FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Thursday, November 16, 2017

8:30 a.m. to 4:05 p.m.

FDA White Oak Campus

Building 31 Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. BADEN: It's 8:30, and we should get started. One member may be caught in traffic and will join us shortly, but we have a packed agenda, much to discuss. I think we need as much time as possible. I'll remind everyone to silence electronic devices and other distracting items if possible.

Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I'd also like to identify the FDA press contact, Theresa Eisenman. If you are present, please stand. She's in the back corner.

My name is Dr. Lindsay Baden. I'm the chairperson of the Antimicrobial Drugs Advisory Committee, and I will be chairing this meeting. I will now call this meeting to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA to my far left.

DR. COX: Good morning, Ed Cox, director of the Office of Antimicrobial Products in CDER, FDA.

DR. NAMBIAR: Good morning. Sumathi Nambiar, director of the Division of Anti-Infective Products, CDER, FDA.

DR. SMITH: Good morning. I'm Tom Smith, the clinical team leader in the Division of Anti-Infective Products, CDER, FDA.

DR. KIM: Good morning. I'm Peter Kim, clinical reviewer, Division of Anti-Infective Products, FDA.

DR. SWENSON: Good morning. Erik Swenson from the University of Washington, pulmonologist and critical care.

DR. HARKINS: Good morning. Michelle Harkins from University of New Mexico, pulmonary and critical care.

DR. CLARK: Nina Clark, infectious diseases, Loyola University, Maywood, Illinois.

DR. CORBETT: Amanda Corbett, clinical associate professor at the University of North Carolina, Eshelman School of Pharmacy.

DR. OFOTOKUN: Ighovwerha Ofotokun, infectious diseases, Emory University in Atlanta.

DR. TESH: Lauren Tesh, designated federal officer for AMDAC.

DR. BADEN: Lindsey Baden, Brigham and Women's Hospital, Dana-Farber Cancer Institute, and Harvard Medical School in Boston, infectious disease physician, and chair of the committee.

DR. GREEN: Michael Green, pediatric infectious diseases, Children's Hospital in Pittsburgh and University of Pittsburgh School of Medicine.

DR. GRIPSHOVER: Barbara Gripshover. I am in infectious disease at Case Western Reserve University in Cleveland.

DR. HAWKINS: Randy Hawkins, internal medicine, pulmonary medicine, Los Angeles, California, consumer representative.

MR. ZIMMERMAN: Jasan Zimmerman, patient representative, Palo Alto, California.

DR. CARVALHO: Paula Carvalho, University of Washington and Boise VA Medical Center, pulmonary

critical care.

DR. ELLENBERG: Susan Ellenberg, professor of biostatistics, University of Pennsylvania, Perelman School of Medicine.

DR. GREEN: Jonathan Green, pulmonary and critical care medicine, and chair of the Institutional Review Board at Washington University in St. Louis.

DR. BRITTAIN: Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases, NIH.

DR. KARTSONIS: Good morning. Nick Kartsonis. I'm an infectious disease physician and vice president of clinical research, infectious diseases at Merck; and I serve as the industry representative on the committee.

DR. BADEN: We have our additional member joining. Thank you very much for making the extra effort to join us.

COL WEINA: It took me longer to get visitor parking and through security than the drive here from Virginia.

(Laughter.)

DR. BADEN: It is further increasing your conditioning. We are just finishing our introduction. I'll try to let you catch your breath, but a brief introduction, and then we'll continue the meeting.

COL WEINA: Colonel Peter Weina, infectious disease physician at the National Military Medical Center, Walter Reed in Bethesda.

DR. BADEN: Thank you for joining us and making the extra effort.

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 ideas and that individuals can express their views without interruption.

Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. 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 the 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, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I will pass it to Dr. Lauren Tesh, who will read the Conflict of Interest Statement.

DR. TESH: We can just let Chris introduce himself for the record.

DR. KADOORIE: I'm Chris Kadoorie, clinical reviewer.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Antimicrobial

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 this committee's compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, 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 U.S.C. 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

special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of the committee have been screened for potential financial conflicts of interest of those, their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. 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 discussion of new drug application 209367, ciprofloxacin inhalation powder, sponsored by Bayer Healthcare Pharmaceuticals, Inc. for the proposed indication of reduction of exacerbations in non-cystic

fibrosis bronchiectasis, adult patients greater than or equal to 18 years of age with respiratory bacterial pathogens.

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 topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Nicholas Kartsonis is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Kartsonis' role at this meeting is to represent industry in general and not any particular company. Dr. Kartsonis is employed by Merck and Co.

We would like to remind members and temporary voting members that if the discussion

involves any other product or firm 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 other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BADEN: I would like to thank the applicants and the FDA for the briefing documents provided to the committee. I don't speak on behalf of the committee, but this is a complex, important issue, and the briefing documents, hundreds of pages, were quite informative as to the complexity of the issue, and appreciate what all have provided to us to facilitate this discussion.

We will now proceed with the FDA's introductory remarks from Dr. Smith.

FDA Opening Remarks – Thomas Smith

DR. SMITH: Good morning and welcome,

everybody. Today, we're here to discuss the new drug application for ciprofloxacin dry powder for inhalation from Bayer Healthcare Pharmaceuticals.

As you heard, the proposed indication is reduction of exacerbations in non-cystic fibrosis bronchiectasis, adult patients with respiratory bacterial pathogens. This is a capsule with inhalation powder containing 32.5 milligrams of ciprofloxacin, and the proposed dosing regimen is 32.5 milligrams twice daily and 14-day on/off cycles.

The development program consisted of one phase 2 trial and two phase 3 trials in patients with non-cystic fibrosis bronchiectasis. The reasons for conducting two phase 3 trials to support this indication were several.

There are no approved therapies for prevention or management of non-CF bronchiectasis exacerbations.

Studies with other inhaled anti-bacterial drugs such as tobramycin, gentamicin, aztreonam, or colistin for the prevention of non-CF

bronchiectasis exacerbations have yielded mixed results, and there are some publications referenced in the FDA briefing document regarding this.

There are uncertainties going into this program regarding what the proper duration of treatment was, the frequency of administration, and the appropriate endpoints for this use considering that there hadn't been successful trials previously.

There are no relevant animal models of non-CF bronchiectasis that could explore the dosing regimen, or the duration of therapy, or provide other supportive information.

Regarding ciprofloxacin, this is a new indication and a new route of administration. Two independent trials would provide replicative evidence of efficacy, and there was a need for an adequate safety assessment.

The phase 2 trial was a randomized, double-blind placebo-controlled trial comparing treatment with Cipro DPI, 32.5 milligrams twice daily versus placebo, for 28 days in 124 patients with non-CF

bronchiectasis. The primary efficacy variable in this trial was total bacteriological load, which included several potential pathogens and was measured as log colony-forming units per gram of sputum during treatment, at the end of treatment, and at some follow-up visits.

For the primary endpoint at day 29, the total bacteriological load in sputum was reduced by over 3 logs per gram of sputum in the cipro group compared with placebo.

Phase 3 trials were RESPIRE 1 and RESPIRE 2. These were randomized, double-blind, placebo-controlled trials, enrolling patients with non-CF bronchiectasis who had two or more exacerbations in the previous 12 months. These were four-arm trials. Randomization in each one was 2 to 1, cipro versus placebo.

There were two 28-day cycle treatment arms with ciprofloxacin and matching placebo powder, and there were two 14-day cycles evaluating ciprofloxacin and placebo. So these were 6 cycles that were evaluated in a 48-week treatment period

for the 28-day regimen and 12 cycles in a 48-week treatment period for the 14-day on/off cycle.

The primary endpoint was time to first exacerbation. And an exacerbation was defined as the presence of fever, malaise, or fatigue along with worsening of three or more of the patients' baseline signs and symptoms, and the need for systemic anti-bacterial treatment.

A key secondary endpoint was frequency of exacerbations defined as the exacerbations that I just described. There was another secondary endpoint that used a different definition of frequency of exacerbations. And then there were the listed additional secondary endpoints, which included pathogen eradication, a couple of patient-reported outcome assessments, forensic new pathogens, and FEV1.

The statistical considerations are important to keep in mind here. Both the 28- and 14-day regimens were each statistically tested against pooled placebo powder under separate hierarchies in each trial. The primary endpoint was tested first,

followed by secondary endpoints in a prespecified order.

Statistical testing stopped after the first nonsignificant finding, and therefore, all other testing is considered exploratory. Statistical testing was done at an alpha of .025 for each ciprofloxacin arm in RESPIRE 1 and was allocated differently in RESPIRE 2 because of the favorable findings in RESPIRE 1 so that the alpha was .001 for the 28-day regimen and .049 for the 14-day regimen.

These are the efficacy results for the primary endpoint of prolongation of time to first exacerbation. What you see here is that for the 14-day arm, there was more than an 150-day prolongation. This was a significant finding. These comparisons are against pooled placebo, so 186 days was the median time to exacerbation for the placebo group.

The event rate, listed down at the bottom, is the percentage of patients who had a pulmonary exacerbation. You can see there were roughly

20 percent fewer patients in the 14-day arm and about 10 percent fewer patients in the 28-day arm.

