.3.1, 1.6.4.1 and 1.6.5.1 for pivotal COPD studies pool; Tables 2.6.1.3, 2.6.2.1, 2.6.3.1, 2.6.4.1 and 2.6.5.1 for COPD safety pool].

“24-hour Holter ECG monitoring

For study M2-125, 24-hour Holter ECGs were obtained from 55 patients who were also taking LABA as concomitant therapy (33 patients in the roflumilast 500 µg and 22 patients in placebo group). The results of the 24-hour Holter ECGs showed no differences in the minimum, maximum, and mean heart rates in the roflumilast group. Rhythm and conduction abnormalities were few and most were considered as not clinically relevant. Clinically relevant findings of episodes of non-sustained ventricular tachycardia were observed only in the placebo group.”

Reviewer’s Comment: There are no reports of torsade de pointes and per the cardiac safety report, sudden death of unclear etiology and ventricular tachycardias were balanced between the roflumilast and placebo groups. The sample size of the holter study is too small to come to any meaningful conclusions regarding concomitant LABA therapy.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of roflumilast’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report cp-069-study-report for roflumilast, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

An Evaluation of the Effects of Roflumilast on Cardiac Repolarization, Pharmacokinetics, Safety, and Tolerability in Healthy Volunteers

4.2.2 Protocol Number

A5821023

4.2.3 Study Dates

15 Dec 2004 to 11 Apr 2005

4.2.4 Objectives

- To assess the effects of multiple-dose orally administered roflumilast on cardiac repolarization as measured by electrocardiogram (ECG) parameters in healthy subjects
- To assess the pharmacokinetics (PK) of roflumilast and roflumilast N-oxide (metabolite) following multiple daily doses of 500 and 1000 µg
- To assess the safety and tolerability of roflumilast 500-, 750-, and 1000-µg once daily (QD) multiple doses when gradually titrated in healthy subjects

4.2.5 Study Description

4.2.5.1 Design

This is a single center, placebo- and active-controlled, parallel group study in 2 cohorts of healthy subjects. The trial was open label on Day 1 when the subjects were taking either placebo or moxifloxacin. On Day 1 (the open label period), the subjects were not randomized to moxifloxacin and placebo. The first forty subjects enrolled into the study received placebo and the second forty subjects received moxifloxacin. Enrollment occurred as 2 cohorts that were dosed a month apart. All Cohort 1 subjects, 34 in total, and six Cohort 2 subjects received placebo. The remaining forty cohort 2 subjects received moxifloxacin.

Table 1: Study Design

Group	Day 1	Days 3 to 16	Days 17 to 23	Days 24 to 37
A	Placebo	Placebo QD	Placebo QD	Placebo QD
		Roflumilast 500 µg QD	Roflumilast 750 µg QD	Roflumilast 1000 µg QD
B	Moxifloxacin 400 mg	Placebo QD	Placebo QD	Placebo QD
		Roflumilast 500 µg QD	Roflumilast 750 µg QD	Roflumilast 1000 µg QD

Group A: 40 subjects received placebo on Day 1; 20 of them received placebo on Days 3-37; the other 20 received roflumilast treatment.

Group B: 40 subjects received moxifloxacin 400 mg on Day 1; 20 of them received placebo on Days 3-37; the other 20 received roflumilast treatment.

Source: CSR page 27.

Reviewer's comments: We cannot accept the study design because (1) there was no randomization between moxifloxacin and other treatment arms, and (2) moxifloxacin was not conducted concurrently with investigational drug.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Open label on Day 1 (placebo and moxifloxacin); double blinded on Days 3 through 37.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The following four treatments were evaluated in the study as shown in Table 1.

- Roflumilast, 500 µg QD
- Roflumilast, 1000 µg QD
- Placebo
- Moxifloxacin 400 mg, single dose

4.2.6.2 Sponsor's Justification for Doses

“During the early development of roflumilast several studies evaluated the safety and tolerability of single and repeat doses of roflumilast greater than the present therapeutic dose of 500 µg QD. From these studies, 1000 µg was determined to be the maximum tolerated dose with dose-limiting AEs of nausea, dizziness, and headache being observed at doses of 2.5 and 5 mg (1 subject exposure).” In a dose titration study conducted in healthy subjects, 1000-µg QD doses were well tolerated. “Therefore, a gradually increasing dosing regimen of 500 µg QD×2 weeks, 750 µg QD×1 week, and 1000 µg QD×2 weeks was chosen for this study. The 2-week dosing periods for 500- and 1000-µg QD doses were to ensure that steady-state concentrations were achieved for both roflumilast and roflumilast N-oxide at the time of the electrocardiogram (ECG) analyses at these doses. A parallel study design was chosen over a crossover design for practicality purposes because of the long study duration.”

Source: CSR Section 3.1, page 20-21.

Reviewer's Comment: Acceptable. 500 µg QD is the proposed therapeutic dose. 1000 µg QD was determined to be the maximum tolerated dose, which might cover the expected exposure for the 500-µg QD dose in patients with mild to moderate hepatic impairment or those co-administered potent CYP3A4 or CYP1A2 inhibitors. 500 µg QD roflumilast was not tested in patients with severe hepatic impairment, thus, not recommended in these patients.

4.2.6.3 Instructions with Regard to Meals

Roflumilast was administered within 10 minutes following the meal in this TQT study.

“Food intake delayed time to maximum concentration of roflumilast by 1 hour, increased systemic exposure (area under the concentration time curve [AUC]) by 12%, and reduced maximum plasma concentration (C_{max}) by approximately 40%. Systemic exposure to roflumilast N-oxide was reduced by just 9% with food, however with no effect on peak plasma concentrations. Food intake did not affect the ‘total PDE4 inhibitory activity’ nor was there any notable difference in the nature, frequency, or severity of adverse events.”

Source: Sponsor's clinical overview, Section 2.5.3 (page 10-11).

Reviewer's Comment: Acceptable. Roflumilast can be administered under fed and fasted conditions.

4.2.6.4 ECG and PK Assessments

“Blood samples were collected Day 16 pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose; and Day 37 pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours post-dose. To demonstrate steady state of roflumilast and roflumilast N-oxide, a pre-dose PK sample on Days 15 and 36 was taken.”

“Standard 12-lead ECGs were evaluated using machine-generated assessments. Triplicate ECG measurements, taken approximately 2 to 4 minutes apart, were obtained on Days -1, 1, 16, and 37 at the following time points, prior to drawing PK samples.”

Source: CSR Section 5.4.1.1 on page 30, and Section 5.5.1.1 on page 33.

Reviewer's Comment: Acceptable. The time points adequately covered the t_{max} of moxifloxacin, and both roflumilast and its active roflumilast N-oxide. Sampling interval is sufficient to cover the potential delay.

4.2.6.5 Baseline

The baseline used for the time-matched analyses was the average of the 3 ECG collected at each nominal time point on Day -1.

4.2.7 ECG Collection

All scheduled ECGs were performed after the subject had rested quietly for at least 10 minutes in a supine position. Single 12-lead ECG measurements were taken at Screening and Closeout. Triplicate 12-lead ECGs were obtained approximately 2 to 4 minutes apart; and the average of the triplicate ECG measurements collected at each nominal time point specified above.

Reviewer's Comments: Further details about ECG interpretation including central read and blinding of readers is unavailable in the study report and the protocol.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

80 healthy male and female subjects with a normal baseline ECG and BMI between 18-30 kg/m² were enrolled in this study. 65 subjects completed the study. Of the 15 subjects who discontinued 4 were due to adverse events and seven were due to withdrawal of consent.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

For the QTc interval analyses, both QTcF and QTcP corrections were used for the statistical analysis. The estimated correction factor for heart rate was 0.4413 which indicated that neither Fridericia nor Bazett correction would properly correct QT for heart

rate. Thus, population corrected QT (QTcP) was used along with QTcF for the primary statistical analysis.

