FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Pulmonary-Allergy Drugs Advisory Committee

WEDNESDAY, APRIL 7, 2010

8:00 a.m. to 4:00 p.m.

Hilton Washington DC/Silver Spring

8727 Colesville Road

Silver Spring, Maryland

Pulmonary-Allergy Drugs Advisory Committee

Voting Members

William Calhoun, M.D. (Chair)
Sealy and Smith Distinguished Professor
of Internal Medicine
Department of Internal Medicine
University of Texas Medical Branch
301 University Boulevard
Galveston, Texas 77555

Paula Carvalho, M.D.
Professor of Medicine
Division of Pulmonary and
Critical Care Medicine
University of Washington
Chief, Intensive Care Unit
VA Medical Center/Boise
500 West Fort Street
Boise, Idaho 83702

Leslie Hendeles, Pharm.D.
Professor of Pharmacy and Pediatrics
University of Florida
Health Science Center (Box 100486)
1600 Southwest Archer Road, Room PG-05
Gainesville, Florida 32610

John Hoidal, M.D.
Professor of Medicine
Chair, Department of Internal Medicine
The Clarence M. and Ruth N. Birrer
Presidential Endowed Chair
The University of Utah
30 North 1900 East
4C104 SOM
Salt Lake City, Utah 84132

Richard Honsinger, M.D.
Los Alamos Medical Center Clinic, Ltd.
3917 West Road
Los Alamos, New Mexico 87544

Daren Knoell, Pharm.D.
Professor of Pharmacy and Medicine
The Ohio State University
Davis Heart and Lung Research Institute
473 W. 12th Ave., Room 405A
Columbus, Ohio 43210

Jerry Krishnan, M.D., Ph.D.
Associate Professor of Medicine and Health Studies
University of Chicago
Section of Pulmonary and Critical Care Medicine
5841 S. Maryland Avenue, MC 6076
Chicago, Illinois 60637

Rodney Mullins (Consumer Representative)
National Director, Public Health Consultants and
Advocates
2960 Risen Star Court
Duluth, Georgia 30096

Thomas Alexander Platts-Mills, Ph.D.
Director, Asthma and Allergy Disease Center
University of Virginia Medical Center
Box 801355
Charlottesville, Virginia 22908

Temporary Non-voting Member

D. Bruce Burlington, M.D. (Industry Representative)
Gaithersburg, Maryland 20878

Temporary Voting Members

Robert Fink, M.D.
Director of the Regional Cystic
Fibrosis Center
The Children's Medical Center of Dayton
One Children's Plaza
Dayton, Ohio 45404

Edna Fiore (Patient Representative)
Littleton, Colorado 80123

Jesse Joad, M.D.
Professor Emerita,
University of California, Davis
University of California Postbaccalaureate Consortium
Sacramento, California 95817

Ganesh Raghu, M.D.
Professor of Medicine & Lab Medicine (Adjunct)
Division of Pulmonary & Critical Care Medicine
Campus Box 356175
Director, Interstitial Lung Disease,
Sarcoid and Pulmonary Fibrosis Program
Medical Director, Lung Transplant Program
Seattle, Washington 98195

David Schoenfeld, Ph.D.
Professor of Medicine
Biostatistics Center
Massachusetts General Hospital
50 Stanford Street
Suite 560
Boston, Massachusetts 02114

Erik Swenson, M.D.
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
University of Washington
VA Puget Sound Health Care System
1660 South Columbia Way, Room 4D142
Seattle, Washington 98108

FDA Participants (Non-voting)

Robert Abugov, Ph.D.
Statistical Reviewer
Division of Biometrics II
CDER, FDA

Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary, Allergy, and
Rheumatology
Products, CDER, FDA

Anthony Durmowicz, M.D.
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA

Curtis Rosebraugh, M.D.
Director, Office of Drug Evaluation II
CDER, FDA

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P R O C E E D I N G S

(8:00 a.m.)

DR. CALHOUN: Good morning. We're going to call the meeting to order. My name is Bill Calhoun. I'm professor and vice chairman in the Department of Internal Medicine at University of Texas in Galveston.

The first order of business is to introduce the committee. And I believe we'll start with Dr. Krishnan. Please introduce yourself and give us a word about your area of expertise.

DR. KRISHNAN: Right. My name is Jerry Krishnan. I'm an Associate Professor of Medicine and Epidemiology, and I direct the University of Chicago's Asthma and COPD Center.

DR. HONSINGER: Richard Honsinger, clinical professor at University of New Mexico. I practice in internal medicine, allergy, and immunology in Los Alamos and Santa Fe, New Mexico.

DR. PLATTS-MILLS: I'm Tom Platts-Mills. I'm a Professor of Medicine at the University of Virginia, and I've been doing research on the role of allergens in asthma for 30 years.

DR. HENDELES: I'm Leslie Hendeles. I'm a professor in the Department of Pharmacotherapy and Translational Research at the University of Florida.

MS. FIORE: Edna Fiore. I'm a patient, and I'm very active in advocacy and COPD awareness.

DR. JOAD: Jesse Joad, Professor Emerita of the University of California at Davis. I'm a pediatric pulmonologist and allergist.

DR. KHUC: Kristine Khuc, Designated Federal Official.

DR. CALHOUN: So Dr. Schoenfeld is not here at present. We'll introduce him when he gets here, and likewise Mr. Mullins.

Dr. Swenson?

DR. SWENSON: Erik Swenson. I'm Professor of Medicine and Physiology at the University of Washington in the Pulmonary and Critical Care Medicine Section.

DR. HOIDAL: John Hoidal, Professor of Medicine, University of Utah, and my interests are in mechanisms of lung injury, including COPD.

DR. RAGHU: Ganesh Raghu, Professor of

Medicine at the University of Washington at the Medical Center. My area of background is inflammation immunology in interstitial lung diseases and fibrosis.

DR. CALHOUN: I see Dr. Carvalho. We'll come back to her in just a minute.

Dr. Knoell?

DR. KNOELL: Daren Knoell from the Ohio State University, Professor of Medicine and Pharmacy; also, in the Davis Heart and Lung Research Institute.

DR. FINK: Bob Fink, Professor of Pediatrics at Wright State University in Dayton, Ohio; interested in cystic fibrosis and pediatric asthma.

DR. BURLINGTON: Bruce Burlington, infectious disease internist after a career at FDA and in industry. I'm now consulting with industry, and the industry rep.

DR. CALHOUN: And we'll give Dr. Carvalho just a minute to get settled.

DR. CARVALHO: Paula Carvalho, Professor of Medicine, University of Washington, in pulmonary and critical care medicine.

DR. CALHOUN: Okay. Thank you. Next, we're

going to proceed with the conflict of interest statement by Dr. Khuc.

Pardon me, and apologies to the agency. Could we have the FDA folks introduce themselves? I'm sorry.

DR. ROSEBRAUGH: Curt Rosebraugh, Director, Office of Drug Evaluation II.

DR. CHOWDHURY: I'm Badrul Chowdhury, Division Director, Division of Pulmonary, Allergy and Rheumatology Products.

DR. DURMOWICZ: I'm Tony Durmowicz, Clinical Team Leader, same division, Pulmonary, Allergy and Rheumatology Products.

DR. ABUGOV: I'm Robert Abugov, Office of Biostatistics.

DR. CALHOUN: Okay. There's a little text I need to read into the record here.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that

individuals can express their view without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I would like to remind everyone present to silence your cell phones and other electronic devices, if you have not already done so.

The committee is also reminded to refrain from discussing the meeting topic during breaks or during lunch. Thanks to all.

So at this point, I guess we're ready for

the conflict of interest statement by Dr. Khuc.

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetics Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has

authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug, and Cosmetics Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of the committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents

and royalties, and primary employment.

Today's agenda involves a discussion of New Drug Application 22-522, Daxas, roflumilast, manufactured by Forest Research Institute, a subsidiary of Forest Laboratories, for the maintenance treatment of chronic obstructive pulmonary disease associated with chronic bronchitis in patients at risk of exacerbations.

This is a particular matters meeting during which specific laboratories related to Forest Laboratories' roflumilast will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the issues being discussed today.

With respect to FDA's invited industry representative, we would like to disclose that

Dr. D. Bruce Burlington is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry.

Dr. Burlington's role in this meeting is to represent industry in general and not any particular company. Dr. Burlington is an independent consultant on pharmaceutical product development and regulatory affairs.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you.

DR. CALHOUN: Okay. Thank you.

As a point of order, we'll have Dr. Schoenfeld introduce himself.

DR. SCHOENFELD: David Schoenfeld from Massachusetts General Hospital, biostatistician.

DR. CALHOUN: Thank you. At this point, we'll proceed with the opening remarks by the FDA by Dr. Chowdhury.

DR. CHOWDHURY: Good morning. Thank you, Dr. Calhoun. On behalf of the FDA and the Division of Pulmonary, Allergy, and Rheumatology Products, I welcome you, members of the committee, representatives of Forest Research Institute, and members of the audience, to this meeting. I hope we will have an interesting and productive meeting.

Today we will be discussing the new drug application from Forest Research Institute seeking approval of roflumilast for chronic obstructive pulmonary disease. In the next couple of minutes, I will give a high-level summary of the clinical program, a summary of efficacy and safety findings. This will set the stage for subsequent presentations by the industry and also with FDA. Then I will talk very briefly about the AC process in very broad terms. Finally, I will mention the issues that we will

discuss later today.

The drug we're discussing here today is roflumilast. It is a new molecule entity and a new drug class. It belongs to a drug class which is a phosphodiesterase-4 inhibitor. As you discuss and deliberate on this drug, there are two other drugs worth keeping in mind.

The first is theophylline, which is available for use by patients with COPD. And theophylline, as we know, is a nonspecific phosphodiesterase inhibitor.

The second drug, which is of the same class, is called cilomilast. Cilomilast was developed by another company for COPD a couple of years ago, and was discussed at an advisory committee meeting approximately six years ago. As you read the briefing documents and you hear the presentations, the cilomilast example will come up multiple times. And also, I will also very briefly touch on it.

So theophylline and cilomilast are relevant for this application.

As you have seen from the briefing document,

the program for COPD for this drug, and other programs, are quite extensive and have spanned over 15 years or so. And ownership of this product also has changed multiple times, including one change within the review period from Nycomed to Forest, as we have seen.

The clinical program for COPD itself has approximately 10,000-plus patients and spans over 10 years, and has many studies. To keep you oriented to the program, in this slide, I'm giving a very high-level summary of the core studies that are important for our deliberation today.

In the slide, I have the study identification numbers on the left side, followed by the duration of the studies and the number of patients in total in each of these studies. Then in the parentheses, I have the primary endpoint for these studies.

As you can see, each of these studies were quite large, and, by itself, any of these could have supported a submission of an application.

Now, the early studies, which are listed as

101 and 107, are now called as dose-ranging studies and they explored two doses of roflumilast, 500 and 250 micrograms compared to placebo. The selection of dose that was carried further was primarily the highest tolerated dose, which is 500 micrograms, and the dosing frequency seems to be supported by clinical pharmacology studies.

Let me take a few moments and talk about the endpoints, and give a very high-level summary of the efficacy.

FEV1 at the end of dosing interval was measured in all the studies, and they're supported from placebo and were statistically significant. The effect size for the FEV1 were approximately 50 ml. As a frame of reference, the other drug which I mentioned, cilomilast, which was discussed at an AC meeting a couple of years ago, also had an effect size of approximately the same magnitude.

Theophylline has been studied quite a bit back in the past, and there's a Cochrane analysis, which we have referred to in our briefing document, which has also given effect size of FEV1. That effect

size for theophylline seems to be larger than this drug, in the magnitude of approximately double.

But again, these are across study comparisons done over a different time period, and there is no head-to-head trial comparing either of these two PDE-4 inhibitors to theophylline.

The SGRQ, as you are very aware of, is a quality-of-life, patient-reported outcome instrument which is commonly used for lung diseases. The cilomilast program was based on assessment on FEV1 and SGRQ. In the program here for roflumilast, the SGRQ did not meet its objective of showing difference on the SGRQ. That was also the case for cilomilast.

The company subsequently moved on and used exacerbation as the co-primary endpoint with FEV1, and you will hear presentations on exacerbations.

The initial studies, 111 and 112, did not win for exacerbation. And these studies are there in our briefing document. Subsequently, two other studies were done, 124 and 125, on a much narrower patient population of COPD, and showed efficacy on exacerbation, and the company has identified 124 and

125 as the two core pivotal studies to support this application.

The last two studies used FEV1 as the primary endpoint, and the intent was to show a benefit for bronchodilatation, measured by FEV1, over other bronchodilators commonly used in COPD patients, such as long-acting beta agonists and long-acting antimuscarinic drugs.

As you hear the presentations and discuss this product, keep in mind the efficacy claim, which is the basis for assessment of efficacy for this product. And here I'm quoting the indication for this product, which is a summary of the efficacy, and which is that roflumilast at a dose of 500 micrograms per day is indicated as maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbation.

Now, the maintenance treatment of COPD is a reasonably broad indication, which is quite reasonable. Typically, from the agency side, for such an indication of maintenance treatment for a drug that was primarily in the (inaudible) fashion, is not

bronchodilatation, we expect efficiency to be shown in more than one variable. In this case, it was FEV1 and exacerbation.

The indication defines the patient population of COPD in somewhat restricted fashion, which is COPD with bronchitis and in patients who are at risk of exacerbation. As you discuss this product, keep this indication in mind. And this is what we will be discussing today and you will be voting on today.

Just as a point of note, as the ownership of this application changed, Nycomed, later in the review period, proposed a different indication, and which is here for your reference.

The indication is somewhat similar, except that the focus had changed from maintenance treatment of COPD to reduction of exacerbation, which is a more focused claim, which is reduce exacerbation specifically. Otherwise, it is somewhat similar. For today, for the purpose of discussion and voting, this is the indication that we will be discussing.

Let me turn it over and talk very briefly

about safety, again, giving a very high-level summary. I'm not going into details; you will hear the details in subsequent presentations.

There are four safety aspects that I would like you to keep in mind and these are neuropsychiatric adverse effects, gastrointestinal adverse reactions, weight loss, and cancer. Let me go through them one by one, again, very briefly.

Adverse effects such as insomnia, anxiety, and deposition, these were seen in the programs, and the frequency of reporting is in parentheses here. And for the 500-microgram dose, the frequency was approximately 1.7 to 1.24 higher for the active moiety compared to placebo.

In the program, there were suicides and suicide attempts totaling five, and all in the drug treatment group, including 250 and 500. Two of the suicides occurred in patients who were approximately three weeks off the drug. Nevertheless, these are something to keep in mind and cannot be discounted easily.

In addition to suicides, completed and

attempts, there was also one case of suicide ideation, and that case of suicide ideation was in the placebo arm. Generally, when one talks about suicide, suicide ideations are relevant and important, but falls in a lower category than completed suicide and suicide attempts.

Now, neuropsychiatric adverse events and suicides are somewhat, we believe, unique for this drug and was not seen in the cilomilast program. And typically, the multiple large COPD programs, including a couple of them that we have discussed here, such as the TORCH study and UPLIFT studies, and these neuropsychiatric adverse reactions is not something that we see commonly.

The second is gastrointestinal adverse reactions, and this is a pretty well-known adverse reaction for theophylline-like drugs, including cilomilast, which was an exception here, with diarrhea and nausea being very commonly reported, and the frequencies are given here.

As far as withdrawal from the study goes, again, diarrhea and nausea were quite common causes of

withdrawal, and, in fact, they were the second and third common cause of withdrawal below the COPD exacerbation.

In some patients, diarrhea were reported as serious adverse reactions. Serious adverse reactions, or SAEs, are regulatory terms, and their definition is in the briefing document that the FDA has prepared. There were 13 cases of diarrhea reported in SAEs, and the imbalance was against roflumilast.

Weight loss was another finding, which was something that we noted and was unique for this product, and you will have much discussions about this. It seemed like the weight loss was more in more severe patients, and more in patients who, to begin with, had lower weight.

The last issue of concern is cancer. Cancer is a concern to us because the drug in rodent -- which is hamster -- carcinogenesis study was positive. And there is a metabolite of roflumilast which was thought to be the reason for the cancer in hamsters, and that metabolite circulates in human blood and is excreted in urine.

If you look at the total cancers in the two groups, roflumilast -- and this is total of 500- and 250-microgram dose -- they are pretty much balanced in the two groups, roflumilast and placebo. However, if you take 250-microgram dose out of this because 500 is the active dose, the number changes somewhat.

If you look at the common cancers, such as the cancers of the lungs, prostate, colon, and urinary tract, there is imbalance, and the imbalance between active drug and the placebo is twofold or higher.

Typically, we do not apply statistics for safety endpoints. But if you do apply statistics, then, for all cancers, minus the common skin cancers, and for the common cancers such as lung, prostate, colon, and urinary tract, some of these differences reaches or approaches a nominal p-value of .05.

In closing, I would point out some expectations or the purpose of advisory committee meetings so that we are all on the same page here, and I am here quoting from the Code of Federal Regulations of the purpose of an advisory committee meeting.

"FDA utilizes or conducts such meetings to

discuss matters of importance that is in front of the FDA, to review the issues involved, and to provide advice and recommendation to the agency."

This is an important process for us to have this advisory committee meeting, and we do bring forward to the advisory committee issues of importance that we need advice on, and we bring it to a committee of experts to give us advice.

Roflumilast is an important product, and it is an important matter, and we are bringing it to you, to the committee here, as you are the experts, and seeking your advice to us on this matter.

For the process of ultimate approval of a product, it's ultimately the FDA's sole discretion. But nevertheless, we take these discussions and advice very seriously, and this forms a very important part of our decision-making.

As you hear the various presentations and discuss the issues, keep in mind there are three high-level issues you will be discussing throughout the day and ultimately will be voting on. These are evidence of efficacy, safety, and approvability. I'll be

coming in front of you later, after all the presentations, and expound on this a bit more.

On closing, Mr. Chairman, I would like to say that I appreciate the time you and everyone else in the committee has taken out of their busy schedules to advise us on this application. This is a reflection of your dedication and commitment to the practice of medicine and public health.

Thank you. I now turn the meeting over to you, Mr. Chairman.

DR. CALHOUN: Thanks, Dr. Chowdhury.

We have one point of order and one point of agenda before we move on to the sponsor presentation. Mr. Mullins, would you be willing to introduce yourself?

MR. MULLINS: Good morning. I apologize for my travel issues here to D.C.

DR. CALHOUN: Mike?

MR. MULLINS: Thank you. Good morning. I apologize for my travel issues here to D.C. I'd like to introduce myself. I am a principal with the Public Health Advocacy and Consultants, and national

director. So I'm pleased to be here. Thank you.

DR. CALHOUN: Thank you.

So both the Food and Drug Administration, the FDA, and public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcome of this meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your

presentation, it will not preclude you from speaking.

At this point, we'll proceed with the sponsor presentation.

MS. TRAVIS: Good morning, Mr. Chairman, members of the advisory committee, and FDA staff. I am Lisa Travis, Director of Regulatory Affairs at the Forest Research Institute. I would like to thank the committee and the agency for the opportunity to be here to discuss roflumilast, an oral PDE-4 inhibitor to be considered for approval in the treatment of chronic obstructive pulmonary disease.

This morning I will start Forest's presentation by sharing with you a brief overview of the roflumilast clinical development program. The unique aspects of its mechanism of action and results of the associated clinical program make it an important new treatment option of patients with COPD.

The system's frozen?

Roflumilast is a new oral, once-daily anti-inflammatory agent. It is a potent and selective PDE-4 inhibitor which is pharmacologically distinct from other COPD therapies targeting key pro-inflammatory

mediators underlying the pathogenesis of COPD and associated exacerbations.

Further, roflumilast has demonstrated clinical safety and efficacy in over 6,500 COPD patients in well-controlled clinical trials.

At the time of the NDA filing, the proposed indication for roflumilast was roflumilast, as indicated, for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.

After assuming sponsorship of the NDA in December of 2009, Forest proposed a modification to the indication in order to more precisely describe the primary action of the product demonstrated in pivotal trials, the reduction of exacerbations.

Specifically, Forest proposed the following indication: Roflumilast, as indicated, as maintenance treatment to reduce exacerbations of COPD associated with chronic bronchitis in patients at risk of exacerbations. This change was submitted to reflect the primary benefit of roflumilast, which is its effect on COPD exacerbations.

Additionally, Forest believes the revised indication is an accurate reflection of the patient population in findings from pivotal trials to be presented, and is prepared to discuss proposed revisions in further detail, should the committee desire.

The division informed the sponsor that because the changes were made late in the review process, the NDA would be reviewed against the original indication. In accordance with the FDA's request, the sponsor briefing book, which you have, only reflects the original indication.

The division, however, has provided both versions of the labeling for you, and because of this, we are also discussing this revised indication here, although the focus, as Dr. Chowdhury said, will be on the original indication.

The modified package insert also includes some additional warnings to reflect the sponsor's commitment to patient safety, specifically regarding findings of weight loss and, also, in reference to rare psychiatric adverse events.

In accordance with the 2007 FDA draft guidance for conduct of clinical programs for COPD, the agency recognizes that a drug can target a specific subset, such as patients with chronic bronchitis. Further, the FDA acknowledges that several types of drugs can be developed for COPD, specifically for the purpose of modifying or preventing COPD exacerbations. Therapeutic drugs that modify or prevent COPD exacerbations will provide a meaningful benefit to patients.

In accordance with the guidance, the proposed indication for roflumilast is supported by two confirmatory, identical Phase 3 trials, Studies 124 and 125, which provide replicate evidence of efficacy for the treatment of patients with COPD with chronic bronchitis who are at risk of exacerbations.

In the pivotal trials, roflumilast demonstrated a statistically significant and clinically meaningful reduction in exacerbations, which was corroborated by consistent improvement on measures of lung function.

The overall roflumilast clinical safety

database consists of over 14,000 subjects exposed to roflumilast across multiple indications, including normal volunteers in various patient populations, of which more than 6,500 were COPD patients exposed to roflumilast in 18 Phase 2 and Phase 3 clinical trials.

The proposed dose of roflumilast, 500 micrograms daily, was selected following Study M2-107. Results from early placebo-controlled Phase 3 COPD trials, Studies 111 and 112, led to the selection of patients with chronic bronchitis symptoms with a history of exacerbations, who were then further studied in two confirmatory Phase 3 trials, Study M2-124 and M2-125. Findings from these studies will be discussed in greater detail in the efficacy and safety presentations.

The efficacy of roflumilast in patients with COPD is additionally supported by two concurrent large-scale six-month trials conducted to evaluate the add-on effects of roflumilast when added to long-acting bronchodilators, salmeterol and tiotropium, in Studies 127 and 128, respectively. The results of these trials will also be discussed during our safety

and efficacy presentations.

Now, I would like to briefly introduce to you the speakers who are participating in our sponsor presentation.

First, Professor Steve Rennard from the University of Nebraska will discuss the medical need for additional treatment options for patients with COPD and the pharmacology of roflumilast.

Professor Klaus Rabe from the University of Leiden will present the efficacy results from our clinical trial experience with roflumilast in COPD, and the logic behind the clinical development program.

Dr. Marco Taglietti, Chief Medical Officer of the Forest Research Institute, will further address the safety findings and issues identified by the division.

Dr. Jim Donohue from the University of North Carolina-Chapel Hill will speak to the risk-benefit provided by roflumilast, and discuss why he believes the safety issues raised by the Division are manageable in clinical practice.

Experts available to the committee to

address any further questions that you might have -- we have them here with us today -- Dr. Neil Barnes, Dr. Peter Calverley, Dr. Phil Schein, Dr. Gary Koch, and Dr. William White.

Now, I would like to introduce -- it's my pleasure to introduce Dr. Steve Rennard.

DR. RENNARD: Thank you very much. I'm Steve Rennard from University of Nebraska Medical Center in Omaha, Nebraska. I'm a pulmonary physician. I've been a roflumilast investigator. I'm here as a consultant to Forest Laboratories, for which I've received compensation. I've also received reimbursement for my travel expenses. I am not a member of Forest's speakers bureau, I do not own any equity in the company, and there is no financial incentives to me for any outcome from today's meeting.

I have the charge today to discuss two topics: first, introduce the medical needs for additional therapies in COPD; and, then to introduce the pharmacology of roflumilast.

Now, COPD is one of the major public health problems facing us today in the United States.

Depending on the estimate, somewhere between 12, perhaps, and 24 million Americans currently suffer from COPD. COPD accounts for about 2 million emergency department visits annually, more than 600,000 hospitalizations, and more than 120,000 Americans die each year from COPD.

Now, COPD is recognized as being heterogeneous. In this particular estimate, where the prevalence of COPD was estimated at a little more than 10 million people, about three-quarters, or 7.6 million, were estimated to have the syndrome of chronic bronchitis, and about 3.7 million, or just a little under 40 percent, were estimated to have emphysema.

Of course, those two add up to more than 10 because people could have both emphysema and bronchitis. So bronchitis is present in a subset, a large subset, of patients with COPD, and the patient population is heterogeneous.

Now, patients with COPD also experience exacerbations. These are events -- and the literature is taken from the -- or the quote is taken from the

American Thoracic Society/European Respiratory Society statement and guidelines on COPD -- they're an event characterized by a change in the patient's baseline symptoms of dyspnea, cough, and sputum beyond the day-to-day variability sufficient to warrant a change in management.

Now, these exacerbations are what drive the majority of the health care burden, the emergency room visits, the hospitalizations, and, in fact, they put individual COPD patients at risk for more dire consequences, such as mortality.

These exacerbations, in fact, do not occur randomly, but individual patients can have risk factors that will identify them for being more likely to have exacerbations. Perhaps most importantly, a history of prior exacerbations, relatively lower lung function, is also a risk factor, as is the presence of chronic bronchitis.

Now, the concept for how COPD develops, the current concept, suggests that in a susceptible individual, when they're exposed, for example, to cigarette smoke or air pollution, an inflammatory

process is initiated in the lungs. This inflammation can, in fact, become chronic, and the chronic inflammatory process can lead to structural changes. The chronic inflammation may also spill over into the systemic circulation and cause some of the systemic features that are characteristic of COPD that really won't be discussed today.

But the structural changes and the inflammatory changes in the lung can lead to bronchoconstriction, edema, mucus production, and emphysema, all of which can contribute to airflow limitation, which is the defining feature of COPD.

Now, in addition to this baseline inflammatory process, individuals with COPD may have exacerbations that are characterized by worse inflammation. And the concept is that exposures to viruses or bacteria or increasing levels of pollution can lead to an acute exacerbation, which is characterized by an acute increase in the same inflammatory cells that play a role in the baseline condition, but lead to increasing bronchoconstriction, edema, mucus production, which

can lead to the symptoms of an acute exacerbation.

Now, to understand what an exacerbation is like from a patient perspective, I think it may be most useful to look at it from patients' own words. And so these are quotations taken -- they're direct quotations from patient focus groups from the EXACT-PRO initiative, an initiative designed to develop an instrument to assess COPD exacerbations, an FDA-initiated project that's actually still in progress.

What patients say is:

"I get short of breath."

"I can't move around much."

"It feels like there's a very, very tight belt around my chest."

"It cuts you at the knees."

"I was coughing, dry coughing, and very bad, and here, like I tell you, it hurts."

"It kind of makes you edgy because your breathing is not normal and you get palpitations."

"I was afraid."

These are events that, in and of themselves, apart from their prognostic implications, are events

that patients who experience them would greatly appreciate not to have to experience again.

Now, our current approaches to COPD therapy are outlined on this slide taken from the GOLD guidelines. For all individuals, of course, avoiding risk factors such as cigarette smoking and exposures to pollution, if you can avoid it, should be recommended. As the disease worsens, going from left to right, and individuals become symptomatic and their lung function becomes compromised, first-line therapy would be to use bronchodilators to improve lung function and to reduce symptoms.

But then as the disease continues to worsen and exacerbations become more common, therapy should be added to reduce exacerbations, therapies such as inhaled corticosteroids added to the other therapeutic regimens. And as the disease gets even worse, then other options, such as oxygen therapy and potential surgical interventions, may be considered.

Now, how well we do at managing COPD can be suggested from the next two slides. This is data taken from the registration trials that allowed a

treatment for COPD exacerbations, tiotropium or Spiriva, from its registration trials. There were two studies, the UPLIFT trial and the so-called VA study, both of which compared tiotropium versus placebo for their ability to reduce exacerbations in COPD patients. And as you can see, the benefits were 14 and 19 percent. This is one of our two approved therapies.

The other is Advair, a combination of fluticasone, 250 micrograms, and salmeterol, 50 micrograms. And there were two studies that looked at this, the so-called Anzueto and the so-called Ferguson studies, named after the lead authors of the publications of these.

These studies had a rather special study design. That is, all individuals who were enrolled in the study were started on inhaled corticosteroids. They were then randomized to be treated with either Advair 250/50 or salmeterol alone. So it was kind of a steroid withdrawal study. And it's thought that steroid withdrawal increases both the frequency of exacerbations and might have increased the effect

size. But there was a 30 percent or so reduction in exacerbations in these studies.

In a more conventional study that is comparing Advair to placebo, and this is a study now using Advair at the 500 microgram fluticasone dose with 50 micrograms of salmeterol, a dosage form that's not approved in the United States for the treatment of COPD exacerbations, where Advair is compared to placebo in the TRISTAN and in the TORCH study, both of these studies using this study design, had a 25 percent reduction in exacerbations.

So to summarize about COPD, it's a common problem in the United States. It's one of our major public health problems that we face today. One of the major features of the disease, which is an important therapeutic target in its own right, is exacerbations, and our current therapies can, to some degree, reduce the exacerbation risk that our patients will experience by, say, 14 to 25 percent. So additional therapies are desperately needed for COPD, and specifically to reduce exacerbations.

I'd now like to introduce the pharmacology

of roflumilast and its active metabolite, roflumilast N-oxide, agents that have the hope to address this unmet need.

Now, the concept for why roflumilast would be able to address this need in COPD is outlined on this slide. Adenylate cyclase is an enzyme that converts ATP to the signaling molecule cyclic AMP. And cyclic AMP, in turn, can do a number of things, including leading to the phosphorylation of proteins.

The phosphorylated proteins, in turn, can act on the inflammatory process, and specifically can inhibit the release of inflammatory mediators that are relevant to COPD in general and its exacerbations, it's believed. And they act on the cells that are most important in the COPD process -- that's neutrophils, eosinophils, monocytes, and lymphocytes.

Now, the phosphodiesterases are a class of enzymes. There's 11 major families, and they -- one of which is the phosphodiesterase-4 class, which includes four members. The phosphodiesterase-4s catalyze the breakdown of cyclic AMP into its inactive metabolite, AMP. Phosphodiesterase-4 inhibitors, like

roflumilast and its N-oxide, inhibit the activity of phosphodiesterase-4. As a result, there's less breakdown of cyclic AMP. The higher levels of cyclic AMP lead to increasing levels of regulatory molecules that down-regulate inflammation, and so phosphodiesterase-4 inhibitors can have an anti-inflammatory effect.

Now, when taken orally, roflumilast is readily absorbed. This slide shows the pharmacokinetics from steady state after the administration of an oral dose of roflumilast. Roflumilast, as you can see, is absorbed relatively quickly in the light blue line. It's then cleared with a half-life of about 17 hours.

Now, roflumilast is metabolized to its N-oxide, which is active and has a much slower clearance, about 30 hours, as you can see in the graphic. As a result, the majority of the exposure to active compound is to the N-oxide. The combined pharmacokinetics with these half-lives makes roflumilast, administered orally, appropriate for once-daily dosing.

Now, a large body of clinical evidence suggests that there's no clinically meaningful drug-drug interactions with a large number of other drugs that patients with COPD are likely to take. Rifampicin, however, which is a known inducer of CYP3A4, which is known to increase the clearance of a number of other drugs, also increases the clearance of roflumilast by about 80 percent. This will result in lower exposures to roflumilast, and while it's not believed that this will contribute to any toxicities, it may have an effect on efficacy.

Now, both cilomilast and theophylline have been mentioned, and it's important to note that roflumilast differs from both roflumilast [sic] and cilomilast -- roflumilast differs from both cilomilast and theophylline. Roflumilast is a highly selective phosphodiesterase-4 inhibitor, but it inhibits all four members of the phosphodiesterase-4 class, A, B, C, and D, equally.

In contrast, cilomilast, which also is a PDE-4 selective inhibitor, is relatively selective for the PDE-4D subtype. And the 4D subtype is believed to

be the major subtype that contributes to the adverse effect of nausea, which may account for more nausea with cilomilast than with roflumilast.

Now, there's more differences between roflumilast and theophylline. Theophylline is a nonselective phosphodiesterase inhibitor, inhibiting not only phosphodiesterase-4, but other phosphodiesterase families. And, in addition, theophylline has actions on a number of other important biological pathways, and, in fact, it's thought that theophylline's actions on these other pathways contribute both to its potential medical benefits and, importantly, to its toxicities, in particular seizures and arrhythmias.

In addition, roflumilast differs, at least in the available clinical data, from both cilomilast and theophylline, as we'll see, in that roflumilast has a consistent effect in reducing exacerbations of COPD.

So to summarize about the pharmacology, this introduction to the pharmacology of roflumilast, it's an anti-inflammatory agent that's appropriate for oral

dosing. Its clinical pharmacokinetic profile suggests it's appropriate for once-daily dosing. And there are no important drug-drug interactions that are believed to be of clinical significance.

With that, I'd like to introduce my colleague, Klaus Rabe, who will present the dose finding and efficacy data.

DR. RABE: Good morning to all of you, members of the committee, colleagues. Thank you very much for giving me the opportunity to talk to this panel on the drug that we've heard about by Professor Rennard so eloquently, and to tell you something about the dose finding procedures and the efficacy of the drug related to the clinical trials.

I'm Klaus Rabe. I'm the Chairman of Medicine of the University of Leiden in the Netherlands. I'm acting here as a consultant to the company, which I have been compensated for. I hold no stocks or equity in the company, and I was not offered any form of incentives in terms of the outcome of this meeting. I guess the only incentive that I have as a longstanding investigator who contributed to many of

those clinical trials and did basic research is a 20-year longstanding interest in the class of drugs and to understand its biology, the pharmacology, and probably its clinical efficacy and utility.

Now, if I may have the first slide on this -- and I can sort of forward this on here, I'm sure -- let me allow you [sic] to take you a little bit through the history of the clinical program as it has been alluded to by the FDA and Dr. Chowdhury in his very good introductory comments and remarks.

The program has been developed -- and it has been something that's been conducted over more than 10 years, with different ownerships, under different ramifications and different interests, if I may say so. Based on a large body of evidence from Phase 1 and Phase 2 trials, that is, in vivo and in vitro experimentation with phosphodiesterases to understand the role of cyclic AMP in modulating inflammatory responses, people have thought, and I share this view, that this is a worthwhile pathway to actually elaborate, to actually understand whether you can modulate inflammatory responses in the lung.