In RESPIRE 2, there were fewer exacerbations, and as you can see from the event rate, fewer than half of patients had a pulmonary exacerbation during the trial period. As a result, the time to prolongation or the prolongation of time to first exacerbation could not be estimated. Another thing to point out here is that the alpha was allocated such that the finding for the cipro 28-day arm, the significance level for that was .001.

Looking at the frequency of exacerbations, which was the key secondary endpoint, this is a valid statistical comparison only for the 14-day arm, and the significance level was .025; so the findings for the 14-day arm would be considered not statistically significant.

You can see in the 28-day arm, the median number of pulmonary exacerbations per subject was roughly the same and a non-significant p-value.

RESPIRE 2, there were fewer pulmonary

exacerbations in the trial, and you can see from the incident rate ratios that -- and keep in mind, for this trial, this is not a valid statistical comparison since the primary endpoint was not met. Therefore, even though for the cipro 28-day arm, there is a small p-value, and this is considered an exploratory analysis.

To summarize the efficacy results, in RESPIRE 1, only the cipro 14-day regimen had a statistically significant finding for the primary endpoint of time to first exacerbation. This treatment effect was not replicated in RESPIRE 2. The ciprofloxacin 28-day regimen did not meet the prespecified primary endpoint in either trial.

As the primary endpoint was not met for 3 of the four test arms, most of the secondary endpoint analyses are considered exploratory. There's a lack of consistency of findings across endpoints, and we do not have any information about the durability of efficacy findings over time.

To briefly summarize the safety, there were over 900 patients in the pooled phase 3 safety

population. Approximately 600 patients received at least one dose of Cipro DPI and approximately 300 patients received at least 1 dose of placebo powder.

There were similar rates of common treatment-emergent adverse events, adverse events leading to withdrawal, serious adverse events, and adverse events leading to death in all groups. Most of the treatment-emergent adverse events appeared to be related to the local effects of Cipro DPI, and these are things like taste disorders, dyspnea, bronchospasm, hemoptysis, and cough.

The comparator arm was placebo powder, and without a comparator arm that didn't receive any dry powder, it's difficult to evaluate adverse reactions that were due solely to inhaling the dry powder.

Patients treated with Cipro DPI were more likely to have treatment-emergent ciprofloxacin-resistant Pseudomonas aeruginosa culture at any time point post-baseline, and it's unknown whether

exposure beyond one year may lead to additional safety concerns, further increasing resistance to fluoroquinolones, or a reduced treatment effect.

So the outline for the day, we'll have some presentations by Bayer coming up next; the FDA presentations from Chris Kadoorie, who will discuss the efficacy findings; Peter Kim with the safety findings; and then I'll be back for a short summary. After that, there will be lunch, open public hearing, and questions for the committee.

These are the questions to be considered. First off, has the applicant provided substantial evidence of the safety and effectiveness for the cipro dry-powder inhaler, 14-day regimen in delaying the time to first exacerbation after starting treatment?

If yes, please provide any recommendations regarding labeling. If no, what additional studies or analyses are needed? And we'd like you to discuss appropriate endpoints, drug regimens, and trial duration.

The second question is the same but for the

28-day regimen. Has the applicant provided substantial evidence of safety and effectiveness for the Cipro DPI 28-day regimen in delaying the time to first exacerbation after starting treatment?

If yes, please provide recommendations concerning labeling, and if not, what additional studies or analyses are needed? And again, it would be to discuss endpoints, drug regimens, and trial duration. Thank you.

DR. BADEN: Thank you, Dr. Smith.

We will now move to the applicant presentations. I do need to read this paragraph before you start.

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

For this reason, FDA encourages all participants, including the applicant's non-

employee presenters, to advise the committee of any financial relationship that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interests in a sponsor, including equity interests and those based upon the outcome of the 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 this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Bayer's presentations.

Applicant Presentation - Jana Napolitano

MS. NAPOLITANO: Good morning, Mr. Chairman, members of the committee, ladies and gentlemen. My name is Jana Napolitano, and I'm from regulatory affairs at Bayer. I would like to thank the FDA for the opportunity to present the ciprofloxacin DPI program for treatment of patients with non-

cystic fibrosis bronchiectasis. And I would also like to thank the patients who participated in our clinical trials, as well as the clinical investigators and the other study personnel at the sites.

Our presentation will include the following speakers. Dr. Pamela McShane, assistant professor of medicine at the University of Chicago and a director of the bronchiectasis clinic, will present on the medical landscape in bronchiectasis.

Dr. Jeff Alder from Bayer clinical development will present the efficacy and microbiology data from our global clinical program.

Dr. Gesa Schomakers from Bayer pharmacovigilance will present safety data from our global clinical trials.

Dr. Timothy Aksamit, associate professor of medicine at the Mayo Clinic and a director of the Mayo Mycobacterium and Bronchiectasis Clinic, will provide his clinical perspective on ciprofloxacin DPI. Dr. Jeff Alder will return to conclude our presentation.

In addition, we have the following experts available to answer the committee's questions. Dr. Anne O'Donnell, professor of medicine and chief of the Division of Pulmonary, Critical Care, and Sleep Medicine at Georgetown University Medical Center; Dr. Kevin Winthrop, professor of infectious diseases, ophthalmology, public health, and preventive medicine at Oregon Health Science University; and Dr. Tim Friede, professor of biostatistics at University Medical Center, Goettingen, Germany.

We submitted the NDA for ciprofloxacin DPI with the proposed indication to reduce exacerbations in non-cystic fibrosis bronchiectasis, adult patients with respiratory bacterial pathogens. Pathogens to be listed will include those that we studied for which sufficient evidence is provided by the data. There are currently no approved drug therapies for this indication.

Non-cystic fibrosis bronchiectasis is a chronic respiratory disease. It's characterized by

abnormal and permanent dilatation of the airways due to chronic airway infection and inflammation. Bacterial growth leads to repeated infections and exacerbations that drive airway damage. The disease is associated with poor quality of life and substantial morbidity as well as increased mortality. Non-cystic fibrosis bronchiectasis is currently incurable.

Ciprofloxacin dry powder for inhalation, or DPI, is designed to break this cycle by reducing the bacterial load in the airways by delivering high concentrations of the antibiotic directly to the site of infection.

Bayer has long experience with ciprofloxacin in systemic use in multiple indications, including respiratory tract infections. In fact, we were the innovator company who brought cipro to the U.S. market in 1987.

Ciprofloxacin is a potent broad-spectrum antibiotic with bactericidal activity against gram-negative and gram-positive pathogens frequently isolated from patients with non-cystic

fibrosis bronchiectasis, and we set out to utilize that known bactericidal activity in a new inhaled formulation of ciprofloxacin with numerous patient benefits.

First, we needed a formulation that would be suitable for inhalation. The PulmoSphere formulation allows deep-lung penetration and delivers high-lung concentrations of ciprofloxacin while minimizing systemic exposure. The majority of the inhaled dose is deposited in the lungs.

The PulmoSphere-formulated ciprofloxacin is contained in a capsule, which you can see in the blister pack here on the left. The capsule is used with the T-326 inhaler, which is approved as the device component of TOBI Podhaler for cystic fibrosis patients with Pseudomonas aeruginosa.

The inhaler is pocket-sized, fits in a patient's hand, is easily portable, delivers the drug in a short period of time, and does not require any special cleaning procedures. It is suitable for patients with bronchiectasis regardless of their lung function status.

Non-cystic fibrosis bronchiectasis is an orphan disease with a high unmet medical need. Ciprofloxacin DPI has many promising attributes supporting its potential to address this pressing need. In recognition of this, the FDA awarded ciprofloxacin DPI the following designations: breakthrough therapy, fast track, orphan drug, and qualified infectious disease product.

We designed the ciprofloxacin DPI clinical program in agreement with the FDA. We then conducted a large phase 3 program in patients with bronchiectasis. This program consisted of two phase 3 trials, RESPIRE 1 and RESPIRE 2. Both trials evaluated two dosing regimens, 14 days on and off and 28 days on and off for 48 weeks. These regimens were tested against placebo, but not against each other.

RESPIRE 1 completed first and the 14-day regimen achieved a statistically significant result for the primary endpoint. We then started the rolling NDA submission based on the RESPIRE 1 study for the 14-day regimen while awaiting the RESPIRE 2

data.

To our surprise, the 28-day regimen outperformed the 14-day regimen in RESPIRE 2. Since both dosing regimens delivered the same total ciprofloxacin dose, we are presenting the totality of evidence for both regimens for your consideration today.

Now, I would like to invite Dr. McShane to the lectern. As a physician who directly cares for bronchiectasis patients, Dr. McShane will share both patients' and physicians' perspectives supporting why bronchiectasis patients desperately need approved therapeutic options.

Applicant Presentation - Pamela McShane

DR. McSHANE: Good morning. I'm Pamela McShane from the University of Chicago Medicine, where I run an active bronchiectasis clinic. I am receiving honoraria from the sponsor to be here today, but I have no financial interest in the outcome of today's meeting. I do, however, have a very strong personal interest in the outcome of today's meeting because my bronchiectasis patients

are the focus of my career. I strive to develop better treatment regimens for these patients and improve their quality of life.