On Day 1 (the open-label period), the subjects were not randomized to moxifloxacin and placebo treatments as stated in the protocol. To test the potential bias due to randomization of moxifloxacin and placebo and to determine whether or not the 2 study cohorts are different, the baseline data of the 2 cohorts were analyzed using an analysis of covariance (ANCOVA) model to assess the effect of cohorts on response variables. The model included cohort as fixed effect and gender as covariates. The results of the ANCOVA model show no cohort effect on the QTcF values at baseline (Day -1), and the difference between Cohorts 1 and 2 was not significant for all time points (p-value range from 0.212 to 0.761).

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 differences from placebo for Days 16 and 37 are displayed in Table 2 below. The largest mean time-matched change from baseline differences from placebo for the roflumilast 500-µg 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-µg group in QTcF was -4.81 ms (placebo higher than roflumilast) and 0.77 ms in QTcP.

Table 2: QTcF and QTcP: Largest Time-Matched Mean Differences From Placebo (Protocol A5821023)

Treatment Group	Hour	Difference [^]	90% CI
QTcF			
Day 1			
Moxifloxacin Day 1	6	6.79	(4.15, 9.43)*
Day 16			
Roflumilast 500 µg QD	4	-3.23	(-6.77, 0.31)
Day 37			
Roflumilast 1000 µg QD	2	-4.81	(-8.61, -1.00)*
QTcP			
Day 1			
Moxifloxacin Day 1	6	6.97	(4.47, 9.46)*
Day 16			
Roflumilast 500 µg QD	1	2.39	(-0.82, 5.60)
Day 37			
Roflumilast 1000 µg QD	1	0.77	(-2.58, 4.12)

* Statistically significant

[^] Difference = Active treatment – placebo.

Source: CSR Table 12 on Page 50

4.2.8.2.2 Assay Sensitivity

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. These differences were statistically significant from zero.

Reviewer’s Comments: We do not agree with the sponsor’s analysis and conclusion of the establishment of assay sensitivity. Our independent analyses results in section 5.2 show that the assay sensitivity is not established in this study.

4.2.8.2.3 Categorical Analysis

Categorical tables include post-dose ECGs from Days 1, 16, and 37. Day 1 following placebo, Day 16 following roflumilast 500 µg, and Day 37 following roflumilast 1000 µg. No subjects treated with roflumilast 500 µg or roflumilast 1000 µg had maximum QTcF increases from baseline 60 ms.

Table 4 displays the maximum post-dose values for QTcF by gender. No subjects had a post-dose QTcF ≥ 500 ms on any treatment. One male subject in the placebo group had a maximum QTcF value 450 ≥ ms (QTcF = 450.13 on Day 16 and 454.3 ms on Day 37). Table 5 and Table 6 present categorical summaries of the QTcP data.

Table 3: Categorical Summary of maximum QTcF Increases from Baseline

		Number of Subjects With Maximum QTcF Increase From Baseline (msec)		
		<30	30-<60	≥60
Placebo	36	35(97.2)	1(2.78)	0(0)
Roflumilast 500 µg	38	38 (100.0)	0 (0.0)	0 (0.0)
Roflumilast 1000 µg	31	31 (100.0)	0 (0.0)	0 (0.0)

Source: CRF Table 13 on Page 50.

Table 4: Categorical Summary of QTcF Maximum Post-dose Values

Treatment Group	Number of Subjects With Maximum Post-Baseline QTcF (msec)										
	Males					Females					
	<430		430-<450		450-<500	≥500	<450		450-<470		470-<500
	N	n (%)	n (%)	n (%)	n (%)	N	n (%)	n (%)	n (%)	n (%)	n (%)
Placebo	26	24(92.3)	1(3.85)	1(3.85)	0(0)	10	10(100)	0 (0)	0 (0)	0 (0)	0 (0)
Roflumilast 500 µg	24	24 (100)	0 (0)	0 (0)	0 (0)	14	12 (85.7)	2 (14.3)	0 (0)	0 (0)	0 (0)
Roflumilast 1000 µg	21	21 (100.0)	0 (0)	0 (0)	0 (0)	10	10 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: CRF Table 14 on Page 50.

Table 5: Categorical Summary of Maximum QTcP Increases From Baseline

		Number of Subjects With Maximum QTcP Increase From Baseline (msec)		
		<30	30-<60	≥60
Placebo	36	36(100)	0(0)	0 (0.0)
Roflumilast 500 µg	38	38(100)	0(0)	0 (0.0)
Roflumilast 1000 µg	31	31(100)	0(0)	0 (0.0)

Source: CRF Table 15 on Page 50.

Table 6: Categorical Summary of QTcP Maximum Post-dose Values

Treatment Group	Number of Subjects With Maximum Post-Baseline QTcP (msec)									
	Males					Females				
	<430	430-<450	450-<500	≥500		<450	450-<470	470-<500	≥500	
	N	n(%)	n(%)	n(%)	n(%)	N	n(%)	n(%)	n(%)	n(%)
Placebo	26	25(96.2)	1(3.85)	0(0)	0(0)	10	9(90)	1(10)	0(0)	0(0)
Roflumilast 500 µg	24	23(95.8)	1(4.17)	0(0)	0(0)	14	10(71.4)	3(21.4)	1(7.14)	0(0)
Roflumilast 1000 µg	21	21(100)	0(0)	0(0)	0(0)	10	6(60)	4(40)	0(0)	0(0)

Source: CRF Table 15 on Page 51.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study. Four subjects discontinued due to AEs of elevated total bilirubin (placebo), flu like symptoms, depression and tooth fracture. Subject 10011041 had a serum creatinine value on Study Day 49 (Closeout) of 2.7 mg/dL. The serum creatinine on the last day (Day 37) of multiple-dose roflumilast was within normal limits (1.1 mg/dL) and values were within normal limits throughout the entire dosing period. Unscheduled follow-up serum creatinine values were 1.4 mg/dL on Day 58 and 1.5 mg/dL on Day 62. On Day 77, the subject returned for a repeat serum creatinine assessment, and the value had returned to within normal limits (1.1 mg/dL). There were no clinically important changes in HR and other vital signs.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results of roflumilast and roflumilast N-oxide are presented in Table 7. C_{max} and AUC values in the thorough QT study were 2-fold higher following administration of the supra-therapeutic dose compared (1000 µg QD roflumilast) with the intended clinical dose (500 µg QD roflumilast). Plasma trough concentrations (pre-dose and 24 hours post-dose) on Days 15, 16, 36, and 37 are similar, indicating steady state was achieved.

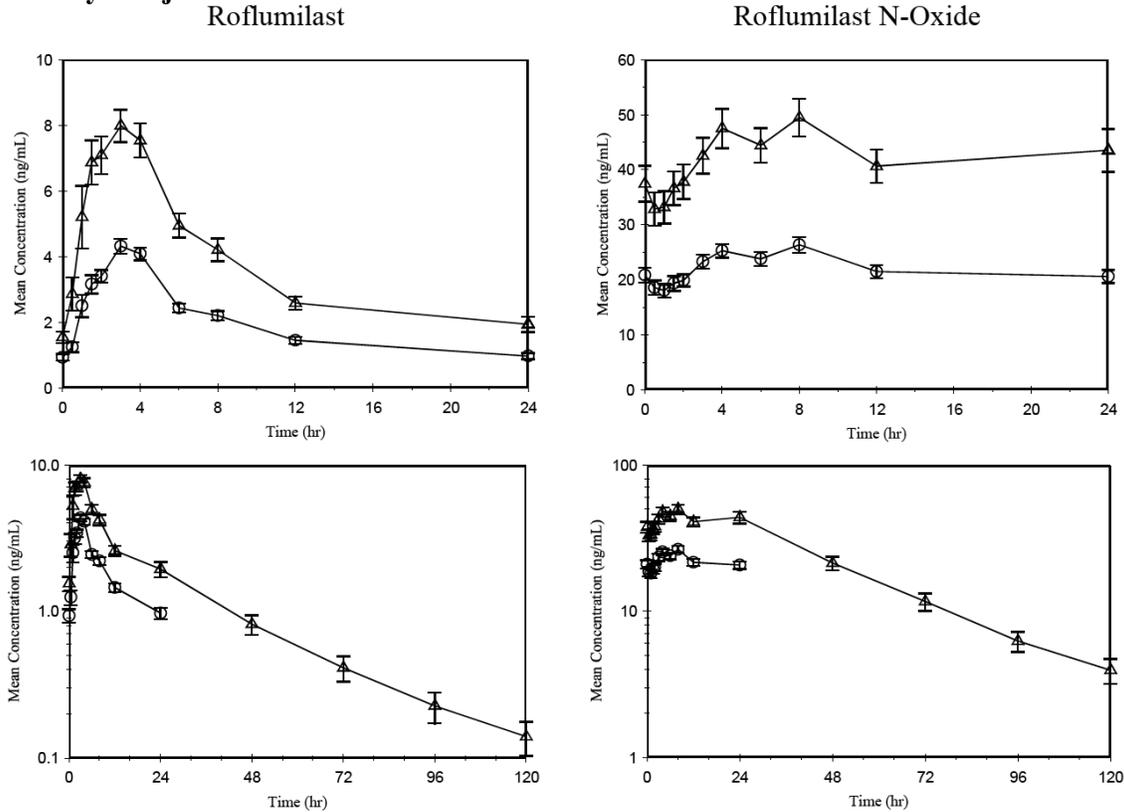
Table 7: Summary of Pharmacokinetic Parameter Values Following Administration of Roflumilast Oral QD Doses to Healthy Volunteers