From this, there were trials being conducted. And one of the first trials that I was involved in, and it's probably irrelevant for the dose finding, is the trial so-called 107, which was conducted in a large group of individuals, and it was looking at different endpoints. It was a randomized controlled trial over 24 weeks. After a single-blind placebo baseline four-week period, people were randomized to either 250 micrograms or 500 micrograms of roflumilast compared to placebo. And it included individuals with moderate and severe COPD only, without any format for the clinical labeling on them.

Now, the endpoints were post-bronchodilator FEV1, and it was quite clear from the study published as early as 2005 already that there was a dose ordering between 250 and 500 micrograms in terms of a mean FEV1 measured post-bronchodilator favoring roflumilast 500 micrograms clearly over the dose of 250 micrograms.

Looking at exacerbations -- and these are the summary of mild, moderate, and severe exacerbations in this trial -- and looking at the

frequency of it, it was quite clear that compared to placebo, there was a significant reduction of the frequency of exacerbation, again, favoring the 500-microgram dose over the 250, with a statistically significant difference between the two doses that led, in terms of efficacy parameters, to the logical conclusion that this would probably be the appropriate dose.

In comparison to that, looking at the side effects, the roflumilast, again, 250 and 500 micrograms, it was quite clear that you were beginning to see a steeper part of the dose-response curve of side effects with slightly more side effects occurring in the 500-microgram dose over the 250.

So weighing clinical efficacy and safety, it seemed to be a logical choice, in this large trial of 1,400 individuals, to go for the dose of 250 micrograms because there was an observed dose-response relationship for FEV1 and exacerbation, and there was the aspects of safety and tolerability that led to that conclusion, as I showed you.

Now, this was done in COPD patients with

moderate or severe disease. Now, moderately severe or severe in COPD terms clinically is related to lung function impairment, which probably is just a partial reflection of real severity of the disease. But at that point in time, this was rendered and believed to be the right population.

Now, after the dose selection trials, people went ahead and said, "Listen, what can we do in terms of clinical efficacy? What about clinical efficacy trials?" And there are the two clinical trials that have been alluded to earlier -- it's Trial 111 and 112 -- that I will talk to in the next couple of minutes.

These trials were after the dose-finding trials, conducted later, 52-week randomized double-blind trials. They also included a large group of individuals in both of them. They were conducted also in severe to very severe COPD. But they were not sort of classifying these individuals as either having chronic bronchitis and/or emphysema.

They were COPD in general, general to be related as being severe by virtue of the fact that,

first of all, the FEV1 was less than 50 percent predicted and a decreased ratio. But the primary endpoints for both of these studies were pre-bronchodilator and post-bronchodilator FEV1 and the rate of moderate to the exacerbations, and the concomitant medications that were allowed in these trials were, for example, inhaled corticosteroids, short-acting bronchodilator, but not long-acting bronchodilator drugs.

Now, if you look at those trials again that were conducted as the first trials for clinical efficacy, and if you want a nonselective COPD population of a particular disease, something was striking.

Striking was that there was a very constant finding of improvement of lung function that was very much comparable to the earlier trials on dose-finding, or the 500-microgram dose, in the range between 40 and 60 ml. These are mean data, obviously, and there's a pattern of distribution. But that was a constant finding that was clear from smaller studies, the dose-finding studies, and this program already.

The next thing that was obvious was the fact that there was a reduction of the exacerbation in this non-further-specified group of 14 at 50.2. But although it was sitting, if you want, on the right side of this equation, you can see that the confidence interval crossed the line of identity, and there was a nonsignificant effect on that.

In further analysis, trying to understand that set of data in these large trials, we've been looking at other factors that may have contributed to the efficacy of the drug in this population. And something was very striking.

First of all, in those individuals that were using concomitant inhaled corticosteroids, there was a significant effect from the drug. We interpreted at that time the use of inhaled steroids to have some form of severity of the disease. A doctor had decided to treat this individual with steroids beforehand.

Secondly, it was individuals with bronchitis, the sign or symptoms of bronchitis, where this effect, reduction of exacerbation, was much more striking than in the overall population.

The third point is -- I think it's very relevant -- that those individuals that have emphysema only, people that did not have chronic bronchitis, there was hardly any effect.

So it was quite clear that there was a subgroup of individuals in the group of severe people with COPD that would respond better or more favorably to the other populations, if you look at them in general. So there was, if you want, a learning curve in that program.

The learning curve was related to hypothesis generation, early studies to actually understand the clinical phenotype that you would be looking for, and generate the hypothesis that you should have confirmatory so-called pivotal trials that looked at the right target population, the right clinical assignment and assessment to actually test the efficacy of the drug, and that was people with COPD that was associated with chronic bronchitis, as listed here, and having the risk of exacerbations.

That led to what we call the pivotal studies. May I just have a little bit of water, if I

may? I do apologize.

Now, this led to the pivotal trials. And the pivotal trials are the trials that are the basis of the submission, and what we are really talking about today. The pivotal trials were very simple. They were one-year trials, done in replicate over 52 weeks, and they compared the dose of 500 micrograms -- I gave the rationale for that -- with placebo, and looked at the same group of individuals in terms of severity.

But people were included when they were severe to very severe by lung function impairment, but they had to have signs and symptoms of chronic bronchitis. That meant chronic productive cough for three months in each of the prior two years, something that is very clinically easily recognizable, and they have had to have an exacerbation history. They had to have had exacerbation in the past, as clinically, if you want, a sign of lack of control or something that is a clinically relevant phenotype, if you want, in conjunction with an impairment of airflow and lung function impairment, as being shown here.

The co-primary endpoints of these pivotal trials were pre-bronchodilator FEV1, and the rate of moderate or severe exacerbations.

Now, the discussion of how and of the best way to define an exacerbation has accompanied the literature and pulmonologists for years. And there is a difficulty in defining an overall acceptable way of doing this.

The way that it was chosen and the definition was chosen as a COPD exacerbation in these trials is an event in the natural course of the disease characterized by change in the patient's symptoms, as referred to by Professor Rennard, that warrant change in management. And that is based, in fact, on the consensus of ATS and ERS. It's something that GOLD has proposed and that was a position by consensus statement that was published in CHEST some years ago by Professor Rodriquez-Roisin.

Important to note that the definition for these trials of a moderate and severe exacerbation is related to the intervention that's been chosen. That means a moderate exacerbation is then an exacerbation

that required the use of a parenteral corticosteroid. So that's something which is not only symptom-driven, that really requires action of a doctor to do something, to treat someone with a steroid. And a severe one is an exacerbation that is associated with hospitalization or death; just for the definition of terms because it comes back during the day, and I think it's important for the discussion that we have.

Now, pivotal Trials 124, 125, what were the demographics and the baseline characteristics? The trials were conducted in individuals that were remarkably well-matched for their age and their gender. They were heavy smokers, with pack-years around sort of 50 pack-years, which is a lot, even in pulmonologist terms. They had a normal body mass index, and the ethnic origin was a little bit favoring, obviously, white individuals from ethnic origin.

Now, if you look at the baseline lung function, and I think it's important for you to appreciate, we are looking at individuals that had a pre-bronchodilator FEV1 of around 1 liter. This is

low. These are individuals that could characterize as having severe and very severe COPD. In fact, two-thirds of the individuals in these pivotal trials could be regarded and were regarded as having severe COPD, a third of them having very severe COPD.

The reversibility of these individuals was very limited. That is part of the definition of the disease, but it's also part of the description of the patient population that you're, in fact, looking at. These are diseased individuals.

The concomitant treatment with long-acting beta agonists consequently was very frequent, that is, a lot of individuals who had been and were concomitantly treated with long-acting beta agonists or short-acting anticholinergics, and they all needed rescue medication, obviously because they were chronically symptomatic. That's a reflection of the severity and top of the lung function impairment.

Now, the data. Again, in these trials that now looked at very severe individuals, categorized and, if you want, specified for the phenotype of those with chronic bronchitis and a history of exacerbation,

the same change in lung function occurred. It was a significant and highly significant change in lung function between 40 and 60 ml. It's debatable, and we can discuss this, whether someone with a liter lung function would benefit from 50 mls, lung function improvement; I would think, yes, he does.

I would sort of suggest that the improvement of lung function is more, however, a sign of overall efficacy of the drug, a drug that, as has been alluded to, is not a bronchodilator, per se, by the way it acts, but it will afford lung function improvement continuously in all these trials, also in these severe individuals. But most strikingly, these effects on lung function improvement are very well sustained.

If you look over the whole period of time over the whole 52 weeks in Trial 124 and 125, you see that this is something that is very continuously reappearing in all the clinical trials, and is sustained over time without any sign or symptoms of developing of tolerance, which is not very likely because there's no receptor involved. It's something that acts very differently in terms of elevated cAMP

levels. So it's something which is consistent and something that is very sustained if you look at lung function improvement.

Turning now to the exacerbations, and that is only looking at moderate or severe exacerbations, exacerbations that actually required the use of a steroid and/or hospitalization and/or death. And you looked at those individuals now and you looked at the efficacy of the drug in the population that was prespecified to have that clinical phenotype, here you see that there is a significant reduction of 15 and 18.5 percent in exacerbation in these individuals.

That meant, for someone like me as a researcher, it was an hypothesis-driven approach to look at the right target population. And bang on, you sort of hit the primary endpoint because now you see, in fact, a significant reduction in exacerbation in both these trials. That means that these trials hit their administered and their agreed primary endpoints, which, in the COPD literature over the last couple of years, has not been the rule rather than the exception, that big trials hit their primary

endpoints. These two trials did.

Now, if you look at exacerbation frequency, there's some other way of looking at the effect of these compounds in terms of what they do to exacerbation, and that is looking at the time to first exacerbation -- again, moderate to severe -- in both of these trials. In both trials, the occurrence of the first exacerbation was delayed from 244 to 309 days or 232 days to 295, respectively, meaning that the first exacerbation would occur 60 days later than you will actually sort of be looking for as if you're not having been given the drug.

Since you're looking for a small event -- that's only the first exacerbation -- it did not quite reach statistical significance in that. But if you look at the analysis of looking, for example, for the second exacerbation to occur in these individuals that are at risk of exacerbation, you see the same trend. There's a significant delay on the onset for the second exacerbation in the duration of the trial. And now, if you look at these events, they become statistically significant.

In fact, if you look at all the exacerbations, from first to second to third to fourth to fifth, with the first or second being a prespecified analysis, you realize there is a decreased risk ratio and hazard ratio for any of these events to occur, again, saying that this is a very continuous effect, not only sustained in bronchodilation, but it is continuously occurring on the exacerbation frequency and the delay of frequency in frequent exacerbations over time.

Now, having sort of discussed the pivotal studies and the basis of why we came to this, the discussion really was, in the program, how would you and how could you use this drug in context of other medications? And this is where Study 127 and 128 come to the discussion. They are, if you want, supplementary and supporting information that could serve for the discussion where and how we should be using these drugs in the first place.

Now, these trials were again conducted in a double-blind, randomized fashion. They compared the use of 500 micrograms roflumilast now on top of other

medications; on top of, A, a long-acting bronchodilator, salmeterol, in the dose of 50 micrograms; or, on top of a long-acting antimuscarinic drug, tiotropium, on 18 micrograms daily dose. And they compared this drug versus a placebo arm with the respective bronchodilators in these large trials.

Again, the trial was conducted in moderate to severe COPD individuals, although they were slightly milder in their lung function impairment. So you have now individuals with an FEV1 predicted from 40 to 70 percent. They did not have any other co-medications such as inhaled steroids, short-acting antimuscarinics, or theophylline. And they were added onto salmeterol or tiotropium in maintenance.

Now, for one of the trials, there was a requirement to have had chronic bronchitis, and another one that they had to have frequent use of short-acting beta agonists to characterize this group. Now, the patient population again is very similar to the pivotal trial that I showed you, 65-plus years, majority of men, heavy smokers again.

You can see, in 1 through 8, 100 percent of individuals had the signs and symptoms of chronic bronchitis, and a large majority had this in the salmeterol trials. The use of a rescue medication was higher in the tiotropium trial than the salmeterol trial. Otherwise, these trials and these populations were frequently and reasonably matched.

As I told you, they were slightly milder in the lung function impairment. Now we're not talking about 1 liter; we're talking about 1.4, 1.5 liter, still making this a group that is moderately to severe. Two-thirds of these individuals were moderate, one-third of them were severe, and they had a very poor reversibility. That's something that is probably worth noting. A reversibility of 5 to 6 percent is low in clinical terms.

Here you come to the results. Lung function. Again, the next trial that looked at post-bronchodilator -- in this case pre-bronchodilator FEV1, sorry, excuse me -- looking at roflumilast over placebo in the trial, compared this to salmeterol or to tiotropium, the same lung function improvement

occurred.

It's the same magnitude that you've seen in the dose-finding trial, in fact, and in the pivotal trial, making it quite obvious that the duration and the efficacy and the mode of action of the drug is very independent from the bronchodilator part of that, that you afford this lung function improvement very continuously on top of other drugs that will act differently in pharmacology on bronchomotor tone directly.

So it is improvement that you see that is 50 to 80 mls that is in this patient population, probably and most likely related to patient-related outcomes, and shows the continuity and the consistency of the findings during the same program.

These trials were not primarily targeted to look at exacerbations. They are too short. They are not big enough. Yet, there was a prespecified analysis to look at moderate or severe COPD exacerbations in this population.

What you see, again, is that there is a trend, and it's, in fact, more than a trend in the

post hoc analysis of 127 -- that's the salmeterol trial -- on reduction of exacerbation also in this population. So the efficacy on top of other bronchodilators is accompanied by a reassuring signal in this relatively short duration of trials, an exacerbation signal, as well.

So what this leads to, in summary, and if I look at the program, that's what I'm trying to tell you in terms of efficacy and comparing this to other programs -- and I've seen the cilomilast program, as well, obviously because I was involved in this, as well -- it's something which I find strikingly consistent, that there is a pre-bronchodilator FEV1 change in all the studies that you have, with 124/125 being the pivotal trials that will be discussed. But it supported by a body of evidence that this is the sort of lung function improvement that you get in individuals, fully reversible, in individuals with severe disease, irrespective of co-medication.

The second point is, and the most challenging one was, at the time when these trials were conducted and it was -- the advice of people like

me was sought, what should you do for patient-related outcomes, we wanted exacerbation to be in. We thought this was the hardest sort of target to get. The advice was, if you don't get it on exacerbation, probably you won't get it at all.

So basically, if you look at the pivotal trials, these trials are significant in their change. And they are also supported by, first of all, trials in nonselected populations and in those trials that looked at concomitant bronchodilators.

But what we're looking at here is a significant effect in exacerbation frequency in the pivotal trials, and they are different -- and I wanted to make this point again -- they're different from 111/112, because although they studied the same sort of severity, they looked at a different patient population, which is the basis of the claimed indication, which I think probably, in my humble opinion, makes sense, based on the data that I see.

Now, if you look at the summary of the clinical efficacy, the conclusion would be that this clinical program so far is extensive. It comprises

5,700 patients on the target dose of 500 micrograms. The results for the reduction of exacerbation, and particularly, also, the improvement of lung function as a measure of overall efficacy, is remarkably consistent. There's not a single trial that doesn't hit that sort of mark, which is probably very different from other programs that I personally have seen.

The pivotal trials, the ones that are the basis of the discussion here, they show a statistically and clinically significant improvement in both primary endpoints that have been predefined and have been discussed with the agency as useful and relevant trials to be made, and that is FEV1 and exacerbation frequency and exacerbation rates.

The effects on FEV1 and exacerbation are, in fact, sustained, something that -- there's no tolerance development in terms of lung function improvement, and there is no sign of a waning effect on exacerbation frequency if you look at sensitivity analyses and you look at the time to first, second, third, or fourth exacerbation, something which is

probably worth discussing.

Secondly, the improvement on lung function is on top of other bronchodilator therapy, which I think for the clinical utility of a drug in that group, patient group, is relevant. It affords this effect on top of a long-acting beta agonist and on top of long-acting antimuscarinic drugs, and, post hoc analysis would show from earlier trials, on top of concomitant ICS medication. That is related to the mechanism of the drug that is novel, and it's something that sort of adds to the existing therapy.

The consistency of the demonstration in efficacy in these patient populations with risk of exacerbation and chronic bronchitis is the basis, I think, for the claim that's been laid down today. And I think it's something that is related to what I regard to be a sensible indication, based on the clinical data that I've seen and have been partly taking part in myself.

Thank you very much for your kind attention. It is now my pleasure to introduce Marco Taglietti, the Chief Medical Officer of Forest Laboratories, who

will address you, as the committee, in terms of safety issues for the program. Marco.

DR. TAGLIETTI: Thank you, Klaus. Gentlemen, members of the committee, FDA staff, good morning. My name is Marco Taglietti. I'm the Chief Medical Officer at Forest Laboratories.

My presentation -- I will give an overview of the safety. My presentation is divided into two parts. The first will be a general, high-level overview of the safety of roflumilast. The second will be more detailed discussions of specific events of interest.

The safety of roflumilast has been well-characterized in a very large safety database, over 24,000 patients in different indications, with over 14,000 with roflumilast. The focus of my presentation will be what we call the COPD safety pool, which includes 14 placebo-controlled trials in over 12,000 patients, with 6,000 patients treated with roflumilast 500 and roflumilast 250. In my presentation, if, on a slide, I use a different safety pool, I will point this out.

The COPD safety pool includes over 6,000 patients treated with roflumilast, but also, and this is very important, a significant, long-term exposure with roflumilast. There are over 1,200 patients treated for one year, and over 3,000 patient-years of exposure. The two treatment groups are very comparable in terms of demographics, concomitant medication, underlying disease, and COPD severity. This will allow us to make a meaningful assessment not only of the most frequent adverse events, but also the less frequent ones.

This is a list of the most frequently reported adverse events. The incidence of patients with at least one adverse event is about 5 percent higher with roflumilast 500 than with placebo, with about one-third of patients which actually did not report any adverse event at all.

The most common adverse event was a worsening of COPD, or COPD exacerbation, which, not unexpectedly, is higher in the placebo group. Diarrhea was the most common -- second most common event, but together with other GI tolerability events,

nausea and decreased appetite, was higher in the roflumilast group, about an incidence of 10 percent in terms of diarrhea.

Most of these events were mild to moderate. Over 90 percent of these events were mild to moderate. There were a few occasional cases of serious diarrhea, and I will discuss these cases when we will talk about the events of interest.

Weight decrease is also a symptom associated with the use of roflumilast, and it occurred more frequently with roflumilast. The same is true for neuropsychiatric events, headache, insomnia, and dizziness. And I will discuss about all these events with events of interest.

One last point I want to highlight in this slide is actually the frequency of infections. Information is an important group of adverse events in COPD because there are other treatments that have been shown to increase significantly the number of infections, specifically pneumonia, in this patient population.

As you can see, the numbers here with

regards to upper and lower respiratory infections -- including pneumonia, here at the bottom, for people who cannot read it, 2 percent versus 1.8 percent -- is similar, if not numerically lower in the roflumilast group. And the same is true when we look at the serious adverse events or death that were associated with infections. Based on these data, we believe that there is no evidence of an associated risk of infection with roflumilast.

The second important point is to look at how many of these overall events resulted in a discontinuation. The discontinuation rate was higher with roflumilast, but this difference of 5 percent in discontinuation between the two treatments was driven mostly by GI events, diarrhea and nausea. All other events -- rather, all other non-GI events, actually, the incidence of discontinuation were the same between the two treatments.

When we looked also at serious adverse events, and I'm talking about overall number of serious adverse events, the incidence between the two treatment groups was the same. The most common

serious adverse event was a COPD exacerbation -- again, it was higher in the placebo group -- followed by pneumonia, which was the same between the two treatment groups.

We observed an imbalance in terms in -- with higher frequency for roflumilast in atrial fibrillation. But the reverse was true for myocardial infarction, with higher incidence in the placebo group. And I will talk specifically about these cardiovascular events later with the events of interest when I will describe and discuss the CV profile of roflumilast.

With regards to deaths, there were a total of 170 deaths in the COPD safety pool between roflumilast 500 and the placebo. They were equally distributed between the two treatment groups. The most common adverse events associated with death -- and these adverse events may not be necessarily the cause of death -- the first one was COPD, followed by pneumonia. And again, pneumonia, there was no difference between the two treatment groups.

We saw an imbalance in terms of cardiac

arrest, a numerical imbalance. And again, I will discuss these specifically when I will talk about the cardiovascular safety of roflumilast in a few minutes.

So before we move now to the events of interest, let me just give a brief overview of what we have seen in terms of a high level. We didn't see any difference in overall number of serious adverse events, no difference in overall numbers of deaths, and the 5 percent difference that we saw in terms of discontinuation was driven mainly by GI events.

Now, let's move to events of interest, starting with diarrhea. We have 16 cases of diarrhea that met the definition of serious adverse events. Three cases occurred before start of treatment. So this means that there are some patients that will experience this type of serious diarrhea just naturally as part of their disease. The 13 cases were mostly -- 10 out of 13 -- in the roflumilast 500.

This is still a small fraction of the total number of diarrhea events that were observed in the study. As I mentioned before, the total number of diarrhea events was, in the vast majority of the

cases, mild to moderate.

When we focus specifically on these serious adverse events, these were not cases of -- intractable cases. These were cases where all of them recovered, and I think it's really noteworthy that 7 out of the 10 cases actually recovered without the patients discontinuing treatment, and the patients continued treatment without any problem after that.

Now, I don't want to minimize the importance of GI tolerability with roflumilast. GI events, diarrhea and nausea, are associated with the use of roflumilast. However, most of these events are mild to moderate. The few occasional cases that are serious were resolved by -- they resolved. The median time of resolution of these events was 11 days.

The point I want to make is that the amount -- this kind of GI tolerability is not uncommon with other drugs that are used for chronic use. And physicians will not be unfamiliar on how to manage this kind of tolerability.

I would like now to discuss the pancreatitis. There is no pre-clinical signal

suggesting that the pancreas is a target organ for roflumilast. And when we looked in our database, we had 16 cases of pancreatitis in the COPD safety pool. Two cases actually occurred before starting on treatment, again, suggesting that pancreatitis may be part of the natural history of these patients.

The 14 cases were equally distributed among the treatment. And when we look and we focus on the serious adverse events, there were six in placebo, six on roflumilast 500, and one on 250, again, well-balanced. All these cases, except two cases where the patients expired due to respiratory failure, were resolved. Actually, four of the six cases on roflumilast 500 resolved without the patients discontinuing the study, and the patients continued treatment thereafter without any further sequelae.

The two deaths occurred in patients, and in both -- in two patients, in both cases due to a worsening of their respiratory condition and due to respiratory failures. And we can discuss the details of these cases eventually in the QA section. But in any case, looking at the distribution of events, we

don't expect pancreatitis to be an increased risk for roflumilast.

Weight loss. Weight loss is an important event of interest for roflumilast. It has been associated with the use of roflumilast in early studies, and, therefore, in the later studies, weight was measured systemically. In my presentation, I will use the COPD pivotal studies, which is a subset of the COPD safety pool. It includes the two pivotal trials, and we selected these two pivotal trials because these are one-year duration and, therefore, allow a better characterization of the weight loss over one year time.

When you look at the effects in terms of weight loss, for the placebo, there was basically no effect at the end of the 12-month treatment, whereas we saw a change of about 3 percent, 2.7 percent, at the end of the 12 months. Most of the change occurred in the first six months, and thereafter, the rate of weight loss started to slow down.

Now, 3 percent, 2-3 percent change, average change over 12 months may not seem like a big change.

However, we were concerned that there may be patients especially sensitive, vulnerable, to this weight loss. And therefore, we did additional analysis to try to characterize not only the weight loss, but also to understand if there were patients that actually had a negative impact in terms of health.

So we looked at two important baseline characteristics, COPD severity and baseline body mass index. With regards to COPD severity, there is basically no difference between patients with moderate, severe, and very severe. Over 12 months, it's a difference of .7 percent, which corresponds to a difference of 300 grams over 12 months. So we didn't see an association between weight loss and different COPD severity.

On the other hand, with regards to BMI, we saw that patients, obese patients, so the heaviest patients, had the largest weight loss with roflumilast, close to 4 percent, compared to patients in other groups and patients, underweight patients, where there was a much smaller difference, 1.6 percent. Now, however, underweight patients is the

group of patients that needs the least a decrease, weight loss. Therefore, we have done additional analysis to check if patients, underweight patients, were having a different or a worse safety profile than the patients -- than other patients on placebo when they were taking roflumilast.

So this is the COPD pivotal pool, and these are actually the underweight patients, patients with a baseline, had a BMI less than 18.5. As you can see, the incidence of adverse events was slightly higher in the roflumilast 500 arm, but comparable to what we have seen for the general population. In terms of serious adverse events, it was the same between placebo and roflumilast. In terms of deaths, it was the name number of deaths and the same incidence, again, between roflumilast and placebo.

We looked also in a subset of patients, underweight patients, who had specifically weight loss. And again, there was no difference in terms of the adverse event profile between roflumilast and placebo.

We did many more analyses to try to

characterize this weight loss. And for the sake of time, I will just give a brief headline and we can discuss further, eventually, in the QA section.

A bioimpedance study showed that the weight decrease was mostly due, about two-thirds of it, to a loss of body fat. We looked again at adverse events and exacerbation analysis by weight loss, without showing a correlation between weight loss with this parameter. In a small group of patients who had weight loss as an adverse event, we followed them for three months and we see, in three months, a regain of some weight.

We looked also if there was a correlation between gastrointestinal adverse events and the weight loss. But for patients with gastrointestinal events, they have a slightly higher weight loss. This does not seem to explain the actual weight loss. So it doesn't seem to be that the weight loss is actually correlated to GI adverse events.

So what is our summary with regards to weight loss? It occurs more frequently with roflumilast, is associated with the use of

roflumilast. The largest weight loss occurs in obese patients, and is mainly due to a loss of fat mass. However, it occurs also in underweight patients. We have evidence of reversibility after treatment discontinuation. And when we did several types of analysis, we couldn't find an identifiable safety finding associated with this weight loss other than the weight loss itself.

So what is our recommendation? Our recommendation is that patients and physicians should be properly warned that weight loss is associated with the use of roflumilast, and the weight of the patients needs to be monitored regularly so appropriate action can be taken if it starts to have an impact on the health of the patients.

I would like now to move to neuropsychiatric events, which is also another important event of interest, as highlighted in the brief introduction from FDA.

In the roflumilast group, we had higher incidence of psychiatric disorders, neuropsychiatric disorders. The most common for psychiatric were

insomnia and anxiety and depression; for nervous system disorders, headache, dizziness, and tremor. However, this higher incidence of treatment-emergent adverse events did not result in a higher incidence of serious adverse events. The number of serious adverse events was actually the same between the two groups, both in terms of nervous system disorders and psychiatric disorders.

However, in the psychiatric disorder, we observed some cases of suicidality behaviors. And this is a very, very serious type of event, and we did a detailed analysis of these cases.

There is a total of six cases of suicidality behavior, five in the roflumilast group, one in placebo. This is a very small number. And given the complexity of assessing these cases, when the NDA was transferred to Forest, we asked Dr. Kelly Posner from Columbia University to perform a blinded C-CASA adjudication of these events.

C-CASA, the Columbia Classification Algorithm Suicide Assessment, is a well-established methodology that was commissioned by FDA and used by

FDA on several occasions because it helps to make sure that there are no other hidden cases of suicidality behavior in a safety database. It is a process that allows a good characterization, a good assessment, and classification of suicidality events.

Let me say that this adjudication was done after the NDA, and the agency didn't have a chance to review these findings. However, we felt that it was important to share this just to assure the committee that these are all the cases that we have in our safety database, and these are the cases we can now focus our attention.

We had two cases of suicide attempts in the roflumilast 500, one suicidal ideation in the placebo and three completed suicides, two on roflumilast 500 and one in roflumilast 250. So let me go through these cases because these are complex cases and with several confounding factors.

Starting with the completed suicides, the first case was an 80-year-old male who was in treatment for 17 weeks. No history of depression. However, the patient was taking Reserpine for blood

pressure control. This is a South African patient. And this drug is known to be associated with risk of suicidality.

There other two cases of completed suicides actually happened in patients that were discontinued from treatment 20 to 22 days after the last dose. So with a 30-hour half-life, as you have seen, by the time the suicide was completed, the drug was long gone. In addition, one of the patients reported depression at the end of a screening period as part of a EuroQol questionnaire that was part of the investigation. So these two cases occurred three weeks, about three weeks, after the last dose.

With regards to two attempted suicides, one patient had a history of depression and use of concomitant administration. The second patient with attempted suicide, history of depression and attempted suicide. The patients, interestingly, after the attempted suicide on-study, continued -- was not discontinued, and continued treatment with roflumilast 500 without further problem.

Finally, the suicidal ideation occurred in

the placebo group, was a 48-years woman with a history of depression and with multiple concomitant antidepressants. The patient was hospitalized for severe depression and for persistent suicidal ideations.

This is a small group of patients. It's a small sample size. There are six cases, one for placebo, five for roflumilast. And at this point, it's our opinion that it's impossible to conclude that there is an association between roflumilast and risk of suicidality. Now, the fact that there is an imbalance, of course, remains an area of concern that needs to be managed properly when the drug will be available.

So this is our conclusion with regards to neuropsychiatric events. There is a higher incidence of adverse events in the roflumilast group. Primarily, it's insomnia and anxiety. There is no difference in serious adverse events compared to placebo. There are five suicidal behaviors, including three completed suicides, with roflumilast versus one placebo. It's an event rate too low to draw a

conclusion at this time about the association.

Our recommendation is that patients and physicians should be informed that there has been observed a higher incidence of these events, including rare instances of suicidal behavior, and physicians should be alerted to be vigilant for any change in neuropsychiatric events. And this was the purpose of the warning that we added in our labeling, proposed labeling, in January in order to make sure that the patients were properly alerted.

Let me now move to tumorigenicity. With regards to pre-clinical findings, there were two studies, two two-year studies, one in mice that did not show any drug-related tumors, and one in hamsters that showed selected nasal -- tumors in the nasal mucosa. However, this tumor in the nasal mucosa is a rodent-specific mechanism due to the fact that these rodents have a special enzyme that humans don't have that can convert ADCP N-oxide into a reactive metabolite.

The precursor of this reactive metabolite is present also in humans, but the level in humans are

hundreds of times lower than the level that are present in animals when no other tumors are observed. So based on these data, the pre-clinical data do not appear to be relevant in terms of assessing carcinogenic risk.

So we looked at our database in terms of tumor events. There is a total of 208 patients in our total safety database with tumors. If you take out one subject, which was in Phase 1 and one patient who was an active control, there are a total of 206 cases, patients with tumors, 80 on placebo, 126 on roflumilast.

Although there is an absolute higher number of cases with roflumilast, when you compute the incidence using the sample size of the safety pool from which these cases were coming, there is no difference between placebo and roflumilast. We also break out this group in the three safety pools, and, again, we showed comparable incidence between the two levels. Asthma was lower than the others, and this is not unexpected because these are healthier, younger patients with lower risk. If roflumilast were a

carcinogenic, we would expect higher incidence, probably, in this group, too.

So let me now focus on the COPD safety pool, where we observed a total of 170 events. The incidence was small in both groups, actually quite comparable to what you expect in this type of patient population. And the most common cancers were lung cancer, observed in 17 patients on placebo, 31 on roflumilast 500 -- again, a small difference, .3 versus .5 percent -- and prostate cancer. And these are the incidence adjusted by gender. All other cancers, they were similar.

Now, we noticed the difference between placebo and roflumilast. Although small, we investigated this difference better to understand where these cancers were coming from. And what we found out is that there was a higher distribution of some tumors in the roflumilast group in the first few months of treatment.

Now, even if a drug is carcinogenic, you don't expect an effect in the first four to six months. However, if you look, for example, at lung

cancer, we observed 22 lung cancers in roflumilast versus six in placebo in the first six months. Beyond six months, they were the same between the two treatment groups. And the incidence we saw, in general, was comparable to what we see in the COPD population. And this pattern of earlier events was observed with other types of solid tumors, again, suggesting that this may have been just a random finding.

So what are the conclusions? It's that there is further work to tumorigenicity, not relevant, but a clinical carcinogenicity signal. There is a similar incidence in the total safety database. When we looked at the COPD, there were tumors, mostly solid, reported early in study for roflumilast, and this is not biologically plausible in terms of all the carcinogenic effects. So our conclusion is that based on this data, there is no evidence of an increased risk of tumors.

Finally, let me talk about the cardiovascular assessment, which is very important considering that there is a certain amount of

underlying cardiovascular disease in these patients. We made a significant, comprehensive program to assess the arrhythmogenic potential of the drug. We didn't see any signal in terms of pre-clinical, in terms of total QTc, in terms of ECG, in our clinical trials or the other monitoring that we did in a subgroup of patients, suggesting that roflumilast does not have an arrhythmogenic potential. However, as I mentioned before, although we didn't see any difference between cardiovascular in terms of overall cardiovascular event between roflumilast and placebo, there were some specific terms in which there was an imbalance. Atrial fibrillation was one, and cardiac arrest was the other one. So what we did was we implemented a blinded adjudication of all the cases of deaths to ensure that these events were not causing some kind of negative effect on the cardiovascular outcomes.

This adjudication was done by a blinded panel of three independent experts, chaired by Dr. William White, who is with us today to answer your questions. This process was done in parallel with the clinical program to ensure that all the deaths were

actually assessed with the same procedures. The fatal events were located in three categories, cardiovascular, non-cardiovascular, and insufficient data. And these are the results.

In terms of cardiovascular, incidence of cardiovascular deaths, this was the same between placebo and roflumilast, actually slightly numerically lower in the roflumilast arm. The largest reason, the most common reason of death was sudden death, which is the same between the groups, slightly lower in the roflumilast arm.

This finding, together with the very small number of deaths due to stroke, suggests that the atrial fibrillation was not resulting in a negative cardiovascular outcome. Moreover, the cardiac arrest was more due to the fact of the way sudden death was actually reported by investigators in different studies in different countries. They were reporting sudden death. So based on this, we don't believe that there is evidence to suggest that there is an increased risk of cardiovascular events.

So our conclusion: The safety profile of

roflumilast has been well-characterized in a large database, and there are three areas that need to be managed.

The first one is GI tolerability. Diarrhea and nausea are more common with roflumilast, associated with the treatment. They are mostly mild to moderate, reversible, and when there seems to be the few occasional serious cases, they recover with no relevant sequelae. But patients need to be informed about this.

The second area is weight loss, which is associated with the use of roflumilast. It has been mostly mild to moderate, more in obese than in underweight. It occurs, however, also in underweight. But there was no clear associated outcome, negative outcome, in terms of a safety profile with the weight loss. We recommend weight monitoring in patients.

Finally, neuropsychiatric events. There is higher reporting rates, including rare events, of suicidal behavior with roflumilast compared to placebo. Physicians and patients should be alert and warned about this, and they need to be vigilant for

changes in neuropsychiatric events. This has been managed with other products properly, with a certain amount of tools that can manage the risk.

Finally, we didn't see any evidence of increased risk for cardiac events, pancreatitis, tumors, and infections.

I would like just to finish saying that Forest is committed to patient safety. And of course, we are looking forward to implement additional appropriate risk management activities to further make sure that the drug would be used safely by the patients. Thank you.