Non-cystic fibrosis bronchiectasis is a very poorly understood disease, and therefore it's a poorly served medical condition. So by way of orientation, I'd like to show you this representative coronal view of normal lungs.

Note that the airways taper as they travel from the center of the chest so that by the time the airways reach the periphery of the lung, they're barely visible. In contrast, bronchiectasis is the pathologic distortion and widening of the airways. And when this occurs, mucus is allowed to accumulate in the airways, and this creates an ideal environment for the growth of pathogens, and then mucus gets transformed to purulent sputum.

The purulence continues to accumulate in the airways, becoming an environment that fosters chronic infection and then a vicious cycle ensues. The result for the patient is a recalcitrant,

debilitating cough productive of copious sputum, as shown in this slide.

I want to note that the sputum in that sputum cup represents a single sputum attempt to give a sputum sample. This is not like a 24-hour collection. This is what these patients produce with a singular cough.

In addition, patients feel shortness of breath, fatigue, and they experience a diminished quality of life. And on top of this, in any given year, my patients experience at least two exacerbations, so that's an acute worsening of their baseline condition.

These exacerbations drive a considerable portion of the morbidity that these patients experience. And as their physician, I have a limited ability to reduce the exacerbations because there are no FDA-approved antibiotics to reduce exacerbations.

There are many challenges in managing bronchiectasis patients. Most notably, bronchiectasis is an extremely heterogeneous

disease. Within the parameters of known treatment strategies, many patients require a customized approach. But there are common threads even among these heterogeneous patients.

I'd like to tell you about a few of my patients who exemplify three very common and significant problems in the therapeutic area of bronchiectasis.

I want to make a note on, the lack of awareness and understanding of the disease, the recognition is poor, so missed diagnosis is the rule rather than the exception.

So here is my patient, Myriam. She's 57 years old. Her chronic cough had been bothering her immensely for 20 years, and Myriam's cough had started to interrupt her daily life so much so that when she was in public, she began to feel marginalized by society.

She had been diagnosed with asthma, and chronic bronchitis, and COPD despite the fact that Myriam was a lifelong non-smoker. Myriam was treated with asthma and COPD therapies, and not

surprisingly, none of these therapies worked.

Myriam had bronchiectasis all along. Her lung exam revealed inspiratory pops and squeaks, chest exam revealed enlarged bronchi and mucus plugging. Her sputum, when finally cultured, grew Pseudomonas aeruginosa.

Pseudomonas, as you know, is an important organism because it's associated with more severe disease and it requires targeted therapy. This had been overlooked during years of being labeled as an asthmatic or COPD patient.

Misdiagnosis is only part of the story. For patients who are able to obtain the correct diagnosis, I find there's a frustrating paradox. And that paradox is between the fervent public concern regarding community antibiotic resistance and the fact that the field of bronchiectasis is rife with extensive use of systemic antibiotics. This is due not only to the lack of disease recognition, but also the lack of available alternatives. So therefore, systemic treatment is the norm for many.

My patient, Elizabeth, is a prime example. Like so many other patients with bronchiectasis, Elizabeth looks well, but her goal is just to feel well. Elizabeth's' condition is characterized by frequent exacerbations related to chronic infection from a variety of bacteria.

From Elizabeth's experience, and frankly for all patients with bronchiectasis, exacerbations can run the spectrum, from an inconvenience to needing to have a PICC line placed for weeks of antibiotics, to even an extended hospitalization.

The specter of repeated hospitalization looms large in the back of her mind. Imagine what it would be like to never really be able to plan anything because of the real possibility of being too sick to carry through with an event, or a commitment, or a vacation.

It can be more than just about making plans, of course. During exacerbations, patients have expressed to me that their coughing fits are so intense, they fear that they won't be able to catch their breath and that that next coughing fit may

literally cause them to choke to death.

For other patients, hemoptysis is associated with exacerbations, and this is truly a life-threatening bleed, and it's completely unpredictable.

Like other patients with bronchiectasis, Elizabeth's exacerbations have been treated with systemic antibiotics. But as you know, this is not an easy answer, either, because the systemic side effects can afflict her with debilitating side effects.

So although they've been necessary to treat her exacerbations, they've undoubtedly been another source of morbidity for her. And most importantly, we know that using intermittent systemic antibiotics does nothing to reduce exacerbation frequency.

We know from numerous investigations that inhaled antibiotics offer targeted treatment for chronic airway infections, but none have specifically been approved for non-cystic fibrosis bronchiectasis. Therefore, as physicians, we are

forced to prescribe complex, off-label uses of antibiotics because of the therapeutic void for non-CF bronchiectasis.

This is Anwar. He's one of my younger patients at 39 years old. And although younger patients are less prevalent, they have the most to lose if therapeutic options do not become available.

Anwar was diagnosed at age 33, and like many other patients, he was told he had asthma for years, and this allowed his bronchiectasis to progress. His disease has become so severe and now he requires supplemental oxygen. He has had to stop working, and unfortunately he will not have a normal life expectancy.

This is tragic because not only is he so young, but he has a wife and young children who will likely lose their father at a young age. So it's important to treat his chronic infection to prevent him from getting worse.

In an effort to minimize his exposure to oral and intravenous systemic antibiotics, the

current strategy is to borrow from the cystic fibrosis treatment approach and use nebulized antibiotics, but regrettably, there's nothing specifically formulated for non-CF bronchiectasis, so we're forced to take the IV preparation of these antibiotics and reconstitute them for nebulization.

But unfortunately, these prescriptions are often denied by insurance due to lack of FDA-approved status. Further problems with availability and coverage issues forces the patient to use pharmacies that won't cover or compound these patients for nebulization, so Anwar, for example, is left to purchase these unreimbursed medications that he has to compound himself at home for nebulization.

This is typical for many of my patients with bronchiectasis, and quite honestly, it often delays their therapy. This is because we have no approved treatments for non-CF bronchiectasis.

Although non-CF bronchiectasis is a heterogeneous disease, the pathogenic mechanism that drives the disease process is thought to be

common among all patients, and it's shown here in this vicious cycle. So let's consider opportunities for intervention as they relate to the vicious components of this cycle.

There's the inflammatory component, and macrolides have been shown to have some positive impact by way of their anti-inflammatory properties. Corticosteroids, however, show no positive impact in non-CF bronchiectasis, and they may even have a negative impact.

Tissue damage is the byproduct of inflammation, and it cannot be treated medically. This is what's causing the irreversible airway abnormalities. Surgery is a last resort, and it's really only reserved for those with local disease.

Airway clearance and breathing techniques with physiotherapy is a critical component of management, but this does not by itself stop the cycle. And it's very, very time consuming, and patients frequently note that it takes them three hours or more to do this every day. Antibiotic use to interrupt this cycle presents a very promising

opportunity, and that's why we're here today.

This slide shows the various therapies that patients in the United States non-CF bronchiectasis registry are receiving. Although not every patient receives the same therapy, 40 percent of patients are using some form of suppressive antibiotic, and a quarter of that group is using an inhaled antibiotic.

In my experience, most patients would prefer using an inhaled antibiotic, but in the past, they've been poorly tolerated, they have not been available, and not to mention they are not approved by the FDA. Nevertheless, we think they do more to reduce exacerbations than systemic intermittent antibiotics.

So I've mentioned exacerbations several times now, and this slide shows a consensus of what an exacerbation is. A working group of experts convened and recently published a suggested definition for an exacerbation.

An exacerbation means that the patient is experiencing a worsening of at least three

symptoms, shown here numbered 1 through 6, and that is worsened cough, change in sputum, shortness of breath, fatigue, malaise, or hemoptysis.

But what clinches the exacerbation is that the physician determines a change in therapy is indicated, and almost always, this means prescribing an antibiotic. So there is an inextricable link between exacerbations and systemic antibiotics. And a very important point to make about exacerbations is that they last a long time.

This graph comes from a prospective study that examined how long exacerbations last in bronchiectasis patients. The Y-axis shows the percentage of patient-reported exacerbations that meet the study-defined criteria for an exacerbation. On the X-axis are the days that the patients have symptoms that qualify as an exacerbation both before and after they receive an antibiotic.

The median duration of an exacerbation was more than 2 weeks long, and for many patients, they

feel symptoms of an exacerbation for as long as 35 days. This really highlights the importance of avoiding an exacerbation.

Can you imagine being a patient who experiences several of these per year? But even if a patient only experiences one exacerbation, they can be sick for as long as a whole month.

Of course, there are even worse parts of an exacerbation. It's been shown that patients have physiologic increase in inflammation, potentially worsening the tissue damage during exacerbations, and they experience a decline in lung function. And unfortunately, this decline in lung function is not always recoverable. So even avoiding just one exacerbation makes a substantial improvement in the lives of our patients.

We discuss the pathophysiologic model of non-CF bronchiectasis, and in this vicious cycle, as you can see, each event contributes to perpetuating the next.

Bacterial infection is a key promoter of this cycle, so an inhaled antibiotic is an ideal

tool. This is especially because it's been demonstrated in the literature that higher bacterial loads are associated with higher levels of systemic inflammation, more symptoms, and most importantly a higher number of exacerbations per year.