Parameter		Arithmetic Mean (%CV) Parameter Values	
		Day 16 (500 µg) N = 38	Day 37 (1000 µg) N = 30
Roflumilast	C _{max} , ng/mL	5.14 (26.2)	10.6 (33.7)
	t _{max} , hr	2.69 (40.0)	2.97 (52.8)
	C _{min} , ng/mL	0.86 (63.3)	1.55 (59.3)
	AUC(0-24), ng*hr/mL	45.6 (34.3)	90.2 (32.3)
	CL/F, mL/min	203 (32.9)	205 (34.9)
	t _{1/2} , hr	ND	21.7 (36.6)
Roflumilast	C _{max} , ng/mL	27.4 (32.8)	53.8 (36.5)
N-Oxide	t _{max} , hr	5.98 (32.9)	8.69 (72.9)
	C _{min} , ng/mL	17.3 (42.5)	33.4 (45.4)
	AUC(0-24), ng*hr/mL	530 (33.2)	1060 (37.8)
	t _{1/2} , hr	ND	26.0 (26.7)

ND = Not determined.

Source: CSR page 5 Table S3.

Figure 1: Mean (\pm SE) Plasma Concentration-Time Profiles for Roflumilast and Roflumilast N-Oxide Following Administration of Roflumilast Oral QD Doses to Healthy Subjects



Upper panels are linear scale with time axis truncated at 24 hours; lower panels are semilogarithmic scale. Error bars represent standard error. Circles = Day 16, 500 µg QD; Triangles = Day 37, 1000 µg QD.

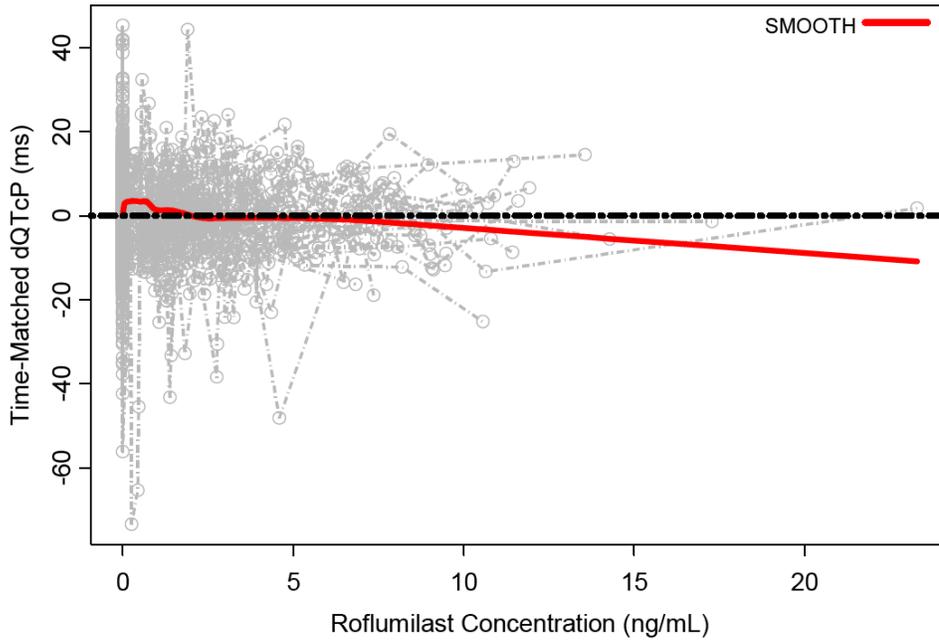
Source: CSR page 43 Figure 1.

4.2.8.4.2 Exposure-Response Analysis

“Plots of Δ QTcP (time-matched QTcP change from baseline) versus roflumilast concentration and dQTcP versus roflumilast N-oxide concentrations are presented in Figure 2 and Figure 3.”

“When the QTcP and plasma concentration data (both roflumilast and roflumilast N-oxide, simultaneously) were modeled to determine the relationship between time-matched change from baseline in dQTcP and exposure using a linear mixed effect model, the slope parameters were not statistically significantly different from zero. The population mean estimates (95% CI) for the slope parameters for roflumilast and roflumilast N-oxide were -0.0282 (-0.0756, 0.0192) ms/(ng/mL) and -0.145 (-0.498, 0.208) ms/(ng/mL).”

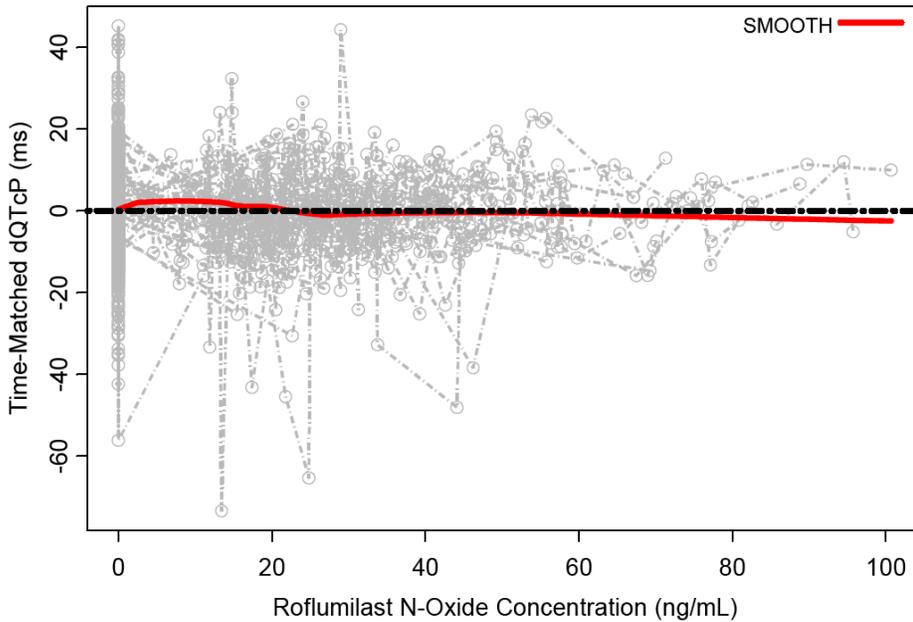
Figure 2: Plot of Time-Matched QTcP Change From Baseline Versus Roflumilast Concentration



The gray circles represent observed roflumilast concentrations, which are connected with in the same individual. The solid line showed a smoothed trend similar to the dotted zero line.

Source: CSR page 54 Figure 7.

Figure 3: Plot of Time-Matched QTcP Change From Baseline Versus Roflumilast N-Oxide Concentration



The gray circles represent observed roflumilast N-oxide concentrations, which are connected with in the same individual. The solid line showed a smoothed trend similar to the dotted zero line.