Now, it is my pleasure to introduce Dr. James Donohue.

DR. DONOHUE: Thank you, Marco. And thank you for the opportunity, Mr. Chairman, members of the FDA, members from industry. I'm here as a consultant to Forest Labs and Nycomed. I've been a study investigator in the past and have received compensation from the company. I have no equity, no stock, and I'm not a member of a company speakers bureau. I have no incentives.

For fair balance, I've also twice now been an ad hoc reviewer for the FDA in the area of orphan drugs, where we award grants to diseases that affect less than 200,000 of our citizens. And I received a stipend also from the FDA for that.

I'm here today on behalf of -- as a clinician. I was asked by the company, the sponsor, to give my perspective and how we would use this medication in our pulmonary practices. And I've been a chest physician for many, many years, and an investigator, and, more recently, I do a lot of data safety monitoring of large trials.

In my clinical practice, both at the university -- I see a lot of very severe stage 3 and stage 4. But I also have assumed a practice in one of the small towns in North Carolina, a pulmonary practice, where we take care of -- my division takes care of, and myself, retired workers and members of the armed forces who are now retired.

That opportunity gives us a very, very wide spectrum of disease severity in many patients, particularly the military, who are still actively

smoking. So that'll give us some -- I think it helps to bring my perspective to the risk-benefit decision.

First of all, from the guidance from the agency, we know, as we've heard from Steve Rennard, there's a pressing need to develop new drugs. COPD, this is the year of COPD, the year of the lung. We have really a number of major efforts in the United States really attacking this disease and trying to increase awareness, increasing screening for it, and developing guidelines for practitioners to help us identify cases of COPD.

But as the guidance from the FDA shows, there's a need for really new medications. A lot of the drugs that we have or run on asthma platform or are bronchodilator class. The prevalence is increasing. So there's a lot of unmet need, and anyone just has to spend a day in clinic with patients to see how many of our patients still are symptomatic, despite even triple therapy or even extensive nebulizer therapy and what have you. So there is a need for our patients to have other options in terms of their treatment of their condition.

There are a number of issues, important issues, raised by the division, Dr. Chowdhury this morning. And again, these we'll be deliberating all day long.

The first would be the relevance of the magnitude of the changes in lung function and numbers bandied about with the FDA and many people in the room here. We had a conference on -- a supplement to the general on COPD -- on minimal clinical important differences. And most of those come from bronchodilator studies, but they tend to be higher.

But here the relevance of these changes must be interpreted in the population that was studied; first of all, the level of their lung function, their degree of reversibility. If they're on concomitant medications, that'll diminish the effect size of the intervention of the drug. And so those are all changes.

Furthermore, we'd be interested -- all these changes went in the same direction in these pivotal studies. And Dr. Chowdhury mentions other PDE-4 inhibitors. That was not the case. There were

inconsistencies in the direction of the lung function changes. But they support the changes in the exacerbations that we saw.

The changes, as Dr. Klaus Rabe mentioned, are consistent, and they persist over the -- they're sustained over the course of the one-year studies. There certainly is no tolerance. There seemed to be no loss of efficacy in either of the two effects, on lung function and exacerbations.

Now, is this relevant to the population of patients that all of us doctors in the room will be seeing? And that's yes. About 80 percent of our patients, it is estimated by the American Lung Association, have features of chronic bronchitis. And the bronchitis, of course, predisposes to frequent exacerbation, and Dr. Rennard took us through a lot of those kinds of mechanisms. So we think the population of patients that we see were reflected in the pivotal studies, and it can be very helpful to inform our decisions as doctors taking care of patients.

We've heard a great deal today about the definition of exacerbations. Primarily, most of the

studies now are driven by outcomes based on health care utilization. Even in asthma, we use oral corticosteroids as the exacerbation, one of the ways of judging exacerbations in asthma. So certainly the definitions of moderate, severe, and severe exacerbations are pretty standard.

Now, I did a literature search here, and as opposed to some of the studies, the pivotal studies for exacerbations in America, namely, the Advair 250/50, they were not placebo-controlled, of course. They had an active comparator, salmeterol.

If we look at the placebo controls, just as for points of discussion -- and you have seen these studies already today -- first, we wanted to look at the change in FEV1 from baseline. And TORCH, of course, is a non-approved Seretide or Advair 500/50, not approved in the United States. And these are the changes in the monotherapy arms and the fixed drug combinations; similarly, in TRISTAN; and, then in UPLIFT and the VA trials.

Then when we look at the effects on exacerbations in these trials, we see the effects

here, minus 18, 15, but then 25, as we saw earlier, 25 for the fixed drug, 14, and 19 in the tiotropium, which was approved for the indication of exacerbations in COPD most recently.

When we add the effects of roflumilast onto the slide -- and these are the one-year pivotal studies, and these are the six-months -- these are the changes that one sees in the lung function, as Dr. Rabe mentioned, a pre-dose FEV1. The split line here, these are six-month studies. So these changes in lung function would really come under more of the additive effects of the drug on top of salmeterol and tiotropium.

So we wouldn't look at monotherapy against placebo. You have to look at the magnitudes of these changes a little bit differently. But they are, to me, fairly substantive and support, more importantly, in the one-year studies, the exacerbation. And as we all know, exacerbations are really -- we had the wording Steve showed from the EXACT-PRO, what the impact of these events are on our patients' lives.

Our patients really dread having COPD

exacerbations. Half of them aren't even reported because the patients get so tired they can't get out of bed. And so anything we can do as doctors to reduce the frequencies of these events really has some very, I think, important impact on the lives of the patients who suffer with this disease.

So, again, these changes, hopefully, you'll find are meaningful and in line with changes that we have seen in other medications, including some that have been approved.

So how do we balance the risks and benefits? And the risk, of course, no one in the room ever wants to do any kind of harm. And that's always one of the great concerns that we have as physicians treating patients.

So the benefits we've heard in the presentations from the doctors ahead of me, the target population who would be benefitting these medications have been identified, as Dr. Rabe shows. Namely, these are folks with chronic bronchitis who have exacerbations, and that is a very large number of patients that we see, we'll see in our practices.

In this program, there has been, to me, very impressive, consistent efficacy in reducing exacerbations and improving lung function, which has been across all the studies. And we didn't see that with some of the PDE-4 drugs that we've studied over the years.

We have a nice additive factor here. Where would be use this medicine? If we follow the GOLD guidelines, we would use a long-acting inhaled bronchodilator as first-line therapy. Then we have the option of perhaps adding this kind of an agent, and PDE-4 inhibitor; or we could go to a fixed-drug combination of ICS LABA. Some patients have side effects with that combination and may prefer a nonsteroid option.

Again, the steroids have been approved in combination, fixed-drug combination, in COPD, for Advair 250/50. Occasionally, a patient will have pneumonia. That safety signal has been identified. There are local side effects that might be relevant to some of the population. So we'd like to have another anti-inflammatory medication.

Lastly, something that I've been very, very concerned about is making the regimens simple for our patients. A lot of our folks are blue-collar folks that aren't as well-educated as all of us in the room here are today. And working with the American College of Physicians, we designed picture books, for example, for the lower literacy patients and what have you. A simple regimen is extremely effective and will support compliance.

So if we use a once-a-day bronchodilator, for example, with a medication, that could be a very simple program to implement, and you could do it effectively in your office. You wouldn't have to spend a great deal of time training on multiple different inhaler devices.

Now, most importantly, what are the risks and how do they stack up against the other medicines that we use in our practices? We've heard that the adverse event rates, from Dr. Taglietti, are similar to other commonly prescribed drugs for chronic use. Most adverse events, of course, as we heard, have been mild to moderate in intensity.

Now, what about weight loss? And as chest physicians, we use often composite indexes when we evaluate our patients, like, for example, the BODE index. And the B in that index is body mass index. And we actually, in the University of North Carolina, include that as a vital sign in our clinics.

Again, patients who are very cachectic, we know, have weakened respiratory muscles. So we have to be concerned, and, as Dr. Taglietti said, we have to monitor weight loss. We might be cautious in prescribing it for someone -- I don't want to pick a dichotomous point, but let's say 18.5 or something like that, which would be -- I would have to look very carefully. Is that patient losing weight? What are the reasons? So we would be careful about that.

Now, the one that concerned the agency was the imbalance in the suicidality. And this would be a great concern to all of us who take care of patients with COPD because so many of our patients have so many losses and then get depression. And it's an integral part, in some patients, of the illness, not all.

Now, the depression can be managed. We

should look for it. If the patient is very stable, of course, it's a co-morbidity factor that you deal with. Recently, in terms of medications, we've dealt with -- the agency noted a chance of increased suicidality in one of the asthma drugs. It turns out that there really wasn't much to it, but we would inform the patient.

Most relevant, though, to the practice of a pulmonary doctor or chest doctor or an internist is the fact that a lot of our patients smoke. So we use pharmaceuticals for smoking cessation, and some of those have been associated, as you know, with suicidality. So how do you handle that in practice? And it's hard. Marco showed, I think, four of the six patients were depressed. There's always going to be one where it's the first event. And I don't think there's any practical way of identifying that one.

But the other patients, you look for signs of instability. You also bring the loved ones into the office, if you can, and many of our COPD patients will be accompanied by their wives or husbands or daughters or sons. And you try to at least make a

great effort, as Marco mentions, to inform the patient as to this, as to the possibility. And again, I think you can deal with it because we deal with it all the time in the smoking cessation drugs, and if there's a change in the patient's mood, that would be noted.

Furthermore, we give high doses of corticosteroids, which have profound psychological effects in some patients. And it's part of the warning of the patient that they'll have insomnia the first night on a big bolus of oral corticosteroids, and they'll get depressed as we lower the dose going forward.

So it's a concern, of course, but one that I think we can manage. And until further studies come in, I think that it would be analogous to what we do with smoking cessation medication.

So lastly, where would I use it in the regimen? I would be informed -- take the information from the pivotal studies, which is a very, very expansive and robust program, much larger than many of the other drugs that we have seen recently. So chronic bronchitic patients who have exacerbations,

who have mostly poor lung function. And then also where would it fit it? It might be, after you're following the guidelines, the initial addition of this agent to an inhaled, long-acting bronchodilator.

So thank you very much for the opportunity to discuss this, and I look forward to your deliberations. Thank you.

DR. CALHOUN: Okay. Thank you. We will now turn to the committee and see if there are questions of clarification for the sponsor. Just by way of order, if the committee members have questions, please raise your hand. Dr. Khuc will recognize you, and then we'll just take things in order.

I think the first hand I saw was Dr. Knoell. And then, Kristine, maybe you can track the rest. Dr. Knoell.

DR. KNOELL: Thank you. I have several questions, but I think for now I'm just going to stick with some of the more general thoughts that I have.

One is I am aware that you paid attention across, I believe, all the studies presented today in terms of patient satisfaction with treatment and

outcome, particularly the St. George questionnaire. And I would ask the sponsor to elaborate on that more for us, since there was none of that information shared with us thus far.

Then another question I have is given the fact that we focused more so through subsequent trials on patients with moderate to severe disease, I am making the assumption that most of these patients were probably fully integrated, to some extent, into a pulmonary rehabilitation program. And if so, were you able to look at secondary endpoints relative to how drug treatment may have enhanced or interfered with their ability to successfully participate in pulmonary rehab, with a particular focus on diet, which we've covered, as well as exercise. Thank you.

DR. ROWE: Paul Rowe, clinical development at Forest.

I'll address the first of your question by starting out that the SGRQ was utilized in the earlier Phase 3 studies. It was not included as an endpoint in our pivotal trials, M2-124 and M2-125. That said, we did have three trials that did utilize SGRQ in

those trials. As you know, the accepted difference in units for that tool is 4 units. And we had variable results in SGRQ, in the range of improvement of about .3 to almost 2 units.

To discuss the impact and the pertinence of the SGRQ changes, I'll ask Dr. Barnes to comment further.

DR. BARNES: I'm Neil Barnes. I'm Professor of Respiratory Medicine at Barts and The London NHS Trust. I've been paid an honorarium for being an advisor to Forest. I have no equity or shares. Neither do any of my family. I'm not on a speakers bureau, and I have no financial interest in the outcome of this meeting.

If I can have slide up, please. As has been said, the SGRQ has been used in a number of clinical trials of various COPD drugs, including in the earlier clinical trials of roflumilast. The trials did show a positive numeric effect of roflumilast on the SGRQ, although, as Dr. Rowe stated, this did not reach the 4 point minimally clinically important difference.

However, we need to set this into context.

May I have the next slide, please? Because this failure to hit the minimally clinically important difference has been seen in many other studies, where we, as clinicians, recognize significant symptomatic benefit.

So here, in the TRISTAN study, if you compare placebo with Advair, you miss the 4-point difference. The same here in the TORCH study. So you're not hitting the minimally clinically important difference, but you are getting a positive effect, and it's in the same range as other drugs.

I think the other thing to point out, though, is that during an exacerbation of COPD, there is a huge reduction in quality of life. And it's been shown in the East London cohort that it takes up to about six weeks for that reduction in quality of life to get back to close to baseline. And therefore, by preventing exacerbations, you are preventing that reduction in quality of life.

Lastly, I think that we have to look upon these drugs, maybe in the future, as like the statins of COPD. Statins reduce exacerbations of ischemic

heart disease, but they have very little impact on current symptoms.

DR. GOEHRING: Udo-Michael Goehring, clinical development, Nycomed.

I want to address the second part of your question that was dealing with the pulmonary rehabilitation. We have in all of our trials included an exclusion criteria of participation in a pulmonary rehabilitation program within three months prior to inclusion to exclude any confounding factors in all of our trials. So actually, your question if this has an impact on patients that are concurrently participating in a pulmonary rehab program cannot be answered with our clinical trial data.

DR. CALHOUN: Dr. Fink?

DR. FINK: Since we're dealing with a drug that has a risk-benefit ratio, in the exacerbation rates, what is the breakdown between the severe exacerbations requiring hospitalization and the more frequent exacerbations requiring oral steroid use?

Secondarily, was there any difference in side effect profile in those patients who had severe

exacerbations versus moderate?

DR. ROWE: Paul Rowe, Forest. To address this question, I'll ask Dr. Goehring to respond.

DR. GOEHRING: Udo-Michael Goehring, clinical development, Nycomed.

In addition to the primary variable, which was defined as the composite endpoint of moderate or severe exacerbations, we also looked at secondary outcomes to the exacerbation categorization that you have now addressed. So the first part of the question was to the exacerbations leading to hospitalizations.

Slide up, please.

So looking into the -- on this effect of the pooled clinical trial results, the severe exacerbation was reduced by roflumilast of 18 percent on the effect size. So the mean rate of exacerbations per patient per year, as it was also shown in other clinical trials in the same patient type, is lower than the composite endpoint.

Therefore, as this was not powered for this, the confidence interval was very broad. But important to note is that, also, these events leading to

hospitalization and/or death was reduced by roflumilast, an 18 percent reduction.

Coming to the next part of the question, which I thought was going into the oral steroid-treated exacerbations alone, which should be E-35, I think, we also looked into this separately. We can actually use E-32, if you want.

Slide up, E-32, please. This is a more busy slide.

But what I want to focus now is on the separated one, which is called the moderate outcome parameter, so the third part of this slide, where you can also see that in each individual trial, as well as the pooled, roflumilast reduced exacerbations that were just purely treated with oral steroids.

So in conclusion, we have analyzed, besides the primary variable, moderate or severe, a lot of categorizations in terms of exacerbation. In any case, the effect of roflumilast shows a very robust and clinically meaningful effect.

DR. CALHOUN: Dr. Honsinger?

DR. ROWE: To address the side effect

profile portion of the question, I'll ask Dr. Taglietti to respond.

DR. TAGLIETTI: Let me make sure I understand your question. Your question was to assess the adverse event profile for patients with severe exacerbation compared to moderate exacerbation. We don't have a slide, actually, right now to address your question. But we will try to provide this information by after the break.

DR. CALHOUN: Okay. We'll try again. Dr. Honsinger?

DR. HONSINGER: I had two series of questions. First, let me ask questions on the benefit of the drug.

I note that the benefit seems to persist throughout the use of the drug. My question is how much of a response? Is this an immediate response? How long does it take that benefit to disappear when the drug is stopped?

The second, we talked about the benefit from the drug from objective data. From subjective data, you did talk about the St. George questionnaire.

Is there any other subjective data, such as exercise data? Do these patients have a six-minute walk?

DR. ROWE: So to frame your question, you have two portions of your question. The first is with regards to the length of time it takes for the benefit to be seen in roflumilast for both FEV1 and exacerbations, as well as --

DR. HONSINGER: My question is how long does it take for the benefit to disappear when the drug is stopped.

DR. ROWE: So to answer this question, I'll ask Dr. Goehring to respond.

DR. GOEHRING: Just to reconfirm, I understand that your question is how long does it take that the efficacy part is stopped when roflumilast is stopped.

We have, in an early trial of this, which was not part of this presentation here, which was called the FK1-103 trial, we have had, in trial setting, where the patients were treated for the first part of the trial for 20 -- for 12 weeks with

roflumilast and then stopped in this treatment arm, where we can clearly see that in this part of the patients, the lung function effect immediately drops down.

Slide up, please.

We see in the upper part the post-bronchodilator FEV1 results that were, at this time point, assigned the primary variable of this trial, whereas in the lower part, the pre-bronchodilator FEV1 is shown. We see that the yellow curve is giving roflumilast 500 over the complete 24 weeks time period, whereas the gray curves always show the roflumilast withdrawal arm, then after 12 weeks, given randomized, in a blinded fashion, to placebo.

What you can clearly see is that already after one week, at least from a lung function perspective -- we have to clearly see that from a lung function perspective -- this effect then is dropping down again. However, also to mention this, which you, I think, nicely see in the white part, that it doesn't go to the baseline back.

DR. BARNES: Neil Barnes. You had a further

question about the SGRQ. I just wonder if you could clarify that.

DR. HONSINGER: No. My question is, were there other subjective data, such as a six-minute walk, as far as exercise tolerance in these patients?

DR. BARNES: The six-minute walk was not done in any of the pivotal trials. I'm not sure if there were some of the earlier trials where, in small, exploratory stuff, the six-minute walk was done. But it wasn't done in the big trials.

DR. ROWE: There was some data with -- exercise data done by a small study that showed beneficial effects with regard to six-minute walk. We don't have that data in a slide, but we can present you that data.

DR. CALHOUN: Dr. Joad?

DR. JOAD: Yes. I had a question for Dr. Rabe about the mechanism of action, where he said that the drug is not a bronchodilator and is anti-inflammatory. And I wondered what data in humans he had for that. For instance, after you give the drug for the very first time at its maximum serum

concentration, is there a change in FEV1? And secondly, do you have sputum mediate or data or anything to show that it's anti-inflammatory?

DR. RABE: Thank you very much. Since the question was directly to me, I'll take the liberty to answer this.

First of all, the question is why isn't this a direct bronchodilator. Phosphodiesterase isoenzymes are distributed in tissues differentially, and it seems that you need the inhibition of the type 3 and the type 4, for example, to have an acute bronchodilative effect. That is based on in vitro experimentation with muscle, where it's shown that the direct bronchial relaxing effect of a selective PDE-4 inhibitor is margin and negligible. So you need other components to be an acute bronchodilator.

Having said this, my comment was referring to if you give the drug once, would you immediately measure, as with a bronchodilator, within 30 minutes, 60 minutes, a bronchodilator effect? No, you would not.

What is the evidence that comes about in

terms of an anti-inflammatory effect? It is inferred by the wide distribution of PDE-4 in inflammatory cells, as was alluded to by Professor Rennard, and the fact that it is a creeping-up improvement of lung function that you measure after two or four weeks, but not immediately.

It is also inferred by the fact that it is in the same range, 40, 60, 70 mls, compared to what you would probably get with an inhaled corticosteroid. And notably, direct comparison in asthma, for example, comparing this drug with 200 micrograms BDP, it showed the same improvement of lung function in earlier trials that are not a basis of the discussion.

So what is the human data, what is the human evidence that we have? The only biopsy trial so far in phosphodiesterase-4 inhibitors was performed some years ago with cilomilast. I was part of this, together with Professor Barnes. And it showed the reduction of inflammatory cells in the mucosa, notably macrophages and CD8-positive cells.

There's no biopsy study with roflumilast performed as yet, comma, but there is evidence from a

lot of in vitro experimentation and one human trial in humans in sputum conducted sort of in our group. And we've been looking at individuals with COPD, not with chronic bronchitis and severe, people that could undergo sputum provocation.

These individuals were treated for several weeks with roflumilast. They, interestingly, got the same improvement of lung function, some 70 mls, and in those population, those individuals, you almost halved the total number of inflammatory cells in sputum when it was retrieved by a standardized technique, notably a significant reduction of more than 30 percent of neutrophils that we believe are very important for those individuals with chronic bronchitis specifically, and notably of eosinophils that are present in sputum of some people that are somewhat unstable in the disease.

That is so far the direct evidence in human experimentation that I can witness of directly, if that answers your question adequately. Thank you.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: Thank you. There's an

apparent paradox to me. On the one hand, you indicate that CYP3A4 and 1A2 are important in the metabolism of the drug. And yet you indicate -- Dr. Rennard indicated there was no clinically important drug interactions with ketoconazole, for example, which shuts off 3A4, and cimetidine shuts off 1A2.

So my question is whether -- what's the role of these enzymes, 1A2 and 3A4, in the conversion of the parent compound to the metabolite, and also in the elimination of the metabolite from the systemic circulation?

DR. ROWE: To address this question, I'll ask my colleague, Dr. Ghahramani from Forest Pharmacokinetics, to respond.

DR. GHAHRAMANI: Parviz Ghahramani, clinical pharmacology at Forest.

The metabolism of roflumilast is mediated by 1A2 and 3A4. But if I can have slide CP-200, please. The summary -- slide up. Based on the main metabolism, it's through the route of 1A2 and 3A4 roflumilast into N-oxide, and further metabolism to the alkylated metabolite of N-oxide. There is also a

minor pathway through the route of dealkylation and then N-oxide, as well. But the majority of the pathway and the metabolism is routed through the one that we see on the right side here.

Now, you brought up the question, if I can clarify, in terms of why the inhibitors don't have higher impact, and we say this is not clinically relevant. Is that correct?

DR. HENDELES: Well, perhaps you can tell us how you determined that ketoconazole, for example, had no clinically relevant when it's going to block enzymes and the conversion of roflumilast to its N-oxide and the elimination of the N-oxide from the circulation.

DR. GHAHRAMANI: Slide up. For example, for ketoconazole, obviously, it's one of the two enzymes. And what we have got is an increasing Cmax and up to about just less than twofold increasing today, you see, of roflumilast. However, the Cmax of roflumilast N-oxide was decreased, and there was no change in the UC.

Now, the point to note here is that the

major moiety which is contributing to the activity is actually roflumilast N-oxide because of the higher concentrations, about tenfold, at least, higher than roflumilast itself. So the major activity is coming from N-oxide, and the changes are relatively -- up to about twofold, it contributes much less into the biological activity of the compound. So to focus on the N-oxide is the major point.

DR. CALHOUN: Okay. I have questions from six additional committee members, and at this point, it's time for our break. And so what we're going to do is put these six questions for sponsor clarification on hold temporarily. We'll take a 15-minute break at this point. When we come back, we'll go to the FDA presentation.

We'll have clarification for the FDA presentations following that set of presentations, and there will be ample time either after that or following lunch for additional necessary clarification for the sponsor.

So at this point we'll take a 15-minute break and we'll reconvene -- actually, it's going to

be a 13-minute break. We're going to reconvene at 10:30. And, panel members, please remember not to discuss the issue at hand during the break. Thank you.

(Whereupon, a recess was taken.)

DR. CALHOUN: Good morning again. We'd like to reconvene. If everybody could find a seat, we'd like to go ahead and reconvene. Thank you.

Next on the agenda is the FDA presentation. And the first of the FDA presentations will be by Dr. Durmowicz.

DR. DURMOWICZ: Good morning. My name's Tony Durmowicz. I'm a pediatric pulmonologist who is the clinical team leader for the roflumilast program. Thank you for being here. I'm going to give a lot of the clinical presentation for roflumilast this morning.

With regard to what I'm going to speak about, I'll try not to go over too much what has already been discussed. However, I will give a brief introduction. I'll talk about COPD trial design a bit, including phosphodiesterase inhibitors. I'll go over,

again, the clinical development program, pointing out the FDA's views on it, and try not to duplicate things too much.

Dr. Abugov, our statistician, is going to go over the efficacy analysis, I'll talk about the clinical perspective, and then we'll go into the safety assessment. And I think what you'll see is that a lot of the data and a lot of numbers are very similar, if not the same. However, as is usual between people at advisory committees, their interpretation might be somewhat different. And the thing for the committee to discuss and weigh upon is the risk-benefit ratio with regard to the use of the drug in what population.

So, saying that, roflumilast was submitted by Nycomed in July of 2009, and, as has already been discussed, the official indication upon the submission was for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.

It's a selective phosphodiesterase type 4 inhibitor, small molecule, proposed anti-inflammatory

action, as already heard. The proposed name is Daxas. It comes -- it will come potentially as a 500 microgram immediate-release tablet, and the dose is one tablet once daily.

As has already been stated, the IND for this program changed hands several times during the 10- to 15-year development period. Most recently was in December of 2009, when it was transferred from Nycomed to Forest Research Laboratories.

As Ms. Travis already stated, in January of 2010, there was a change of indication when a new labeling supplement was submitted. And while this is not the exact wording, the point is that the indication was changed from more of a global treatment of the COPD as a disease, maintenance treatment of COPD as a disease, to a more focused indication of maintenance treatment to reduce exacerbations of COPD. So that's the main crux of the change.

In addition, warnings and precautions sections of the label were updated to include neuropsychiatric adverse events, as they weren't mentioned at all in the initial label that came in in

July.

The change of indication six months into the review period is somewhat problematic. By that time, the review period is half over, and since the review focuses on the label -- and it shifted the efficacy analysis, which is based on that original label indication. So that's why what we're discussing today, at least officially, is the focus on the original proposed indication, which is the more global indication.

COPD is a progressive disease of the chronic inflammation and destruction of the airways, as everybody, or most of the people here, know. There is progressive airflow destruction. It's not fully reversible. As has already been alluded, there's a spectrum of pulmonary processes, symptoms such as chronic bronchitis, with cough and excess sputum production, as well as emphysema-related symptoms. And again, it's a major cause of morbidity and mortality in the United States and the rest of the world.

With regard to therapies for COPD, most

therapies are bronchodilators. There are long- and short-acting beta-adrenergic agonists and antimuscarinic agents. And these mostly treat the reversible component of the airflow obstruction. As has been mentioned, I think by Dr. Donohue, tiotropium is now indicated for reduction of exacerbations of COPD, a long-acting antimuscarinic agent.

There are several combination products that are used to treat COPD. They are inhaled corticosteroid and long-acting beta agonist combinations. The one we've heard most about is Advair Diskus, 250 micrograms of fluticasone propionate and 50 micrograms of salmeterol xinafoate. And that combination therapy is approved for maintenance treatment of both airflow obstruction and for reduction in exacerbations of COPD, and as has already been shown, it reduces COPD exacerbations, depending on what trial you want to believe, but in the label it states by over 30 percent.

Symbicort is a combination therapy of 160 micrograms of budesonide and 4.5 micrograms of formoterol fumarate. It is approved to treat the

maintenance -- maintenance treatment for airflow obstruction of patients with COPD.

As Dr. Chowdhury brought up, theophylline is a nonspecific PDE inhibitor, which has been used for many years to treat obstructive lung diseases.

Now, the clinical trials in COPD, the endpoints are based on the proposed benefit. Therefore, if you improve airflow obstruction, like a bronchodilator would be, that's what you get in the label; if you can improve quality of life, you can relative symptoms, as is proposed here, reduce exacerbations, or even increase survival.

FEV1 is a common objective efficacy endpoint for bronchodilator drugs, and it does reflect the extent of airway obstruction. The resultant indication, as I mentioned, for bronchodilator drugs which show a clinically relevant benefit and improvement in FEV1 would be reflected in the label, with an indication of for maintenance treatment of bronchoconstriction.

Patient-reported outcome measures, such as the St. George's Respiratory Questionnaire, the SGRQ,

are also used in clinical studies for COPD. The SGRQ is probably one of the most recognized PROs in pulmonary disease. It assesses different aspects of the effect of COPD on a patient's life. This could be symptom relief, such as reduction in cough, sputum production, or dyspnea.

It's graded on the scale of zero to 100, the less being better. As has already been mentioned, the minimal clinically meaningful effect is a 4-unit change; 4 units to the negative would be a clinically meaningful beneficial change, the minimum. Differences of minus 8 and minus 12 units would denote more and more meaningful benefit if they occurred.

COPD exacerbation prevention and reduction, as somebody already stated in the FDA COPD guidance, is viewed as a clinically relevant endpoint for patients with COPD. However, once again, there is no consensus definition of what a COPD exacerbation is. Its most commonly intervention-driven definitions are used, and that determination rests on a decision, mostly by a clinician, to intervene in the care of a patient, mostly by either prescribing a medication or

putting the patient in the hospital.

Now, these intervention-driven definitions can be problematic, and they raise concern because the definition to intervene may be a subjective decision by a clinician that might vary, depending on who the clinician is, where they practice, what the local practices are, and et cetera. Therefore, we felt and feel that it's important to try to standardize the definition of a COPD exacerbation as much as possible. And we suggest to link a decision to intervene in the care of the patient with specific sign and symptom criteria that have to be met.

That was accomplished in the Advair Diskus program, which I mentioned is approved for COPD exacerbations. In that program, major and minor symptom criteria were laid out prospectively that had to be met and documented that a patient who had a worsening of his illness or increase in symptoms had to meet before calling it an exacerbation.

While the clinical program for roflumilast did have a suggestive COPD exacerbation definition of an improvement -- an increase in symptoms that

required increased care, there's no specific criteria outlined that had to be met.

With regard to phosphodiesterase inhibitors, theophylline, at this time, is the only PDE inhibitor marketed in the United States. The mechanism of action, which I believe -- I want to say Dr. Barnes for -- no, Dr. Rabe -- stated was mostly PDE type 3 and 4 inhibition. It's not generally viewed as a potent dilator by itself.

There was a Cochrane meta-analysis in 2002 which looked at the bronchodilator effect of theophylline, and it looked at 20 randomized studies. The baseline FEV1 in these studies ranged from .96 to 1.15, which is very, very similar to the baseline FEV1 in the trials that the sponsor today is calling pivotal. The FEV1 improvement was, on an average, 100 milliliters, with a confidence interval -- I have ranging from 40 to 100, but that's really 40 to 160. That was a typo.

We've talked a little bit about cilomilast this morning. Cilomilast is a selective PDE-4 inhibitor that's been studied in COPD fairly

extensively. There were four Phase 3 clinical trials conducted with cilomilast. The co-primary endpoints were lung function, measured by FEV1, and the patient-reported outcome, the St. George's Respiratory Questionnaire.

The FEV1 change from placebo was approximately 30 to 40 mls. This difference was statistically significant in two of the four studies, Phase 3 studies. The SGRQ change from placebo was anywhere from minus 4 to plus .7. And again, this was statistically significant in two of the four studies; however, in just the one study out of four did it meet a minimally clinically meaningful standard to show some efficacy.

Cilomilast was presented in 2003 at a Pulmonary-Allergy Advisory Committee meeting. Using the data -- maybe a little bit more extensive than I just said, but using the data I just mentioned, the question was asked, has cilomilast shown efficacy to support approval for maintenance of lung function? That would be the FEV1 endpoint. The vote at that time was yes-3 and no-7.

With regard to safety, the cilomilast program safety profile had significant GI adverse events, just as we feel it's a class effect with PDE-4 inhibitors. In addition, there was an issue with gastrointestinal vasculitis that was seen in non-clinical studies, in animal studies. However, it did not have a non-clinical carcinogenicity signal, as is seen with roflumilast, nor did it have any increase in neuropsychiatric adverse events, nor any weight loss issues, as is seen in roflumilast.

With that information in mind, at this time, the committee was asked, is the safety in patients with COPD sufficient to support approval? At that time, without those extra adverse event issues, the vote was yes-9 and no-1.

Finally, the composite question of, does the efficacy and safety data provide substantial and convincing evidence that support the approval of cilomilast for the maintenance of lung function, the vote reverted back to what it was initially with the efficacy, yes-3, no-7.

Now, I'd like to go over the clinical

program a little bit. And I'll try not to belabor the points, but there are a few issues and things I'd like to just bring out.

The program, as you already know, was relatively large. There were a very large number of clinical trials that encompassed six indications. COPD and asthma were the biggest of those, but they also were studied in osteoarthritis, diabetes, allergic rhinitis, et cetera.

In the COPD studies, the doses of 250 to 500 micrograms were focused upon. There were 18 fairly large Phase 2 and 3 trials. The COPD safety pool entails 14-plus double-blind, placebo-controlled parallel group trials, with an N of over 12,000 patients.

On this slide, I'm going to go through the core roflumilast COPD program as we've kind of defined it, if you will. There are some other very large parallel group studies which have been alluded to. However, these were what we felt were the core studies. And I should mention that any of these studies that we're going to talk about were designed

such that they could show benefit, if positive, to support the safety and efficacy of a drug for approval. So any of these trials could have been "pivotal" trials if they were positive.

Studies FK-101 and M2-103 were six-month trials we're going to call, for lack of a better word right now, the dose-ranging trials. M2-103 was discussed a little bit this morning. FK-101 was the actual dose-ranging trial, as designated by the IND sponsor at that time. Of note, they were again, 24 to 26 weeks. There were about 2,000 patients in these studies. Roflumilast 250, 500, and placebo were studied.

In this set, FK-101, just to mention, the difference between roflumilast 500 and 250 was 4 milliliters. The difference between roflumilast 250 and 500 in the 107, as you've already seen, is about 20 milliliters. And that range is about 1 to 2 percent.

M2-111 and 112 were one-year studies that were designed to assess COPD exacerbations in addition to FEV1 lung function. They were, again, large trials

with over 2,600 patients. These trials ended up not showing a significant difference in exacerbations. And therefore, trials 124 and 125 were conducted -- again, year-long studies, over 3,000 patients.

The patient population for 124 and 125, as you've already heard, was derived from post hoc analyses of the studies that failed. And they ended up with a patient population that was somewhat narrower than the initial population. They were severe COPD, FEV1 less than 50 percent. They had to have the symptoms of chronic bronchitis with cough and sputum production. And they had to have recent exacerbations.

Studies 127 and 128, again, were Phase 3 trials, six months in duration, to look at the effect of roflumilast added onto a LABA, which is Study 127, and a LAMA, or antimuscarinic, tiotropium 128. You've already seen a very similar slide like this, and it just shows that the clinical trial design is fairly simple, and all of them are very similar. And there's a run-in period of two to four weeks, a treatment period anywhere from six months to a year. After the

run-in period, patients are randomized to placebo or roflumilast 500, or in the dose-ranging trials, 250.