The bar graph on the right comes from a study that investigated the relationship between the bacterial load and sputum and exacerbation frequency. Increasing bacterial load is on the X-axis and exacerbation frequency is on the Y-axis. And as you can see, as bacterial load increases, the number of exacerbations per year also increased.

The specific bacteria involved in non-CF bronchiectasis are listed here. H. influenzae is the most commonly identified organism, and Pseudomonas is present in up to one-third of non-CF bronchiectasis patients, but it exists at a much higher prevalence in patients with more severe disease.

Other bacteria such as streptococcus,

moraxella, and staphylococcus can be the primary culprit in chronic infection as well. Stenotrophomonas and burkholderia are seen in more advanced disease, but not very commonly.

We do see multiples of these organisms seen together in some of our patients. This graph from a study of bacterial type and exacerbation frequency demonstrates that all pathogens are associated with increased exacerbation frequency. And regardless of the organism, patients with long-term infection have more exacerbations than patients who are not chronically infected.

This graph demonstrates the impact of a higher rate of exacerbation. The X-axis shows an increasing number of exacerbations in the previous 12 months. As the number of exacerbations increase, mortality and hospitalization rates increase. But so do exacerbations themselves, and that is exacerbations are predictors of future exacerbations. And so not surprisingly, health-related quality of life diminishes with greater rates of exacerbations.

Now, you've probably noted that lung function or FEV1 has not been included in the graphic data that I presented here. Lung function in the context of bronchiectasis is largely due to the permanent anatomical abnormalities that are inherent to this disease, and therefore, it's generally impossible to influence lung function in a positive way. We do know, however, that frequent exacerbations cause a more rapid decline in lung function.

Within the non-CF bronchiectasis community, there's a consensus for treatment goals: reduce exacerbations, improve daily symptoms, maintain pulmonary function, and identify and treat the underlying cause if possible. We can only achieve these goals by breaking the vicious cycle.

Treating the bacterial load in the lungs of our patients is an important strategy. With your help today, these patients may finally have an FDA-approved agent for just such a purpose.

Now, I would like to introduce Dr. Jeff Alder, who will present the efficacy and

microbiology data of ciprofloxacin DPI therapy in non-cystic fibrosis bronchiectasis patients.

Applicant Presentation – Jeff Alder

DR. ALDER: Good morning. I'm Jeff Alder from Bayer. I'll be giving the efficacy and microbiology presentation today.

Ciprofloxacin DPI, dry powder for inhalation, was built on the successful legacy of oral and IV cipro. Cipro's already approved for treatment of respiratory tract infections with similar pathogens to what is found in NCFB patients, including Pseudomonas aeruginosa and Haemophilus influenzae.

The rationale is to reduced exacerbations through direct application of drug into the lung, and that is accomplished through a specialized formulation of PulmoSpheres and a dry-powder inhalation device that is easy, fast, portable to use. The device is already approved for use with tobramycin for CF patients.

There are two factors about the formulation, both the small size and the dispersion

characteristics that yield to deep penetration into the lung. On the left-hand side, we see an electron micrograph demonstrating the small size, which are less than 5 micrometers in diameter, and on the right side is the scintography representation showing even and deep penetration into the lung.

The PulmoSpheres achieve high local concentrations in the lung and correspondingly low systemic exposure. The two green boxes here are showing the concentrations achieved in sputum -- that's the upper box -- and in plasma, the lower box with Cipro DPI dosing.

The concentration in sputum is up to the saturation limit, i.e., 120 milligrams per liter, and that's the limit for unbound cipro. Higher concentrations than that in sputum are simply insoluble.

The lower green box is showing the levels achieved in plasma, which are quite low, and that's the goal. The plasma Cmax following a Cipro DPI dosing is less than 0.1 microgram per mL. The red

line is showing a typical plasma concentration with oral dosing, i.e., about 2 micrograms per mL.

So what that means is that the concentration achieved in sputum through Cipro DPI is 58 times higher than what's achieved in plasma with a typical oral dose, but systemic exposure is 24x lower with the DPI dosing. What that translates into is a 1400x concentration at the site of infection.

The cipro 14-day-on and 14-day-off dose was based on phase 2 trial results. The trial shown here has as its primary endpoint log CFU reduction. That's on the Y-axis, the logarithmic scale, and of course time on the X-axis.

Patients had one cycle of 28 days on and 28 days off. That's depicted by the lighter green shaded box for the on cycle and the gray box for the off. The Cipro DPI group is depicted in the lighter blue and the placebo in gray.

What was noted is that maximal log CFU reduction is achieved quite early in the treatment cycle, in fact within 10 days. The remainder of

the on cycle more or less maintains the bacterial reduction without further improvement. During the off cycle, when the patient is not on therapy, there's a pretty rapid regrowth nearly back to the level of placebo.

This was the genesis of the idea of shortening the typical on and off cycle, the 14 days on when the maximum bacterial reduction is achieved, and most importantly, shortening the off cycle to 14 days. That's the vulnerable period when bacterial regrowth occurs.

The phase 3 program for the first time tested two different dosing regimes, the cipro 14-day-on and 14-day off, and that's depicted throughout the presentation in the forest green color you see at the top, and the cipro 28-day-on and 28-day off, that is an established standard for cyclic anti-bacterial therapy. It was first utilized in CF patients and has been utilized elsewhere.

It's very important to note that the dose is the same in both treatment regimens,

32.5 milligrams twice daily. The Cipro 14 doubles the number of treatment cycles in the same time frame, but the exposure is the same. The number of days on and off therapy is equal in both dosing arms and overall exposure is equal.

The RESPIRE programs enrolled were both global, and they enrolled a total of 937 patients. That's the largest phase 3 effort ever into studying NCFB patients.

The inclusion criteria were designed to enroll a large and representative sample of NCFB patients. There are three criteria in particular that are important. First, they had to have NCFB as documented by CAT scan of two or more lobes. Secondly, they must have a history of 2 or more exacerbations in the previous year.

It's important to note that the definition used within the trial is much more rigorous and exacting than a patient recall as far as number of exacerbations in the previous year. But they must have had a recorded history of 2 or more; and the third, very importantly, proven culture for at

least 1 of the 7 pathogens that you saw in Dr. McShane's presentation.

NCFB is not a disease of just one pathogen or just Haemophilus, or just Pseudomonas. Any of the seven pathogens, either alone or in combination, can cause exacerbations, and we meant to study the broad array of NCFB patients.

The efficacy involved eight different endpoints and four different parameters. First, exacerbations, as was stated in the FDA introductory remarks, time to event was the primary endpoint, and the second and third endpoints involved frequency of exacerbations.

The first secondary was based on a more rigorous standard of three or more signs and symptoms deteriorating over 2 days, and the second was involving one or more sign or symptom. That was to capture a broader array of exacerbations.

There were two endpoints that were microbiology related, pathogen eradication and prevention of acquisition of new pathogens. New pathogen acquisition has been implicated in causing

exacerbations in NCFB patients.

There were two patient-reported outcomes that were used, the St. George Respiratory Questionnaire, the symptom component score, and the quality-of-life respiratory symptoms domain were both utilized throughout the trial.

Lastly, the FEV1 was measured throughout the trial. As you've heard from Dr. McShane's presentation, FEV1 is an especially difficult parameter to effect in NCFB patients. It was placed eighth in the hierarchy.

For the purposes of today, we'll be focusing primarily on the exacerbation-related endpoints, but we will show you the results for all 8 of these. The definition of exacerbation is especially important since the primary and first two secondaries depend on it. So a qualifying exacerbation had to meet criteria that fell into basically three buckets.

The first bucket was at least three of these signs and symptoms that had to have worsened for at least 2 consecutive days, and these signs and

symptoms matter to the patient.

The dyspnea and cough were graded on basically a 4-point scale from none to severe. Wheezing was a binary yes/no, and sputum volume was collected over 24 hours. Sputum purulence was also tabulated, and we can tell you that over the course of the exacerbation, over 40 percent of these patients would report severe cough.

The second bucket was fever and/or malaise. During an exacerbation, over 99 percent of patients reported an increase in malaise and fatigue. And then lastly, there was a need for intervention with systemic antibiotics specifically to treat the exacerbation. All three of these buckets had to be met for a qualifying exacerbation.

The subject disposition across RESPIRE 1 and 2 demonstrated that there was a high completion rate over the course of the trial. The Cipro DPI arm, Cipro 14 and Cipro 28, showed an 81 to 86 percent completion rate. And by that, we mean they completed the follow-up visit. The pooled placebos were a bit lower, 76 to 82 percent. And

within RESPIRE 1 and RESPIRE 2, the Cipro DPI arms always showed higher completion rates than the corresponding placebos.

As mentioned earlier, patients with any of seven pathogens were enrolled. Within the trial, Pseudomonas aeruginosa was the primary pathogen, and the pathogen array was well distributed between the three treatment arms and between RESPIRE 1 and RESPIRE 2.

The Y-axis is showing the percentage of patients with the pathogen; X-axis of course is pathogen group. So in both trials, Pseudomonas was by far the most prominent pathogen. Staph aureus and H. flu were number 2 and number 3, and they swapped places in RESPIRE 1 and 2. But over RESPIRE 1 and 2 together, the proportion of staff in H. flu was about the same.