Source: CSR page 55 Figure 8.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

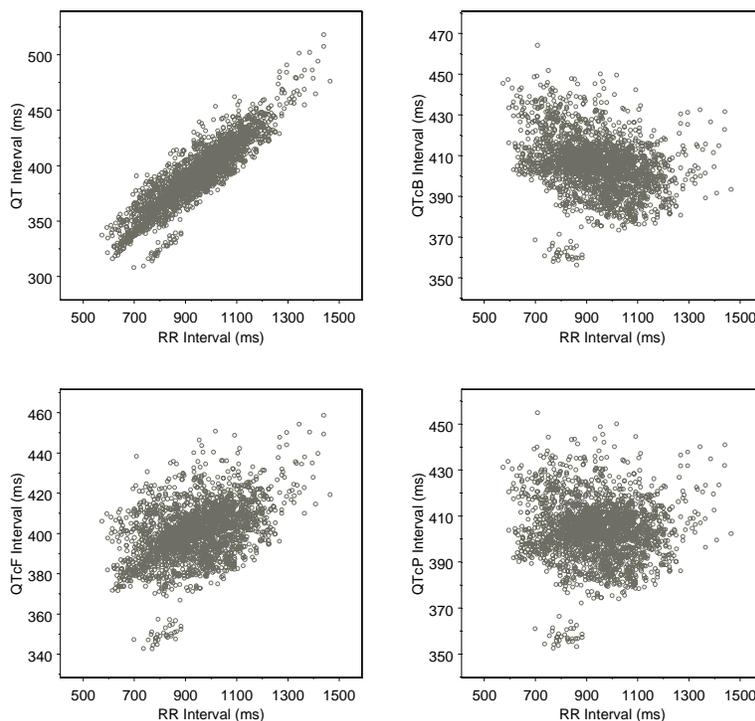
The QT-RR interval relationship is presented in Figure 4 together with the Bazett's (QTcB), Fridericia (QTcF), and population correction (QTcP).

We also evaluated the linear relationships between different correction methods (QTcF and QTcP) and RR. We compared the slopes of QTcF and QTcP vs RR. The absolute values of slopes of QTcP are smaller than the absolute values of slopes of QTcF. The differences between the slopes are statistically significant across all the treatment groups. Based on the results listed in the following table, it appears that QTcP is significantly better than QTcF. Therefore, this statistical reviewer used QTcP for the primary statistical analysis.

Table 8: Slopes and P-value of Slope Difference between QTcF and QTcP

Treatment Groups	Slope of QTcF	Slope of QTcP	diff_p_value
Moxifloxacin	0.0597	0.0280	0.0205
Placebo	0.0413	-0.0020	0.0000
All	0.0464	-0.0004	0.0000
Roflumilast 1000 µg	0.0416	-0.0022	0.0000
Roflumilast 500 µg	0.0440	-0.0132	0.0000

Figure 4: QT, QTcB, QTcF, and QTcP vs. RR



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Roflumilast

As mentioned in the study design, most subjects in Group A were enrolled at least one month earlier than the subjects in Group B. As demonstrated later, data from the two groups were different; therefore, this review was performed by group analysis. We used mixed model to analyze the Δ QTcP effect. The model includes Treatment as a fixed effect and Baseline values as a covariate. The analysis results are listed in **Table 9**. Based on by group analysis, some upper bounds of 90% CI for $\Delta\Delta$ QTcP are above 10 ms for both doses of roflumilast in Group B. This is mainly due to a larger negative Δ QTcP placebo effect in Group B.

Table 9: Analysis Results of Δ QTcP and $\Delta\Delta$ QTcP by Group

		Day 16				Day 37			
		Placebo	Roflumilast 500 μ g			Placebo	Roflumilast 1000 μ g		
		Δ QTcP	Δ QTcP	$\Delta\Delta$ QTcP		Δ QTcP	Δ QTcP	$\Delta\Delta$ QTcP	
group	Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	LS Mean	Diff LS Mean	90% CI
A	1.0	-2.5	-2.7	-0.1	(-4.9, 4.7)	-2.4	-6.0	-3.7	(-8.0, 0.7)
	2.0	-4.0	-1.6	2.5	(-1.7, 6.7)	-2.7	-4.2	-1.5	(-5.9, 3.0)
	4.0	1.8	0.7	-1.1	(-5.5, 3.2)	-0.9	0.2	1.0	(-3.1, 5.1)
	6.0	0.9	0.2	-0.7	(-5.3, 4.0)	0.0	-0.8	-0.8	(-4.6, 2.9)
	8.0	1.0	1.9	0.9	(-4.3, 6.0)	1.4	3.1	1.7	(-1.3, 4.7)
	12.0	0.1	1.9	1.8	(-2.0, 5.5)	0.7	-1.1	-1.8	(-7.1, 3.5)
	24.0	2.5	1.3	-1.2	(-5.0, 2.5)	0.8	0.6	-0.1	(-4.4, 4.2)
	B	1.0	-6.5	1.3	7.7	(3.8, 11.7)	-6.3	2.1	8.4
2.0		-2.1	-1.7	0.4	(-4.9, 5.7)	-5.0	-1.7	3.4	(-1.3, 8.0)
4.0		-2.5	-0.2	2.3	(-3.0, 7.7)	-4.6	-0.1	4.6	(-0.7, 9.8)
6.0		-3.6	0.7	4.3	(-0.9, 9.5)	-0.7	2.0	2.7	(-2.4, 7.8)
8.0		-4.9	0.3	5.2	(0.7, 9.6)	-1.7	-1.1	0.6	(-4.8, 6.0)
12.0		-3.9	-0.4	3.5	(-0.5, 7.5)	-1.4	2.6	4.0	(-1.4, 9.4)
24.0		-4.0	1.9	5.9	(0.7, 11.2)	-1.8	1.5	3.3	(-2.3, 9.0)

We used the same model to analyze two group combined data. The results are listed in **Table 10**. As pointed out early, because of the discrepancy between Group A and Group B, the results based on the combined data are nor reliable.

Table 10: Analysis Results of Δ QTcP and $\Delta\Delta$ QTcP for Combined Data

Time (hrs)	Day 1				Day 16				Day 37			
	Placebo	Moxifloxacin			Placebo	Roflumilast 500 μ g			Placebo	Roflumilast 1000 μ g		
	Δ QTcP	Δ QTcP	$\Delta\Delta$ QTcP		Δ QTcP	Δ QTcP	$\Delta\Delta$ QTcP		Δ QTcP	Δ QTcP	$\Delta\Delta$ QTcP	
	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	LS Mean	Diff LS Mean	90% CI
1.0	-2.8	3.2	6.0	(3.3, 8.8)	-4.5	-0.7	3.7	(0.6, 6.9)	-4.2	-1.9	2.3	(-0.7, 5.2)
2.0	-0.5	5.2	5.7	(3.1, 8.3)	-3.1	-1.6	1.6	(-1.7, 4.8)	-3.7	-3.0	0.7	(-2.4, 3.8)
4.0	1.6	8.4	6.9	(4.3, 9.4)	-0.4	0.3	0.8	(-2.6, 4.2)	-2.7	0.1	2.8	(-0.5, 6.1)
6.0	-3.6	2.7	6.3	(3.6, 9.0)	-1.2	0.4	1.6	(-1.8, 5.0)	-0.2	0.6	0.8	(-2.2, 3.8)
8.0	-2.2	1.9	4.0	(1.6, 6.5)	-1.8	0.9	2.6	(-0.8, 6.1)	0.0	0.9	0.8	(-2.4, 4.0)
12.0	0.9	3.5	2.7	(0.6, 4.7)	-1.7	0.6	2.3	(-0.5, 5.1)	-0.2	0.7	0.8	(-2.8, 4.5)
24.0	1.0	3.0	2.0	(-0.2, 4.1)	-0.6	1.5	2.1	(-1.2, 5.4)	-0.3	1.0	1.3	(-2.1, 4.7)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in **Table 10**. The largest unadjusted 90% lower confidence interval is below 5 ms (4.3 ms), which indicates that the assay sensitivity is not established in this study.