Now, this slide goes over some of the principal differences between the four sets of studies, if you will. And again, I don't want to belabor things too much, but I think there's some important points to bring out so you can look at the totality of the program.

As mentioned, with regard to COPD severity, the dose-ranging studies and the add-on studies had a more broader definition of COPD severity, if you will. They included moderate as well as severe COPD patients. With regard to the Phase 3 trials sandwiched in the middle, 111 and 112, 124 and 125, they focused on more severe patients, FEV1s that, baseline, were around 1 liter, less than 50 percent of predicted. As I'd already mentioned earlier, the 124 and 125 trials had requirements for bronchitis and a recent COPD exacerbation.

With regard to endpoints, the endpoints for the dose-ranging trials were FEV1 and SGRQ as the primary endpoints. Exacerbations was not a primary

endpoint in those trials. Therefore, there's not a primary endpoint for exacerbations from a dose-ranging issue.

The FEV1 was an endpoint, as you've already known, in all the trials. The trials that were a year long, as I've mentioned, were designed to assess for COPD exacerbations. The Phase 3 add-on had FEV1 by itself as a primary endpoint.

Now, finally, but this is a significant issue that is probably -- we'll be able to discuss later -- is the use of concomitant medications in the groups of patients that were in these trials.

In the dose-ranging trials, patients got roflumilast and a rescue medication. There were no inhaled corticosteroids allowed, no long-acting beta agonists allowed, or no LAMAs allowed. So there's no therapies allowed that would be standard of care.

In the Phase 3 Studies 111 and 112 that failed, inhaled corticosteroids were permitted, but there was no LABA or LAMA allowed.

Now, in the Phase 3 study that won, statistically, with exacerbations, LABAs were

permitted in about 50 percent. Even those patients with severe COPD, only 50 percent were on a LABA. They could not take inhaled corticosteroids or a LAMA.

The add-on studies, nobody could get an inhaled corticosteroid. Patients in 127 had to get a LABA, but couldn't be on a LAMA. Patients on 128 had to be on a LAMA, but couldn't get a -- had to be on a LAMA, but couldn't get a LABA. I'm going to tongue-twist myself here.

Now, I'd like to pause and have Dr. Abugov come up and discuss the efficacy results.

DR. ABUGOV: Thank you, Dr. Durmowicz. Good morning. My name is Robert Abugov. I'm the statistical reviewer for the roflumilast program. To help orient you to the main points in this presentation, I'll start by providing a brief introduction to the analyses.

We first examined roflumilast effects on pre-bronchodilator FEV1. Roflumilast increased pre-bronchodilator FEV1 by approximately 50 milliliters. And so we next looked at results from the St. George's Respiratory Questionnaire to help determine whether

this improvement increased quality of life. In four studies, the largest mean decrease from baseline SGRQ provided by roflumilast relative to placebo was 1.7.

Next, we'll quantify the effects of roflumilast on rate of moderate and severe exacerbations. And finally, we'll assess whether roflumilast changes the overall rate of mortality.

In the remainder of this presentation, I'll briefly describe the study endpoints and analysis methods used by the applicant, focusing on the two 52-week studies, 124 and 125, whose patient populations most closely correspond to the proposed indication. Where relevant, I'll also bring in additional endpoints and analyses from the other studies in the core program, and I'll then discuss results from these analyses, and conclude with a summary slide.

In the two dose-ranging studies, 101 and 107, the primary endpoints were changed from baseline to final measurement of pre- or post-bronchodilator FEV1, and changed from baseline of St. George's Respiratory Questionnaire. In the four 52-week studies, primary endpoints were the mean change from

baseline to week 52 of pre- or post-bronchodilator FEV1, and the rate of moderate or severe exacerbations. In the two 24-week studies where roflumilast was used as an adjunct therapy to a LABA or LAMA, the primary endpoint was mean change from baseline to week 24 of pre-bronchodilator FEV1.

The primary analyses were conducted in all treated patients. The goal of the analyses for the 52-week and add-on studies was to compare roflumilast 500 micrograms per day to placebo.

The definition of exacerbation differed across the 52-week studies. First, a typo on this slide should be corrected. Study 111 should be next door to Study 112.

In Studies 124 and 125, a moderate exacerbation was defined as one requiring administration of oral or parenteral steroids, and a severe exacerbation was defined as an exacerbation which resulted in hospitalization or death. In Studies 111 and 112, severe exacerbations were defined as those requiring hospitalization, but not necessarily including mortality, and moderate

exacerbations included a need for antibiotics.

I'll give a brief overview of the analysis methods.

In the six core program studies, change from baseline of pre-bronchodilator FEV1 was evaluated using a repeated measures analysis of covariance, with fixed effects based on factors potentially affecting outcome.

Three of the four 52-week studies conducted to examine the effect of roflumilast on exacerbation rate employed a general linear regression model with Poisson distribution and log link. The independent factors were the same as described in the previous slide for the analysis of pre-bronchodilator FEV1. Instead of a Poisson regression analysis, the primary analysis for Study 112 used a Wilcoxon Rank-Sum Test.

In Studies 112, 124, and 125, a hierarchical approach was used to avoid problems with multiplicity. The effect of roflumilast on exacerbation rate was not to be assessed unless a significant difference between roflumilast and placebo was seen on FEV1. In Study 111, instead of a hierarchical approach, a significant

difference between placebo and roflumilast in both FEV1 and exacerbation rate were required before effectiveness could be declared.

Change from baseline of St. George's Respiratory Questionnaire, SGRQ, was examined in four of the core studies using an analysis of covariance. Mortality in six studies, which had a large number of individuals per treatment, was examined using a proportional hazards model. As in the analyses discussed earlier for FEV1 and exacerbations, the statistical models for SGRQ in mortality included factors potentially affecting outcome. And with that, we can now move to the results of the efficacy analyses, some of which you've seen before.

The effect of roflumilast on change from baseline of pre-bronchodilator FEV1 in these six studies ranged from 39 to 80. In a pooled analysis of Studies 111 and 112, which both prohibited use of long-acting beta2 agonists, roflumilast increased pre-bronchodilator FEV1 by 51 milliliters. In the next two studies, which both prohibited use of inhaled corticosteroids, the pooled change was 48 milliliters.

In Studies 127 and 128, which included patients with moderate, as well as severe or very severe COPD, and in which roflumilast was used as an add-on therapy to salmeterol or tiotropium, roflumilast had an effect of 49 and 80 milliliters, respectively.

This table for exacerbations differs a bit from that in the briefing document in that it presents results from the analyses prespecified by the applicant. You can see that the difference between roflumilast and placebo was significant only in Studies 124 and 125.

For Study 112, the prespecified analysis was a Wilcoxon Rank-Sum Test, so no Poisson exacerbation rate is provided in the above table.

As a post hoc study, the applicant repeated the analyses of 111 and 112 using the criteria for moderate and severe exacerbations employed in Studies 124 and 125, using a Poisson regression. In both of these post hoc analyses, roflumilast did not significantly differ from placebo.

Changes from baseline of St. George's

Respiratory Questionnaire were measured in four core studies. In all four studies, the difference between roflumilast and placebo-treated patients was less than 2. And you can see the maximum change was 1.7.

Because the proposed indication is for maintenance therapy with implicit approval for long-term administration, I conducted exploratory analyses to examine roflumilast's effects on rate of moderate or severe exacerbations over time. This graph examines exacerbation rate on the Y axis as a function of time, which is on the X axis.

In both the roflumilast and the placebo treatments, the number of exacerbations per patient year decreased over time. The exacerbation rate among patients treated with roflumilast, represented by the solid line, tended to be less than the exacerbation rate among patients treated with placebo, represented by the dotted line.

For Study 124, however, this graph also suggests that the difference between roflumilast and placebo may have attenuated, even disappeared, after eight months of treatment. A similar pattern was

observed for Study 125. Again, the graph seems to suggest that the difference between roflumilast and placebo-treated patients may have attenuated, even disappeared, after eight months of treatment. However, it is unclear whether the apparent loss of effect is due to actual attenuation in treated patients or, instead, reflects patterns of patient withdrawal.

Roflumilast did not appear to affect the rate ratio of moderate exacerbations differently from how it affected severe exacerbations. For example, in Study 124, the rate ratio was .84 for moderate exacerbations and .89 for severe exacerbations. However, roflumilast reduced the absolute rate of severe exacerbations less than it reduced the rate of moderate exacerbations.

For example, in Study 124, the reduction of moderate exacerbations provided by roflumilast, given in the diff column here -- that's the absolute difference in the rate of exacerbations -- was 0.17 exacerbations per patient year, while the reduction of severe exacerbations was 0.01 exacerbations per

patient year. Overall, in a pooled analysis of Studies 124 and 125, roflumilast reduced the rate of moderate exacerbations by 0.21 exacerbations per patient year, and reduced the rate of severe exacerbations by 0.03 exacerbations per patient year.

No statistically significant differences between roflumilast and placebo in overall mortality rate were seen in any of the studies in this program. For example, in Study 124, 17 of 765 patients administered roflumilast died, compared to 17 of 758 patients administered placebo. The hazard ratio, calculated from a Cox proportional hazards analysis, did not differ significantly from 1. For Study 128, no hazard ratio is given because its calculation would have involved a division by zero.

In summary, roflumilast provided a 48 milliliter increase in pre-bronchodilator FEV1, reduced SGRQ by a maximum of 1.7, and reduced the rate of moderate or severe exacerbations by 0.24 exacerbations per patient year. Of roflumilast reduction in exacerbation rate, 0.21 per patient year would have been moderate, requiring administration of

oral or parenteral steroids, and 0.03 per patient year would have resulted in hospitalization or death.

Exploratory analyses suggest that eight months after commencement of treatment, the effect of roflumilast may lessen, and it may no longer reduce exacerbation rate. However, whether the apparent loss of effect is due to actual attenuation among treated patients or, instead, reflects patterns of patient withdrawal is unclear. There's no evidence that roflumilast changed the overall rate of mortality.

Thank you. I'll turn the presentation over to Tony once more.

DR. DURMOWICZ: So I'm coming back up, first, to give a somewhat more clinical perspective on the efficacy analyses that Bob did, and adding a couple other comments. Actually, that's not the right one. This is it.

As has been demonstrated by the company's presentation and Bob's presentation, there's a consistent but, we would say, modest 50 ml increase in FEV1, and that's consistent with other spirometry-based endpoints -- post-bronchodilator FEV1, pre-

bronchodilator, and other permutations of FEFs, et cetera -- that there were consistent but small improvements.

The question that is for discussion is, are these improvements clinically relevant? The 50 mls is about a 3 to 5 percent improvement in FEV1 in these patients with an FEV1 of about -- mid-baseline of about a liter. It's notable, as I mentioned earlier, that in the Cochrane meta-analysis for theophylline, pre-bronchodilator FEV1 increased about 100 mls. Patients had the same baseline FEV1 of about 1 liter, so that would be a 10 percent increase.

It's also notable that neither the cilomilast program nor the roflumilast program -- there's never been a head-to-head analysis of efficacy with regard to pulmonary function between theophylline, a nonspecific PDE inhibitor, and the type 4 PDE inhibitor. The companies with roflumilast -- I don't know whether it was Nycomed or an earlier company -- did conduct a drug/drug interaction study with theophylline, but there's no FEV1 data, I don't think, for that.

With regard to the COPD exacerbation endpoint, it reached statistical significance in two of the four year-long trials. 111 and 112 did not reach statistical significance. 124 and 125, on the more narrowed population, did. Dr. Abugov has already mentioned that the exacerbation, moderate or severe exacerbation, difference was minus .24 per patient year. That splits out to minus 0.21 for moderate exacerbations. So that means if you have a patient with COPD, it takes five years to get the benefit of not having one exacerbation, defined by corticosteroids.

For the more severe exacerbation, the hospitalization, there was a minus .003. So if you have one patient, that patient has to be on the drug for 30 years to show a benefit of not having a hospitalization from taking roflumilast.

Dr. Abugov also mentioned that post hoc analysis suggests attenuation. We've already discussed a little bit that it's a narrowed COPD population. And importantly, there's no LAMAS or ICSs that were in the pivotal-type studies that showed

benefit, and 50 percent were on LABAs, despite the fact that they were severe COPD patients.

The SGRQ, as a patient-reported outcome, was measured in more than four studies across the clinical development program, but we didn't want to bring in superfluous studies for other issues. But in any study that it was assessed, either as a co-primary endpoint or a secondary endpoint, it failed to meet the minimal clinically meaningful difference compared to placebo.

There are a lot of other secondary endpoints that were conducted in the pivotal trials, and I'm going to focus on the pivotal trials right now. But Dr. Abugov didn't mention them; he was sticking mostly with the major endpoints. But I want to touch base on some of those now.

Clinically relevant secondary endpoints included dyspnea, as measured by the BDI/TDI, Transition Dyspnea Index, questionnaire. The change from baseline was 0.23 for Study 124, and change from baseline was 0.29 for Study 125. That is a positive change. However, the minimally clinically meaningful

difference, as published for the BDI/TDI Dyspnea Index, is greater than or equal to 1. So that did not show a benefit.

The use of rescue medications -- these would be short-acting bronchodilators like albuterol or salbutamol -- there was a minus .2 to minus .4 puffs per day decrease in the roflumilast-treated patients in Studies 124 and 125. Now, a dose is two puffs, in general, for these types of medications, so you're looking at a difference of one-fifth to a half a puff of a dose a day -- one-tenth to one-fourth of a puff -- of a dose per day in a benefit. And I don't think people would think that would be that clinically relevant.

Time to study withdrawal was assessed. Roflumilast-treated patients withdrew earlier than placebo patients, on an average of 20 and 14 days in Studies 124 and 125, respectively. That was mostly driven by adverse event profile.

Other secondary endpoints such as shortness of breath, quality of life as measured by the European quality of life scale that was alluded a little bit

earlier, or time to mortality showed no differences.

I think an important point to mention in this drug, for this drug, that is being framed as a drug that helps severe patients with COPD, with bronchitis, and who get exacerbations, is that the use of standard therapies for COPD was very heavily restricted in the program. There were no inhaled corticosteroid/LABA combinations used. LABAs were restricted in some of the major studies, and LAMAs were restricted in the major studies.

The point being that while not required from a regulatory standpoint, the use of roflumilast in addition to standard treatments in these patients with severe COPD would have allowed a better characterization of efficacy and determinant of what we want to discuss later, the risk-benefit in the population that we want to treat.

Now, I'm going to go into the safety overview. And first I'm going to discuss a little bit of the nonclinical considerations. We've heard a little bit about the tumor situation earlier from the company. And then I'll discuss the clinical safety

aspects.

Now, nonclinical studies are done for specific reasons in drug trials or drug development programs. They characterize the toxicity profile in animals, not that it has to carry you on into humans, but to get an idea of what type target tissues there might be. It looks at, as I mentioned, the target tissues and determines the reversibility of that toxicity. And again, it looks for carcinogenicity. There's genetic toxicity studies. You look for studies on the fetus in pregnancy, and growth and development is relevant for that drug.

There is eventually a margin of safety for clinical doses that's determined. And that safety margin differs depending on what the drug is, what indication it is. For instance, if it's a cancer drug, you might not have that much of a safety margin because it's a very, very, very severe, life-threatening disease.

With regard to the nonclinical findings for carcinogenicity, nobody's going to argue that the drug is carcinogenic in rodent animals, i.e. hamsters,

where there was a dose-related increase in undifferentiated carcinomas in the nasal cavity. And with regard to the nasal cavity, I think that it's already been brought out that the nasal cavity, at least in hamsters, metabolizes the drug in a somewhat special manner, a different manner, where there's a higher concentration of the carcinogenic metabolites in there.

The effect of the carcinogenicity appears to be from the metabolites -- this is a little typo; it's ADCP N-oxide and ADCP N-epoxide. And the N-oxide metabolite was initially felt to be irrelevant for humans, because when this study was done five or six or seven years, the carcinogenicity study, it wasn't believed that ADCP N-oxide was in the metabolic pathway for humans. So it was not felt to be relevant.

Subsequently, it's been determined that ADCP N-oxide metabolite is produced in humans, and accounts for 10.5 percent of the dose in human urine. Now, it's not -- I don't think the humans have the nose issue with regard to hamsters, and that's why the

hamster tumors and adenocarcinomas were probably in the nasal cavity.

But the fact that 10.5 percent of the dose is recovered from the systemic circulation means that this carcinogenic metabolite is circulating. It might be lower levels than in the nasal cavity of a hamster, but you have to take that into consideration. Thus, the FDA Executive Carcinogenicity Committee subsequently changed their position and stated that it's not irrelevant for humans and it could be relevant for human studies, human patients.

With regard to the clinical safety profile, which I'll try to go through now, we've already mentioned that there's a large safety database, greater than 12,000 COPD patients. I'll look quickly at patient exposure -- we've already looked at deaths, adverse events, serious adverse events -- and then, again, go through the psychiatric and GI and weight loss and malignancy issues. And again, like I mentioned earlier, a lot of the data are the same. The issue is risk-benefit interpretation.

The COPD program was large. There are a lot

of patients that got 500 micrograms of roflumilast, many, many fewer with a 250 microgram dose of roflumilast, because the 500 dose, which we feel is the maximally tolerated chronic dose, was selected for the larger year-long exacerbation trials. And again, about 5,400, 5,500 in the placebo group.

That translates into patients that were treated for a long period of time so you can assess some of these rare adverse events; 2,200 patients, six months to a year for roflumilast 500, 2,400 or 2,500 patients for placebo. And again, like I mentioned, not very many people were studied long in the roflumilast 250 because the decision was made to go with the 500 dose.

All-cause deaths are about the same. Common causes of death are about the same. It's already been presented. With regard to death-related adverse events that were greater with roflumilast, we've already seen cardiac arrest, seven to one. Don't know what that means. Cardiac disorder deaths were the same. This is a subset, and it's hard to understand that.

You already know that there are three suicide deaths in roflumilast-treated patients versus none. You already know that there are two acute pancreatitis deaths in the roflumilast-treated patients versus none in the placebo group. I will come back to the suicides and acute pancreatitis issues when we talk about special safety signals later.

Serious adverse events, again, as the company has presented, total SAEs were very similar between the 500 and the placebo group, at 14 percent. Serious adverse events that were greater with roflumilast are listed here. There are some to highlight, and they're bolded compared to some of the common ones that you would not think were potentially real or something like that.

We've already talked a little bit about atrial fibrillation, 24 to 9. Diarrhea, that's a serious adverse event. So serious adverse event, from a regulatory definition, at least in the context of this table, is an adverse event that would be considered life-threatening or an adverse event that

would be resulting in a hospitalization. We already talked about death, so that's not included here.

Prostate cancer, 12 to five. Suicide attempts, again, it's already been mentioned there have been two suicide attempts in the roflumilast group and not any in the placebo.

Now, more common and more frequent adverse events concentrate on the GI and a little bit on the nervous system. Again, total adverse events are not that different, although there are a lot of them because these are sick patients.

Withdrawals due to adverse events is somewhat different. There's about 321 more withdrawals due to adverse events from the roflumilast 500 dose group than there is with the placebo group, and that's about a three times increase. Weight decrease, now this is as an adverse event. We'll talk about it later as weight decrease which was monitored in clinical trials. But this is weight decrease as an adverse event, is 394 versus 101.

Again, GI, nausea, that's about a 5 percent to 1 percent. We go down to headache and insomnia.

Insomnia was a significant issue, 148 to 50. Dizziness and decreased appetite were also more prominent as generally common adverse events in roflumilast-treated patients.

Now, I'm going to go into the adverse events of concern. Again, the data are very similar in some aspects to what the company presented, but I'll try to just highlight the FDA perspective for those.

With regard to psychiatric adverse events, there were, all told, about double in roflumilast 500 microgram-treated patients versus placebo, 403 to 190. The common ones, as the company has already stated, are insomnia and sleep disorder, anxiety and anxiety disorder, and depression.

Other more rare, but consistent increases in psychiatric adverse events are seen more in the roflumilast group versus the placebo group, roflumilast 500, and they include nervousness, restless, agitation, mental disorder. Again, I'm going to talk about the suicide and suicidal attempts in a little bit.

Because we saw this in COPD patients, we

looked at some of the other clinical data from the company to see is psychiatric adverse events carried across different indications, such as asthma or diabetes or other things. And you've seen this data, essentially, in the first line. This is the COPD program.

This is a COPD in Japan program that was submitted that is not part of the safety database. This is a large asthma program database that entailed over 5,000 patients. And this data come from other indications -- the diabetes, the allergic rhinitis, the osteo and rheumatoid arthritis patients.

The point I want to make is that it seems like there is a consistency across indications of an increase in psychiatric adverse events in roflumilast 500-treated patients compared to placebo. Again, we've seen this data -- 24/16, which is 10 percent to 6 percent, 4 percent to 2 percent, 5 percent to 1 percent.

If you look at the individual adverse events, they're somewhat similar to what you see in the COPD. There's the anxiety, the depression, and

the insomnia that are the prominent ones.

Now, with regard to the suicides, because that's a big topic of discussion, as you know, the company has stated they conducted, through Dr. Posner at Columbia University, a suicidality assessment, I believe, of the COPD trials only, not the total roflumilast database, which you would want to look at.

We weren't invited to participate in that request to have that analysis. And when the FDA looks at these kinds of analyses, it's usually a company/FDA joint decision of what trials to include, what trials not to include, and how to assess it.

Saying that, nobody can deny that there were three suicides in the roflumilast group and two suicide attempts, versus none in the placebo group. The three completed suicides all received roflumilast, 500-2, roflumilast 250-1. All were male. None had a known history of depression or known psychiatric problems.

Now, the company presented some information that said on a baseline European quality of life questionnaire, one of the patients may have had a

history of depression. That's not in the CIOMS adverse event report for this, nor is it in the company narrative. So we don't know what that means.

With regard to the suicide attempts -- well, let me go back. We also know that two of the three patients committed suicide about 20 to 21 days after they stopped roflumilast therapy. So that raises the question, is it in their system, or why should it be attributable to roflumilast?

Well, I think that what we don't know is we don't know the link between the pharmacokinetics and what the pharmacodynamic effect of the drug would be. A lot of neuropsychotropic drugs take a while to have an effect because they change brain chemistry and take a while to go out of effect, if you know what I mean.

The issue with these patients is that nobody stopped the drug because they had a COPD exacerbation or anything like this. A lot of them were having -- not having anxiety or depression symptoms before they took the drug. They started while they were on the drug, and then the drug was stopped, and 20 days later they killed themselves.

With regard to the suicide attempts, they were both in women, and these women took 500 micrograms of roflumilast. They both -- one of the women had a history of depression, and one had a prior suicide attempt before she was on the roflumilast trial. There was one case of suicidal ideation in the placebo group, and we don't lump these things together.

Specifically, it might be right or wrong from a psychiatric standpoint, but actually doing something about it, i.e. committing suicide or attempting to commit suicide, is viewed, at least by us and I think by other people, as different than thinking about it.

With regard to gastrointestinal adverse reactions, GI toxicities were prominent, 22 percent, about a doubling in the 500 versus placebo groups. Withdrawals from GI toxicity played a large part in the increase in withdrawals from the roflumilast program, 294 to 44.

With regard to GI adverse reactions, again, acute pancreatitis. Two people died with acute

pancreatitis listed as an adverse event in the roflumilast groups and none in the placebo. And we also went back and tried to look at the serious adverse events at other kind of rates of pancreatitis.

It is true that if you look at pancreatitis serious adverse events reported under the terms "acute pancreatitis" or just "pancreatitis," that it's a fair balance. It's seven with roflumilast, six with placebo, and one person got montelukast. And we're putting that to the side because it was active control trial.

But the point is that if you look further in the analysis and look further at the narratives of these things, it's hard to decide whether there is a signal or not, to be honest. And that is because if you look at the SAE data, with seven in roflumilast and six in the placebo patients, six in the placebo patients for serious adverse events for pancreatitis, three of the placebo patients had normal amylases.

I don't know what to make of that, because an elevated amylase is usually one of the diagnostic criteria, confirming criteria, for pancreatitis. But

it throws a little bit of a haze on the data and how to interpret it and what to make of it. So I don't know 100 percent what to make of that, to be honest with you.

Again, this data here you've seen before. It's the serious adverse events that were diarrhea, again, life-threatening or requiring hospitalization, and the regular adverse events, with diarrhea, nausea, and decreased appetite, which focused on the GI tract.

With regard to weight loss, this is a very busy table and I'm just going to point out a few things on it. This is somewhat similar to what the company presented, but there's a different twist because we're comparing weight loss in the roflumilast group to placebo. And I want you to focus on this set of numbers, which is underweight patients, and underneath this set of numbers, which is the COPD severity patients.

Roflumilast is in these two columns. These are the weights that they began with, and this is the change. Placebo, here's the weight, here's the change. And what you'll note is that as a percent of

body mass, underweight patients lose more of a percent of their body mass than lesser underweight patients, I'll say. And in addition, with the severity of COPD, the COPD patients who are very severe lose an increased amount of their body mass as a percent than the less severe patients.

The point here is that although it's not a dramatic difference, these are the patients that can least likely tolerate a decrease in weight. And these patients are the ones that -- well, I think that patients that lose weight with COPD is a not-good sign for like death and things like that. But I'll let the experts determine that.

So that's the information about the characteristics of the weight loss. I think the point of being mostly fat is that I think the way the human metabolism is is everybody loses fat before they start losing muscle and other things. So that's not a surprise with regard to bioimpedance measurements.

Finally, let's talk a little bit about malignancy, because that is another interesting topic. This is raw data. The total database for roflumilast-

placebo over everything is up top, with 131 versus 86. Now, right now in this table, roflumilast, when you're looking at the COPD safety pool, 250 and 500 microgram doses are lumped. Placebo is placebo, if you will.

In all the other adverse event profile-type tables I showed you, they're not -- they're split apart. Here they're kind of lumped. And I have some additional data that splits them apart, which might give a little bit more representative issue that we could talk about later when the discussion comes.

But there's a total of 105 to 80. The general incidence, if you divide by these larger numbers, is very similar. It's 1.7 and 1.6 percent, somewhere in that ballpark. But the point being that I want to make, at least on this slide, is that for common cancers, irrespective of the imbalance up top of a number of patients, that there's kind of a -- at least a doubling of some of the more common cancers -- lung cancer, prostate cancer. Skin cancer is very similar, and urinary tract cancer and colorectal cancer.

The skin cancers, when we do cancer

analyses, we usually exclude those because they're such common things caused by the sun, et cetera, that we just take those out of the groups to not dilute the database. So I just want to make that point that in the context of a carcinogenic metabolite, I don't think we can ignore this data. And again, I'm sure that will be an interesting point for discussion.

So in summary, with regard to safety, there's a higher incidence of psychiatric adverse events, including suicide. This occurs across all programs, as far as we know. There's a higher frequency and severity of gastrointestinal adverse events. There's weight loss that's most prominent in those least likely to tolerate it, those who are underweight and patients with severe COPD.

With regard to malignancy, there's a carcinogenicity signal in non-clinical studies, coupled with an imbalance for common cancer types. And we know that that carcinogenic metabolite is excreted in humans, and they're exposed systemically to it.

Thank you.

DR. CALHOUN: Okay. Thank you. So we'll now open the FDA's presentation to members of the committee. And again, I'd like to focus our questions on the presentations of Dr. Durmowicz and Dr. Abugov. And we'll come back at a later time to the sponsor's presentations, if there's additional question on that.

Dr. Knoell?

DR. KNOELL: I would like from the FDA some perspective. Coming back to the SGRQ -- we've talked about that earlier today -- we just talked about it again. And we're focusing on the data as a lack of notable clinical significant improvement in the SGRQ. Yet we were provided with a perspective earlier that if you put that into comparison in the context of previous COPD-related trials where we've approved other medications previously that were well-designed clinical trials, point being those drugs were approved with similar data.

It leaves me confused as to what the importance and/or weightedness of this type of data should be for this particular medication, but in the broader perspective, of expectations at the FDA across

the board when we come up for discussions like this with drugs of this nature to treat a disease like COPD.

DR. DURMOWICZ: As you already know, the SGRQ was a primary or co-primary endpoint in large Phase 3 early trials that could have been used to support efficacy. So to look at the totality of data across the program and not just focus on two studies out of eight that won, if you will, on exacerbations, we presented data on a patient-related outcome which is well-respected by the pulmonary community and has been used as a co-primary endpoint.

That is the reason why we included the SGRQ data in the COPD studies here. It also plays a role into looking at what kind of ancillary effects you might get, because it was used as a secondary endpoint, as well.

So if the committee wants to discuss the two primary endpoints that were used in what's called the pivotal trials, these would be ancillary data to support or refute that benefit, if you think it's clinically meaningful or not.

DR. CALHOUN: Dr. Chowdhury?

DR. CHOWDHURY: I would just make some comment about the specific use of SGRQ in efficacy endpoint measures for a COPD program. That was your focused question.

For other studies, which was mentioned by the applicant and you've also seen the data, SGRQ was looked at, for example, in the combination in the corticosteroid and long-acting beta agonist products, and also in other programs. And the numbers that you saw mostly did not reach the threshold of 4.

But these studies for other products were done with different intent, mortality or COPD exacerbations or other endpoints. And on those endpoints, it actually had 1.

So the point to look at it is what is the drug, and what is the expected benefit you are looking from a drug? For a drug whose primary mechanism of action is bronchodilatation, such as a beta agonist, you probably would not expect a large increase in SGRQ; whereas if you're looking at a drug which is, for example, theophylline, as has been discussed here,

which does something beneficial to the patients, although not necessarily a large bronchodilatation, you would want to support that with something else, including SGRQ or something else.

If we look back at the cilomilast program, which is the same class, there were trials, and two of the trials actually won on SGRQ statistically. Of the two, there was one trial which actually crossed the threshold of 4. So in the cilomilast program, there was actually one trial which had crossed the threshold of 4. Here we have a threshold that has been crossed is less than 2.

So if a company is to come in and wants to get a broad maintenance treatment of COPD, then we would want two co-primary endpoints to win. One of them could be SGRQ or something else.

DR. CALHOUN: Thank you.

Dr. Swenson?

DR. SWENSON: My question's on the weight loss issue, and there's lots of things that come from it. But the first question would be, with respect to the apparent higher detection of cancers in these COPD

patients, a group that has a fairly high risk for cancers, both lung and elsewhere, to what extent was the detection of cancer picked up simply by the weight loss?

Was that what drove the detection of these cancers? And could you then argue that perhaps the weight loss just focused a physician's attention a bit more, and we just picked up cancers a bit earlier that would otherwise arise in the next year or two?

DR. DURMOWICZ: I don't know if weight loss was a trigger for assessing for cancer or whether a patient had a cancer in these studies, and I don't know if we'd be able to find that out. The company might have a comment about that. But I don't think that was a reason, at least that we could investigate, as a cause of why the cancer was diagnosed or not diagnosed.

DR. SWENSON: Would it be appropriate to have the sponsor discuss that point?

DR. DURMOWICZ: If they have that information, that would be fine. But I'd be interested in knowing.

DR. CALHOUN: Does the sponsor have information on that specific point, or is that something that you can get to us after the lunch break?

DR. TAGLIETTI: Marco Taglietti, chief medical officer. I think that this is a very good point for which, however, we may not have full information in the sense that this was not a study about cancer. This was a study about COPD.

However, there is some indication that something is happening in terms of detection of these cancers, because the fact that a large part of the cancers was actually detected very early during the study, when there is no biological plausibility for a tumorigenic effect, may actually be one -- maybe actually we came to a conclusion that may be due to the fact that there may be some more investigation, including some of it due possibly to weight loss or some of it GI, other GI events, that may have resulted in further investigations.

But the study was not designed for that. There was no prospective randomization in terms of

risk factor for cancer. So we cannot have a definitive answer. But I do believe that some of the evidence that we have may suggest this. And if this is a topic that we can further elaborate, I may have Dr. Schein actually comment on this aspect because I think it's a very critical one.

DR. CALHOUN: Can we comment with respect to data as opposed to interpretation?

DR. TAGLIETTI: So in terms of clear evidence that the weight -- investigation of weight loss resulted in a early detection, no. This was not -- is not the type of information that we have available.

DR. CALHOUN: Okay. Well, then, with respect to Dr. Swenson's question, if you guys can develop data over the lunch break, then, and come back with that?

DR. TAGLIETTI: Certainly.

DR. SWENSON: I have just one question for Dr. Abugov. Your finding of attenuation of this effect on exacerbation rate, you pose the thought that you hadn't analyzed the -- there was a question around

some lack of data, maybe, in the last months there in terms of maybe the dropout rates affecting that. Can you elaborate further? How robust do you think that attenuation effect is?

DR. ABUGOV: I'd be hesitant to say. I've been burned by speculating before. But I will note that the reason I did mention that is because the dropout rate for exacerbations was higher in the placebo group. And if some of those individuals were those in which exacerbation rate was higher, that could reduce the overall exacerbation rate in the placebo group, because the individuals with exacerbations could have been dropping out more.

So as to whether that's true or not, we're clearly missing the data that patients withdrew. So I hesitate to say more than that. But there is a mechanism by which patient withdrawal could be associated with this attenuation.

DR. CALHOUN: Dr. Hoidal?

DR. HOIDAL: I think Dr. Swenson asked two questions I had. But maybe expand on one, and that's either Tony or the company, on the distribution of the

cancers in the two -- in the treated and placebo groups over the course of the year. You kind of tangentially mentioned it. But a little more information on that?

DR. DURMOWICZ: Kristine, could you pull up the backup slide for me? I think it's the second one. The next one.

Now, this is a somewhat complicated table that Bob made. Do you want to speak to it or --

DR. ABUGOV: Go ahead and speak to it.

DR. DURMOWICZ: Okay. I'll talk to them about it. And this further analyzes the malignancy signal. And what we did here are multiple things in this table, and I'll explain them, and then, Dr. Hoidal, you can tell whether this addresses your question or not.

What we did was we broke out the roflumilast 250 microgram group from the total numbers that we had seen on my last slide and compared that to the placebo group. And then the numbers don't make as much of a difference because they're very similar.

Then we also took out, as I mentioned, the

skin cancers because skin cancers occur very commonly and they're due to sun, et cetera. And people commonly, when they look at cancer data, take out the skin cancers, the non-melanoma skin cancers.

What we found is that if you look for those common cancers that are occurring, there were 29 lung cancers to 17 in the roflumilast versus placebo group. The proportion is under the PROP, and the incidence is under INC. So the incidence is three times -- no, the incidence is higher in the roflumilast group.

But if you look at the p-value of the Kaplan-Meier incidence, it's significant for the lung cancer. And in the same manner, with prostate cancer, it's significant. In the same manner, with the colorectal cancer, it's significant. Now, this data is on a database that's relatively large. But it's unusual to see significant differences in types of cancer in clinical trials.

Now, it doesn't address, I think, what one of your major questions was, and Bob may have the answer in his brain or not, about did these cancers occur all early, and, therefore, should you discount

them? I think that might be part of your question.

DR. HOIDAL: It relates to whether there's vigilance with early detection, as was -- or is there a bimodal distribution that differs later during the year that might have -- imply more of a biologic effect, or a pathobiologic?