The remaining four pathogens are lumped together here for convenience. We can break them out later this afternoon if you want to see. They were primarily strep pneumo and M. catarrhalis. Stenotrophomonas was present in about 10 to 15

patients total across both trials, and the Burkholderia was quite rare.

Now we'll get into the efficacy data for RESPIRE 1 and RESPIRE 2. This Kaplan-Meier shows the treatment effect for delaying time to first exacerbation in RESPIRE 1. Once again, Cipro 14 is the forest green line that's on top, Cipro 28 is the lighter blue, and the pooled placebo is gray.

The dotted lines are Weibull survival fits. They're here simply for illustrative purposes. There was no statistical test involved with the extrapolations. These are simply to allow a projection of meeting days to first exacerbation when the line did not reach the median during the course of the trial.

Cipro 14 had the larger treatment effect, and that was statistically significant. Cipro 28 also had a favorable treatment effect, but that did not reach statistical significance.

Numerically, that Kaplan-Meier is presented here in this table. On the very top portion are descriptive results. The proportion of patients

that had one or more exacerbations was 57 percent in the pooled placebo, and you see 47 and 39 in the two DPI groups.

Statistically, Cipro 14 achieved statistical significance in the primary endpoint, that 0.005. In the secondary for reduction of frequency of exacerbations, we will point out that p-value of .038 did not reach statistical significance. The alpha was set such that a p-value of 0.025 is needed for formal significance.

Cipro 28 also showed favorable treatment effects, but did not reach statistical significance, as seen here.

Now, to show you the overall balance of what happened in RESPIRE 1 is important. You've heard about the mixed results in the FDA briefing document, and that's fully acknowledged. So looking at the RESPIRE 1, all 8 endpoints are listed here.

For convenience, we've grouped them in a slightly different order than the hierarchy. That's for illustrative purposes only. Of course,

you cannot do formal testing for significance if the primary endpoint does not reach significance, so there are no p-values here. We're simply showing the point estimates in the CI.

FEV1 is at the very bottom, and FEV1 was frankly flat in both RESPIRE 1 and RESPIRE 2. The point estimates basically straddle the line. For the other seven endpoints, we see that the treatment effects consistently favor Cipro 14 and Cipro 28. Some of those would reach nominal significance, but of course formally cannot be tested, and some would not. The argumentation today is going to be based on totality of the evidence and figures such as this, showing positive point estimates for Cipro DPI.

The exacerbation-related endpoints are in the upper left. Those are the first three. The next two are pathogen eradication and prevention of acquisition of new pathogens. Those are the next two on the top. The PROs are on the bottom, fairly wide confidence intervals, and then FEV1. So this is a totality of data argumentation.

For RESPIRE 2, the Kaplan-Meier graph shows two distinct differences. First, Cipro 28 is showing greater treatment effect than Cipro 14. And secondly, the entire graph is right-shifted. If you'll recall from the first trial, the pooled placebo had 210 median days to first event. In RESPIRE 2, that's been increased to 388 days, and that's by the Weibull survival fit. None of the groups actually reach the median line.

Cipro 28 showed greater treatment effect followed by Cipro 14 in comparison to pooled placebo, And you can see the median days that were projected by the Weibull survival fits.

Numerically, this is what the data looks like. Now, you see the pooled placebo had 42 percent of the patients who suffered one or more event compared to 57 percent in RESPIRE 1. You see, once again, the decrease in proportion of patients with an event, 33 percent and basically 38 percent in the two Cipro DPI groups.

Cipro 28 did not reach statistical significance for the primary endpoint. You see the

p-value there or 0.05, and that did not reach significance. The first secondary cannot be formally tested because of failure to reach the primary. The p-value was 0.0003. That would have been nominally significant, but of course in the hierarchy, the primary did not reach significance.

The forest plot -- and once again, the exacerbation-related endpoints are in the upper left -- show once again the consistency of favorable effects. FEV1 is again straddling the line, but of the other seven endpoints, three are exacerbation related, two microbiology, and two are patient-reported-outcome related. Fourteen of 14 of the point estimates favor Cipro 14 or Cipro 28. Again, the goal is to show the overall treatment effect within RESPIRE 1 and RESPIRE 2.

Statistically, in forest plots, this is what the data would look like. This is for time to first event, the primary endpoint. The RESPIRE 1 and RESPIRE 2 forest plots are using the prespecified analyses, integrated analysis at the bottom, and I believe the FDA calls that pooled.

What it basically is, is combining the Cipro 14 from RESPIRE 1 and 2 compared to the pooled placebo from RESPIRE 1 and 2, and similarly combining Cipro 28 from RESPIRE 1 and 2 compared to pooled placebo.

So we see that as far as a range of treatment effects, the range is on the Cipro 14 side as far as delaying time to first event, with hazard ratios of .53, which reach significance in RESPIRE 1, and .87, which did not reach significance in RESPIRE 2. Cipro 28 was more consistent across the two trials with hazard ratios of basically .7173.

Both treatment regimens come to the same place, though, in hazard ratio in the integrated analysis. The integrated analysis was prespecified, but it's exploratory. It's not part of the formal hierarchy of testing. And in the integrated analysis, we see the hazard ratios are at 0.68 and 0.71, basically very similar effects.

Looking at the frequency, it's a similar story, except the range of treatment effects are in

the Cipro 28 side with incidence rate ratios of 0.86 and 0.56. That's basically a 14 percent reduction in frequency of exacerbations in RESPIRE 1 and a 44 percent reduction in frequency in RESPIRE 2.

Again, both treatment regimens come to about the same place with incidence rate ratios of 0.72 and 0.75, i.e., a 25 to 28 percent reduction in frequency of exacerbations.

So a key question is what happened between RESPIRE 1 and RESPIRE 2? There are clearly differences. The pooled placebo had a lower exacerbation rate and took longer to have the first exacerbation in RESPIRE 2 compared to RESPIRE 1.

In addition, Cipro 14 showed more favorable treatment effect in the first trial, and Cipro 28 showed greater treatment effect in the second trial. So what happened between RESPIRE 1 and 2?

Numerous analyses were done shown here, geographic, regional, disease history, demographics, resistance, MIC pattern, time, seasonality, including exacerbation by month, by

season, and by quarter.

There was screening of groups and subgroups in various combinations that amounted to 30,000 different group and subgroup combinations screened. None of these provided a meaningful explanation for the lower exacerbation rate in pooled placebo in RESPIRE 2 or the treatment differential, where Cipro 14 shows more favorable effect in the first trial and Cipro 28 in the second trial.

Overall, we can certainly find differences within a particular country where Cipro DPI might perform particularly well or not so well, but none of it translated into a medically meaningful explanation.

What we believe we're looking at is simply the heterogeneity within NCFB patients. This Kaplan-Meier is simply superimposing the two placebo groups from RESPIRE 1 and RESPIRE 2 onto the same graph so you can see the variation from the first trial to the second trial.

It's important to note that these patients are receiving best available therapy plus a

placebo, and their median day to first event varies by more than 100 days. It's also important, though, that within each trial, the Cipro DPI arm, Cipro 14 and Cipro 28, showed favorable treatment effect on top of each of the corresponding pooled placebo lines.

So we're looking at considerable variation within the NCFB patient population, but positive treatment effect within RESPIRE 1 and within RESPIRE 2.

What that treatment effect looks like in more laymen's terms or medical terms is shown here. This is showing the RESPIRE 1, 2, and integrated analysis in days delay in time to first exacerbation.

In RESPIRE 1, Cipro 14 showed a 222-day delay. That was the statistically significant result; a 43-day delay in RESPIRE 2, and you see when you combine across both trials, it comes to 144 days. Cipro 28 was more consistent across RESPIRE 1 and RESPIRE 2. And perhaps it's reassuring that these two treatment regimes, which

had equal doses and equal exposure, come to basically the same treatment effect, about a 140-day delay in time to first event.

Similarly, on the frequency, now Cipro 28 showed the range in treatment effects, with 14 percent reduction in frequency in the first trial, 44 percent reduction in the second, while Cipro 14 is showing more consistent reduction in frequency.

Again, both treatment arms come to basically the same place, 25 to 28 percent reduction in frequency. So the two treatment arms become cross-validating as far as equal exposure, equal doses, and coming to overall more or less equal treatment effects.

Now, we'll look at microbiology for a moment. Resistance is of key importance. Patients are being exposed to cyclic ciprofloxacin over a year and we tracked resistance carefully. This is a simple way to look at it. Simply, is the patient present, do they have a culture, and was that culture resistant or not? So this is looking at

the overall resistance rates in the most conservative manner without regard to present and susceptible or present and resistant later.

Baseline resistance rates are basically in the low 20s across groups. That's before any therapy. That shows the patient population has been heavily exposed to fluoroquinolones previously, probably through treatment of exacerbations, and they are harboring pathogens with 20 percent resistance.

I'll say that for resistance, we're utilizing systemic breakpoints for all descriptions of resistance that may or may not apply for aerosol therapy. By the end of the study, the resistance rates in patients that are present produce sufficient sputum for a culture, grew something, and were evaluated is just about 20 percent in both Cipro DPI arms.