5.2.1.3 Graph of $\Delta\Delta\text{QTcP}$ Over Time

The results of by group analysis are graphically displayed in Figure 5 and

Appears This Way On Original

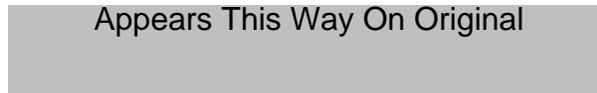


Figure 6. The time profile of $\Delta\Delta\text{QTcP}$ for different treatment groups based on the combined data is displayed in

Figure 7.

Appears This Way On Original

Figure 5: Mean and 90% CI $\Delta\Delta Q_{TcP}$ Timecourse by Group for Roflumilast 500 μg

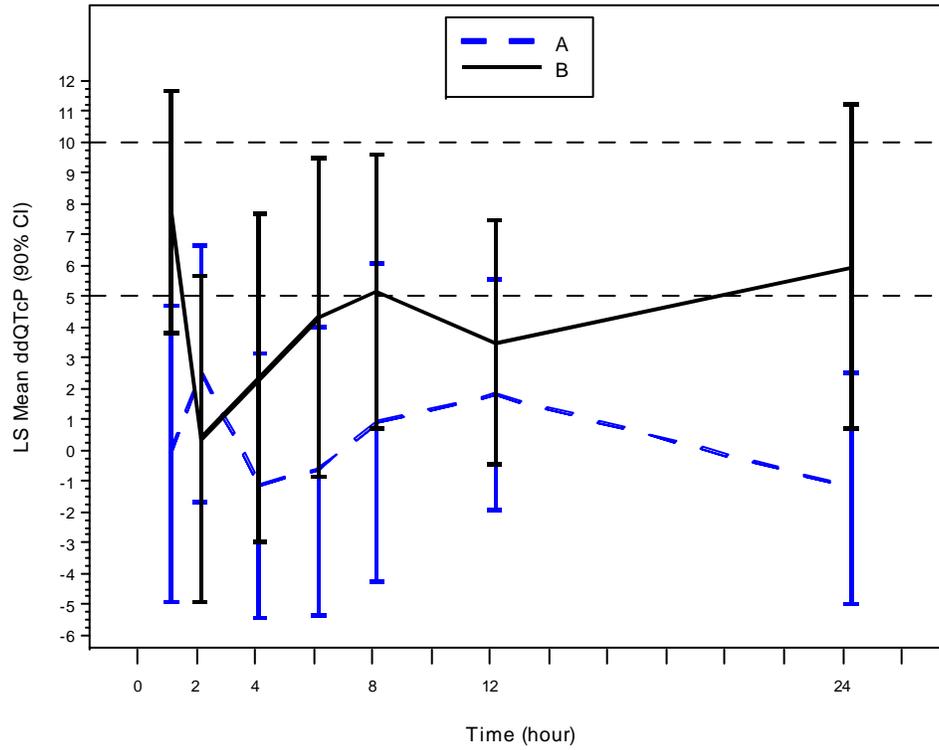


Figure 6: Mean and 90% CI $\Delta\Delta$ QTcP Timecourse by Group for Roflumilast 1000 μg

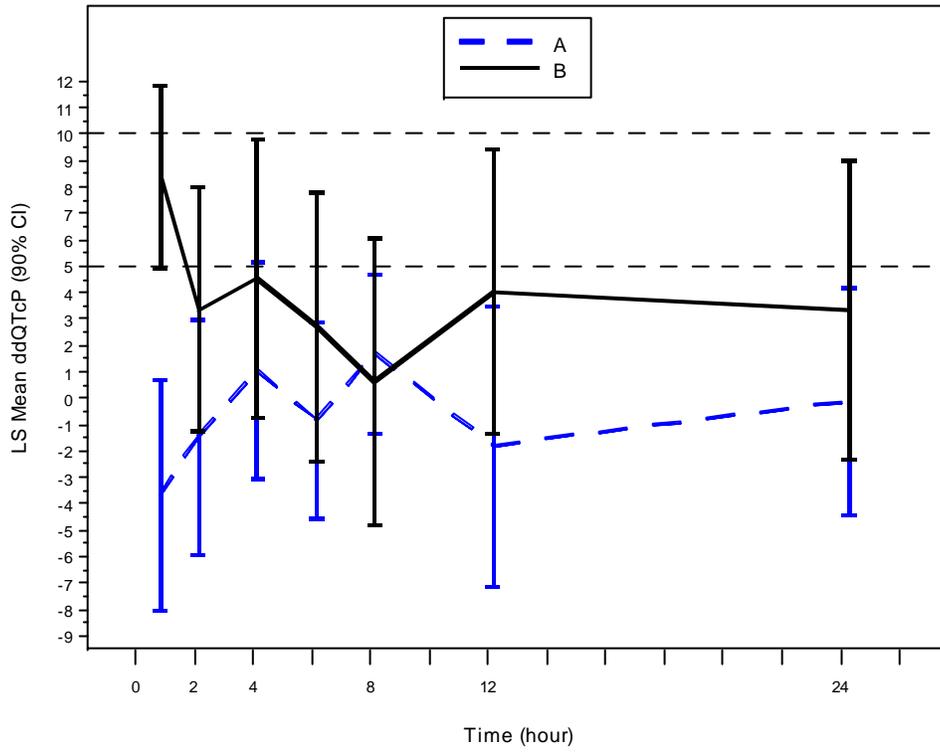
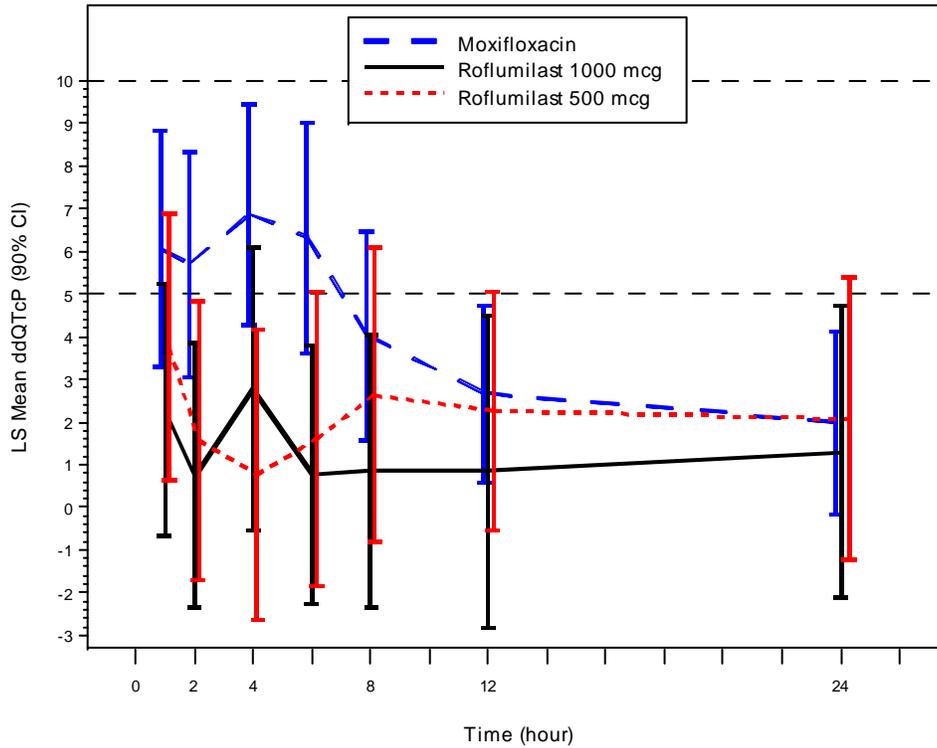


Figure 7: Mean and 90% CI $\Delta\Delta$ QTcP Timecourse for Combined Data



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcP values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcP was above 480 ms. No subject's change from baseline was above 60 ms.