DR. PLATTS-MILLS: Can we get a clarification?

DR. CALHOUN: If it's a clarification on this particular question.

DR. PLATTS-MILLS: I think it's important to note that prostate cancer is not as lethal as COPD. It doesn't have the mortality rate. And probably colorectal is probably not as rapidly lethal as COPD, whereas lung cancer probably is. But there are real differences in the implications of these.

DR. DURMOWICZ: No. I think that the issue is not whether having a cancer signal would prevent some kind of use of this drug in a population. The issue is taking these adverse event profiles as a whole -- cancer, psychiatric, et cetera -- into the risk-benefit assessment. I think that's where we're

coming with the cancer kind of situation.

I think if you look at the next slide, it's censored to cancers that occur after 365 days, so it cuts out the late cancers, and you see very similar data. But I don't think we have any that censor from the first few months.

DR. CALHOUN: A point of order from Dr. Chowdhury.

DR. CHOWDHURY: The question here was the time to cancer. And I would ask Dr. Abugov to comment on and analyze the two data on the Kaplan-Meier curve.

DR. ABUGOV: Looking at the Kaplan-Meier curves, which I don't have as a backup slide, the rates did seem to diverge over time, the proportions. So I would guess that it wasn't all early cancers.

With regard to commenting on the weight loss versus cancer issue, whether there was some observational bias caused by, more generally, adverse events -- if a patient has a serious adverse event, you're more likely to examine them -- the fact that it doesn't seem to happen in a lot of other trials seems to suggest that maybe cancer truly is associated with

the roflumilast groups.

But there is data which could be looked at examine that. And we could simply ask whether adverse events, serious of moderate, were correlated with cancers. So the data is there for the company to examine.

DR. CALHOUN: For the sponsor, if you have a response with data, then that would be fine. If it's interpretation, then that's probably not fine.

DR. TAGLIETTI: It's a response with data.

DR. CALHOUN: Okay.

DR. TAGLIETTI: Please, slide up. It's one of the points that I think I verbalized in my presentation. And it's just showing the number of cancer that -- lung cancer, in these cases -- that were detected in the initial period of treatment.

The first three months, there were 10 versus two. And in the subsequent three months, it was 12 versus four. And without interpreting, I just leave this data showing that there was clearly an imbalance in the first six months of treatment between roflumilast and placebo.

If I may have Dr. Schein just to make a short comment on this?

DR. SCHEIN: I'll stay specifically to data. Phil Schein. I'm a medical oncologist, pharmacologist, visiting professor in cancer pharmacology, University of Oxford. I'm a consultant to the company. I have no shares, no equity, no position on their speaking group, and I have no incentives based on the outcome of this meeting.

You've seen here the lung cancer data. Let me give you the data for the entire study in terms of all cancers. As you see, within three months, you have one-third, roughly, of the lung cancers. It is the same for all tumors. One-third of all tumors, roughly 30, occur in the first three months. Two-thirds of all tumors detected occurred within six months.

I'll just leave you with that fact. I'll be happy to interpret that later in the meeting. But I think that has to be put into context in terms of the relevance for this in terms of any potential carcinogenic activity.

DR. CALHOUN: Okay. Thank you.

Moving now, Dr. Burlington.

DR. BURLINGTON: Thank you. A couple times, FDA has pointed out the change in indication in mid-review here, and has expressed concern about it. And I would like to comment that this is not unusual. Certainly, I mean, over my career, I have taken many, many drugs through the approval decision on either side of the table.

FDA always interacts extensively on the label. Changing and narrowing the indications is frequent in many of the other divisions at FDA. And of course, although this is not Europe, one always gets into that discussion with CHMP.

So that leads me to say, or ask, why is FDA really concerned about this? If we have a noisy, less precise definition of exacerbation, that may make it harder to demonstrate superiority. But still, the sponsors overcome that.

Is there something else that FDA is concerned about? Is there evidence the blind was broken? Is there a treatments-by-center interaction?

Is there a treatments-by-region interaction? Or what is your concern?

DR. DURMOWICZ: I think you're correct in that the FDA, in general, does sometimes change the indication throughout its review of the NDA, and might focus it more, focus it less, depending on how the data are.

That is generally an FDA-driven issue, at least in the United States. From what you say, in Europe it might be different. This was specifically a company-derived issue that occurred after we had done a substantial amount of review on the entire NDA. And from our standpoint, that changed the way we looked at things, and in preparation for an advisory committee meeting and subsequently, we decided to stick with the initial indication.

So that's my answer, whether you're frowning or not frowning. You know, that's my line and I'm going to stick to it right now.

[Laughter.]

DR. DURMOWICZ: I don't know if Dr. Chowdhury wants to comment further.

DR. CHOWDHURY: Yes. Just to add on that, I mean, a couple of points that you raised towards the later part of the question is the points that we would have liked to assess, if there is an effect that we need to look at to formally come here and say exacerbation-only is an indication that we can feel very comfortable to discuss.

The change for the indication proposal to us came month 6, month 7, into the review cycle, approximately two or three months before this meeting, and the briefing documents were due approximately a month before the meeting. So simply we did not have time to look at the changed indication and what implications it would have on the labeling.

But again, we do not necessarily have an issue of a more focused indication than a broad indication. In fact, as we discuss, I'm certain there will be some comments about that. And later on, if risk-benefit is fair for the drug, it is entirely possible that a changed indication or indication different than what has been proposed will be entertained for final decision-making.

Thank you.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: Questions for the FDA about the carcinogenic effect of this drug. As I look at carcinogenic effects, a carcinogenic effect on a drug usually becomes -- or any substance becomes apparent after long, long use, not immediate use. Certainly, tobacco, benzene, asbestos, anything else we look at that we think of as a carcinogen seems to have an effect.

We do have years of data now, at least 10 years of data, on more than 12,000 patients to look at for this drug, if we could get that data. On the other hand, we're talking about -- I don't know if we're talking amino-dichloropyridine, or ADCP. I don't know about that chemical.

I need to ask the FDA if this is a known carcinogen, or is this drug really a carcinogen, or does this drug do something to suppress your immunity so your cancer that's already there becomes apparent? A cancer that occurs in three months certainly was there before three months. So that did the lung

cancer, the prostate cancer, the bowel cancer, did those become more apparent where they'd be preexisting? We gave this drug, and it suppressed your ability to keep that cancer suppressed?

But maybe you can answer me about the ADCP.

DR. DURMOWICZ: I think you raise a good question with regard to the promotion of a cancer that's already there versus a de novo cancer that would occur very early is very unlikely in those aspects.

With regard to the ADCP, I'll state that the -- as I mentioned in our talk, the FDA Executive Carcinogenicity Committee viewed that as a carcinogenic molecule. Maybe our pharmacology/toxicology person could elaborate on that, if there is something to elaborate. But that's what I know right now.

DR. SHEA: I'm Dr. Molly Shea. I'm the pharmacology supervisor in the division.

Basically, the ADCP N-oxide is the metabolite of interest, as well as it's further metabolized to the epoxide. Just based on the

preliminary data that Dr. Durmowicz already covered, the original assessment of the Carr studies in the hamster, we did feel that that data showed the N-oxide and the epoxide of the ADCP was specifically a rodent tumor because of the locality, being generated by the specific CYP enzyme in the nasal cavity of the hamsters.

This was also supported by data that was available at that time that demonstrated there was no ADCP N-oxide in humans. Based on current information, we do see the ADCP N-oxide in human plasma and in the urine at significant levels to suggest there is some potential that having that circulating in the human plasma and the urine, that there could be potential for carcinogenicity. Therefore, the hamster data, although you're seeing it located with the tumor formation specifically in the nose, it doesn't necessarily mean there can't be any toxicities in there.

As for immunosuppression, no data is really available to us to suggest that that's the mechanism resulting in tumor formation in the animal studies.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: I have a question for Dr. Durmowicz, which is really a clarification. The company, I think, has presented data focusing on two criteria; that's exacerbations and lung function. And in your presentation, at several points you mentioned standard of care.

I'm not clear about whether you were implying that the company really ought to do full trials of everything against all standard of care, and in which case, why is pulmonary rehab not included? We heard that pulmonary rehab was excluded from one study, and clearly that's an important issue.

The real issue is for the FDA. What are your standards? To get the simplicity, to get the results that the company's shown, they have to simplify -- as far as I can see, you'd have to simplify the studies. You can't have every drug in the world thrown in.

The question is, what are you implying when you say standard of care?

DR. DURMOWICZ: Well, I think that's an

important topic for general discussion, once we get over the cancer things and other things like that, and that is, where does the risk-benefit profile of this drug fit in with the patient population?

I think that if you look at a patient population that has severe COPD, has chronic bronchitis, and they've had exacerbations fairly frequently, then I think these patients are going to be already on three medications which are, right now, standard of care -- a combination inhaled corticosteroid and a LABA, and a LAMA on top of that.

Now, if you'd say to yourself, the risk of this drug is such that we don't want mild people with COPD to take it because of its risk profile, then I think you have to discuss whether it should be added as an add-on therapy, like a lot of drugs for rheumatoid arthritis are, or for other types of diseases, to what is existing therapies.

I think that's the point that I think is important for the committee to discuss because I think the ultimate risk-benefit profile of this drug is what we're here to discuss. We know there are some

benefits, and we know there are some adverse event issues.

So that's what I was trying to get at when I was pointing those things out, if that's helpful.

DR. CALHOUN: Dr. Joad?

DR. JOAD: This is a quick question to Dr. Abugov about when you showed that graph about that over time, exacerbation risk seemed to go down, the company showed a graph about time to exacerbations that they said showed that there wasn't a drop-off over time, if I heard them right.

I just wondered if you wanted to comment on their statistical evaluation, and why you think yours is a better one or a more accurate one, if you do. I just don't know.

DR. ABUGOV: I'm going to try to explain this. I did additional analyses, which looked at existing individuals who had already had one exacerbation, and looked at the time to a second exacerbation.

I'm going to call that a conditional analysis because I'm only going to look at people who

have the condition of one exacerbation before looking at whether they had a second one. My belief is that among patients who had a first exacerbation, roflumilast did reduce the rate at which they had a second exacerbation.

Then I took the individuals who had a second exacerbation and looked for time to third exacerbation. Roflumilast, again, had a small effect reducing the rate of exacerbation. I did the same thing for patients who had three exacerbations, and looked at four. So my belief is that among those analyses, roflumilast did have a -- I won't use an adjective "small," but it did have an effect.

So that's why I didn't argue with the sponsor's analysis. The easiest explanation for me is that -- given that analysis, the easiest explanation for me is that the apparent loss in roflumilast effect was perhaps due to patient withdrawal. But how to prove that mathematically when we're losing randomization over time as patients withdraw is kind of problematic, and I don't think it can be solved with this data set.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: My question is for Dr. Abugov. What is the impact of patients withdrawing from the active treatment group on the assessment of frequency of adverse effects? And is there any way to carry that forward or to see so that at the end -- in other words, if people who had adverse effects dropped out, you'd have an underestimation.

DR. ABUGOV: So could you repeat your question? I'm just having trouble parsing it.

DR. HENDELES: So did the withdrawal of subjects in the active treatment group result in an underestimation of adverse effects?

DR. ABUGOV: Well, I think this points out a problem with having patients withdraw from a study in general. You really don't know what happened to them afterward.

There are some hints at the FDA of asking sponsors, "Okay, once a patient withdraws treatment, maybe you can study -- look at them 'til the end of the study," and then we'll have an idea of what would have happened.

But in this study in general, once treatment was withdrawn, adverse events weren't necessarily followed.

DR. HENDELES: Maybe I'm not clear. I understand that. But does that cause, ultimately, an underestimation of the frequency of adverse effects for this drug?

DR. ABUGOV: Again, I couldn't say because I don't have the data.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: Thank you. I want to go back to this question of weight loss that was brought up by Dr. Swenson. As I look at the FDA slides and, for example, looking at all-cause deaths, slide 26, serious adverse events, slide 27, essentially they're equal in terms of proportions of those adverse events.

The question I have is, we then have this weight loss signal. And I'm trying to understand if this weight loss signal, again, is part of what we're seeing in terms of the adverse events. It's part of the phenotype of that adverse event, or it's helping uncover adverse events that are going on.

So I guess what I want to know is, did the FDA look at different amounts of weight loss that participants had, and how that is related to the incidence of adverse events?

DR. DURMOWICZ: I think the short answer to that is no. I think the discussion point or the interesting part about it is there are patients in the clinical trials that had anywhere from one to nine exacerbations of COPD. Some of the patients had nine over the course of the year.

You bring up the point of potentially what happens to the weight of the patients who have four, five, six, seven, eight, nine exacerbations of COPD, and how does that change things? And I think that information could be generated, potentially. I'd have to ask Bob about that.

But I think that's what you're getting. But the short answer is no.

DR. KRISHNAN: I'm sorry. Just to clarify, I'm not sure I was getting at that exact question. It was more, I'm trying to understand if there are populations in which we can identify as having more

adverse events, sort of a risk profile. And in that way, I was wondering if we can understand the relationship between weight loss and other adverse events.

DR. DURMOWICZ: I don't know the answer to that question right now.

DR. CALHOUN: Dr. Fink?

DR. FINK: Clearly this is going to be an issue where we look at the risk-benefit ratio. And if we're looking at exacerbations, and we only have one dose that's used, and there's no dose-ranging trial for this drug with the endpoint of pulmonary exacerbations, is this drug approvable, from an FDA standpoint, without a dose-ranging trial looking at exacerbations? I.e., a 250 microgram dose would clearly be safer. If it has the same benefits, that changes the risk-benefit ratio dramatically.

DR. DURMOWICZ: I think that from a regulatory perspective, there is no regulatory requirement to have a specific dose-ranging program with a nice S-shaped curve or something like that for dose-ranging. So to answer the first part of your

question, they're not required to have that.

However, if there is a significant adverse event profile difference, then you can say, from a safety perspective, was the right dose chosen, and should other doses be assessed? Especially since, as you pointed out, exacerbations was not one of the major endpoints in the dose-ranging trials.

DR. CALHOUN: Does the sponsor have new data regarding this question, or just a different interpretation?

DR. TAGLIETTI: No. It's new data. Actually, first of all, for the first -- just the previous question, we have done actually several analyses. But we can present them actually later, after the break. But we have done analysis to correlate weight loss to actually the safety profile in different groups of patients. So we can go more in details in this.

Actually, we did also additional analysis for exacerbations. So, of course, we can show the results now or after the break.

DR. CALHOUN: It's probably relevant to this

question. So if you have the data, let's see the data.

DR. TAGLIETTI: Yes. Slide up.

This is, for example, an analysis looking at exacerbational rates based on weight loss because we were interested to know if the weight loss was actually resulting in a lower efficacy.

So we divided the patients in three groups: patients with no weight loss, which means patients with actually either were stable or their weight was increased; patients who had had a zero to 5 percent weight loss, which we can consider sort of a moderate weight loss; and a greater than 5 percent weight loss.

The grouping was based on sort of a standard definition of what the percentage weight loss, but also to make sure that we have an adequate number of patients to calculate, actually, the ratio. And as you can see, in terms of exacerbations rate, we didn't see, really, a correlation between the patients who were losing weight and their benefit in terms of hazard ratio.

I would like now to show another slide. And

of course, we can come back later.

Slide up, please. Of course, one of our major concerns is the patients who are underweight. So we look in patients who are underweight, and we looked how was their profile. As I mentioned this before, the overall number of adverse events in underweight patients is similar between the two treatments.

Weight -- of course, there was a higher weight decrease in the roflumilast 500. We are not arguing that weight loss is actually associated with the use of roflumilast. We had, however, a higher number of COPD actually in the patients, in the placebo patients. And all the other parameters were, let's say, comparable to the general population.

We did also an additional analysis. And this, of course, we are starting to slicing and dicing, with all the caveats that we should do for such type of presentations.

So slide 28, please. Yes. Slide up.

So we look, actually, here at the smallest group of the underweight, which are those patients

that actually lost weight. So this is 62 patients in roflumilast 500. Of course, it's a larger number because there were more patients who lost weight. And again, the number of adverse events, still considering the small sample size, suggests that the profiles between the roflumilast and the placebo were comparable.

We may go also more in details later on. What we saw is a higher number of COPD exacerbation, actually, in the patients who lost weight in the placebo group, and similar numbers of -- this was one of our concerns, the possibility of higher number of infections in underweight patients that were losing weight. And we didn't see this.

Slide up.

This is another analysis. And I don't want to overwhelm, so please stop me when you think I show enough data.

[Laughter.]

DR. TAGLIETTI: Here the number again is divided by the four groups that we identified. These are the underweight, the normal weight, the

overweight, and the obese patients. And these are -- again, we looked at the mortality to assess if -- mortality, in terms of BMI, to check if there was a difference.

Of course, we saw higher mortality in the patients with lower BMI. This has been shown, lower BMI, to be actually -- yes. I will close my statement quickly. But there is clearly a comparable, comparable in terms of mortality, between the different groups.

Slide down.

So our point is that we have done quite an extensive -- quite extensive analysis because, of course, weight loss is associated with roflumilast. And we want to make sure that we understand how this can impact, therefore, the patients.

DR. CALHOUN: Thank you. Jerry, does that address your --

DR. KRISHNAN: [Nods affirmatively.]

DR. CALHOUN: Okay. Dr. Schoenfeld?

DR. SCHOENFELD: So I always have a great deal of difficulty when the issue is sort of the

estimates and not the significance tests, because then the question is, how good is good enough, and how big are these numbers? And I often defer to the subject matter experts, who see patients, who kind of have an idea of what's a big improvement and what's a little improvement.

But it's often good when looking at estimates to worry a little bit about their variability, which is a statistical issue. And so I was trying to do some back-of-the-envelope calculations, and I'm getting -- and I'm having trouble doing it. So I was asking -- my main question is to ask somebody else to do it, either Robert from the FDA or somebody from the company, to just give us those.

So the one I was able to do easily was that we know the FEV1 value to plus or minus about 15 milliliters. And thus, we know that the difference is about anywhere from something like 65 -- I think it's actually good to look at the better end of that confidence interval to give a compound the benefit of the doubt, basically. So that the best it could be

would be about 65.

I think that it's up to the subject matter experts to interpret that. It's about -- it's, I think, about one-third of -- I'm not exactly sure. It's about one-third -- and this is something you might look at -- it's about one-third of the variation in the population that this would be about. But I don't know whether that's -- the standard deviation in the population, I don't know if that's relevant.

Now, in terms of the other figures, the statement was made that it's about one moderate or severe exacerbation in five years. And so I was trying to calculate what would be the lowest confidence interval of that. In other words, what's the best it could be, one every three years or one every two years? I would like to see that calculated. So if we're going to bandy about one every five years, we might as well know what the best it could be.

Then the severe exacerbation rate, we were talking about one every 30 years, I think it was. And so I'd like to know the best and the worst that could be. And I couldn't calculate that too quickly. I

don't know. I'm sure it's easy to calculate, but it's hard to do with the -- both of you, both the people in the company and the FDA, are much closer to the numbers than I am.

So those are the two questions I have. And I don't really need an answer right away because I think that if I can't calculate it in two or three minutes, I'm sure you can't, either.

The other question -- the other comment is that it is very, very hard to actually determine whether the hazard of an event is going down or what it's due to over -- in a serial study like was shown here. It's just very hard because there's -- because it sort of makes the assumption -- the picture kind of makes the assumption that the Poisson model is really the right model. And all of us know that the Poisson model is fine for statistical tests and so on, and won't lead us too far astray, but it's -- in reality, it's unlikely that things are that simple.

So you could begin fitting frailty models, and you could write a couple of statistical papers on whether or not the rate went down, and so on. But

it's probably hard to know for sure. And I guess you would agree with me on that, or I'd want your comment on that.

DR. CALHOUN: Jerry, did you have a question about this particular matter?

DR. KRISHNAN: I did, David. I want to be, I guess, cautious in taking that .2 exacerbation rate and multiplying it out and deciding that we want to know how many exacerbations might it save when followed over multiple years, or how many excess people would benefit from the use of the drug.

The reason I say that is because exacerbations cluster in individuals. There are exacerbators and non-exacerbators. So we ought to be a little bit careful in averaging that out and calculating the number needed to treat in order to save one exacerbation. Right?

DR. SCHOENFELD: Yes, I know. It's very hard to quantify these things. And I'm not sure that's the best way to do it. But at least we should get some idea of what the variation is of when we look at the absolute benefit of the drug, if there's some

way of quantifying that so that we know the best it could do -- not only the worst it can -- we always compare the worst it can do to zero. Okay? That's the worst. Drugs that the worst it could do would be zero we don't usually approve.

But when we're trying to -- try to judge the estimates, probably we should look at what the best it could do, knowing that, in fact, clinical trials -- that some drugs do actually better in practice than they do in clinical trials. But we can't really quantify that.

DR. CALHOUN: Okay. We're going to take one more question before the break. And then as with the earlier session this morning, we'll come back and catch two more people who are in the queue.

So, Dr. Carvalho?

DR. CARVALHO: Thank you. This is a follow-up question to Dr. Honsinger's, which is back to the question of lung cancer.

What I'm wondering is if the FDA or if the sponsor has any information regarding the cell types of those lung tumors. There are some tumors that are

typically much more fast-growing, and I would wonder if there's any deregulatory effect of this protein that may hasten those along, as compared with tumors that are typically slower-growing.

DR. DURMOWICZ: The adverse event term that I see is bronchial carcinoma. That's the one I see. I don't have it broken down into any different types of it, whether it's an adenocarcinoma versus something else versus something from asbestos, a mesothelioma.

DR. CALHOUN: Yes, sir?

DR. TAGLIETTI: We don't have this information available. First of all, we have to realize that these were cancers collected in a period of probably 10 years, many different studies. And we don't have additional information other than the one just mentioned.

DR. CALHOUN: Okay. Thank you.

So just from a point of order, if it is possible for you over the lunch break to poll your clinical database to address from the AE reports Dr. Carvalho's question, I think that actually would be both helpful and perhaps relevant to the biology.

If it's not possible, then it's not possible.

Okay. At this point we're going to take a lunch break of 42 minutes. We'll reconvene at 1:00 p.m. Panel members, please remember that there should be no discussion of the issue during your lunch break. Thank you.

[Whereupon, at 12:18 p.m., a lunch recess was taken.]

A F T E R N O O N S E S S I O N

DR. CALHOUN: Good afternoon again. So let's call ourselves to order again.

So in terms of structure for this afternoon's proceedings, we have three questions from the committee that relate to the FDA presentation. So those are questions of clarification for the agency.

At the end of that period of time, we have some data from the sponsor that was requested during the discussions this morning. And so we'll ask them to present those new data at that point.

Then following that, we've got questions from six of the panel members that are hanging from the sponsor's original presentation this morning. We'll take care of that, and then we'll move on to the deliberations.

So at this point, the first question for the agency is Dr. Raghu.

DR. RAGHU: The question that I had for Dr. Durmowicz was to do with this business of the discordance of what's significant in terms of the FEV1. Granted, there is a 50 cc change. And

acknowledging that these patient populations are quite sick, with an FEV1 to start out with a liter, so some improvement is potentially considered as improvement.

But going onto those two data -- the St. George's Respiratory Questionnaire tool, which is a very good tool for the COPD and chronic bronchitis patient, as well as your BDI/TDI, it is my perception, and I want you to correct me if I'm wrong, is that for a given patient, that 50 cc change in the FEV1 is not going to be noticeably different, based on the BDI/TDI as well as the St. George Questionnaire. Is that a fair assessment?

DR. DURMOWICZ: Are you saying -- are you asking that a 50 ml change in FEV1 would not be reflected in the BDI/TDI and the SGRQ? Is that the question?

DR. RAGHU: No. If that change is not reflected by the patient's perception of feeling better as far as shortness of breath is concerned.

DR. DURMOWICZ: Well, I think that what the data show, it doesn't seem like the patient's -- the global change in 50 mls, as an average, is globally

reflected in the BDI/TDI or the SGRQ, although there are very minor positive, nominal changes in those. So it could be, but it's not -- doesn't reach the minimally clinically significant point.

But I think that the question that you allude to overall for us to discuss is the relevance of a 50 ml change.

DR. RAGHU: Yes. The other question I had was to do with this arbitrary zone of definition of acute exacerbation based on patient's own subjective symptomatology, which is, granted, that's how it is done. Were there any geographical differences in the acute exacerbation, if anybody did a post hoc analysis on this?

Because I see at least in the 125, there are over 330 patients coming from India and 300-some patients coming from Italy and Spain and 290 patients coming the United States. So I'm just wondering if there is a fair amount of differences in terms of the acute exacerbation as being perceived by the patients, and the cultural changes in their behavior in terms of treatment.

DR. DURMOWICZ: I think, given the definition that was used for exacerbation and carrying that throughout the studies that you mentioned, I don't think we did see a geographic change across countries.

DR. RAGHU: Okay. And likewise, there wasn't any seasonal variation, nor taking into account whether these patients were receiving a pneumovax or flu vaccinations and other preventive measures, so to speak?

DR. DURMOWICZ: I don't think those last two data sets were collected, whether they got vaccinations or what season it was when they had exacerbations.

DR. CALHOUN: So as a point of clarification for Dr. Raghu's question, does the sponsor have information on the prevalence of influenza and pneumovax vaccination, and do you have data on the seasonality of the exacerbations?

DR. GOEHRING: Udo-Michael Goehring, clinical development, Nycomed. I want first of all to answer the data question that was asked concerning the

regional differences of our trials.

Slide up, please.

Here you can see a prespecified subgroup analysis that we performed in each of the trials, here given in the pooled, pivotal trial analysis, where you can see, subdivided by the baseline region of North America or rest of the world, that there's no regional differences in the effect of -- limited differences in the -- in the regional aspect of this trial in perspective of reduction of exacerbations. And in fact, the same is true also on the other lung function variables, pre-FEV1.

Slide down.

The other question that was posed as a second part, and if I can shortly reconfirm this, was in aspect of vaccination, if this is correct. Based on the inclusion criteria, vaccinated status was allowed to be enrolled in the trial. However, this status should be preserved already three months prior to inclusion of the trial so nothing -- no changes stipulated during the course of the trial. So we cannot have any input in this data perspective.

DR. CALHOUN: Okay. Thank you.

Dr. Burlington?

DR. BURLINGTON: Sure. I wanted to ask, among the patients with excess -- or the excess patients treated who had depression symptoms, how were those collected in the first place? Was it systemic, or were these spontaneous? And how were they evaluated? And then there's a third item. Were all of them part of the Columbia review?

DR. DURMOWICZ: I think the depression data were not collected actively. They were collected like adverse events are usually in a trial, where they would either ask "How are you feeling" at visits or potentially in a patient diary.

The Columbia classification that was performed, I don't know the exact patient population that it was performed on. I believe, at best, it was the COPD safety pool. At worst, it was a sub-class of that safety pool. But it was not the whole -- it was not the whole roflumilast population. I don't know if that's helpful.

DR. TAGLIETTI: So I want just to confirm,

yes, that depression was just collected as an adverse event. And the Columbia was performed only COPD safety pool. However, we looked into the full data set in terms of the other indications to make sure that there were no adverse -- actually, this was also following a request from the agency. And there were no additional cases of suicidality in the rest of the database.

DR. CALHOUN: Okay. Thank you.

Ms. Fiore?

MS. FIORE: Well, I'd like to make some observations from a patient's perspective. I heard something about 50 ml improvement, would you feel it. Hey, I'd be flying with 50 more mls. And I'm at .8 now. You can imagine what it would do for me.

Also, when it comes to the weight loss, have you taken into consideration that the patient -- the medication is effective. The patient is feeling better, becoming more active, doing things that they want to do, and that is causing the weight loss.

As far as depression and COPD is concerned, they're twins. They walk hand in hand. And I think

that the patients probably have expectations. They're looking for Son of Tiotropium. And when that doesn't happen, they become -- it increases the intrinsic depression of COPD.

DR. CALHOUN: Okay. I've been advised that the sponsor has developed information over the lunch break in response to four questions from the committee earlier this morning. So at this point, I'll invite the sponsor to present those new data.

DR. TAGLIETTI: Absolutely. So we are planning to address, actually, four questions that were raised. The first one will be the safety profile, the adverse event profile, in patients who had moderate and severe exacerbations. The second question is about the exercise data. The third one will be to clarify some aspects about tumorigenicity, and specifically, also, on the role of ADCP N-oxide. And the last one will be to answer the question of Dr. Schoenfeld about some statistical issues.

So let me start with the first one, which will be the safety profile of patients who had moderate exacerbations.

Slide up, please. So this is the group of patients who had moderate exacerbation in the safety population. So this is -- there were a total of 629 subjects, and 718 in placebo, which, as you expect, there are more in the placebo group.

The overall number of the events -- and I apologize; all our slides, usually, we have roflumilast on this side. So in these two slides, actually, they will be inverted. You can see the difference in terms of any adverse events is higher on the roflumilast -- in the roflumilast 500. But it seems to be the same ratio that we have seen, this difference of 5, 6 percent that we have seen also in the general population.

The most common event is weight decrease, which is not unexpected. And again, it's similar to what we are seeing in the general population. Diarrhea, again 10 percent, which is what we expect based on the general population.

COPD exacerbations are higher in the placebo group, and all the other events tend to be similar. And also we have -- our last one is pneumonia, where

we have a comparable number between the two treatments.

Slide A-4, please. Okay. Slide up.

This is actually for AEs for subject who had severe exacerbation. Now, all subjects had at least one adverse event, and this, of course, is because of the definition of exacerbation, which was hospitalization, and, therefore, had to be recorded as an adverse event. In fact, basically almost all patients had a COPD exacerbation in this group.

All the other events, they seem to follow the same common pattern, with weight decrease higher, diarrhea higher. There is a higher incidence of pneumonia, but it seems to be small, relatively small in the sample size. Again, I've been -- we have been talking about pneumonia before. And also, the other events, we have nasopharyngitis and hypertension and insomnia.

So the safety profile, I hope these address the question of the committee. The safety profile of the AE patients with moderate or severe exacerbation seems to be comparable to what we have seen in the

general population.

Slide down.

Now, I would like to have Dr. Calverley talking about the exercise data.

DR. CALVERLEY: Thank you very much. I'm Professor Peter Calverley from the University of Liverpool in the U.K. My conflict of interest of interest statement is identical, I think, to four other people in that I am receiving, I sincerely hope, travel expenses to attend this meeting, as well, fortunately, as an honorarium.

I've acted as an advisor to the people who've conducted these studies, and developed several of the trials, and published them. I am not part of a speakers bureau. I don't have any financial involvement in any way, shape, or form. And the outcome of this hearing is not going to influence any remuneration on my part. So I hope that covers that.

The issue which was raised by Dr. Honsinger is an important one, which is -- it actually ties in with our patient representative's very important comments about what this drug might do to

breathlessness. And there have been two studies that were conducted very on in this trial, this trials package.

One was a six-minute walking study, which, in retrospect, was underpowered and showed virtually no difference, and numerically it favored the roflumilast, but certainly wasn't statistically significant, so I've not got that on a slide for you.

There was an exercise test, study, done by Dennis O'Donnell in Kingston, Ontario, who's a doyen of this field, which showed, again, an improvement and a trend towards improvement in the patients on roflumilast, but certainly wasn't statistically significant.

I think that reflects people who were recruited who, to my mind, wouldn't constitute the patient population, who, in retrospect -- a great thing, the retrospectoscope (ph) -- we would now identify as being the targeted people because, in fact, these studies have shown us how our ideas about COPD have evolved, from trying to treat everybody with one drug to trying to specifically phenotype people.

And the data with roflumilast have helped us do that.

I think it's a little unfair to say they kept rolling the dice until they got two trials they liked because each trial has been built scientifically on what came before, and has been part of a structured idea, which now fits in with other data. The benefit of an anti-inflammatory agent like this one will be in preventing exacerbations, and the magnitude of that benefit is relevant to patients in that context. Thank you.

DR. ROWE: The next topic we'd like to address is related to the issue that ADCP N-oxide in and of itself is not carcinogenic. And Dr. Martin will start this discussion.

DR. MARTIN: Terry Martin, Forest toxicology.

So we've heard several times that ADCP N-oxide is carcinogenic. We think it is not. ADCP N-oxide is actually converted in the nasal mucosa of rodents into a reactive metabolite, which is an epoxy ADCP N-oxide. That is directly toxic to the nasal mucosa of the hamsters and other rodent species,

actually.

We have done other studies to support this, to know that ADCP N-oxide is not the toxic entity. We have done CYP inhibition studies, where ADCP N-oxide has been tested or found in the rodent mucosa, and shown that when you give a CYP inhibitor, you get increased levels of ADCP N-oxide, but no toxicity at all.

We've also done in vitro studies where we had CYP antibodies against the actual CYP isozyme that converts ADCP N-oxide to the epoxy. So we've shown that when you inhibit the CYP2G1, which is the CYP enzyme, that you do not get formation of the reactive metabolite.

So for these reasons, we believe that ADCP N-oxide is not the carcinogenic agent.

DR. GHAHRAMANI: Parviz Ghahramani, Clinical Pharmacology, Forest.

Just to add to what Dr. Martin said, the human data in terms of human liver marker zones, and also the human liver product that we've tested before with respect to the metabolism, also showed no

conversion of the N-oxide, ADCP N-oxide, to hydroxy ADCP N-oxide. So that's very specific to hamster with the 2G1 enzyme, which is making that conversion.

Also, there's evidence out there in 2007 papers published by Dr. Zhao's group in New York showing that 2G1 is also not functional in humans, which is further establishing that. Plus the fact that in the human studies, at least in one study, we did measure and try to detect whether there's any hydroxy metabolite of ADCP N-oxide, and we could not detect that.

DR. SCHEIN: Phil Schein, consultant.

Just to give you a clinical perspective on these data, having searched the preclinical information, I found no evidence that any of these agents are genotoxic in vitro. There's no evidence of adduct formation. Basically, there's no evidence of a direct-acting carcinogenic effect.

In regard to the potential relevance of the hamster data, there is one case of head and neck cancer in the COPD database of roughly 6,700 patients. So it's very hard to make a direct correlation by any

means.

Perhaps, while I'm up here, there was a question related to the distribution of histologic types of lung cancer. So over the course of lunch, we went through the database, to the extent we could. We did surface 35 lung cancer patients in the active treated group. I can show you the distribution is sort of garden-variety of lung cancer, the predominate expression being non-small cell lung cancer.

The more aggressive histologic types would be small cell. But even there, hopefully I'll have an opportunity later in the session to discuss the issue of biologic plausibility and these time frames. We found only four cases of small cell in the entire series that are designated such, but even those could not possibly have arisen in the course of three to six months after drug exposure. But hopefully, I'll have an opportunity to readdress that later.

DR. TAGLIETTI: We would like also to answer one specific question with some data.

Slide A-11, please. There was a specific question on if the -- if there was a higher incidence

of tumor in patients who had GI events. And so this is the slide. Slide up. We just prepared this, so sorry if the slide is just the basic information.