That's relatively consistent throughout the trial. Resistance levels waxed and waned throughout the trial, but by the beginning and the end were at about the same resistance level for

both Cipro 14 and Cipro 28.

The efficacy by baseline pathogen is shown here. Baseline pathogens of Pseudomonas, Staph aureus, Haemophilus influenza, or the other four, are grouped together. You see in the darker-shaded column, the exacerbation frequency for patients who have, for example, Pseudomonas at baseline.

There is a reduction in frequency demonstrated for Pseudomonas and Staph aureus, and for the other four lumped together. Again, that's primarily strep pneumo and M. catarrhalis.

The Haemophilus influenza data is a bit more ambiguous. You see the resistance frequencies. Say that, for Haemophilus influenza, Cipro DPI was particularly efficient at achieving eradication. Eradication rates of baseline H. flu were above 90 percent for both treatment arms.

So we're not sure what's occurring with Haemophilus influenza other than the bug is being eradicated by Cipro DPI, and you see the frequencies of exacerbation. None of these groups

were designed to be a standalone statistical test.

To summarize the overall efficacy, there is perhaps an easy and simple way to look at overall effect. Without modeling, without graphing, we're simply looking here at the top part of the percent of patients on Y-axis, and the X-axis is the proportion of patients that have zero, i.e., they were exacerbation free, or 1, 2, 3, or 4 more events.

The zero-side, taller bars are better. You want to keep your patients free of exacerbations. You see for the two Cipro DPI arms, there's about a 10-percentage point improvement in keeping patients exacerbation free.

On the right side of the dotted line, lower bars are better. We want to reduce the number of exacerbations in patients who have one or more. And we see, again, for both Cipro 14 and Cipro 28 that there is a reduction in proportion of patients that have one or more exacerbations across the board, including 4 or more.

What that totals to is shown on the bottom.

This is simply patient total enrolled and the total number of recorded exacerbations. Again, both treatment arms come to virtually the same place, 188 and 184 total exacerbations compared to 248 in the pooled placebo. That's a reduction of 60 and 64 exacerbations, respectively.

This is an integrated Kaplan-Meier, i.e., the results from RESPIRE 1 and RESPIRE 2 combined. There's a very similar graph in the FDA briefing document as well as in our briefing document. We've added the Weibull curve fitting. That's for illustrative purposes only, and none of this was statistically tested.

But what this integrated graph shows is twofold. Number one, Cipro 14 and Cipro 28 are virtually superimposable in treatment effect. There's not any difference at all in the overall positive treatment effects of the two active regimes; secondly, clear separation between both Cipro 14, Cipro 28, and the pooled placebo. This is one way to summarize a lot of data. It's shown to you here, and it is in both briefing documents.

In summary, for the treatment efficacy, the RESPIRE program was two global phase 3 trials with a total of 937 patients enrolled in two different dosing regimes. It's important to note both regimes had equal doses and equal exposures. There were a range of treatment effects that favored Cipro DPI. Those treatment effects were in exacerbations, but also in the microbiology and in the PROs.

The argumentation is not based on formal statistical significance because, as it's quite easy to see, one of the four primary endpoints reached statistical significance. Instead, the argumentation for efficacy is based on a totality of data in that, outside of FEV1, of the remaining 7 endpoints, all 7 consistently favored Cipro 14 and Cipro 28 every time across both trials.

Overall, what that translated to in exacerbations is about a 140-day delay in time to first event and about a 25 to 28 percent reduction in frequency of exacerbations.

Now, I would like to introduce Dr. Gesa

Schomakers, who will be giving the safety presentation for the RESPIRE program.

Applicant Presentation – Gesa Schomakers

DR. SCHOMAKERS: My name is Gesa Schomakers. I am therapeutic area head in pharmacovigilance at Bayer, and I would like to present the safety data of ciprofloxacin DPI.

The ciprofloxacin safety profile is well known and established by our 30 years of postmarketing experience. The non-clinical safety evaluation of ciprofloxacin DPI was performed according to guidelines for products administered chronically by inhalation. There were no toxicological effects determined that would prohibit the chronic long-term use of ciprofloxacin DPI.

I will present to you details of the clinical safety analysis from the phase 3 studies in the following slides. The safety data from RESPIRE 1 and RESPIRE 2 were pooled. Pooling was appropriate due to the consistent adverse event profile in the individual studies. I'll focus my

presentation on the most relevant events, treatment-emergent adverse events that were all events that occurred from first administration of study medication to 30 days after last dose.

The pooling was done by combining the respective treatment arms. This yielded a safety population of 310 patients treated with Cipro 14, 312 Cipro 28 patients, and 311 patients that inhaled placebo.

There were more females in this study. The mean age was around 62 years. There was no upper age limit, so the eldest patient was actually 91 years old. The pooled population was representative of a typical NCFB population with regards to demographic factors and medical history.

Let me show you a high-level overview of the phase 3 study data on the next slide. This is a comparison of the pooled active treatment arms to pooled placebo. The incidence rates are very similar across the treatment groups. The majority of patients experience adverse events, and around 20 percent of patients experience serious events

with no increase in the active treatment arms. There was also no increase in AEs leading to discontinuation or AEs with fatal outcome.

The majority of adverse events in the phase 3 trials were mild to moderate. In general, there was low variability between the treatment arms. Among the most common events, headache and dyspnea were increased in the active groups, but the most frequently observed events, hemoptysis and bronchiectasis, were balanced between the treatment arms.

Serious adverse events were again very similarly distributed across treatment arms. Looking at them by system organ class, it is apparent that most were reported to occur in the respiratory system. In fact, the majority of serious events in this system organ class were bronchiectasis.

Other events were infections, which might be expected in the study population due to the underlying disease. There was no pattern observed in the serious adverse events that would point to a

drug-related effect.

Observation of deaths was not unexpected, given the morbidity of the included population as well as the length of the observation period. There were 15 cases observed in the treatment-emergent time window, again with the most frequently reported cause of death directly linked to the underlying disease, bronchiectasis, with no increase in the active groups compared to placebo.

During the review, we have looked at specific topics of interest. I will present to you more details on bronchospasm and hemoptysis that were observed with similar incidence rates and active treatment arms and placebo in the next slides.

Let me also comment on observations of positive aspergillus in the sputum that were more frequent in the active treatment arms. Aspergillus sputum tests were not part of the clinical study protocol, so the baseline colonization status of the study population is unknown.

Testing during the study was driven by local

clinical practices. The majority of these observations came from Australia and New Zealand, notably 4 of the 17, even from one single site, in New Zealand. Importantly, these were clinically silent and did not lead to any treatment or clinical consequences in the affected patients.

What you can see for events of bronchospasm is that they were mostly reported on cycle, meaning during inhalation for active treatment as well as for patients inhaling placebo. The status displayed in the lower part of the table and the on-cycle events include events reported as a consequence of spirometry measurements, which was done during the first cycle. There was one serious event occurring on cycle in the Cipro 28 arm.

Hemoptysis was another event of special interest. Again, incidence rates were similar in hemoptysis, and also, serious hemoptysis was seen in patients inhaling placebo. However, here the events occurred on cycle as well as off cycle, which could point to some of the events being related to the underlying disease.

You have already seen this graph in Dr. Alder's presentation, and I would like to focus here on the lower part of the graph that shows the plasma concentration after inhalation, which is around 24 times lower compared to an oral dose of 500-milligram BID.

This might be important when assessing the potential risk of systemic side effects. There were no increased risks seen during the review for potential systemic fluoroquinolone class effects. Hypersensitivity was observed in all treatment arms.

This is a composite, including events such as bronchospasms, but also skin reactions and allergic rhinitis. No serious case of anaphylaxis or angioedema was reported.

Hepatic disorders included mostly elevations in liver function tests. Serious hepatic events were only reported in one placebo patient. Tendon disorders were non-serious and no tendon rupture was observed. There was no Clostridium difficile gastroenteritis observed in patients treated with

Cipro DPI.

Let me now summarize the main points regarding the RESPIRE 1 and RESPIRE 2 safety data. The adverse event profile was consistent across studies and treatment regimens. Most AEs were mild to moderate, with no clinically relevant differences between treatment arms.

There was no increased rate for deaths, SAEs, or discontinuations in Cipro DPI-treated patients, and there were no increased risks for class effects seen with a systemic fluoroquinolone.

So overall, we can conclude that ciprofloxacin DPI has a favorable safety profile and was well tolerated in the phase 3 program. Thank you for your attention. I would now like to hand over to Dr. Timothy Aksamit, associate professor of medicine and director of the mycobacteria and bronchiectasis clinic at Mayo Clinic Rochester to bring the presented efficacy and safety data into clinical perspective.

Applicant Presentation – Timothy Aksamit

DR. AKSAMIT: Good morning. My name is

Timothy Aksamit. I am a consultant, associate professor of medicine and director of the Mayo Mycobacterium and Bronchiectasis Clinic, the Mayo Clinic in Rochester, Minnesota. I would share with you that all contractual and honorary monies for being here will be paid directly to my employer, Mayo Clinic.