Table 11: Categorical Analysis for QTcP

	N	Value<=450 ms	450 ms<Value<=480 ms
Treatment Group			
Baseline	80	80 (100%)	0 (0.0%)
Moxifloxacin	40	40 (100%)	0 (0.0%)
Placebo	58	58 (100%)	0 (0.0%)
Roflumilast 1000 µg	31	31 (100%)	0 (0.0%)
Roflumilast 500 µg	38	37 (97.4%)	1 (2.6%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. Only results based on the combined data are presented here. The largest upper limits of 90% CI for the PR mean differences between roflumilast 500 µg and placebo and roflumilast 1000 µg and placebo are 2.1 ms and 0.7 ms, respectively. The outlier analysis results for PR are presented in Table 13.

Table 12: Analysis Results of Δ PR and $\Delta\Delta$ PR for Combined Data

Time (hrs)	Moxifloxacin				Day 16				Day 37			
	Placebo				Placebo	Roflumilast 500 μ g			Placebo	Roflumilast 1000 μ g		
	Δ PR	Δ PR	$\Delta\Delta$ PR		Δ PR	Δ PR	$\Delta\Delta$ PR		Δ PR	Δ PR	$\Delta\Delta$ PR	
	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	LS Mean	Diff LS Mean	90% CI
1.0	-1.2	2.2	3.4	(0.9, 5.8)	0.5	-4.4	-4.8	(-7.4, -2.3)	1.3	-7.2	-8.5	(-12.2, -4.7)
2.0	2.5	2.1	-0.4	(-3.1, 2.3)	1.3	-1.8	-3.1	(-5.7, -0.5)	1.4	-3.6	-5.0	(-8.2, -1.8)
4.0	0.4	0.0	-0.3	(-2.7, 2.1)	0.6	-0.1	-0.7	(-3.5, 2.1)	2.7	-2.0	-4.7	(-7.6, -1.7)
6.0	-2.0	-2.4	-0.5	(-2.5, 1.6)	1.0	-1.8	-2.8	(-6.0, 0.4)	2.3	-1.1	-3.4	(-6.4, -0.4)
8.0	-3.6	-1.7	1.9	(-0.4, 4.1)	1.0	-1.7	-2.6	(-5.4, 0.1)	2.4	0.4	-2.0	(-4.8, 0.7)
12.0	-1.5	-2.8	-1.3	(-3.4, 0.8)	0.6	-1.9	-2.5	(-5.6, 0.5)	1.8	-3.3	-5.1	(-8.6, -1.7)
24.0	-2.9	-1.1	1.8	(-0.2, 3.9)	1.3	-1.6	-2.9	(-6.2, 0.3)	1.3	-2.8	-4.1	(-8.2, 0.0)

Table 13: Categorical Analysis for PR

	N	PR < 200 ms	PR \geq 200 ms
Treatment Group			
Moxifloxacin	40	37 (92.5%)	3 (7.5%)
Placebo	58	55 (94.8%)	3 (5.2%)
Roflumilast 1000 μ g	31	31 (100%)	0 (0.0%)
Roflumilast 500 μ g	38	37 (97.4%)	1 (2.6%)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. Only results based on the combined data are presented here. The largest upper limits of 90% CI for the QRS mean differences between roflumilast 500 μ g and placebo and roflumilast 1000 μ g and placebo are 2.3 ms and 3.3 ms, respectively. The outlier analysis results for QRS are presented in Table 15.

Table 14: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Combined Data

Time (hrs)	Day 16				Day 37			
	Placebo	Roflumilast 500 μ g			Placebo	Roflumilast 1000 μ g		
	Δ QRS	Δ QRS	$\Delta\Delta$ QRS		Δ QRS	Δ QRS	$\Delta\Delta$ QRS	
	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	LS Mean	Diff LS Mean	90% CI
1.0	0.3	0.5	0.2	(-1.3, 1.7)	0.1	0.5	0.4	(-1.2, 2.1)
2.0	0.8	0.8	-0.0	(-1.5, 1.5)	0.4	0.6	0.2	(-1.4, 1.8)
4.0	1.0	1.4	0.4	(-0.8, 1.6)	0.7	1.9	1.3	(0.1, 2.4)
6.0	0.1	0.7	0.6	(-1.0, 2.1)	0.2	1.0	0.7	(-0.7, 2.2)
8.0	1.3	-0.7	-2.0	(-3.5, -0.6)	0.3	0.2	-0.2	(-1.6, 1.2)
12.0	0.2	1.1	0.9	(-0.5, 2.3)	-0.8	1.2	2.0	(0.7, 3.3)
24.0	0.6	-0.6	-1.2	(-2.8, 0.4)	1.2	0.3	-0.9	(-2.2, 0.4)

Table 15: Categorical Analysis for QRS

	N	QRS < 120 ms	QRS \geq 120 ms
Treatment Group			
Moxifloxacin	40	40 (100%)	0 (0.0%)
Placebo	58	57 (98.3%)	1 (1.7%)
Roflumilast 1000 μ g	31	31 (100%)	0 (0.0%)
Roflumilast 500 μ g	38	38 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

Due to the design defect, time-matched Δ QTcP change from placebo was not available for subjects in the roflumilast treatment group. The relationships between $\Delta\Delta$ QTcP, roflumilast and roflumilast N-oxide concentrations are visualized in Figure 8 and Figure 9 with no evident exposure-response relationship.

Figure 8: $\Delta\Delta$ QTcP vs. Roflumilast Concentration

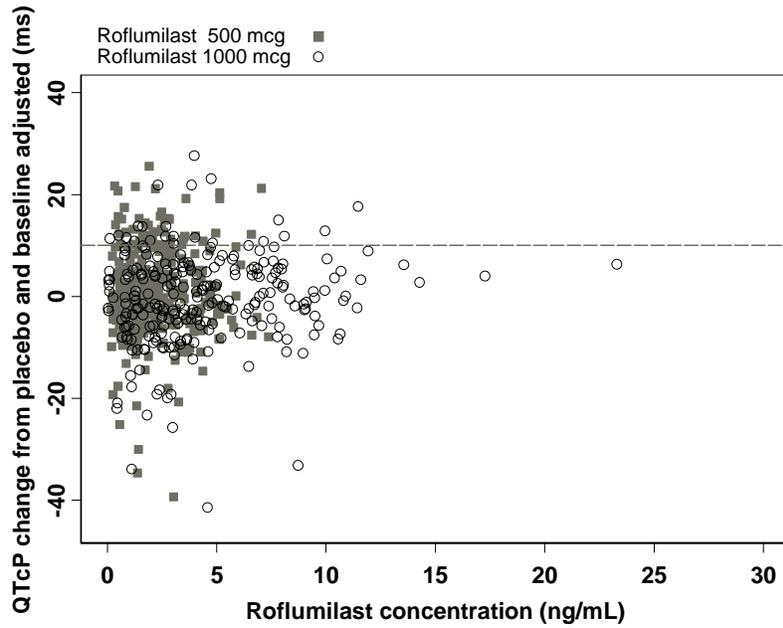
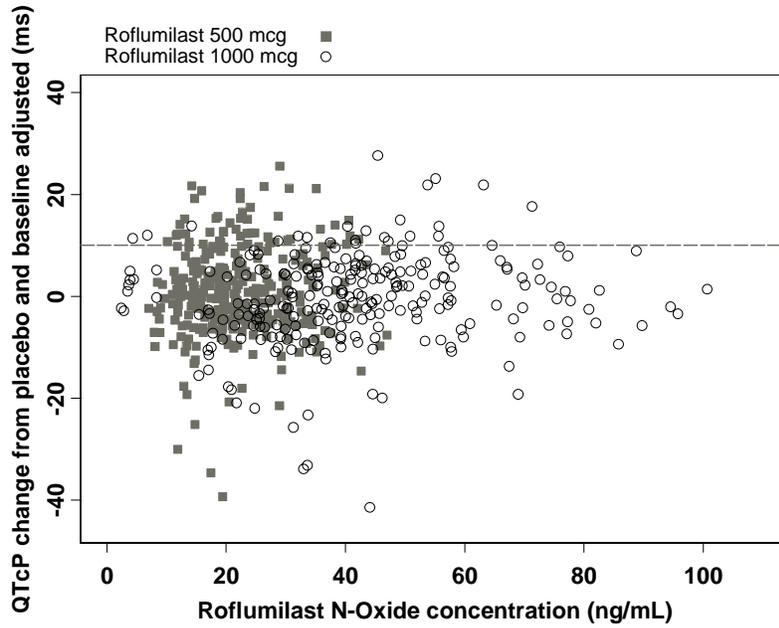