This is the tumor incidence in patients with GI events. And this is the incidence of tumors in the two groups, suggesting that the patients with GI events actually probably, I think, were suggested by one of the members of the committee that could have been to further investigation.

Slide A-12, please. Slide up.

The same is true for weight decrease, where there is -- there appears to be patients with weight decrease having a higher incidence than no weight decrease, and this appears to be, again, a possibility, at least, and I think, more speculative, that the higher number of investigations may have resulted in higher diagnosis.

DR. CALHOUN: Erik, those data went to your specific question. Do they address what you needed to know?

DR. SWENSON: [Nods affirmatively.]

DR. CALHOUN: Okay.

DR. ROWE: And then the last issue we wanted to address had to deal with Dr. Schoenfeld's statistical inquiry. Dr. Koch will address that.

DR. PEI: Mr. Chairman, can I respond to that carcinogenesis?

DR. CALHOUN: If we could, why don't we hear the end of this, and then I'll -- then we can move on to your view.

DR. RAGHU: If I can ask the sponsor a question? The question that is bugging me about this cancer is how did these patients get diagnosed with cancer? Because this was not a cancer screening study design. So was it patient symptom-driven? Of course, it is -- a weight loss is one driven situation. But in other words, are there more patients who have not surfaced as lung cancer or any other cancer? So how did it get picked up?

DR. CALHOUN: Can we come back to you, Dr. Raghu, when we finish?

DR. RAGHU: Yes.

DR. CALHOUN: Put him on the list, please. Thank you.

Go ahead, sir.

DR. KOCH: Gary Koch. I am a professor of biostatistics at the University of North Carolina at Chapel Hill. My activity here with respect to Forest is through a cooperative agreement between Forest and the University of North Carolina. That agreement provides funds that support part of my university salary, as well as for travel reimbursement.

Dr. Schoenfeld had some questions about precision of results from the pivotal studies. For the change in FEV1, the point estimate was 39 from 124, and it had a confidence interval of 18 to 60. So the confidence interval was roughly plus or minus 21, and the background standard deviation was 209. So the ratio of the effect size to the standard deviation would have been about 20 percent.

In Study 125, the change in FEV1 was 58. The confidence interval was from 41 to 75. And again, the standard deviation was near 200, so there the effect size was about 30 percent of a standard deviation. So on average, the effect size is in the vicinity of 25 percent of a standard deviation.

That's what 50 would represent relative to 200.

For the exacerbation rates, the risk difference in the exacerbation rates were approximately .2 for one study and about .3 for the other study. And based on the p-values from the two studies, we've determined that the standard error would be somewhere in the vicinity of .1.

From there, we have done a calculation of number needed to treat. And for the 124 study, the number needed to treat is 5.3, with a confidence interval from 2.8 to 48.5. And for the 125 study, the number needed to treat is 3.6, with a confidence interval from 2.2 to 11.1.

If possible, I'd like to also provide some clarifying comments about the role of the time to first event/time to second event/time to third event with respect to the sustaining of effect. Would that be okay?

DR. CALHOUN: Yes. That's relevant. Yes.

DR. KOCH: So as was indicated in the FDA presentation, they examined what was going on in the latter part of the trial by looking at event rates in

the latter intervals of the trial -- numbers of patients with an event among those at risk during the last eight weeks of the trial, or the preceding eight weeks, or the preceding eight weeks to that.

They basically saw the trends that they reported in the presentation. But they also noted that discontinuations could have an impact on that, particularly patients in the placebo group with high rates of exacerbation early on in the trial. Discontinuing the trial would not contribute to these event rates calculated by interval in the latter part of the trial.

So that is why the sponsor chose to -- and slide up -- use the information in time to first exacerbation, time to second exacerbation, and time to third exacerbation, as well as what you saw in the main presentation for time to fourth and time to fifth, to evaluate the issue of sustained effect because these analyses are time to event analyses. So everything begins at the time of randomization, and then continues through the time of the occurrence of the event.

There was some mention of looking at time from first to second, time from second to third, time from third to fourth, showing similar trends. But those analyses are not protected by the randomization. Those analyses only involve the people who had a first event or who had a second event.

So these analyses begin at the time of randomization. Now, I could show you that people tend to have second exacerbations at later points in time than they have first exacerbations. They have third exacerbations even later, and fourth and fifth exacerbations later than that.

So by preventing time until the later exacerbations, which are occurring at later points in time, that is the way in which the treatment is having a sustained effect throughout the follow-up period.

DR. CALHOUN: Thank you. So at this point, I'm going to invite the FDA to respond to this question of the carcinogenicity of the ADCP N-oxide, which the sponsor has just asserted is not carcinogenic. And you have data to the contrary?

DR. PEI: I don't have data to the contrary,

but I just need some clarifications.

One, there was no dispute about the evidence that roflumilast --

DR. CALHOUN: Could you introduce yourself? I'm sorry.

DR. PEI: Oh, I'm Luqi Pei. I'm a pharmacologist in the FDA, and I did a review of the nonclinical data of this application.

First, there is no dispute about the evidence for the tumorigenicity of roflumilast given to hamster for two years can cause nasal tumors. This tumor is dose-related, and I think the -- and the tumor incidence rate was zero for roflumilast 4 milligram or less, 3.3 percent for 8 milligram per kg, and is 12.5 percent for the 16 milligram per kg per day. And that's a little bit different from, say, isolated nasal tumors in hamster. That's 12.5 percent.

As far as when the tumor was found in the hamster, the sponsor did quite extensive mechanistic studies. I'm not going into detail into how the study was done, but there was good evidence shown that the

roflumilast N-oxide, a pathway, is the -- may incorporate in this finding.

If you plot the roflumilast N-oxide pathway, that means if an ADCP N-oxide is not produced, then there is no nasal toxicity in the hamster or the rats. And because the nose is a major target of roflumilast toxicity in the rodents, it was believed that the carcinogenicity was related to the direct nasal toxicity.

We do not have direct evidence that says, well, if you completely block the tumor agent, the ADCP N-oxide pathway, there will be no tumor produced in hamster. But it's a possible pathway. We believe that's plausible. So we believe that pathway plays a role.

Because the ADCP N-oxide in the hamster is converted -- because the ADCP is converted to ADCP N-oxide in the rodents by enzyme called CP2-T1, and this same enzyme will further convert this N-oxide to epoxide. That is much more active and could bind the two proteins and -- could bind two proteins or cause DNA adducts or protein cross-links. That's a

plausible pathway for tumorigenicity.

When we first got this data during our review, the sponsor, the applicant, argued that humans do not produce this ADCP N-oxide. And the data, we don't have that -- at that moment, it was indicated that. So the FDA expert committee, called the Carcinogenicity Assessment Committee, concluded that this tumor formation in the hamster may not be relevant to humans because humans do not produce ADCP N-oxide.

However, during this NDA application, we found that that statement is no longer true, and humans do produce this N-oxide. But we don't know what enzyme is involved. And because in the rodents the same enzyme converted ADCP to N-oxide, and further converted to epoxide, and the humans -- we don't know first if the ADCP N-oxide was produced, and now we found out it is produced, but we don't know what enzyme is involved. Furthermore, whether it's converted into the epoxide, which is probably the culprit of this action, and we don't know what happens in humans.

DR. CALHOUN: Okay. Thank you. I think we heard that line of reasoning this morning, as well.

We have Mr. Mullins regarding clarification of the FDA presentation?

MR. MULLINS: Right. This question is for Dr. Abugov. I had a question about the psychiatric observations. And I wanted to clarify, and I wanted to frame it from the standpoint of a consumer.

If you were speaking to a consumer, aren't there clear indications, based on the observations in sleep disorders, suicidal attempts, depression -- would you clarify that or would you feel comfortable saying that this particular therapy is mood-altering?

Secondly, do you feel comfortable that we -- based on the data that you reviewed, is this -- does this data speak to what were the precursors, the preliminary indicators for the extreme cases of the psychiatric -- the severe psychiatric cases that attempted suicide?

Were there any indicators for consumers so that they know -- when do we know when someone is reaching that danger zone, and if you are getting to

that point, where this is a point where it's fatal? So I'd like you to speak to those two issues, please.

DR. DURMOWICZ: I think that I'm probably a better person to speak to those issues as the clinical person than Dr. Abugov, who's the statistical person. So let me just try to address some of those issues that you just brought up.

First, the definition of what's a mood-altering drug is very broad. And in that context, if you say can a drug cause you to be anxious, not sleep, be nervous, have other issues related to psychiatric thoughts, then I'd say it is a mood-altering drug. Does it cause you to go to sleep? No. That's a mood-altering drug. Does it cause you to get hyperactive? No. That's another thing.

So in that specific subset of adverse events that we saw, I think there's the potential for it to be "mood-altering." But that's a very, very, very kind of broad wastebasket kind of term.

With respect to -- I think your second point was what would you tell a patient, or how you would you decide what to do or what signs you would look at

to say you can't take it anymore. I think that that's what you were kind of getting to.

I don't know how you would make that decision. I think that it was brought out by several people, including our patient representative, that there's a baseline, fairly high incidence of "life is miserable" with people with severe COPD. And when to pull the trigger and say, "I'm worried about this person's going to have a major psychiatric adverse event or not" is a thing that's part of that risk-benefit profile that is hard to answer.

So I don't really -- I'm not able to tell you specifically. Could you say that, in some, you would have to link some early symptom that you could hang onto that was -- like insomnia that was correlate and say take him off the drug? But I don't think we would really know. That's as good as I can do.

DR. CALHOUN: Okay. Dr. Raghu?

DR. RAGHU: Yes. I was referring to the -- how did this cancer get surfaced in this patient population. Was it driven by patients' particular symptoms like hemoptysis or whatever besides the

weight loss? In other words, they were not being screened for cancer. So are there more subclinical cancers in this patient population?

DR. DURMOWICZ: Are you asking me or --

DR. CALHOUN: Well, these are questions that are directed to the FDA for clarification.

DR. DURMOWICZ: Oh, I'm sorry. I don't know. There was no prospective -- this is not a cancer study, as you just brought up and as the company brought up before. So again, cancers would probably be reported, quote unquote, "passively," or found out about by a patient seeing their own private physician. Or, again, in these studies every four to six weeks they were seeing an investigator. So potentially, there was more observation of patients, more examinations.

Now, you would say that that could be one of the reasons why cancers were detected earlier. The interesting point about that is that since these studies were so well randomized and stratified, why would there be an imbalance? And I don't know.

DR. CALHOUN: Okay. The last question for

clarification to the agency is from Dr. Krishnan.

DR. KRISHNAN: Thank you very much. My question is about trying to better understand whether, from a patient-centered standpoint, they would notice a benefit from taking this medicine.

We have some information that it reduces exacerbations. But I want to go back to the SGRQ, which is often used as a marker of whether or not patients feel better. Any analysis the FDA did in terms of the proportion of people who noted a clinically meaningful benefit, so the proportion of people that had a 4-unit improvement in the SGRQ and how that relates to the placebo condition?

Because while the mean change might be smaller than the 4-unit mean change, there might be some number of people that actually benefitted. And they may be the same groups that actually had fewer exacerbations, for example.

DR. ABUGOV: We didn't perform such an analysis. But I invite the company to come forward if they did.

DR. RABE: Klaus Rabe from Leiden. I'm not

the company; I'm a consultant, as you know from the presentations earlier. Thank you for this opportunity.

What we have been looking at specifically at the discussion about the definition of exacerbations, how they would or would not track with symptoms. What you need to know from these clinical trials is that it was not only censored by the investigator whether or not somebody had an exacerbation, there was a diary card by patients also.

So what we tried to do is we tried to relate do, in fact, symptoms that would be associated with an exacerbation track with the actual diagnosis of having an exacerbation which gets, I think, close to what you're getting at.

DR. KRISHNAN: I mean, it sort of does, although that becomes a co-linearity because it's the symptoms that drives physicians to potentially treat. So rather than answering the questions based on diary cards, I guess I would prefer if you had information about the proportion of people who had at least a 4-unit improvement in the SGRQ and how that relates to

the placebo.

DR. RABE: No, we don't.

DR. KRISHNAN: Is that something the sponsor has?

DR. RABE: That's something that I wouldn't know. But maybe, Paul, over to you.

DR. ROWE: The responder analysis was not performed for SGRQ, but there was one performed for TDI in the pivotal trials, and perhaps that may shed some light on the topic as well. It's more specific, as you know, for breathlessness.

Slide up, please.

So the TDI responder analysis was performed for both pivotal trials, M2-124 and M2-125. And as we see here, in the roflumilast groups in both those trials, we saw a 38 percent response in the roflumilast active treatment groups. And that was consistent with what was seen in the earlier one-year trial of 39 percent response there.

Slide down.

DR. DURMOWICZ: Can I just make a comment that it's interesting to note that the responder

analysis for the SGRQ was better in the MT-111 study, and that's one of the studies that failed on exacerbations. So there seems to be a potential disconnect between some of these secondary endpoints and what the primary endpoints are.

DR. CALHOUN: Okay. Thank you.

Dr. Joad?

DR. JOAD: Yes. I wanted the FDA to comment on the comment that I think I heard the sponsor say, that they thought these degree of side effects were in the realm of what you usually expect with a chronic medication. I believe they said that. Do you believe that most chronic medications have this degree of side effects?

DR. DURMOWICZ: Well, I think that that's a very interesting question, and it's not something that you can state across all drugs and all indications because I think that taking into context side effects, you also have to take into context what disease it's treating.

For instance, if I -- 20 years ago when HIV was a big issue with regard to not having therapies or

people taking certain cocktails, you might tolerate a whole lot of toxicity. So it becomes an individual basis.

Now, for drugs for COPD, this has got a quite different toxicity profile from other drugs that are approved for COPD, i.e., bronchodilators or inhaled corticosteroids, where the safety profile for COPD, at least, is relatively benign. Here they're more varied, and that's a point of discussion, and again, to take into the risk-benefit. So that's about as far as I'm willing to go on that one.

DR. CALHOUN: Dr. Swenson?

DR. SWENSON: Yes. To the FDA's presentation, I was somewhat curious about the intention to treat and per-protocol analysis that you provided on pages 39 and 40, and was curious in that although there was -- it appeared that there was quite a bit of protocol violation and maybe only about two-thirds of the patients could be considered in the per-protocol analysis, it was interesting to see how robustly the per-protocol analysis matched the FEV1 across both studies.

But then in the exacerbation rate, the data on page 40, there is not that concordance. And surprisingly, one would think that the per-protocol analysis would show even more robust benefit, and it didn't on at least one of the studies.

Could you elaborate on that? You didn't present it in this morning's discussion.

DR. DURMOWICZ: No. We didn't present it. You are quite correct in that there is a difference in the significance of the Study 124 with and without the early withdrawals and the patients that withdrew, the ITT population, which is all people randomized or all people given one dose, and the per-protocol, which is actually the patient population that completed the study, took all the drug they were supposed to.

As you mention on page 39 of the document, clinical briefing document that we had, the ITT population wins and the per-protocol population loses on exacerbations. And like you said, that's quite unusual. You would think, in most studies that we see, the per-protocol pollution is the population that does better. And that's why we stick to the ITT

population, because that's the most conserve estimate.

This is flip-flopped. And the only rationale I could think of in doing that is there are a whole lot of patients, I think up to 20, 30, 40 percent, that take medications they're not supposed to take, i.e., inhaled corticosteroids, or a LAMA when they're not supposed to take a LAMA because of the concomitant medication rules for the study. And they would not be in the per-protocol population because they were a major -- what do you call it -- protocol violation.

So that's the major difference, is that patients that had major protocol violations -- and that's mostly taking drugs they were not supposed to take for COPD -- changed the results of the per-protocol population. You'll note that it's not just a numbers issue because the effect size goes down. It's not just nonsignificant because there's 300 less patients in the study.

DR. SWENSON: Well, that does sort of get to the point of out in the real world, people are taking different medications. And it's hard to recreate

what's really going to be the standard practice when you develop these studies. But it speaks to a confounding issue, I think.

DR. CALHOUN: Okay. So that concludes the questions of clarification for the FDA presentation portion. We now have six questions that are still in queue from this morning that were relevant to the sponsor's presentation.

The first of those is Dr. Hoidal.

DR. HOIDAL: The first question -- I have two questions. The first relates to the slide 55. After the initial improvement, was there any -- do you have any evidence of the rate of decline being different in the control and treated group, either?

DR. ROWE: Paul Rowe, clinical development.

So just to clarify your question, you're asking for over the course of the one-year treatment period, did we see any declines in FEV1?

DR. HOIDAL: No. The rate of decline after the initial improvement with the drug. So if you compare the placebo versus drug, is the rate of decline changed?

DR. ROWE: Slide up, please. So here is the lung function in pre-bronchodilator FEV1. Change from baseline is on the horizontal access, and the 52-week interval for both trials. And as you see, at about a month in, you see the effect in FEV1 improvement in both trials. And it's pretty consistent, and appears to be parallel to the placebo lines in both trials.

Further comments on this, I'll ask Dr. Calverley to comment.

DR. CALVERLEY: I think that's a fair summary of what the data are. I just would like to kind of put in a small health warning. People have tried to look at data over one-year trials to extrapolate rate of decline, and clearly this is -- there's a major statistical effect of the initial offset which you identified.

I've published a number of papers about that, including some with positive results and some with negative. And it's clear that the data over one year is, at the very best, hypothesis-generating. I wouldn't want to go away with looking at those graphs and making any conclusions about whether the lines are

closer together or not. It's just not a robust scientific test of that hypothesis.

DR. HOIDAL: The second question was, was there any difference in -- so about a third to half of the people in the pivotal trials were smokers. Was there any evidence that there was a difference in smoking cessation in the treated versus the placebo group?

DR. ROWE: To address this question, I'll ask Dr. Goehring to respond.

DR. GOEHRING: Concerning the smoking effect on roflumilast, we have in the totality of the database no -- we see a consistent benefit of roflumilast in patients, either current smokers or formerly smokers.

Slide up, please.

What you can see here is the effect on roflumilast in the subgroup of patients by based on smoking status of the pooled pivotal trials, where you can see that in both treatment groups, the effect is conserved and is clinical meaningful.

I think your second part of the questions,

or what might add, is that the same is also true for if you look into the second primary outcome variable, lung function. I think your second question or the second part of this question was concerning change in smoking status during the course of the trial.

Actually, we have also looked into this one, but the change in smoking status during the course of the trial was below 5 percent, independent of what you look at, which treatment arm and which study. So therefore, we have not had any subgroup analysis to this due to the limited number of patients there.

Slide down.

DR. ROWE: May I request from the chairman that we address the discrepancy between the per-protocol and ITT analysis?

DR. CALHOUN: Yes. Let's do that briefly.

DR. ROWE: Okay.

DR. GOEHRING: Concerning the PP analysis, it's definitely true or just to summarize what was said earlier, all the per-protocol analysis that we performed in terms of lung function has seen the robust effect of roflumilast.

What was also seen in the -- with the same protocol violation rules in the Study 125 in the reduction of exacerbations, we have seen, in fact, a higher benefit if you look into the effect size in the reduction of exacerbations. In Study 124, we also -- we have seen this as it was described that there is a little bit lower effect size that we have seen in the other trials.

If you pool both together, again from kind of a robustness perspective, then the effect sizes are still having the same as we have it in the ITT. So there was some speculations already what the effects were, and we have carefully also looked into these perspectives.

The most important statements to these are that the primary variable that we're going to focus on these and assigned to be on the confirmatory pathway is in the superiority trial, the ITT-1, which hit the endpoints. And it was also true what was -- what was postulated, that these patients in a one-year trial that have taken prohibited medications were the more sicker patients and had a higher background rate of

exacerbations.

In the 1 to 4 model, these patients over placebo have dropped out, leading to a bias after the randomization procedure. But I think here, definitely Gary Koch is the colleague to better look into the statistical aspects.

DR. KOCH: Yes. I would agree with the points that were made, as you would have seen the p-values for the FEV1 were all below 001. So that makes them more robust to excluding patients from the analysis, even if those exclusions start to compromise the comparability of the groups, as originally conveyed by randomization, which, of course, always makes per-protocol analyses difficult to interpret.

For exacerbation, many of the patients who had protocol violations ended up having high exacerbation rates. So they did not benefit in any way, so to speak, from whatever violation they had. and when you exclude these patients because of a protocol violation, even though they have a high exacerbation rate, you, in some sense, are misinforming the analysis.

DR. CALHOUN: Okay. Dr. Platts-Mills?

DR. PLATTS-MILLS: Yes. Thank you. I have some questions about the nature -- perhaps about the nature of the disease a bit. But in one of the studies, you've got an 11 percent reversibility. But of course, that's M2-125, where they're very severe. So the chances that there were any significant number of asthmatics is low.

On the other hand, you keep suggesting that this is an anti-inflammatory drug. And at times, I had the sense that there was the hope that if it was said often enough, it would become true.

Given the data that inhaled steroids really don't work in active smokers because active smoking is profoundly anti-inflammatory to smokers, do you have any data that the effects of this drug are really different on inflammatory markers in active smokers than in ex-smokers?

DR. ROWE: To address this question, I'll ask Dr. Calverley to respond.

DR. PLATTS-MILLS: And I have two more questions.

DR. CALVERLEY: I'll do my best. I think that the analysis is fine. I absolutely agree with you about the situation in asthma, and Neal Thompson has shown that very clearly; although, interestingly, of course, when you stop asthmatics smoking, you don't always get the same rebound responsiveness to corticosteroids, so there's a continuing effect.

It's some years ago we published, looking at acute steroid trials in COPD, that, indeed, continuing smokers/current smokers got a smaller acute steroid response. It's been an immense disappointment over the subsequent decade to me personally that that hasn't been reflected on any of the trials of inhaled steroids.

That also includes combination treatment like those licensed in the U.S., where there are, I think, really reasonably consistent data from several studies of airways biopsies -- Neal Barnes has done one, but there's also data from Canada, from François Maltais, that you do get changes in inflammatory cells that aren't really related to smoking status when you give these medications.

So there's a disconnect between what seems to affect inflammation in the airways of a COPD person and an asthmatic. And therefore, the analogy, which is very attractive, at least of acute smoking exposure and stopping, which you would think would work, doesn't seem to work in COPD. And my speculation is because the damage was done long ago, and even if they're ex-smokers, that continues.

But the medication can still have some effect, as shown by the biopsy studies. I hope that's not too confusing.

DR. PLATTS-MILLS: And can I -- a simple question. Do you have any pharmacogenetics on this response that would help to understand differences?

DR. ROWE: Let me confer with my colleagues on that question.

No, we do not.

DR. PLATTS-MILLS: A few years back there was a lot of speculation about fungal colonization of the lungs in patients with atopic -- with severe COPD. And occasionally, we get patients coming in with aspergillus in their lungs who have COPD, which is a

major severity.

Do you have any data on colonization of the lungs, or the effects of this drug on colonization, in relation to exacerbations?

DR. ROWE: Dr. Rabe will address this question.

DR. RABE: The simple answer to the question is we don't. I guess that the description of fungal infections in the general population of COPD patients is scanty. The evidence for that is. It is, however, true that obviously, in the future, individuals, for example, with bronchiectases, individuals that have COPD plus bronchiectases and the colonization pattern would be very -- of relevance to look at.

I think in the future you will be looking at individuals that have a mixture. Chronic bronchitis symptoms could be on the basis of the COPD only and/or coexistent exacerbation, or coexistent bronchiectases. And there, I think, that's more relevant.

Has that been specifically studied in the pivotal trials, or do we have any sort of colonization data of that, sir? No, we don't.

DR. CALHOUN: Dr. Burlington?

DR. BURLINGTON: I wanted to ask the sponsor to elaborate on the across-studies comparison that they had in slide 105, in which they are comparing the effect size on Spiriva, Advair, and roflumilast. In particular, FDA has pointed out the roflumilast patients are not on maximum background therapy.

So when looking at the two comparator sets of studies, what patients are enrolled? Are they comparable? What sort of background therapies are we looking at? What is the duration of observation? And what do we understand about those factors in terms of predicting the effect size?

DR. ROWE: Paul Rowe, clinical development. It's important to note that when making comparisons of that nature, it's important to take into account the duration of the trials, the types of populations in those trials, as well as the designs of those trials. I believe that in the presentation, Dr. Donohue did speak to that there were some differences there.

To discuss these differences in detail, I think that would be pertinent to have Dr. Calverley,

who was an integral part of a few of those trials, to comment further on the differences between populations.

DR. CALVERLEY: Thank you very much. My past is beginning to haunt me. Could you put up the slide, please? Thank you very much.

I think this is the relevant slide which was referred to just now. My connection with this is really with the purple, orange, and light blue part of that slide, because I was instrumental in those studies. And I think that it illustrates accepting the things that Jim said about the dosage being different. I don't think that's crucial, as has been a topic here previously.

I think that the effects in terms of comparability, if you look at the yellow bars of M124 and M125, half of the people in there, as was said earlier on, were taking a long-acting beta agonist, predominately salmeterol. So the comparisons there relative to placebo should really be looked at relative to the impact on lung function and exacerbation rates in the light blue bars in TORCH and

TRISTAN.

TORCH, of course, was a four-year study which did not require people to have a history of prior exacerbations, although if you go sub-analyze that, you'll find, surprisingly enough, that those with exacerbations had larger rates.

The really comparable group, because I think in many ways it is similar, is the TRISTAN data that we published in the Lancet in 2003. The subjects there had to have a history of prior exacerbations, which is very like the story that you are seeing here. They had to have some history of bronchitis. So we're actually looking at a rather similar population historically in the TRISTAN data, which is the second threesome of bars there along from the left.

The UPLIFT and VA trial data, UPLIFT is quite different. UPLIFT is an effect of tiotropium on a background of a population which were largely using many of those colored compounds to the left. The VA was done earlier by Dennis Niewoehner, and there you have some people using -- about half of the people used inhaled steroids, and there was some interaction

and perhaps a diminution of the impact, if you analyze that as a subset. This was done in the Annals paper.

So the point about that is the TRISTAN data is probably the most comparable to the data that you're looking at in the other studies, particularly with respect to exacerbations. And I think it's easy to say that perhaps the effect of roflumilast is quite small and not terribly important, but perhaps this slide sets it in context and says that, yes, it's what you would expect when you were using that kind of therapy on that kind of background.

DR. CALHOUN: Dr. Raghu?

DR. RAGHU: My question is with reference to the mechanism of action, going back to the concept of this being an anti-inflammatory drug working as a systemic effect, and perhaps at the bronchial level with decreased neutrophils that has been brought up by Dr. Rabe.

We see that in both the 124 and 125 studies, the FEV1 goes up by about 50 cc or so after four weeks, or four to six weeks, and then it sustains. If this were to be a chronic anti-inflammatory agent

suppressing the neutrophil influx into the bronchial levels or the airway distal, wouldn't you expect the FEV1 to continue to longitudinally increase a little bit more over time?

DR. RABE: Klaus Rabe again. I think, with due respect, this is a speculative question, isn't it?

DR. RAGHU: Yes.

DR. RABE: Okay. So since we left the level of -- a little bit of what the data could actually sort of demonstrate, I would be happy to speculate on this.

It seems, and I think it's very relevant to the question earlier from Professor Platts-Mills, the type of inflammation of COPD is distinctly different from the type of inflammation you see even in chronic and chronic severe asthma. It is driven by neutrophils. It is something that persists even though you take, for example, the noxious agent of smoking away, for years. It persists for years, including then to neutrophilia.

So it seems to be that neutrophilia, as a hallmark of the disease also in the patient population

that we look at, is something that is a continuous process that, once switched on, is very difficult to stop. It's difficult to see that neutrophils, by their -- on their own, over years would subside if you stop smoking. And therefore, it is a continuous and chronic disease that there is.

Would you speculate that you can -- halving the number of neutrophils in sputum -- that's the data that we have -- that it could directly contribute to a further increase of lung function? I think that's Professor Raghu's question. Theoretically, you could construct this. But I think -- I don't know of any other agent of an anti-inflammatory nature that has been used in lung diseases where this relation has actually been found.

So it would be nice exploring, for example, in a biopsy study, something that needs to come at some stage, obviously, as for other agents. But it remains speculative, widely, at that point in time.

DR. RAGHU: I thought CRP was looked into. And I wonder if there were any biomarkers of information that were looked into, because the whole -

- yes, it is speculation. But the whole concept of this being an anti-inflammatory with some vascular modeling, as well as extracellular metrics, modeling is supposed to be the mechanism of action, isn't it?

DR. RABE: I would agree with you with this question. And with hindsight, you would say, wouldn't it have been nice in all these trials if we had genotyping, if we had molecular markers, if we did have serum markers. The only serum marker that's been looked at were CRP. There was no significant decrease in CRP in these individuals. But we didn't sort of look at this prospectively.

If we would design these trials nowadays, obviously, the study design would be different. It would be different in the sense that you would look at co-morbidities. You would look at it in effects and probably in serum markers, yet to be defined as to be of any relevance for the cause of disease, by the way.

DR. CALHOUN: Thank you.

DR. CALVERLEY: Just one additional fact, really, which I might contribute. One of the problems is that we've looked for biomarkers very hard. And

there are a number of prospective studies -- there's one called SPIROMICS which includes a biomarker component people are familiar with.

I've been involved with one called ECLIPSE, which has just finished its data analysis. And we had high hopes for identifying nice, clear panels of biomarkers. We're still working on the longitudinal data. But looking at the cross-sectional data, which might be relevant to this discussion, CRP was not really helpful. And in fact, the variability there has been unhelpful.

Indeed, even interventions that cut down exacerbations, there's been a nice study published in the blue journal, the American Journal of Respiratory and Critical Care Medicine, by Professor Wedzicha from the Royal Free in London showing antibiotics, macrolide antibiotics, cut down the number of exacerbations, order of magnitude slightly greater, if anything, than we're talking about today, but no change in CRP.

So I'm no longer surprised. I am disappointed, but no longer surprised that that

doesn't happen.

DR. CALHOUN: Dr. Swenson?

DR. FREIRE: Jose Freire, preclinical pharmacology. If I may basically sort of address the question regarding the anti-inflammatory activity of roflumilast. And of course, it is very difficult to show in clinical trials the precise mechanism of any drug. We can speculate a lot. Usually, speculating on the studies can help you to try and to basically understand that and sort of -- if I may address, what I would like is sort of to basically address two points. First is sort of regarding the CRP and the fact that in the clinical trials, they did not show a statistically significant effect. I want to remind the panel just that actually the levels of CRP are quite broad. And normally, and sort of for many patients and what now becomes sort of more common to hear, is the very low levels that are associated with cardiovascular.

These are not really the levels that you will see sort of under true systemic inflammatory conditions. Those are levels that are just between --

around 3 nanograms per ml, while basically sort of systemic inflammation from other conditions such as rheumatoid arthritis, those levels will go higher, sort of around 100, 500. And just to put it in sort of perspective. And even if you look sort of at the data, the literature in terms of the cardiovascular and the effects in there, that will be.

But actually, going back, it's sort of -- in particular, it's sort of addressing maybe sort of the differentiation between roflumilast as an anti-inflammatory agent and corticosteroids. If I can have the slide up, please.

This again -- take it with some degree of salt -- is a preclinical study. These are guinea pigs, are not humans, but these are sort of a classical model of COPD. So exposing guinea pigs to cigarette smoke, and that it will induce an inflammation into the lungs that somehow is sort of resembling some of the pathology.

You can see here, sort of looking at the total neutrophil levels in this study, so sort of are animals that basically are exposed to just normal air

or tobacco smoke. You see an increase in the number of neutrophils in the lungs. When you treat it with roflumilast, you see a decrease on the numbers of neutrophils and methylprednisolone, a corticosteroid, does not have an effect. If I can have the next slide, please.

Slide up.

DR. CALHOUN: Okay. Thank you. I think the chair and the committee will appreciate if we stay on point.

Dr. Swenson?

DR. SWENSON: Well, my question is to the sponsor. So if it's outside the purview of this -- okay.

In dissecting out the basis for the weight loss on the drug, one could ask whether it's some change in basal metabolic rate that just amps up basal metabolism or, as our patient representative said, could this represent a positive effect on people getting up and being more active, or is it linked to the GI side effects and is it just a subsequent result of the decreased intake from people that feel

nauseated and all.

I wonder if the sponsor has any basis for understanding this weight loss.

DR. ROWE: To discuss the potential link between the GI AEs and weight loss, Dr. Taglietti will respond. With regards to potential mechanism of weight loss, with regards to the mechanism of action, I'll ask Dr. Freire to follow.

DR. TAGLIETTI: So we investigated, actually, specifically because this was one of the initial hypotheses, that GI events could have been the one driving, actually, the decrease in weight loss. But when we looked in patients with GI events, we didn't see really a significant difference. Patients with GI events had an average weight loss of -- I think it was 2.6 kilograms, versus patients who didn't have weight loss was a difference -- a decrease of 2 kilogram.

On the other hand, so this is what we know. We didn't collect, and as -- it was one of the things with hindsight -- more information about the mobility of the patients. This could have been very

interesting data to see, if this weight loss was due to an increase in mobility in the patients.

If we want to stay in the realm of speculation, actually, I would like to ask Dr. Freire to comment on some of the mechanisms that have been suggested as a possible explanation.

DR. FREIRE: Yes. So we look extensively, or trying to look as extensively as possible, to the potential mechanism for roflumilast to have an effect on body weight. We have not seen this effect in our preclinical studies.

We look at food intake as a potential sort of effect. We look also at increased metabolic rate. None of these effects will actually, in themselves, account for the effect on body weight.

So we believe that, actually, this is potentially a multiple factor that we are at this stage here. The only thing sort of that is probably in the literature is an association between some PDE-4 and PDE-3 inhibitors has increasing lipolysis. This has been done sort of using rat adipocytes, but it has not been confirmed using human tissue. So that's the

sort of evidence that we have at this point.

DR. CALHOUN: The last question to the sponsor, then, is by Dr. Krishnan.

DR. KRISHNAN: I think my question was answered earlier, so I'll pass. Thank you.

DR. CALHOUN: So this ends the questions left over from this morning.

We have no registered speakers for the open public hearing session, and, therefore, we will continue with our discussion. At this point, Dr. Chowdhury is going to come address the committee and give us the questions and the charge.

Dr. Chowdhury?

DR. CHOWDHURY: Thanks again. I'm here to give some introductions to the questions and some regulatory aspects. Here I will be wearing my regulatory hat.

I've shown this slide before, and here, there again. Before going into the questions, I would like to bring up and mention some regulations so that you, as a committee member, have a better understanding of the FDA standards for approving a

drug, standards for assessing efficacy, and standards for assessing safety. And for this portion, I'll be using language as specifically picked up from the Code of Federal Regulations.

Here is a Code of Federal Regulation citation for the standards for approval of an application, and I will read it for you here. "The FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling."

The regulation also goes on to say that there are many kind of drugs that are subject to those standards, and the wide ranges of users of these drugs demands flexibility in applying standards. And FDA is required to exercise scientific judgment. And for this scientific judgment, we are here in front of you discussing this application and calling on you to help us in the scientific judgment.