Over the past 20 years, I have participated in multiple clinical trials involving bronchiectasis, including the RESPIRE ciprofloxacin DPI trials and am the global PI for the RESPIRE 2 trial.

In addition, I chair the U.S. bronchiectasis and NTM research registry, which currently captures data from over 2,300 patients. This registry involves 15 U.S. academic sites with expertise and academic interest in bronchiectasis, and is supported by the COPD Foundation with a mission to advancing the science of bronchiectasis and to support the development of new pharmacologic and non-pharmacologic treatments of bronchiectasis through clinical trials.

Over the next few minutes, I'd like to share my perspectives and opinion that there is a large unmet need for my bronchiectasis patients seen at Mayo Clinic, as well as bronchiectasis patients nationwide, including those in the U.S. registry.

By way of introduction, as we deliberate the proposition of ciprofloxacin DPI for use in non-CF bronchiectasis patients, I'd like to share with you some history of the use of inhaled antibiotics from my own institution.

This Mayo Clinic note is taken from a patient I currently care for that was seen by my colleagues previously as part of a comprehensive and individualized approach to non-CF bronchiectasis patients.

She was evaluated in 1951, no less than 66 years ago. Recommendations included the use of solubilized penicillin tablets in sterile saline or water put directly into a DeVilbiss nebulizer. Further down in the note, my colleague also recommended that if the patient is not responsive, use of inhaled streptomycin should be considered.

My point here is that the use of inhaled antibiotics to treat airway infections is not a new idea. Although the cystic fibrosis community has been doing this for some time with great success, the best use of inhaled antibiotics for non-CF bronchiectasis patients has previously been elusive.

So where does that bring us today? Let me put the data presented earlier by the sponsor in a broader context by sharing with you some data from the U.S. bronchiectasis research registry.

This is an analysis of patients with two-year follow-up data. I might add that in current hands of registry PIs, the use of off-label and unapproved inhaled antibiotics varies between 1 and 6 and 1 and 3 patients.

Although there is an unmet need for all non-CF bronchiectasis patients, those that exacerbate 2 or more times per year make up just under 20 percent of the registry in this two-year follow-up cohort.

Interestingly, this subgroup has an

eightfold increase in hospitalizations. As such, they represent patients that most likely would benefit from ciprofloxacin DPI.

I would like to again be clear that ciprofloxacin DPI is not for all non-CF bronchiectasis patients, but what it does represent is a potential high impact on those that are in most need. And what of this unmet need?

As we have already heard in detail, non-CF bronchiectasis represents a complex and heterogeneous chronic progressive lung disease. Patients with exacerbations experience symptoms and feel unwell for days before seeing the physician. And even after antibiotic has started, these symptoms may be slow to respond.

My experience and that of my clinical colleagues is that bronchiectasis exacerbations burden the healthcare system daily with physician time, hospital bed utilization, and the trappings that exacerbations bring. These trappings include the loss of quality time with family, time off work, and the additional disruptions associated

with courses of oral or parenteral therapy, including the placement of a PICC line and home health services.

Sadly, there's a tragic void for approved tools and management options. Current non-CF bronchiectasis management options, including inhaled antibiotics, are all off label, as was presented by Dr. McShane earlier and discussed in the U.S. registry patient data.

This need for patients and physicians not only is compromised by the lack of any FDA-approved therapeutics, but also reflects the gap in knowledge of non-CF bronchiectasis and structured data safety monitoring.

So my request today is for a recommendation of approval for a safe and effective tool, ciprofloxacin DPI, for use in select patients with non-CF bronchiectasis. This leaves us right here and now in an important and meaningful moment to be able to further advance the science of bronchiectasis and make available an important, safe, and effective treatment option for non-CF

bronchiectasis patients.

RESPIRE is the largest clinical program of non-CF bronchiectasis to date and has addressed important points for studying an established drug with a new route of administration, new treatment regimen, and new indication.

As demonstrated in the Kaplan-Meier curves of both ciprofloxacin DPI regimens, these data of delaying exacerbations by approximately 140 days, or almost 5 months, would provide a meaningful answer to those days and weeks of symptoms related to exacerbations. And as importantly, this also represents an opportunity to decrease systemic antibiotic exposure, be it oral or parenteral route, that otherwise would be needed to treat these exacerbations.

These data summarizing trends in efficacy, including integrated analysis, have already been presented. But what does the improvement in frequency of exacerbations mean? I understand that a 25 percent decrease in frequency of exacerbations in almost 20 percent of U.S. bronchiectasis

registry patients has the potential to favorably impact healthcare resource utilization.

While I clearly acknowledge that, although the RESPIRE program doesn't have perfect results, what it does have and what the data do mean is a consistent and positive effect on exacerbations across a large non-CF bronchiectasis cohort.

For my patients and in my practice, this means less symptoms, less hospitalizations, and less attack, less time away from family and work activities.

So today, it is my opinion that an opportunity exists based on the data presented for recommendation for approval. This translates into a meaningful improvement in patient lives where none now exists and who are currently burdened by the prolonged symptoms related to frequent exacerbations and the negative consequences on their personal, family, and work lives.

In addition, the RESPIRE program has leveraged the important points of studying a very well-known antibiotic with a known track record

using a new route of administration with a new indication.

As we have seen, ciprofloxacin DPI is safe. It has a low systemic exposure, adverse event rates that are similar to placebo, and employs the convenience of a dry-powder inhaler. I judge that, on behalf of my patients and the non-CF bronchiectasis community, the clinical use of ciprofloxacin DPI in frequent exacerbators is an important tool sorely needed for these patients.

Large clinical studies are complex, and imperfect as they may be, can still provide meaningful signals and important results as in the case of the RESPIRE program, encouraging us to not let perfection kill success.

The opportunity exists now rather than waiting years for the completion of an additional study for my colleagues and myself to provide an effective, safe, and approved clinically meaningful treatment for non-CF bronchiectasis patients.

With my last slide, let me share my perspectives as to the deliberations to date.

Bayer is asking for approval of ciprofloxacin DPI for the use in non-CF bronchiectasis patients. The totality of the data gives me the assurance that the 14- and 28-day regimens are efficacious. While many of my patients have shared their preference for a 14-day on/off regimen, I understand similar effectiveness compared to the 28-day regimen.

Having options in my clinical toolbox for using an either 14-day or 28-day regimen based on individualized patient preferences cannot be overstated. Increasing the number of options for patients is an important element for best care.

So for whom would I recommend ciprofloxacin DPI? In my opinion, only patients with frequent exacerbations of 2 or more per year and infected with a specified pathogen, including but not limited to Pseudomonas.

Why does an approval bring additional benefit? An approval for ciprofloxacin DPI not only will improve the prolonged and debilitating symptoms associated with frequent exacerbations, but will allow for a path forward from the decades

of use of unapproved and unproven therapies and a chance to decrease systemic antibiotic exposure.

The safety profile presented assures me that this drug will be well tolerated in the majority of patients in contrast to other inhaled antibiotics. I can also share that the U.S. bronchiectasis research registry's existing infrastructure could provide a framework for assisting and efficiently collecting data that may be needed in a post-approval setting.

In summary, I very much hope, on behalf of my patients and the clinical and research bronchiectasis communities, that moving forward today means a recommendation for an approval and a new beginning, a beginning for bringing much needed hope to non-CF bronchiectasis patients as well as for making available effective and safe tools to clinicians and a portal for advancing the science of bronchiectasis.

With that, I will turn this over to Dr. Alder, and he'll leave you with a few concluding remarks. Thank you.

Applicant Presentation - Jeff Alder

DR. ALDER: Jeff Alder, Bayer, and very brief concluding remarks.

The proposed indication would be for Cipro DPI, 14 or 28, as indicated for reduction of exacerbations in NCFB patients, adults greater than 18 with the following pathogens, and that pathogen list is subject to final label approval by the FDA. It's also important to note that this proposed indication would be for patients with a history of two or more exacerbations. As you saw from Dr. Aksamit's presentation, patients with 2 or more exacerbations would apply to about 20 percent of the NCFB patients in the registry.

Now, we've shown a lot of data today. We'd like to bring you back to a couple of brief analyses that nicely summarize the treatment effects of Cipro DPI.

First, this is the integrated Kaplan-Meier analysis that appears in both the Bayer and FDA briefing document. This is showing the Kaplan-Meier graph for all patients who receive Cipro 14,

all that receive Cipro 28, or all that received the placebo. Similar treatment effect is apparent for both Cipro 14 and 28, and the clear separation.

This graphic speaks directly to the two important FDA questions. Has the applicant provided substantial evidence of the safety and effectiveness of the 14- or 28-day regime in delaying time to first exacerbation after starting treatment? So this graph speaks directly to the efficacy portion of that question.

Next, this is an integrated analysis, again, all Cipro 14, all Cipro 28, or all pooled placebo across the 8 endpoints. Again, the exacerbation related are on the upper left.

You've heard the trials described as imperfect, as they are. And what is directly meant there is, statistically, in the primary endpoint, one of the four treatment arms, Cipro 14, RESPIRE 1, reached statistical significance. The other three arms did not.