Figure 9: $\Delta\Delta$ QTcP vs. Roflumilast N-Oxide Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study with roflumilast.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. The median representative beat from 12 lead overlay seems to have been used for interval assessments. R-peak was not annotated, so PQ and QRS intervals seem to have been estimated. According to the automated algorithm, about 1.2% of the ECGs were reported to have significant QT bias but the histograms of the distribution was narrow and the annotations seemed adequate on review of a sub-set of these ECGs. Overall ECG acquisition and annotation in this study appears acceptable but details about ECG interpretation including central read and blinding of readers is unavailable in the study report and the protocol.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on the PR interval and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	500 mcg once daily	
Maximum tolerated dose	1000 mcg once daily	
Principal adverse events	Principal adverse events at therapeutic dose of 500 mcg once daily were nausea, headache and dizziness. Dose limiting adverse events at doses of 1000 mcg include more severe and frequent events of nausea, dizziness, headache, lightheadedness and diarrhea.	
Maximum dose tested	Single Dose	5000 mcg
	Multiple Dose	1000 mcg for up to 14 days
Exposures Achieved at Maximum Tested Dose	Single Dose	In the single-ascending dose study (Study FHP002), PK parameters were available for 1 subject after administration of 5000 mcg single dose and for 2 subjects after 2500 mcg single dose. Roflumilast C _{max} and AUC, determined using an early bioanalytical method, after 5000 mcg were 35.3 ng/mL and 700.2 ng.hr/mL, respectively. Mean C _{max} and AUC after 2500 mcg were 24.2 ng/mL and 303.7 ng.hr/mL, respectively.
	Multiple Dose	Following repeated doses of 1000 mcg for 14 days in Study CP-069 (Thorough QT trial), Mean (%CV) for: Roflumilast C _{max} was 10.6 (33.7) ng/mL and AUC ₀₋₂₄ was 90.2 (32.3) ng.h/mL Roflumilast N-oxide C _{max} was 53.8 (36.5) ng/mL and AUC ₀₋₂₄ was 1060 (37.8) ng.h/mL
Range of linear PK	AUC of roflumilast and roflumilast N-oxide increased in a dose-proportional manner in the dose range of 250-1000 mcg/day. C _{max} of roflumilast and roflumilast N-oxide increased in a dose-proportional manner at 500 mcg/day compared to 250 mcg/day. Less than proportional increases in roflumilast C _{max} were observed at 750 mcg/day compared to 500 mcg/day.	
Accumulation at steady state	Following repeated dosing of roflumilast (500 mcg/day) roflumilast had little or no accumulation: Mean accumulation ratio for AUC and C _{max} were 1.14 and 0.96, respectively. Mean accumulation ratio for roflumilast N-oxide was 1.07 for AUC and 2.3 for C _{max} .	
Metabolites	There are two active moieties, namely roflumilast and roflumilast N-oxide metabolite. The N-oxide metabolite has about 3 times higher free concentrations and 2-3 fold less intrinsic pharmacological activity compared to roflumilast. The plasma concentrations of roflumilast N-oxide metabolite are about 12-fold higher than roflumilast. Therefore,	

	overall the main moiety contributing to the PDE4 inhibitory activity in plasma is related to roflumilast N-oxide metabolite. There are hydroxy-derivatives and their conjugates of roflumilast and roflumilast N-oxide detectable in human plasma but they have pharmacologically no/little activity.	
Absorption	Absolute Bioavailability	Mean absolute bioavailability of roflumilast is 79% (90%CI: 69-92)
	Tmax	Median (range) for parent roflumilast following 500mcg single dose was 1.25 h (0.5-2.0) and following multiple dose 500mcg/d was 1.0 h (0.5-2.6) Median (range) for roflumilast N-oxide metabolite following 500mcg single dose was 8.53 h (4.0-13.0) and following multiple dose 500mcg/d was 3.0 h (2.0-5.9)
Distribution	Vd	Roflumilast Vd Mean (%CV) is 2.92 (20.9%) L/kg.
	% bound	In humans, at a concentration of 10 ng/ml Mean (CV%) bound roflumilast was 98.9% (16.7%) In humans, at a concentration of 100 ng/ml Mean (CV%) bound roflumilast N-oxide metabolite was 96.6% (11.8%). Protein binding was consistent with the values stated above over range of concentrations (0.1-10 ng/ml for roflumilast and 0.1-100 ng/ml for roflumilast N-oxide).
Elimination	Route	Roflumilast is extensively metabolized via phase 1 (CYP450) and phase 2 (conjugation) reactions. The major metabolite found in human plasma is the roflumilast N-oxide. The formation of the N-oxide is mediated by cytochrome CYP450 3A4 and 1A2, with the former being the major contributor to the N-oxide formation. The major metabolites identified in urine included glucuronides of both the hydroxy-derivatives of roflumilast and its N-oxide metabolite. In humans, excretion after oral or IV administration occurred almost exclusively in the form of roflumilast metabolites and mainly via the kidneys (~70% of the dose). Fecal elimination accounts for approximately 20% of the dose.
	Terminal t _{1/2}	Across 11 Phase I studies with repeated doses of 500 mcg/day roflumilast, Median (Range) for roflumilast t _{1/2} was 16.6 (8.2-30.9) hr. Median (Range) for roflumilast N-oxide t _{1/2} was 29.7 (10.6-46.5) hr.

	CL	Mean (%CV) Roflumilast CL was 0.1446 (33.5%) L/hr/kg.
Intrinsic Factors	Age	In healthy elderly subjects (≥ 65 years of age), roflumilast and roflumilast N-oxide mean AUCs were greater by 27% and 19%, respectively, compared to healthy young subjects (18-45 years of age). Mean peak concentration (C_{max}) of roflumilast and roflumilast N-oxide was higher in the elderly by 16% and 13%, respectively, compared with the young. No clinically significant differences between middle-aged subjects (46-64 years of age) were observed compared to the young.
	Sex	For roflumilast and roflumilast N-oxide, in all age groups, higher systemic exposures and peak concentrations were noted in females, when compared with male subjects. These differences were not considered to be clinically relevant.
	Race	Based on the population PK analysis for roflumilast, subjects of black race have 14% lower clearance, and subjects of Hispanic ethnicity have 30% lower clearance. Subjects of black race or Hispanic ethnicity are expected to have slightly higher systemic exposures than non-black, non-Hispanic subjects. These differences are not considered to be clinically relevant.
	Hepatic & Renal Impairment	For hepatically impaired subjects with Child-Pugh A, mean C_{max} and AUC for roflumilast were higher than normal subjects by 3% and 51%, respectively. Mean C_{max} and AUC for roflumilast N-oxide were higher by 26% and 24%, respectively. In subjects with Child-Pugh B, mean C_{max} and AUC for roflumilast were higher than in normal subjects by 26% and 92%, respectively. Mean C_{max} and AUC for roflumilast N-oxide metabolite were higher by 40% and 41%, respectively.
Extrinsic Factors	Drug interactions	No pharmacokinetic interactions were observed in the following DDI studies, i.e. Test/Reference ratio for AUC and C_{max} were within 80-125% limits: albuterol, antacid such as magnesium aluminum hydroxide, budesonide, digoxin, formoterol, oral and intravenous midazolam, montelukast, sildenafil, and warfarin. Drugs that have been shown to produce modest PK interactions when co-administered with 500 mcg roflumilast were:

		Ratio of Geometric Means for AUC and Cmax (90% confidence interval.)			
		Roflumilast		Roflumilast N-Oxide	
		AUC	Cmax	AUC	Cmax
	Erythromycin	170 (150, 192)	140 (125, 158)	104 (91.6, 117)	66.4 (61.0, 72.3)
	Ketoconazole	199 (171, 231)	123 (106, 143)	103 (91.5, 115)	62.3 (56.8, 68.3)
	Fluvoxamine	256 (218, 301)	112 (100, 124.5)	152 (132, 175)	80.3 (73.6, 87.7)
	Enoxacin	157 (120, 206)	120 (105, 137)	119 (97.4, 147)	85.9 (75.7, 97.5)
	Cimetidine	184 (146, 232)	146 (125, 169)	127 (103, 156)	96 (82, 112)
	Theophylline	128 (109, 151)	106 (NC)	107 (98, 116)	101 (NC)
	Oral contraceptive (gestodene & ethinyl estradiol)	151 (122, 187)	138 (121, 158)	114 (96.6, 134)	87.6 (80.4, 95.5)
	Rifampicin	20.6 (15.8, 27.0)	32.0 (26.3, 38.8)	44.2 (35.8, 54.7)	130 (114, 148)
		NC=Not Calculated			
Food Effects	Following administration of roflumilast with high-fat food, mean AUC for roflumilast the N-oxide metabolite did not change significantly. Mean Cmax for roflumilast decreased by 41% but no significant change was observed for the N-oxide metabolite. Because the major active moiety is roflumilast N-oxide, these differences are not clinically relevant.				
Expected High Clinical Exposure Scenario	In theory, the maximal exposures that could be expected are approximately 2-fold higher exposures (AUC or Cmax) for roflumilast or the N-oxide metabolite compared to average observed exposures. Roflumilast contributes much less to the PDE4 inhibitory activity and, therefore, an increase in roflumilast exposures of this magnitude (i.e., 2-fold) is not likely to be clinically relevant. Exposures >2-fold (e.g., exposures associated to 2500 and 1000 mcg doses) would be unlikely to occur due to self-limiting tolerability issues (i.e., nausea and vomiting).				

6.2 TABLE OF STUDY ASSESSMENTS

6.3 TABLE OF STUDY ASSESSMENTS

Table 2. Study Schedule (Protocol A5821023)

Study Day(s)	-28 to -2 (Screening)	-2	-1	1	2	3	4 to 14	15	16	17	18 to 22	23	24 to 36	36	37	38	39 to 42	47 to 49 (Closeout)
Orientation and Informed Consent	X																	
Complete Medical History ^a	X																	
Physical Examination	X							X										X
Vital Signs	X		X	X		X		X	X	X	X	X	X	X	X	X		X
Clinical Laboratory ^b	Chemistry	X	X		X			X			X				X			X
	Hematology	X	X		X			X			X				X			X
	Urinalysis	X										X						X
	Serum Pregnancy Test ^{c,d}	X																X
	Urine Pregnancy Test ^{c,d}				X		X	X										
	Serum FSH ^e	X																
	Drug and Alcohol Screen ^d	X	X				X	X										
Standardized Diet			X	X ^f				X							X			
Electrocardiogram (12-Lead) ^g	X		X	X	X			X	X						X	X		X
Blood Collection for Pharmacogenomics ^h				X														
Blood Collection for PK Analysis ⁱ							X	X	X					X	X	X	X	
Administration of Study Drug ^j				X		X	X	X	X	X	X	X	X	X	X	X		
Confinement to Clinic		X	X	X	X ^k	X ^k	X ^k	X	X	X	X	X	X	X	X	X	X	X ^k
Concomitant Medications			X															
Adverse Events	X																	

^a Includes use of all prescription and nonprescription drugs, vitamins, dietary supplements, alcohol, and tobacco
^b Subjects are required to fast for at least 4 hours prior to Clinical Laboratory Assessments.
^c For all females of childbearing potential
^d Results must be negative in order to continue with trial procedures.
^e Serum FSH concentrations for 45- to 55-year-old postmenopausal females, defined as being amenorrheic for at least 2 years
^f Subjects will not consume breakfast and will fast until lunch.
^g ECG measurements will be obtained as defined in Appendix A1, Final Protocol.
^h A pharmacogenomic sample will be obtained, shipped, and analyzed as defined in Appendix A1, Final Protocol.
ⁱ PK samples will be obtained as defined in Appendix A1, Final Protocol
^j Dosing of study drug is defined in Appendix A1, Final Protocol.
^k For convenience, subjects may remain in confinement from the evening of Day -2 through the morning of Day 42.
Source: Appendix A1

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/

JOANNE ZHANG
03/05/2010

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DSI CONSULT: Request for Clinical Inspections

Date: Jan 07, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Xuemeng Han Sarro, M.D., Clinical Reviewer, DPAP
Anthony Durmowicz, M.D., Clinical Team Leader, DPAP
Lydia Gilbert-McClain, M.D., Deputy Director, DPAP

From: Carol Hill, M.S., Regulatory Health Project Manager/DPAP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22522

Applicant/ Applicant contact information (to include phone/email): Forest Research Institute, Inc.,
Harborside Financial Center, Plaza Five, Suite 1900, Jersey City, NJ 07311

Phone: 201-386-2031, Fax: 201-524-9711

CP: Lisa L. Travis, M.S., RAC, Director, Regulatory Affairs, Email: Lisa.Travis@frx.com

Drug Proprietary Name: Daxas

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): COPD

PDUFA: May 17, 2010

Action Goal Date: May 17, 2010

Inspection Summary Goal Date: May 1, 2010

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	# of Subjects	Indication
Site ID 7176 (US) PI: Neal Moser, MD Internal Medicine Associates, 2900 Chancellor Drive, Crestview Hills, KY, 41017 Office Phone: 859-341-0288 Fax: 859-341-0203	M2-124 (pivotal)	12	Efficacy concerns (FEV1 outlier)
Site ID 6675 (Poland) PI: Dr. Halina Batura-Gabryel Department of Pulmonary Diseases, Marcinkowski University of Medical Sciences, Poznan, Szamarzewskiego 84 str. Office Phone: +48 61 84 17 061 Fax: +48 61 84 17 061	M2-125	33	Violations of GCP per previous EMEA inspection

III. Site Selection/Rationale

NDA-22522 is for a new drug class, phosphodiesterase 4 inhibitors (PED4). The applicant designated studies M2-124 and M2-125 as the pivotal trials. Both M2-124 and 125 were multicenter, multinational studies and together they involved 355 sites from 15 countries in Europe, North America, Asia and Africa.

The rationale for the site selection is based on the link between the efficacy claim of the proposed product and its approvability. Sites with best outcome and largest number of enrollment were considered first. However, due to the large number of sites involved and small number of subjects per site, selection of candidate sites for inspection has been difficult. Only a handful of sites that had outcomes favoring the proposed product had more than 10 subjects. Some sites had larger number of enrollment (between 20 and 50) but the outcomes were equivocal.

We selected 2 candidate sites, one from the United States (M2-124) and one from Poland (M2-125). While other study sites reached statistical significance preFEV1, study site 7176 in the United States was the only domestic site that reached the statistical significance in pre FEV1 and had N of greater than 10. Site 6675 from Poland has been selected for inspection for cause; a previous inspection by the EMEA identified significant violations.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify): see rationale
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites (approximately 75% of subjects enrolled in the clinical program were from foreign sites). Also, a previous inspection by EMEA revealed violations at the Polish site.

IV. Tables of Specific Data to be Verified (if applicable)

NA

Should you require any additional information, please contact Carol Hill, RPM at 301-796-1226 or Xuemeng Han Sarro at 301-796-4205

Concurrence: (as needed)

Anthony Durmowicz, M.D., Medical Team Leader, DPAP

Lydia Gilbert-McClain, M.D., Deputy Division Director (Acting Division Director), DPAP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22522	ORIG-1	NYCOMED GMBH	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/

CAROL F HILL
01/07/2010

LYDIA I GILBERT MCCLAIN
01/07/2010