Today we are going to talk about and vote on and discuss on the safety and effectiveness portion only. We are not discussing about manufacturing and

controls, and not about labeling. And one point to know for your consideration for recommending approvability, the clause for the clinical standard is "and safety and effectiveness." So both are required to be shown. It should be, therefore, quite unlikely if one is to conclude safety is not shown or efficacy is not shown, or either/or, to go back and recommend approval. That should be somewhat unusual.

Now, I would like to go on and talk a bit more about the efficacy standards that we consider, and also the safety standards.

Here is again some language from the Code of Federal Regulations. And this is on the clause when FDA will refuse to approve an application, and borrowing some language here to lay out for you to consider the efficacy standards: "The substantial evidence consisting of adequate and well-controlled investigations that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

So the efficacy standard is pretty much

high, and it should be certain, without any doubt, and needs to come from investigations, with an "S," which we have interpreted to be more than one clinical trials. And the efficacy is linked to the labeling, and you have the labeling in front of you.

Now, on the question that we have, where we would ask you to vote on efficacy, and also for you to vote on approvability, you would take the question as is, with the proposed labeling -- and the labeling language is in there, in the questions -- and vote as such; meaning that if you think that the proposed labeling that you have and the claims that you have is supported by the submitted clinical trials, then you would vote a yes. If not, you would vote a no.

If you think that the labeling, other than what is in the question, or some other language that you think is supported as far as efficacy goes or safety goes, we would still like you to vote following the question, and after that give your comment, and possibly say if you would recommend approval if the efficacy claim or the labeling claim was somewhat different.

So we take these discussions into consideration as we move on for regulatory decision-making. So therefore, to hear your opinion on efficacy claims or efficacy that you think it's having which is different than the question, different than the labeling claim, please say so as you comment on the question.

As far as the safety standard -- this is again from the same section of the Code of Federal Regulations -- and there are three conditions that need to be met for concluding a drug is safe, or if these conditions are not met, then you will conclude the drug is not safe.

The first clause is the studies do not include adequate tests by all methods that assess safety. In other words, simply, efficacy was not assessed by adequate controlled trials.

The second clause has an "or" in between, so there are two parts of it. If you conclude that the results of the test show that the drug is unsafe, which is the first clause before the "or," or if you conclude that the drug product -- the clinical trials

submitted do not show that the drug product is safe, then you will conclude the safety standard has not been met.

The third clause, which is the last item here, if you think there is insufficient information to assess safety, then also the safety standard has not been met.

So basically, then, there are four conditions to be met for assuring safety and recommending approval from the safety standpoint. Number one, you will vote a no if there are no adequate tests; also, if the drug is unsafe, and that is a conclusion; and if your conclusion is results do not show the drug is safe; and finally, is insufficient information to conclude whether the product is safe.

So with this background, I'll very briefly introduce the questions. I will not read the questions, for sake of time. These are there in print. And you will see the questions later on.

The first question is a discussion question, and this is on efficacy and the proposed dose, and

with the labeling claim embedded in the question. The second is also a discussion question, and this is on the safety.

The third is a question again on efficacy, and this is a voting question, and we're asking you to vote whether you conclude efficacy has been shown or not. And there's a sub-clause to it. If you conclude efficacy has not been demonstrated, what other efficacy data should be obtained by the company?

Question four is again a voting question, and this is on safety, again a similar clause. If you conclude safety is not shown, what other data you would expect or ask the company to generate.

The final question is a combination of safety and efficacy built into it, and this is a question on approvability. And again, the question has the same language as the previous question, which is the label claim or the proposed indication.

With that, I'll close. Thank you.

DR. CALHOUN: Thank you, Dr. Chowdhury.

At this point, the panel is open to discussion of either the sponsor's data, the FDA's

analysis, or the interaction between those two. And we can spend a few minutes talking about that, but I want to move pretty quickly to the first discussion question.

As we think about the questions that we're going to discuss, please use those questions to inform the discussion. There are lots of things we can do that would be somewhat tangential, and I'd like to keep our attention focused on these questions, because from the advisory committee standpoint, those are the discussions that will be most helpful to the agency as they work through the data.

So for the committee members, try and make your questions to the point and specific. And to the sponsor, brevity is a virtue. We don't need to be exhaustive. Brevity is a virtue.

Okay. And with that, I think the first on the list is Dr. Honsinger.

DR. HONSINGER: I had several questions about the side effects of the drug. One was the gastrointestinal side effects. I mean, we heard you present that. I didn't see any data. We certainly

saw data -- excuse me. We saw data on cilomilast, that there is a mesenteric vasculitis.

Of course, this was autopsy data on animals. We don't have any evidence for that. I'd like to ask if we had any evidence in people if the GI side effects were more than just a gastric irritant. And with comment on that, we saw that there were -- four weeks later, there was gastric irritation and gastric inflammation in the mucosa of rats. And we saw this vasculitis in other animals.

Was anything done as far as looking at CRP, sed rates, any of the inflammatory markers that we see in inflammatory bowel disease looked at in these people that had GI side effects? That's question number 1.

Question number 2 is regarding the cardiovascular effects of this drug. I'm an older physician that spent a lot of time using theophylline. I always worried about the cardiovascular side effects, thought this drug wouldn't have it, and then I hear that we have an increase in cardiac events, an increase in atrial fibrillation. Sure, it didn't

increase the QT.

Do we know if it had an effect on cardiac output, stroke volumes, other cardiac effects like we saw with theophylline?

DR. RABE: Well, I will start to address your first question about eventually effects that could suggest ischemic colitis.

Slide 175, please.

To summarize the key point -- and this was actually one of the reasons why this was not part of the core presentation -- slide up, please -- is that when we look at the actual data, what we did, based on the history of some of the PDE-4, like cilomilast, we actually conducted the fecal occult blood test in five studies.

The result was that there was a higher number of patients on roflumilast that had a positive test. But this was a relatively small difference, especially considering that these patients had, in general, a higher number of GI events, and patients with GI events went through more FOB tests.

More importantly, patients were -- not all

patients with a positive FOB test, but most of them, will -- actually had a colonoscopy. And these colonoscopies were negative, and there were no data suggesting that there was any evidence or indication of the possibility of ischemic colitis.

There were five cases of colitis, five in the roflumilast group, one in the placebo. And there were -- oh, excuse me, five in roflumilast and seven placebo; and, two suspected cases of ischemic colitis, one in roflumilast, one in placebo. And actually, these two cases, after further analysis, looked like they had other justifications. I hope that this addresses your question.

With regards to the second question about the cardiovascular profile, actually I would like to have Dr. William White to make a few comments.

DR. WHITE: Thanks very much. William White from the cardiology center at the University of Connecticut and a professor of medicine.

I served last year and this year as the chair of a blinded adjudication committee which evaluated all the deaths and all the serious

cardiovascular events in the roflumilast COPD pool, along with two other committee members, Peter Calverley from Pennsylvania and Glenn Koch from Ohio State, both cardiovascular experts.

Slide 359, please. Slide up.

Now, these data have not been seen by anybody at the FDA yet because they have recently been evaluated by us. And I would like to point out that we had 170 deaths and 99 nonfatal, serious cardiovascular events to evaluate for either a nonfatal MI, nonfatal stroke, or cardiovascular death, some of which you've already seen before in the case of the fatal events.

All of these events had a lower event rate on roflumilast relative to placebo, including -- so the same direction for nonfatal MI, nonfatal stroke, and cardiovascular death. So the composite, which we frequently utilize in noncardiac drug studies -- it's call MACE or APTC events; like I say, that is CV death, nonfatal MI, and stroke -- was reduced by 34 percent on roflumilast relative to placebo, which was, in fact, statistically significant in a post hoc

analysis. Next slide, please.

This is the time to event curve for these various cardiovascular events of both the fatal and nonfatal variety. So I'd point out that after about three to four months of double-blind therapy, the separation began to occur so that the events were lower on roflumilast relative to placebo. And that was consistent throughout the rest of the one year.

DR. CALHOUN: Okay. Thank you.

So at this point, we're going to move on to the first question. And the question is, as Dr. Chowdhury noted, a discussion question. And the question -- each of the questions -- let me just make clear, reemphasize something that Dr. Chowdhury said -- it will be most helpful if the committee focuses their attention on the precise wording of the question, and discuss the question that's asked as opposed to some question that might be like that, that might perhaps be more interesting to you. But from the standpoint of what's going to be useful for the agency, I would like you to focus your attention on the specific wording of the question as written.

So question number 1 is to discuss the evidence to support the efficacy of roflumilast at a dose of 500 micrograms once daily for the maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations.

Dr. Honsinger?

DR. HONSINGER: I think we've heard the data today. I would want to modify that, and we probably can, to say moderate to severe COPD, because as we look at COPD, we didn't see the effect on mild, and that's these studies were done using the moderate to severe. And the moderate and severe patients are much more meaningful than the mild.

DR. CALHOUN: Dr. Knoell?

DR. KNOELL: A couple things that are still puzzling me. One is a point of reconciliation. So in Trials 127 and 128, when we looked at the data, we focused upon the primary outcomes, which were to look at the exacerbation rate and the change in FEV1 over the study period of time.

What is confusing me, and I don't know whether I should be hung up on this or I should get

over it, in Trial 127 there was a decrease in exacerbation frequency of 36.8 percent, yet there was a change in FEV1 of 49 milliliters. In contrast to that, in Study 128 we had a decrease in exacerbation rate of 23.2 percent, but an increase in FEV1 of 80 milliliters.

So this is, at face value, counterintuitive to me, but yet I think it's relevant because we're talking about subtle changes in FEV1 and whether it's clinically significant. And in this case, between those two trials at face value in the treatment arm, we have a 49 ml change and an 80 ml change, but yet opposite and contrasting effects upon exacerbation rate frequency. So I find that data a little bit puzzling. Then related to this, I think there was a very nice presentation earlier in the day by the sponsor that educated us on how they ended up getting to the trial design for 124 and 125. That is, when they started to look more carefully at patients that have chronic bronchitis as a major phenotype as opposed to emphysema, it seemed like that is where the effect was.

But yet when they moved on with subsequent trials, looking more specifically at that patient set in their trial design, the differences in exacerbation frequency and change in FEV1 were not that remarkably different from the previous trials, if I understand this correctly.

So I'm having a hard time, in my mind, reconciling that data set as well.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: Yes. I think, in part, if you look at Trials 124 and 125, whereas you say they've become focused on chronic bronchitis, they're also focused on severe or moderately severe disease. The mean FEV1s are either 1 or .95, which is severe disease.

Clearly, the thing that I find very reassuring is there's a consistency of the FEV1 data. But FEV1 data in COPD is remarkably -- I mean, you can't use it the same way that you use it in asthma at all.

So the increase that you see, this 50 milliliters, is an indication that something's

happened in the lungs. But I don't think the size of it tells us whether they're better or not. You see patients who are going along with an FEV1 ratio of 30-something percent of predicted and coughing, and they can't function at all. You stop the cough, and their FEV1 is exactly the same, and they're fine.

So that why people get better in COPD is a little bit different from a simple change in FEV1. Nonetheless, the FEV1 data is consistent. But if you go to that data in 124 and 125, the other issue is we're now in severe COPD. And once you're in severe COPD, this is a very severe disease which has a very high mortality rate, consistently. And the exacerbation -- to get clear exacerbation data, significant in this disease is very difficult.

The fact that there's a discrepancy between the 51 versus the exacerbation rate or the size in the change may be, in part, due to a different baseline level of FEV1. I think that 124 and 125 are more severe.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: Thank you. And this question

is along the lines of Dr. Platts-Mills', as well as Dr. Knoell.

It still, again, confuses me a little bit, focusing on Studies 124 and 125, where LABAs were allowed, but inhaled corticosteroids and LAMAs were not allowed. And what I was hoping for from this agent is to see whether we could decrease exacerbations. I was still hoping for the anti-inflammatory process to be there.

The FEV1 increase of 50 ccs to a patient may be very significant, but all in all -- and the quality of life in the St. George's assessments, we're not really getting that information. So if we look at table 12 on page 27, again we have a very well-laid-out by week between roflumilast and placebo, and the numbers of exacerbations, and we, again, do not see that difference and that still concerns me.

DR. CALHOUN: So I'm taking my turn and not asserting chairman's privilege here.

My concern here turns on the issue that Dr. Durmowicz actually raised in his presentation, and that is that the studies in which the evidence of

efficacy is present are those studies in which, in general, those patients should probably be on inhaled corticosteroids because they've got significant airway obstruction.

They're in the severe to perhaps even very severe, as we saw the demographic. They should probably have been on an inhaled steroid, which we know reduces exacerbations. And so we don't really have any comparative data to address the question of whether steroids or roflumilast might be a better option for reducing exacerbations.

I think that to the extent that one could look at subsets, you might be able to get a little bit of a sense of that question. But we didn't see any breakdown in that regard.

Dr. Fink?

DR. FINK: I think there's a critical issue in this question, and that is that this question is worded to say daily maintenance therapy, not reduction in exacerbations. And I think they have shown a reduction in exacerbations in their trials. I don't know that they have reached the bar for daily

maintenance therapy.

It's hard to say that a drug is effective for daily maintenance therapy in a chronic disease when there is absolutely no effect on quality of life. I think daily maintenance therapy, to me, implies quality of life, not reduction of exacerbations.

So the wording in this is different than what the company has proposed. But in this case, if we stick just to this wording, I would say it has not proven effective for daily maintenance therapy.

DR. CALHOUN: Dr. Swenson?

DR. SWENSON: This might be best posed to the sponsor because maybe they have the data. But to try to get a grasp on this FEV1 change of 50 mls, or the neighborhood of 51 mls, is that -- what I'd also like to know is what happened to vital capacity or historic capacity.

When people are this severely obstructed, there is often considerable hyperinflation. And in fact, bronchodilation sometimes affords a modest improvement in FEV1 but a much bigger improvement in volumes, particularly, say, something like the

historic capacity.

So just to get a better grasp on whether that 50 is meaningful, does the sponsor have any further pulmonary function data? And I should say patients that experience some deflation from their very hyperinflated lung volumes often feel very grateful.

DR. GOEHRING: Udo-Michael Goehring, clinical development, Nycomed.

Slide up, please.

Very brief, we have also not only looked into pre-bronchodilator FEV1, as well as post-bronchodilator FEV1 as the primary variable and the key secondary variable, we also have a long list of further spirometric variables, which all show a benefit of roflumilast.

Here is the data of the 124 and 125, as well as the pooled analysis in terms of forced vital capacity in the status of a pre-assessment. And you see then an improvement in roflumilast, placebo-adjusted of 90 ml in the 124 trial and 110 ml in the 125 trial.

The same -- and very important to say is also that the same values you have in the maximized bronchodilator effect you have in post-bronchodilator FVC values.

Slide down.

DR. RABE: Maybe if you'll allow me, Klaus Rabe, to add a clinical note to that question. Since the patient population is chronic bronchitis at risk of severe exacerbation, while I fully acknowledge your mentioning about other lung volumes that would be plethysmographic measurements, it is exactly not that patient population that would show that degree of hyperinflation.

If you compare this, for example, to a bronchodilator drug as tiotropium that showed a big effect on IVC, these are individuals that primarily have emphysema with a high degree of hyperinflation. You note that the effect size on the emphysema patients -- I showed you the data compared to the chronic bronchitis -- was very, very small.

So therefore, I would think it's worthwhile to study plethysmographic data on exercise capacity

and volumes. But the target population would not be the primary population that would be characterized by the high degree of hyperinflation, just as a clinical mentioning.

DR. ROWE: And just to add, we believe that the effects that we have on FEV1 are modest and in line with what is expected with an anti-inflammatory therapy. And getting back to Dr. Platts-Mills' point, this patient population in 124/125 are severe and very severe patients with low reversibility, and that has to be taken into account, as well.

When looking at patients with low reversibility, there are meta-analyses that have been performed for bronchodilators such as salmeterol and formoterol that show changes of about 50 mls in patients with low reversibility, as well. Slide up, please.

This is some other data that we have looking at responders in M2-124 and M2-125. And as you see, looking at pre-bronchodilator FEV1 with changes of greater than or equal to 100 milliliters, 34 percent of the population in M2-124 and 31 percent of the

population in 125 did have changes of 100 milliliters or greater in FEV1 baseline to every visit during treatment. That corresponds to approximately 10 percent change in FEV1.

Slide down.

DR. CALHOUN: Okay. Thank you.

Dr. Krishnan?

DR. KRISHNAN: Sure. I want to make two comments. One was this -- so just by way of background, I direct an asthma/COPD center and provide care to a substantial number of people with severe COPD, many of them oxygen-dependent.

Along the lines of whether maintenance therapy could construe an improvement in exacerbations, I would like to argue that it is actually beneficial for a patient to feel that they're going to not have as many exacerbations, because when they do get exacerbations and one is forced to use systemic corticosteroids, it certainly affects their life for a certain number of weeks. And I think most patients would like to have fewer of those events.

So I'd like us to maybe think through

maintenance therapy as not just a bronchodilatory effect we'd like people to have and perhaps a respiratory symptom on a particular day, but also the prevention of catastrophic illnesses, including exacerbations.

The second point I wanted to make is that there is a tremendous need for reducing exacerbations. And we do have inhaled corticosteroids, of course, and they have been of benefit. But a substantial number of patients don't like to use corticosteroids for a variety of reasons.

There are adverse effects of corticosteroids that I think we're all familiar with, and then there are effects also on bones, on the skin, and moreover, a number of people have difficulty using inhalers for a variety of reasons, despite how many times they're taught.

So I think there is a need for an alternate agent. So I actually feel that the reduction in exacerbations is a very important, clinically relevant endpoint in this population. And the fact that we have an agent that is not inhaler-based and non-

corticosteroid-based is of value.

So I'd like us to sort of think about that as we proceed with the discussion.

DR. CALHOUN: Dr. Platts-Mills?

DR. PLATTS-MILLS: Dr. Calhoun, you suggested that these patients should be on inhaled steroids, or would be on inhaled steroids, as if the inhaled steroid effect was bigger than this.

But I think the point is that in TORCH and TRISTAN, inhaled steroids on their own are not having an effect bigger than this. They're having very much the same effect. And for many years, of course, we --

DR. CALHOUN: Agreed.

DR. PLATTS-MILLS: -- all of us didn't really think that inhaled steroids did anything in this disease. And it's the combination of salmeterol. And LABA was allowed in those studies.

DR. CALHOUN: No. I wasn't indicating by my remarks that there was no benefit. It was simply that the benefit was comparable to what was seen with inhaled steroids, just as you say. Yes.

Dr. Burlington.

DR. BURLINGTON: In looking at this question, as the sponsor went through the hypothesis-generating exercise from 111/112 and began to focus on patients with exacerbation and more chronic bronchitis systems than simply maintenance and COPD, they saw a diminished effect when they got to 124/125 versus what had been in their hypothesis-generating.

Well, that's not very surprising because we see that all the time. I mean, that's the reason we do the confirmatory trial rather than just rely on the hypothesis-generating data.

But the other thing relative to that is that when you look at that Kaplan-Meier curves on exacerbations from 124 and 125, almost half the patients didn't have any exacerbations during the period of time. So they really did not have a highly enriched population to study here of individuals with very frequent exacerbations.

In relationship to the point that Dr. Fink just made about whether this is really maintenance or not, it's hard to understand how one would develop a strategy for prevention of exacerbations or

maintenance, if you will, without chronic therapy. I mean, treatment of an exacerbation would be a very different drug development strategy than what the sponsor has undertaken here.

DR. CALHOUN: Okay. Are there other comments regarding efficacy? Dr. Raghu?

DR. RAGHU: To me, the acute exacerbation episodes that seem to be reduced in this study, both 125 -- both studies, is mainly a moderate exacerbation, based on patient symptoms and corticosteroids used at home or outside the hospital. And the severe episodes of acute exacerbation requiring hospitalization, respiratory failure, mechanical ventilation, et cetera, does not seem to have made a difference in this particular study.

So when we're thinking in terms of whether there is a true reduction of acute exacerbations and chronic bronchitis in COPD in this patient population, I share with the concerns that, yes, even though these patients seem to be at high risk to have manifested chronic bronchitis and acute exacerbation, the episodes were not that significant enough for me.

DR. CALHOUN: Dr. Knoell?

DR. KNOELL: Just one last question related to efficacy. It occurred to me that given the extensive number of trials, patients' exposures, patient years, although mortality, of course, was not a primary endpoint in one-year studies or shorter, are there any patients in your cohorts that were maintained on the drug for extended periods of time out to, say, two, three, four years that you have data on that can give us inference about impact on mortality since, obviously, reduction in exacerbation we would hope would translate overall to a reduction in mortality?

DR. RABE: If you'll allow me, since I'm standing here. Thank you very much for the question. No, there are no data of people sort of staying in the trial for longer than this one year or an extended period of three to four years. The only trial that ever addressed mortality as a primary endpoint, as you know, is a three-year study with a huge number of individuals.

So we can't answer the question, although I

think that the cardiac data are reassuring. And since it was mentioned on the exacerbation frequency that actually sort of was of relevance to that, I would want to make a comment in relation to Professor Raghu's comment, if I may.

It is true that, obviously, the bulk of effect is seen at moderate exacerbations. But that has to do with the frequency of events of the very severe. You've seen there is a numerical difference. But the number of events that are very severe -- that is, hospitalization or death -- is very low.

I think what is important in the core presentation slide set, number 59, when I went through this this morning, when we looked at the continuous effect that is from the different exacerbations, what I didn't mention -- slide up, please -- what I didn't mention explicitly, and I would hope that you would pick that up -- is that if you look at the total number of exacerbations on the observation period in Study 124 and 125, you're talking about a difference between 1,638 events, moderate or severe, versus 1,285.

So what you do and what you see in these trials is in terms of risk rates, what have you, a tangible outcome is that more than 300 of these events did not occur in the treated group. And I think that is important in terms of putting this in the clinical perspective. Thank you very much.

DR. CALHOUN: Thank you.

Dr. Hoidal?

DR. HOIDAL: Just from that data and the general effect, the patients that seem to benefit from this in terms of exacerbations are those, in particular, that have recurrent exacerbations, which is a relatively small number to the total treatment for the indication that's provided.

DR. CALHOUN: Dr. Schoenfeld?

DR. SCHOENFELD: I don't think we actually know that. I mean, we actually haven't -- I don't think we've been presented data on -- as far as I can tell -- on whether the -- on the mechanism of this drug relative to the individual person who, in fact, either has lots of exacerbations or few exacerbations.

The data that you just showed about the time

to the first, the second, the third, the fourth, one of the problems with that way of expressing things is that it basically conflates the time to the -- the time to the third exacerbation, or the time to the fourth or the time to the fifth, is -- that Kaplan-Meier curve is dominated by the people who didn't have any.

So 50 percent of the people didn't have any, and they're in all of those curves. So each of those curves is actually using data from the other curve. So although they look like -- they look like sort of sequence data, they're really not.

So we don't really know from the data -- from the way the data's been presented, we don't have a model for how this drug works and whether it really prevents people -- sort of frequency in exacerbations among the many -- among the people who exacerbate a lot versus whether it affects just sort of the same -- whether it has the same effect on everybody. I don't think that's been presented to us.

The other issue which I just want to comment on relative to efficacy is that numerically, the

effect on severe exacerbations is about the same as the effect on moderate, on the non-severe exacerbations. So again, we don't know, really, whether these -- there's not enough data to really know that these are different. They don't look different.

So I guess the best guess would be that it would be the same, and that if we reduce one by 20 percent, we reduce the other by 20 percent. That's what the data seem to show. But of course, with 90 or 100 severe exacerbations per treatment group, it's kind of a little difficult to know that, to let -- the data can't really tell us that. But that's what it is numerically, at least as far as I can see.

DR. CALHOUN: Do you have a response for Dr. Schoenfeld?

DR. KOCH: Yes. Gary Koch, University of North Carolina.

I agree with what you're saying when you look at time to first, time to second, time to third. They're including all patients. The advantage is they are intent to treat analyses, and patients who do

better are in the "no" column, and those who are doing worse become progressively in the "Yes" column.

The main point of those analyses was to address sustaining or persistence of effect, basically showing that there was benefit in later points in time through those intent to treat analyses. Now, if we just -- no, go back to the previous one that you had. The sponsor did do a -- no, not that one, either.

The sponsor did do a number of analyses that looked at whether or not -- yes, this one here -- treatment effects varied by subgroup. And this would be one of them. This is exacerbations in the previous year to doing the study. And on the left is a group that had only one, and on the right is the group that had two. And the rate ratios are comparable for that.

I think they had previously shown something broken down by smoking, current smokers and ex-smokers. And I think the rate ratios were the same for that, as well.

So I don't know that there's any particular subgroup or population that the sponsor has identified that identifies the type of patient where the effect

size is bigger, which I think was where the original question was starting.

DR. CALHOUN: Okay. Thank you.

Dr. Hendeles?

DR. HENDELES: I have two thoughts. One is, overall, that the evidence for efficacy, as the question asks us to discuss, is really minimal, especially in terms of my concept of what maintenance means. Maintenance means it keeps you less symptomatic and you're able to do more.

The second thought is that because it's a specific PDE-4 doesn't mean it's better. We already have a nonspecific PDE-4 on the market, and removing the effects on PDE-3 may be a disadvantage. There's no data to demonstrate that this has an advantage over lower-dose theophylline, which is very safe, even in this population.

So those are my thoughts.

DR. CALHOUN: Thank you.

Dr. Joad?

DR. JOAD: I would also like to support the idea that the indication would need to be very much

the same as in the pivotal trials, which is severe COPD with frequent exacerbations, and certainly not this.

But the other comment I was going to make is it doesn't seem like -- it seems effective for preventing exacerbations, and it has a consistent improvement, FEV1, none of which are better than the tiotropium or the inhaled steroids or the salmeterol or the combination of the steroid and the LABA.

So when we get to the next part, it is -- it just gets at the issue that you said to me, which is you have to look at the other -- how effective is this compared with how effective is everything else that's already available, to put it into perspective.

DR. CALHOUN: Okay. Are there points of efficacy? Just a point of order from the agency that we've not dealt with that you'd like us to discuss?

DR. CHOWDHURY: No. You've discussed it adequately. Thank you.

DR. CALHOUN: Dr. Schoenfeld?

DR. SCHOENFELD: As I understand sort of the FDA rules about this, we're really not supposed to be

judging whether or not this is as effective as something else. The basic idea is to judge efficacy of each thing by itself, and not to judge whether this would be as efficacious or more efficacious than theophylline.

Do I understand that correctly?

DR. CHOWDHURY: You do understand it correctly, and that is correct what you're stating. But again, discussing that actually is helpful for us to hear what your perspective is. And as you go to the question and approval of the question, if you want to discuss that and bring that into consideration, that will be very appropriate there, as well. Thank you.

DR. CALHOUN: Great. All right. Well, let's move on, then, to question 2, another discussion, nonvoting question. Question number 2 is to discuss the overall safety profile of roflumilast.

Dr. Hendeles?

DR. HENDELES: So I have two concerns. One is that the withdrawal of subjects from the active treatment group could potentially underestimate the

amount of adverse effects, firstly.

Secondly, I have some real concerns about how the drug interaction studies were done. And in particular, they passed out this handout on ketoconazole, and I want to point out to my colleagues on the panel that they only gave a single dose of roflumilast, of the active compound.

If they did that, gave a single dose, if you give multiple doses, the blood levels increase over time, especially with a drug that has a 40-hour half-life. And I'm guessing that they were not able to truly measure the clearance rate. But the half-life does indicate that it was significantly prolonged with the addition of ketoconazole.

Secondly, I don't see on the list where they've tested the effective inhibiting cytochrome P450 1A2. And that might have the opposite potential. If 1A2 is involved in converting the parent compound to the metabolite which is the active, and you inhibit that enzyme, then you may get the effect of lowering the dose to the 250. In other words, you get less of the active metabolite, and, therefore, it may have an

adverse effect that way.

DR. CALHOUN: Dr. Schoenfeld?

DR. SCHOENFELD: Just I'm trying to put all this data in perspective for myself. And so I did, again, some calculations, and I'll just present them. And if they're wrong, please, either from the agency or from the sponsor, please correct me, although only correct me if they're very wrong, because they're sort of to one decimal place.

[Laughter.]

DR. SCHOENFELD: So roughly among 1,000 patients in this disease, there'll be 50 deaths, just to put a -- in a year, basically. To put things in perspective roughly, that's the death rate.

The excess cancer risk, if we believe that actually the estimates given there are actually the reality, there would be three cancers, three extra cancers. There would be roughly 25 extra severe or worse -- that is, requiring hospitalization or death -- exacerbations. That's what we're preventing with the treatment. And there would be about 200 all exacerbations that we'd be preventing.

So we're preventing 200 exacerbations in 1,000 patients. We're preventing 25 hospitalizations/deaths from exacerbation. And we're causing, if we believe the data just as is, about three cancers. And the suicides and so on would be much less than the cancers, as -- so it would be fewer, way fewer suicides.

So that's sort of just trying to put the numbers in perspective.

DR. CALHOUN: Thank you.

Dr. Platts-Mills?

DR. PLATTS-MILLS: I just want to say about two of the side effects, which are the GI side effects and the loss of weight, that it seemed to me that what we were told, these are clearly within the terms of manageable side effects of the kind of drugs that we're using all the time.

I think in the GI ones -- yes, I think they were -- diarrhea is obvious, and the patients who become severe come off the drug, and that's not a problem.

The loss of weight, there are five times

more overweight patients in these studies than there are underweight patients in these studies, whereas I would be suspicious that in the United States, that would be an even worse ratio, that there would be even more overweight patients. I don't know why I got that idea.

[Laughter.]

DR. PLATTS-MILLS: This psychiatric stuff, clearly this is a disease that ought to make people depressed, and certainly does, so that seeing the differences -- but remember that prednisone has extraordinary psychotropic effects, and we're using high-dose steroids, and that if you can avoid a course of high-dose steroids, that's really a positive thing.

DR. CALHOUN: Thank you.

Dr. Knoell?

DR. KNOELL: A couple last questions. One is, to go back to the issue of new cancer formation, I may have missed this, and if I did earlier in the day, I apologize now. But we talked a lot about toxicity, different models, new tumor formation. But I want to go back to Dr. Rennard's talk at the very beginning.

Based upon the known mechanism of action of this compound and its active metabolite, is it plausible to consider that as a direct extension of its known activity, by virtue of altering phosphorylation of downstream proteins, has it been shown in any model, in vitro on up, that by virtue of doing exactly that, it could lead to activation of, say, a proto-oncogene, or inactive a tumor suppressor? That's my first question.

DR. CALHOUN: Is there a response from the agency or from the sponsor?

DR. FREIRE: Jose Freire, preclinical pharmacology. There is no preclinical data to support an effect of PDE-4 inhibition in promoting cell growth. That's the evidence. Actually, it's sort of -- inhibition with PDE-4 in many cases actually is low, with the growth of many cell types.

DR. CALHOUN: Thank you.

DR. SCHEIN: If I could respond just quickly to this issue as to whether there's any biologic plausibility to some of the cancer data you've seen, is there a risk; is there a risk of even three new

cases out of the 1,000 that have been hypothesized?

Again, as we emphasized earlier, the cancers are coming very early. One-third of them are occurring in the first three months, two-thirds in the first six months, and then the remaining portion over the next six months. What do we know about cancer biology? It is recognized that it takes about 30 cell doublings to go from a transformed cancer cell to one where we can actually detect it, perhaps at 1 centimeter in size. Thirty doublings.

How long does it take for a cancer cell to double? For solid tumors, in particular, the estimate is about two months. So you do the simple math, it's about five years.

Now, what do we know about the latency of human solid tumors? As was mentioned, the case of cigarette smoke or asbestos exposure, you're talking about a decade or decades. In the case of estrogens, which may act as a tumor promoter rather than a direct-acting agent, it takes about five years of exposure in a post-menopausal woman who's receiving estrogen to control the symptoms of menopause to begin

to evidence a risk for breast cancer.

In the case of alkylating agents, used in the treatment of cancer, which may provoke the development of acute myelogenous leukemia, several cases may be seen in about two years. But the real risk occurs at five years or longer.

In the case of colon cancer, the American Cancer Society currently proposes that the guidelines for colonoscopy as a screening tool would be administered every 10 years, in recognition of the biology of that human tumor, that it takes 10 years for a cell to transform, to grow, to form the polyp, which may enlarge and eventually become malignant. Ten years.

We're talking here about three months. This would be a rather unique -- totally unique situation. It is more probable that the patients entered the trial with a preexisting cancer. And as you recognize, the studies were not designed to dice out a cancer. The protocols accepted patients with a prior history of cancer, and indeed, 15 percent of patients diagnosed on the trial with a cancer had that history.

There was no screening for cancer. There was no stratification for risk factors. There was no organized attempt to diagnose cancers that might emerge during the trial. Overall, it seems much more probable that the patients came to the study with a preexisting tumor, and during the course of observation and testing, a tumor was found.

But plausibility is very unlikely in terms of a direct relationship of the drug.

DR. CALHOUN: Two points of order. First, sponsor's folks, please identify yourself for the record. And, Dr. Durmowicz, you wanted to respond to that particular question, I guess.

DR. DURMOWICZ: I wanted to respond a little bit to the question, or to the statements made. And I think that it is very important to point out, as he made at the very end, that these aren't cancer studies. And nobody's going to argue that you're going to see a new cancer develop in two or three months from a drug de novo, so it is the likelihood that something was potentially going on prior to the entry.

People weren't screened for cancer. People

were observed more during the trials, probably, than they would be normally because they saw a physician or somebody every four to eight weeks. But it's hard to start making definite conclusions about the cancer issue when you're looking at a study that's not designed to look at it.

DR. CALHOUN: Thank you.

Dr. Honsinger?

DR. HONSINGER: I agree with Dr. Platts-Mills. I certainly have more patients who want to lose weight than those who want to gain weight. And that may be an advantage of this drug. And as I look at the GI side effects, yes, if they get GI side effects, you'll stop the drug. It doesn't look like they're long-term.

The suicide, it was interesting that the majority of the suicides were after they'd stopped the drug. Is this because the drug was actually making the patients better, and when they got worse, that's when they committed suicide?

The other question is, of course, the cancer. To me, if this drug has anything to do with

cancer, it may be the same thing that other drugs have to do with cancer. That is, drugs we use that suppress the immune response, drugs that block tumor necrosis factor, cause cancers to grow faster. And this drug may have some of those effects, to make preexisting cancers more evident.

DR. CALHOUN: Dr. Joad?

DR. JOAD: Just to get back a bit to the comparison, if this were the only drug that could prevent exacerbations, then you would look at the side effect profile in one way.

But given that there are other drugs, there are other ways to do this, I think the side effect profile is very not good. I mean, I think 10 percent diarrhea, and some of it intractable that puts you in the hospital; I think anxiety, insomnia, in a disease that already has those -- depression, already has those problems, how would you ever pick it up and know whether it was the drug or the disease? The same thing with the weight loss would fit in there.

So it just seems like there are a lot of significant, bothersome, some of them serious, but

many of them bothersome kind of things. And I don't think the argument about high-dose corticosteroids is a very good one, because although it does have neuropsychological changes, it's brief. It's during the time of the exacerbation. And we're talking about a drug that we plan to give every day.

So I just think, in context, this is a lot of side effects.

DR. CALHOUN: Dr. Swenson?

DR. SWENSON: Well, I just have a concern about the weight loss and this cancer question, and worry that, obviously, anybody experiencing weight loss, whether it's desirable weight loss because they're starting overweight, or they're normal or underweight and losing weight, is going to occasion the usual cascade of workup, which would probably involve a high-resolution -- or a CT scan at a minimum, with the detection of possibly insignificant lesions and then difficult discussions about how to proceed at that point.

I wonder if the sponsor has any data -- maybe not because it wasn't planned for this -- but to

what extent were workups engendered by weight loss specifically for this question of cancer?

DR. TAGLIETTI: Excuse me. Marco Taglietti, chief medical officer, Forest. I'm not sure I understood the question.

DR. SWENSON: I wonder if you have data on the issue of whether weight loss stimulated workups for cancer, and in what fraction of patients this might have occurred, and maybe some estimate of the expense and the false positive detection rate.

DR. TAGLIETTI: I don't think we had the data. But let's say something may be related to this and it has been raised is the possibility of the fact that roflumilast has an effect on TNF alpha, which has been raised as a potential explanation.

I would like just to raise -- to bring two facts. One is that the amount of TNF inundation is relatively low, especially if you compare it with monoclonal antibody, which have almost 100 percent. We really were talking a 10, 15 percent.

The second aspect of it I would like to stress with the other diseases that are known to be

increased, actually, or activated due to inhibition of TNF alpha -- examples are tuberculosis or viral information like herpes zoster -- this we didn't see any event.

We had 496 patients with a positive tuberculin test, all previously studied for tuberculosis. None of them reactivated during the study. And we had almost 100 subjects with positive herpes zoster that did not reactivate it during the study. So I think to address some of your question, but does it?

The second point I would like briefly to make is just to better characterize one of the statements I made during the core presentation that I could not expand any further, which was the fact that we may have drugs that may have a safety profile not dissimilar from what we see here. Slide up, please.

When I was mentioning with regards diarrhea and nausea, certainly there are drugs belonging, for example, to antidepressants or antidiabetics, like just to think metformin, where you may have a high incidence of these adverse events.

There are also drugs like Topamax that actually cause quite a significant weight loss, close to 7 to 10 percent, compared to what we have seen on average, in our case, of 2.4 percent. And of course, there may be other effects in the neuropsychiatric event.

All this is not to minimize the safety profile of roflumilast. As I mentioned in my presentation, GI tolerability, weight decrease, and an increase of these events is certainly observed and associated with the use of roflumilast. But there appears to be adverse events for which the physician would be familiar how to manage these events. Thank you.

DR. CALHOUN: Dr. Burlington?

DR. BURLINGTON: I'll pass. Every comment I had has been made.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: Sure. I wanted to address the issue of adverse events, as well. I just want to remind the committee members that, for example, the FDA's own analysis on page 14, slide 27, indicates

that while serious adverse events are common, they appear to be equally as common in patients treated with roflumilast 500 versus placebo at 14 percent.

That, in part, is because this is a population that has a lot of things going on. They're going to have a variety of events that are going to be appropriate for saying is an adverse event -- pneumonia, atrial fibrillation, bronchitis, diarrhea, prostate cancer probably less likely as a new event you would pick up, but acute renal failure. These are all events listed in the FDA table that are common in this population.

So I would be careful in applying perhaps our clinical experience with asthma in looking at this table and wondering about where there are so many adverse events.

I do share the concern, though, that some have raised about the issue of potentially malignancy, and we have heard considerable discussion that it's not so clear why that's happening. Perhaps we're uncovering disease that was already there. And that, I think, is just hard to tell. We don't have the data

to feel confident that it's actually being caused by the drug versus just because they're under an observation period, we're detecting these things earlier.

DR. CALHOUN: Dr. Knoell?

DR. KNOELL: Yes. Just one question and one comment to follow up on. One is a simple question, but I don't think I heard this earlier today.

So for the sponsor, is there any reason to think that there would be a need for dose modification in an individual with, say, altered kidney or liver function?

DR. ROWE: To address this question, we'll ask Dr. Ghahramani to discuss this.

DR. GHAHRAMANI: Parviz Ghahramani, clinical pharmacology, Forest.

Dedicated clinical pharmacology studies have been done on renal impairment and also hepatic impairment in healthy -- basically, in subjects who are not COPD, but they have got hepatic impairment.

In the renal impairment patients, there was no effect, especially at the severe group, on the

concentrations of roflumilast or N-oxide. So there is -- no dose adjustment is needed for renally impaired patients.

For mild hepatic impairment, there was about 40 to 50 percent increase into the exposure. And that's within the variability of the drug we see, and clinically, that doesn't relate to any clinically relevant increase.

However, for moderate and severe hepatic impairment, expect it to be significantly higher concentrations. And therefore, as the label shows, we are not recommending those patients to take it.

DR. KNOELL: Thank you.

DR. CALHOUN: Dr. Fink?

DR. FINK: I would think, looking at the side effect profile of this drug, that a study at lower dose would really be critical before the drug is approved because it would be hard to have it performed after approval of the drug. And that would give us two pieces of data.

One, it would show whether a lower dose caused decreased side effects, which is highly likely.

It would also address the issue of, at a lower dose, do we lose the efficacy of decreased exacerbations.

If we lose the endpoint, then maybe the increased side effects are tolerable. But at this point, I have no information to tell me that we couldn't achieve the same endpoints with fewer side effects because that study hasn't been performed.

DR. CALHOUN: Okay. Thank you.

At this point we're going to take a 10-minute break. It's 3:15 by my watch. We'll reconvene at 3:25. Once again, panel members, please don't discuss the issue.

(Whereupon, a recess was taken.)

DR. CALHOUN: Okay. We're going to reconvene.

So we have spent most of the day hearing presentations and discussing the issues that have been raised there. I have had a request by the sponsor, and I'm promised that they will be brief, to show us two pieces of information that are relevant, one, to Dr. Hendeles' question regarding the PK study, and the other regarding the lower dose.

So with that --

DR. GHAHRAMANI: Parviz Ghahramani, clinical pharmacology, Forest.

Just to address the drug/drug interaction question which was raised as a concern with regard to single-dose use, obviously the studies have been done according to the FDA guidance for drug interactions. Roflumilast has got a linear kinetics, and therefore, the ratios for increasing concentrations apply to all ranges observed.

Therefore, a single dose is predictive of the steadier state concentration, just to address the question whether that had the steady state of N-oxide, there would be higher increases. It wouldn't be because, obviously, of linear kinetics. And it's been shown.

Your second brief question was about what happens if you inhibit 1A2, which is also involved. We have done a study with fluvoxamine, and again, the maximum increase in the N-oxide concentration is about 50 percent magnitude. The fact is that the drug is metabolized by three enzymes, so blocking one enzyme

is not going to affect a very significant increase in the concentrations level. So it has to be a multiple factor.

DR. HENDELES: But doesn't it decrease the amount of oxide formed? If the sole source of the oxide is from the parent compound and you block that pathway, don't you get less oxide?

DR. GHAHRAMANI: Well, the N-oxide is also further metabolized by 3A4. So if you block that, really, the formation is also reduced, correct, but also the elimination is reduced, as well. So therefore, N-oxide remains more or less the same.

DR. HENDELES: And if a patient takes both cimetidine and ketoconazole, what happens?

DR. GHAHRAMANI: Indeed, we have done with fluvoxamine, which is a mixed inhibitor of 1A2 and 3A4. That's a mixed inhibitor. And again, the maximum increase, as we see, is about or less than twofold.

DR. CALHOUN: Okay. Thank you. And then the question of the 250 milligram dose?

DR. RABE: Yes. Thank you very much for this opportunity. I was just slightly irritated --

maybe I didn't make it quite clear -- in terms of the doses of 250 and 500. In fact, the trial -- can I have E-35, please, and up -- the trial 107 is, in fact, a trial that is not in a small group of individuals. It's 1,400 individuals, looking at 250 and 500 micrograms.

If you, in fact, looked at the -- it's E-35. And if you look at the chance of actually inhibiting exacerbation with the lower dose, the prediction would be right. You would very likely lose that signal. There was a clearly significant difference between the 250 and the 500 in the efficacy of the drug to afford this.

So I would, with all due respect, think the suggestion to make yet another trial in this group of individuals would probably be superfluous, seeing the data that we have. Thank you very much.

DR. CALHOUN: Thank you, Dr. Rabe.

DR. RABE: Put the slide up just for illustration. It's always nice to see the graphs to prove that I'm right, what I said. So it's between 250 and 500. That's a significant difference. Thank

you.

DR. CALHOUN: That was my recollection, as well. Thank you very much.

Okay. We're going to move on, then, to question 3, which is a voting question. And the way we'll do this is to have whatever discussion needs to occur surrounding the question prior to the vote. Again, we're going to focus our attention on the question as written, and we're going to try to focus our comments to inform the voting.

So question number 3 is, considering the totality of the data, has roflumilast at a dose of 500 micrograms once daily demonstrated substantial evidence of efficacy for the indication of maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbation? And if not, if in the negative, then what further efficacy data should be obtained?

We're not voting yet. We're open for discussion of this point. If there is any further -- if there's anything else that needs to be said that has not yet been said?

[No response.]

DR. CALHOUN: And if not, I guess we are ready to vote. We will be using the electronic voting system. Each of you have three buttons on your microphone, a yes, a no, and abstain. Once we begin to vote, please press the button that corresponds to your vote.

After everyone has completed their vote, the vote will be locked in. The vote will be displayed on the screen, and I will read the vote from the screen into the record. Next, we'll go around the room and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did.

So if there is no further discussion, we will begin voting on question 3.

[Voting.]

DR. CALHOUN: Okay. The vote is 6- yes -- I'm sorry -- 9-yes -- I'm not actually dyslexic -- 6-no, and zero abstentions.

So we'll walk around the committee, and what we'd like to do is have you reaffirm your vote and

then give us a brief sense of why you voted the way you did. And I believe we will start with Dr. Krishnan.

DR. KRISHNAN: Sure. Jerry Krishnan. I voted in favor, as yes, because I believe that the sponsor has demonstrated that it does reduce exacerbations. There is a modest effect on FEV1. And I believe that the reduction of exacerbation is important for the maintenance treatment of patients with COPD.

DR. CALHOUN: Thank you.

Dr. Honsinger?

DR. HONSINGER: I voted yes. It was difficult. I would have had an easier time if it had said moderate to severe COPD and if it had said recurrent chronic bronchitis, because I think those two really emphasize the usefulness of this drug.

DR. CALHOUN: Thank you.

Dr. Platts-Mills?

DR. PLATTS-MILLS: I voted yes because I think I was impressed with the consistency of the significance in relation to lung function, which seems

to go across all the studies. And I think they have clearly shown an effect on exacerbations.

DR. CALHOUN: Thank you.

Dr. Hendeles?

DR. HENDELES: I voted no because I think that the evidence is minimal. And in particular, the way it's worded, this drug could be approved for use as the sole maintenance medicine, and I think there's no evidence that that would be of a clinically relevant benefit.

There is some confusion between the two sets of studies. The 112 had a co-administration of an ICS, and in that study there wasn't a significant reduction in exacerbations. And I think it's more likely that this drug would be added to a regimen that included either a combination product or both an inhaled corticosteroid and a LABA or LAMA. And therefore, adding this agent in that population didn't reduce exacerbations.

DR. CALHOUN: Thank you.

Ms. Fiore?

MS. FIORE: I voted yes because I know from

personal experience that an anti-inflammatory is very, very effective in maintaining the COPD patient. But as Dr. Hendeles says, it should be used in a combination with a LABA and tiotropium. But I personally -- if it isn't available here, I'm going to get it from Europe.

[Laughter.]

DR. CALHOUN: Thank you.

Dr. Joad?

DR. JOAD: I voted no, although I think it is effective, especially in preventing exacerbations. The reason I voted no is I would -- it has to do with the wording and the indication that maintenance to me does mean everyday symptoms, and certainly they have not shown that. And so I would like -- not like the word "maintenance treatment" to be part of the indication. And also "moderate to severe COPD" should be added. Then I would be all right with a yes.

DR. CALHOUN: Thank you.

Calhoun. I voted yes, and I did so because of the consistency of the FEV1 signal. I remain unconvinced that we know anything about the mechanism

of action. But from a practical standpoint, it doesn't matter. The consistency of the FEV1 signal across all the studies is reasonably strong.

The evidence that the drug reduces exacerbations in patients who are selected to have a likelihood of exacerbation because they've got chronic bronchitis and because they've got moderate to severe COPD is reasonably strong. I think the flexibility of a nonsteroid agent is important. I think the once-a-day pill for many patients is important. And so those are the reasons I voted affirmatively.

Dr. Schoenfeld?

DR. SCHOENFELD: I voted yes, and it was a difficult decision because I don't really have good criteria for knowing how to deal with situations in which you have statistical significance. But the effect is relatively modest, and so it's -- and in those situations, it's extremely difficult for me to actually judge how important the point estimate is, the estimate of the effect is.

So I guess I could have voted no. But I voted yes, I guess, because the estimate was similar

to estimates of other point estimates in the literature of other drugs for the same indication. And that seemed to be a reasonable criteria. But it would be nice to have a better one.

DR. CALHOUN: Mr. Mullins?

MR. MULLINS: This was a tough vote for me, but I voted yes because of a couple things. I feel that the drug was not overwhelming in the sense of how efficacious it was, but it was consistent. I looked at the FEV results. I also looked at the fact that it's in tablet form. And many patients have struggled with inhalers, and so this gives them an alternative.

So I did struggle with this vote because of several issues, because, like I said, the data was not overwhelming. It was not compelling. But I do feel there is some mild consistency there, so I am conflicted on this vote. Thank you.

DR. CALHOUN: Thank you.

Dr. Swenson?

DR. SWENSON: I voted yes, for many of the same reasons that were stated, and I won't repeat them. The only thing is the semantics of this labeling

are difficult, and I think that possibly the best outcome would be to probably move toward the sponsor's labeling request simply because I think it will help to position this drug at the rightful place in the step therapy of COPD.

DR. CALHOUN: Thank you.

Dr. Hoidal?

DR. HOIDAL: I voted no. First, the efficacy claim, I thought, was too broad. And secondly, the clinical significance of some of the findings, particularly with regard to the FEV1, I think, is really uncertain.

DR. CALHOUN: Thank you.

Dr. Raghu?

DR. RAGHU: I voted no, primarily because of the way that the question has been worded, an indication of maintenance treatment of COPD as a broader term. This particular study was targeted at a very specific high risk of patient populations, so I don't think that the question is pertinent to this particular study. So I said no. Plus, also, the effects on the FEV1 were relatively small. And

thirdly, the patients didn't seem to sense the improved quality of life for BDI.

DR. CALHOUN: Thank you.

Dr. Carvalho?

DR. CARVALHO: I voted no, also, for several of the reasons that some of the panelists have noted, one being the labeling, another being the borderline interpretation of efficacy. I would actually be much more comfortable with the data if there had been a study done with inhaled corticosteroids, LAMA, and LABA against this agent.

DR. CALHOUN: Thank you.

Dr. Knoell?

DR. KNOELL: I did vote no. I struggled a great deal throughout the day. I'm very exhausted at this point in time.

[Laughter.]

DR. KNOELL: I agree that the wording was, for me, an obstacle that I couldn't overcome. I think it's too generalizable. I especially think that's a problem considering this is an ideal drug, in a pill form given once a day. I think there's high abuse

potential for misguided dosing of COPD patients. So I'm very concerned by that.

Also, I think that the efficacy is undeniable, but mild at best. And unfortunately, it was not complimented by things we spent a lot of time talking about today -- outcome surveys, St. George Respiratory Questionnaires, exercise, treadmill testing, these kinds of things that had I seen that data and seen evidence that these patients really felt better, I think it would have been a much easier yes vote for me.

DR. CALHOUN: Thank you.

Dr. Fink?

DR. FINK: I voted yes, reluctantly, for many of the same reasons that have been stated. I think it does show efficacy similar to many other drugs approved for COPD. But I do think the label has to be very carefully worded, because I think there is a very high potential for misuse and abuse of the drug. But an oral agent in COPD clearly has some benefits.

DR. CALHOUN: Okay. So I think one of the

messages that the agency has heard is that the label needs attention. So I'm sure that the agency can work with that post-meeting.

All right. Let's move on, then, to question number 4, which again is a voting question. Is the safety profile for roflumilast for the maintenance treatment of COPD sufficient to support approval? And if not, what further safety data should be obtained?

First, are there points of discussion on this matter? Dr. Fink?

DR. FINK: Yes. I think in this issue, I'm particularly bothered by the fact that there were no open label add-on studies to provide anything beyond 12 months of therapy because maintenance therapy really implies years of use in these patients, and we really have no data about safety or maintenance of efficacy beyond 12 months, particularly the safety standpoint of usage beyond 12 months.

DR. CALHOUN: Okay. Thank you.

Mr. Mullins?

MR. MULLINS: I think on the issue of safety, I'm concerned because there never was -- I

think there are a lot of questions around the issues of the psychiatric observations. I don't believe we received full clarity on the primary causes for those exacerbations, and I don't feel we understand what led up -- what were the precursors to some of those psychiatric exacerbations. I feel there are a lot of questions.

I'm also concerned that we never did an investigation of some of those suicide attempts. There has never been given any adjudication of how those deaths occurred, just a full understanding so that consumers will understand what's going on with some of those psychological effects.

So I think there are a number of safety questions when it comes to this therapy. Thank you.

DR. CALHOUN: Thank you.

Dr. Knoell?

DR. KNOELL: Yes. I want to add onto that. I think earlier today we heard pretty clearly what the labeling might look like from the sponsor's behalf, so I appreciate that. However, I don't think we heard much in terms of what their -- if the drug were to be

approved, what their release intentions would be in terms of post-marketing surveillance, making sure that the medication gets into the right type of patient and avoid using in the wrong kind of patient, which we spent a long time talking about today. I don't know if we can get clarification of that since we haven't heard anything on that.

DR. CALHOUN: Looks like we might. Please.

DR. TAGLIETTI: Yes. I'm ready. Marco Taglietti, chief medical officer.

First of all, let me make a premise. We didn't have an opportunity to discuss a risk management plan with the agency. This was not part of the NDA. So what I can present is some of the thoughts that we as a sponsor have. And of course, these thoughts will need to be vetted, discussed, and agreed with the agency. Slide up, please.

DR. DURMOWICZ: I don't think we should be discussing risk management plans during the questioning period for a drug to determine whether it's safe or not. I don't know if anybody else has any specific opinions, but that's not the place for

this at this time in the committee meeting.

DR. CALHOUN: Okay. I'll take your point.

Dr. Platts-Mills?

DR. PLATTS-MILLS: Yes. I would just like to reinforce that I think that the side effects -- I think we've seen a very adequate description of the side effects. This is a large database and a lot of detail, and that for a disease as severe as this, personally, I do not find the side effect profile a problem. And so I approve that.

I think what Dr. Knoell is asking is something quite interesting. What you want to see is actually what the direct to public marketing would look like, that is, that you can't quite see how this drug would play out unless you know how it's going to be marketed. And that's an issue that I think will come up again and again in relation to the issues we discuss here.

DR. CALHOUN: Dr. Krishnan?

DR. KRISHNAN: Dr. Calhoun, I'd like to maybe ask the FDA, since we are concerned about adverse effect -- we've spent considerable time on

it -- I would like to ask why is it not reasonable to hear from the sponsor about what their particular approach would be to mitigate these effects? Is that just not policy part of FDA, or is this particular to this discussion?

DR. CALHOUN: Should this be Dr. Chowdhury or Dr. Rosebraugh or Dr. Durmowicz?

DR. CHOWDHURY: I think Dr. Durmowicz can open the discussion here, and I can add in later on.

DR. CALHOUN: Okay. Thank you.

DR. DURMOWICZ: Well, I think the adverse event profile and the safety data are being presented. Now, the question of whether it can be adequately addressed by label or risk mitigation strategies is not part of the discussion, I don't believe, for this meeting.

The company will, depending on what your vote is and depending on what the approval is, enter into some kind of negotiation or discussion with us to try to frame the risk mitigation strategy appropriately.

But to have a new risk mitigation strategy

sprung upon us at this point in time, without any kind of further discussion or vetting throughout what you're thinking, what we're thinking, during the approval process, which is still going on, the review processes, which is still going on, is not, I don't think, appropriate. That's my feeling about it. I don't know if Badrul feels --

DR. CHOWDHURY: I'll just add to that. I mean, the risk evaluation and mitigation strategies, or the risk mitigation strategies, can become quite complicated. And if it is just mentioned on the fly, without really going through all the full details about it, it is very difficult to understand what the proposal is. Is it something logical? Is it something that can be applied in the real life or not?

It needs extensive review, extensive understanding, for discussion at a forum like that. And part of the application did not have a REMS or, in the risk mitigation strategy, submitted to us for our review.

The second point is I would like you to remember what I stated as safety standard. And we are

trying to interpret the safety of this product according to the Code of Federal Regulations, which I presented earlier. And the standard is the regulation of safety, and that's what we're asking you to assess, whether it is safe or not.

We can take this into considerations later on, and if we think it is reasonable to allow marketing of the drug, we can work with the sponsor on the REMS or other strategies, if it is appropriate.

DR. KRISHNAN: Dr. Calhoun, do you mind if I just respond real quick?

DR. CALHOUN: Sure.

DR. KRISHNAN: I guess the reason I'm asking this question, of course, is that given the potential safety issues that we've discussed, it is conceivable that a strategy could be developed that would mitigate further whatever safety concerns are among the panel members.

That's why I'm wondering if the vote is really about the safety profile. Safety profile, in part, means to me, what would you expect would be potential problems that you would need to worry about?

And the strategy the sponsor may use to mitigate that might help influence how I think about this question.

But if this is the policy of the FDA, I'm not asking it to be revised. I'm just putting it out there for discussion.

DR. CHOWDHURY: It is not only the policy of the FDA. It is a regulation that I am citing here, which was also pointed out earlier, that assessment of safety is based on standards, which is in the Code of Federal Regulations, and that assessment is whether the drug is safe or not under conditions of labeled use.

We four or five standards of safety, which I alluded to earlier, and the risk evaluation mitigation strategy does not necessarily change the safety profile of the drug. It may change how the drug can be used.

DR. CALHOUN: And as the discussion and the voting goes on, remember that there is a second piece to question 4, which is, if not, what further safety data should be obtained? And I think if there are specific recommendations of the committee, we can

certainly make those recommendations without the force of policy. We can make those recommendations to the agency.

DR. ROSEBRAUGH: Yes. Let me just kind of add in, because I think your point is very well taken. It is not unusual for sponsors, if there is a risk issue, to present at a meeting their risk mitigation strategy.

However, it's usually one that's been submitted to us so that we can kind of look at it, not one where we see the panel members seem to be upset about this; let's see if we can throw something out that will appease them for the meeting. So I think you're hearing some concern about that from the FDA side.

On the other hand, it would be very helpful to us if you said, look. Some of these I just don't think are an issue. The suicide, maybe it is, and you ought to have some kind of plan to monitor for that or to check post-marketing or whatever. That would help us because then we could go back and develop a plan for that.

DR. CALHOUN: Thanks. That's helpful.

Okay. Other points of discussion on the safety before we move to the vote?

[No response.]

DR. CALHOUN: If not, we're going to vote. Again, press yes, no, or I hope you don't abstain.

[Voting.]

DR. CALHOUN: Okay. So the vote is yes-9, no-6, abstain-0. And just as a point of order, let me apologize for opining that you should not abstain. That's not part of what the chair should do. Sorry.

So at this point, we'll start with Dr. Fink.

DR. FINK: I voted no on this issue because the indication is maintenance therapy. And the limitation, at least at 12 months, when we're talking about some side effects that are potentially bothersome, I think it may be because this drug has been owned by multiple sponsors that there have not been add-on open-label trials to generate additional safety data.

But at least my experience in multiple clinical trials, if a sponsor has a drug they think is

going to be approved, they will usually continue patients who have participated in a trial on the drug until it is approved for marketing to gather that additional safety data. And I find it somewhat striking and disturbing that that's missing in this instance.

DR. CALHOUN: Thank you. Dr. Knoell?

DR. KNOELL: So I voted yes. I believe that there are some very significant safety signals that were addressed today and require further investigation if this drug were to be approved. I think a majority of those that are clinically relevant can be managed by specialists, in particular, and general practitioners, in particular.

I will say that I was not convinced today that enough work has been done in the context of understanding individual variation, particularly with respect to genetic predisposition as a responder/ non-responder, as well as drug/drug interactions, given the fact that CYP 3A4 metabolizes 50 to 60 percent of the drugs that are commonly prescribed in this country.

So I would advocate that a lot more needs to be known in that area.

DR. CALHOUN: Thank you.

Dr. Carvalho?

DR. CARVALHO: I also voted yes for this one. I think that the sponsor has recognized that there are some safety signals. But some recommendations have already been made for monitoring those that are well worked out.

DR. CALHOUN: Thank you.

Dr. Raghu?

DR. RAGHU: I said no, primarily because of the way that -- how it is worded because of the maintenance treatment. I remain concerned about the unintentional weight loss, which needs to be explained. I also remain concerned about the cancer signal that needs to be explored. So the long-term effects of this is unknown, so I said no.

DR. CALHOUN: Thank you.

Dr. Hoidal?

DR. HOIDAL: I voted yes. I think the risks and side effects are not out of line with other

treatments for this disorder. I would encourage post-marketing studies, which would include continued evaluation of neuropsychiatric events and incidence of cancer.

DR. CALHOUN: Thank you.

Dr. Swenson?

DR. SWENSON: I voted yes, with the exact same caveats that Dr. Hoidal mentioned, that I'll trust the agency to come up with post-marketing monitoring of these important events.

DR. CALHOUN: Mr. Mullins?

MR. MULLINS: I voted no because I think there are a lot of questions about the carcinogenicity of the drug. And I think there are some questions about just managing the exacerbations, because even in the environment of a clinical trial, the study, we struggled to see signals to understand some of the exacerbations, particularly the psychiatric exacerbations. So that concerns me.

In the general context of a normal consumer's life, I feel that it would not be as rigorous as this environment that we had in the study.

So I think they'll be vulnerable. I think that it concerns me. So thank you.

DR. CALHOUN: Thank you.

Dr. Schoenfeld?

DR. SCHOENFELD: I voted yes, but I have nothing to add in terms of reasons.

DR. CALHOUN: Calhoun. I voted yes. The principal reasons are that most of the adverse effects, in my view, are tolerability issues and not safety issues. The two safety issues that come to the level of my concern are suicide, and I think that the agency ought probably to work with the sponsor to work on some way of monitoring and gathering more data; and as Dr. Raghu mentioned, the weight loss issue, I think, probably requires some follow-on.

I personally am unconcerned about the malignancy signal. I think the biological plausibility isn't there. But I am actually quite disappointed with the sponsor in not having provided some explanation for what is a pretty clear difference.

I think the sponsor might have spent a

little more time and effort in digging into those cases to try to sort out whether this was -- how this was misdiagnosis or whether you were just remarkably unlucky in your randomization, that so many folks with preexisting malignancies ended up in your treatment group.

Dr. Joad?

DR. JOAD: I voted no, for the reasons I stated earlier. But if the drug is approved, I would strongly encourage a very rigorous follow-up study to look at the issues that have all been brought up here.

DR. CALHOUN: Ms. Fiore?

MS. FIORE: I voted yes because apparently the sponsor has given a lot of thought to all of the safety considerations. And as a patient with chronic lung disease, my life didn't come with a guarantee. I need all the help I can get. And it didn't come with an expiration date, either.

DR. CALHOUN: Thank you.

Dr. Hendeles?

DR. HENDELES: I voted no because I think the degree of benefit doesn't outweigh the adverse

effects. I think the benefit can be achieved with other drugs by the inhaled route. And if patients can't use dry powder inhalers or metered dose inhalers, they can get the same drugs by nebulization. And those are virtually without side effects.

I think that the -- in answer to the second part question, what other studies, I think the drug interaction studies for a drug that has a half-life of 40 hours of the metabolite, the studies were flawed. I think they've missed clinically important potential drug interactions, and that needs to be readdressed.

DR. CALHOUN: Thank you.

Dr. Platts-Mills?

DR. PLATTS-MILLS: I voted yes because I've said before I think most of the common side effects are not a major problem in general management for a disease as severe as this. I think the two signals that I see are suicide and tumor, and I think that clearly they should be followed up. I don't see a rationale that they're directly related to the drug, and so they are something that should be followed carefully in post-marketing.

DR. CALHOUN: Thank you.

Dr. Honsinger?

DR. HONSINGER: Honsinger. I voted yes, with the same caveat, that we need continued follow-up post-marketing or post-release on suicidal and neuropsychiatric effects and on cancer.

DR. CALHOUN: Thank you.

Dr. Krishnan?

DR. KRISHNAN: This is Jerry Krishnan. I voted no. This was a difficult vote for me, but I voted no in the end because I think there's some uncertainty, in my mind, about the reasons behind the psychiatric effects.

I also worried that the weight loss is a marker of some systemic effect that's happening that is not good. And I didn't feel I had enough information from the sponsor to help me understand it. I was hoping that by hearing what the sponsor might think would be a reasonable approach for risk mitigation, it might make me feel better. But in the end, since I was not afforded that opportunity, I voted no.

DR. CALHOUN: Okay. Thank you.

We will now move on to question number 5, which again is a voting question regarding the efficacy and safety data. Do they provide substantial evidence to support the approval of roflumilast at a dose of 500 milligrams once daily for the indication of maintenance treatment of COPD associated with chronic bronchitis in patients at risk of exacerbations?

Are there other points of discussion?

[No response.]

DR. CALHOUN: Seeing none, let's move on to vote.

[Voting.)

DR. CALHOUN: Okay. So the results are yes-5, no-10, abstain-0.

We'll start with Dr. Krishnan.

DR. KRISHNAN: Jerry Krishnan. So I felt, because of my uncertainty regarding the safety data, that I could not feel comfortable that I appreciated the efficacy-safety balance. Therefore, I voted no.

DR. CALHOUN: Thank you.

Dr. Honsinger?

DR. HONSINGER: Honsinger. I voted no. I felt the benefit of this drug, although it's there, it's meager. We didn't have a lot of patient evidence that they thought it was a good drug, and the drug does have side effects.

I think we need to compare this drug with existing drugs such as theophylline or inhaled steroids, and to show that it has as much benefit, or less side effects, before it's released.

DR. CALHOUN: Thank you.

Dr. Platts-Mills?

DR. PLATTS-MILLS: I voted yes because I think that they've clearly shown that this drug has as much effect as many of the other drugs, and that this is a disease in which clearly there's a need for other drugs.

The correct place of this drug in the management of COPD, as Dr. Swenson said, will be worked out. It's a very complicated clinical problem to work out, but will not be worked out in clinical trials premarketing. And the side effects, as I've

said before, are not severe by comparison with the disease.

DR. CALHOUN: Thank you.

Dr. Hendeles?

DR. HENDELES: Well, all of my comments before still stand. And I just -- for the meager degree of benefit, and it's got side effects, and I don't think there's anything unique.

In terms of the second part of the question, if there had been data presented showing this meager advantage in patients who are already on other standard therapy, I might have voted differently. And so that's the study that needs to be done that would convince me that there's a group of patients that would benefit from the addition of this to existing therapy that probably causes fewer side effects.

DR. CALHOUN: Thank you.

Ms. Fiore?

MS. FIORE: I voted yes because I can't take theophylline because of the cardiac effects, and I see this as an alternative there. I know that theophylline benefits me. But, as I say, I can't take

it.

DR. CALHOUN: Thank you.

Dr. Joad?

DR. JOAD: I voted no. The efficacy, I thought there was efficacy, but it was not more than what's already out there. And the side effects, I thought, were greater than the alternatives that are there. So if there -- so I'd agree with previous speakers that if there is a place for it in addition to other therapies, that would be great studies. But at this point, I would say not.

DR. CALHOUN: Calhoun. I voted yes, for the reasons that I stated previously, that I think that there is an efficacy signal, although, as indicated, modest. And the safety issues, I think, are addressable. And I think for pulmonary physicians who care for patients with moderate to severe COPD and for COPD patients to have another option is a good thing.

Dr. Schoenfeld?

DR. SCHOENFELD: Yes. I voted yes, for basically the same reasons as you.

DR. CALHOUN: Mr. Mullins?

MR. MULLINS: I voted no because I think the American public needs clear, definitive, and comprehensive answers to many of these questions. And we spent a lot of time discussing the hypothetical situations surrounding some of the unanswered questions.

So I think that the patients, the consumers are hopeful, and we need to give them objectivity and clarity and valid facts and evidence that there is clear evidence of effectiveness with this therapy. And I don't think I found that today. Thank you.

DR. CALHOUN: Thank you.

Dr. Swenson?

DR. SWENSON: I voted yes. I think the efficacy is reasonable. And as Dr. Calhoun said, I think options are necessary for individual patients. So I would like that option. And the safety signals are real, but I think addressable in post-marketing, and I think we'll come to the truth at some point about whether these represent dangers or not.

DR. CALHOUN: Dr. Hoidal?

DR. HOIDAL: I voted no because I think the

robustness of the clinical efficacy is not strong.

DR. CALHOUN: Dr. Raghu?

DR. RAGHU: I said no, for the reasons that I have said before. But also, I was thinking about it more as we were going along. And the other clinical trials, looking for COPD exacerbations in clinical trials, we do not see the increased incidence of the side effect profile that we are concerned about -- the weight loss, the neoplasm, and the psychogenic aspect. So I said no overall.

DR. CALHOUN: Thank you.

Dr. Carvalho?

DR. CARVALHO: I voted no, for the same reasons that a lot of the panelists have already mentioned.

DR. CALHOUN: Thank you.

Dr. Knoell?

DR. KNOELL: I voted no, primarily for modest efficacy effect. Also, having said that, in the context of the data that we reviewed today, I voted no. That's not to say that I don't think that this particular molecule does have potential for

future treatment, given additional studies, as already identified by the group.

DR. CALHOUN: Thank you.

Dr. Fink?

DR. FINK: I voted no because I didn't feel the risk-benefit ratio was favorable for this drug, with the lack of studies where there was a better standard of care. If they could demonstrate that there was an additional benefit for patients who are on good standard of care treatment, then the risk-benefit ratio would change, in my mind.

DR. CALHOUN: Thank you.

Okay. To the agency, are there matters of discussion that have not come up, or are there points of clarification that you'd like for us to amplify for you?

DR. CHOWDHURY: No. I think you have covered all the topics that we wanted you to cover, and the discussions were very comprehensive and very informative and useful for us. Thank you very much.

DR. CALHOUN: Okay. Thank you. So let me first thank the panel members for their work in all

the review and listening to this.

I thank the sponsor for a very comprehensive presentation.

Thank you to the FDA for their insights and the detailed statistical analyses.

At that, we are adjourned. Thank you.

[Whereupon, at 4:09 p.m., the meeting was adjourned.]