The argument is based not on simply statistical analysis of the primary endpoint, but a

totality of data. As you see here in the integrated analysis, treatment effects consistently favor the two Cipro DPI arms in exacerbations, microbiology, and in the patient-reported outcomes. The FEV1 was of course flat throughout RESPIRE 1 and RESPIRE 2.

In summary, the rationale for Cipro DPI in this patient population is based on three pillars. Those pillars are NCFB has a high unmet need. It's an orphan drug indication, is underserved, and there are no approved therapies for reduction of exacerbations in this patient population.

Secondly, Cipro DPI has demonstrated favorable treatment effects, most especially in exacerbations, but also in the PROs and in the microbiology. And it is perhaps reassuring that these two different treatment regimes, which have equal doses and equal exposures, produce similar treatment effects overall, the 140-day delay and the 25- to 28-percent reduction in frequency of exacerbations.

Last, Cipro DPI has demonstrated a favorable

safety profile, and that's consistent with the need for long-term therapy. Overall, ciprofloxacin DPI has a favorable benefit-risk profile. Cipro DPI can help fulfill a critical unmet need in these NCF patients who have no approved therapies for reduction of exacerbations.

Dr. Baden, that concludes the sponsor presentation.

Clarifying Questions

DR. BADEN: Thank you very much for covering a lot of data conceptually as well as through the studies conducted. At this time, are there any clarifying questions for Bayer? Please remember to state your name for the record before you speak, and if you can please direct your questions to a specific presenter.

For the panel members, please get Lauren or my attention, and we'll add to the list. What I will also say to our panel, if we can build on a theme, it would be useful to try and ask two or three questions that build on a theme to minimize bouncing around. So indicate to me if it's

building on the theme that's being discussed.

I guess Dr. Brittain has the first question.

DR. BRITTAIN: I have two quick questions. One, I just want to truly clarify. When you had your discussions with the FDA, when you were designing the protocol, was the understanding that you did want to see a significant result in both trials for both regimens?

MS. NAPOLITANO: Yes, that is correct. These were designed as replicate trials.

DR. BRITTAIN: I understand. So there was no discussion about maybe it could be more open ended?

MS. NAPOLITANO: No.

DR. BRITTAIN: No? Okay.

The other thing, I just wanted to mention, CC-88 or the similar plots like that -- and by the way, it was a really nice presentation. I wanted to say that.

MS. NAPOLITANO: Thank you.

DR. BRITTAIN: So this is impressive, but at the same time, I'm wondering how much these

endpoints are all correlated with each other so that it's not really independent pieces of information we're getting.

If you had an exacerbation, was it predictable? How would you want all the variables down the line?

MS. NAPOLITANO: I will ask Dr. Alder to address your question.

DR. ALDER: Thank you. The eight endpoints that are shown here, some are certainly interrelated. You would certainly expect time to first exacerbation be related to frequency over the course of the year.

Some of these, though, are clearly unrelated, the microbiology endpoints, eradication and prevention of acquisition of new pathogens. We think that's related to exacerbation, but there's nothing that would directly correlate, i.e., what happens to Pseudomonas eradication doesn't directly cause exacerbation time to event to change.

Similarly, the two PROs are certainly independent of the microbiology and somewhat

independent of the exacerbation frequency. The PROs were measured at multiple time points during the trial. I think you could say the FEV1 is probably related to exacerbations, but we did not observe any such trend.

DR. BADEN: Any follow-on questions to this?

DR. OFOTOKUN: Igho Ofotokun. I want to ask the two clinicians that presented to comment on the significance of the quality-of-life data. How important is that? Just a follow-up.

MS. NAPOLITANO: I will ask Dr. Aksamit to address your question.

DR. AKSAMIT: To answer the question of the quality-of-life data, we think that there is positive trends there, and what I would propose is I would like to ask Dr. Alder to share with you some data first, and then I'll follow that up with additional perspective.

DR. ALDER: Thanks, and we'll try to keep this brief for you.

Tiff, that's Papa Quebec 1, 2, 3 and 8, please. The PRO application in NCFB is a bit

problematic. As you might know from the literature, there have been three macrolide studies done that all showed reduction in exacerbations. They also had PRO, the SGRQ and, in those 3 studies, two of them showed no effect by a PRO, even though there was reduction in exacerbations, and the third one barely showed an effect.

Slide 1 up, please. This is deep drilling down now into the PRO. This is the least favorable one, but we want to show you this for a point, the quality of life, and we're looking at point differentials, being on the right side of the line favors the Cipro DPI arms. You want to increase the point total for favorable effect. We see pretty minimal effects, 1 to 2 points, which was nowhere near statistically significant.

Slide 2 up, please. What that literally meant -- this is within RESPIRE 1 -- the lighter blue bars are baseline scores; the darker blue is at the end of the trial. You want the bars to go up. You won't to increase your point total. And you see it's pretty much the same between the

placebo and the two treatment arms.

That sort of effect was also noted in the macrolide trials. Placebo seems to improve the PRO scores. However, there is underlying data that isn't captured by just looking at the beginning and the end of treatment. The QoL-B was measured at 10 different time points during the trial.

Slide 1 up, please. This is from RESPIRE 1, the Cipro 14. What you're looking at are the purplish dots are showing the differential between Cipro 14 and placebo 14 following the on cycle, so after 14 days of therapy.

The green dots are showing the differential following the off cycle after they've been off drug for 14 days. Every time, the differential is greater following active drug treatment cycle compared to the off cycle.

That's nice for one trial, but is this pattern consistent for both drugs across both trials?

Slide 2 up, pleas. This is showing the results for across both trials. The Cipro 14 is

across the top, RESPIRE 1 on the left, RESPIRE 2 on the right, and similarly for Cipro 28.

Every time, every time, the point differential is greater following an off cycle than the on cycle. Now, it's been written that measuring PRO effect just at the beginning and the end when you have cyclic therapy is probably not the optimal way to capture drug effect.

This is clearly not a statistical test, but we're showing you overall what happened within the trial, that there appears to be good treatment effect of cipro, but it's amplified following the on cycle and narrows during the off cycle.

DR. AKSAMIT: In follow-up, I would also add that there was a meeting here at the FDA in 2012 to look at instruments for PRO data, and what our community has experienced is that this is a very, very difficult issue to have reliable validated instruments.

We certainly know that the St. George respiratory quotient is not validated for bronchiectasis, and even the QoL-B, which was

discussed specifically at the FDA conference here in 2012, does not necessarily perform as well as clinicians would like to think, which brings me to this point. And I think, to answer your question, as I think it has a huge impact, that this is a very positive response to decreasing symptoms that patients have.

They feel really crummy. As was pointed out by Dr. McShane and any of you that take care of patients, they really do have considerable symptoms of fatigue, sputum. They're off work. It disrupts their life. And to have options to minimize or to decrease the frequency of prolonged time to exacerbation will have a very positive impact on quality of life.

That translates into day in, day out, not having to worry about take time off work, what to do with the kids, what to do with these other issues. We wrestle with this all the time. And from even quality-off-life data, these patients are very engaged in trying to fill out pre-authorization forms and paperwork, trying to lobby

to get unapproved therapies for non-CF bronchiectasis.

MS. NAPOLITANO: Thank you.

DR. BADEN: Any follow-on questions from the panel on this theme?

(No response.)

DR. BADEN: If not, then I would like to ask a question moving to the microbiology. In the briefing document, it was not clear to me what the definition of eradication was and also the frequency of microbiologic sampling and how that was done in the determination of resistance. And if that could be clarified, and then I have some follow-on questions to that.

MS. NAPOLITANO: I will ask Dr. Alder to address your question.

DR. ALDER: Dr. Baden, if I understood, it's a two-parter. The first was regarding definition of eradication and how is that accomplished.

DR. BADEN: That definition, and then the frequency of microbiologic sampling, given the determinations of resistant organisms being

present, how was that made.

DR. ALDER: Sure. Fair enough. The definition of eradication is, by the end of the trial, the patient has a sample -- or a sputum sample that's adequate for culture, and is the baseline pathogen present or absent.

Now, that definition could certainly be imperfect in that the efficiency of a sputum culture maybe is 50 percent give or take.

DR. BADEN: So it's by culture?

DR. ALDER: I'm sorry. That's all you want?

DR. BADEN: Yes, by culture.

DR. ALDER: Yes, it's by culture, yes.

DR. BADEN: It's not PCR.

DR. ALDER: No.

DR. BADEN: Then you're not at baseline sampling multiple isolates, because when you make declarations of related or unrelated, how well did you speciate the baseline within a species?

DR. ALDER: So for baseline sampling, it was done at the local hospitals. And if the technician noted, for example, two different Pseudomonas

phenotypes, as they often do, then both would be isolated and worked up. So it wasn't simply one Pseudomonas. If they saw two or three, or two or three H. flus, they were all worked up independently.

DR. BADEN: The frequency of sampling during the course of the study, was it monthly?

DR. ALDER: It was based on the visits and would be up to 12 times during the course of the 48-week trial. So they were sampled quite frequently, a bit more in the Cipro 14 arms and the placebo, and a couple less in the Cipro 28, placebo 28.

DR. BADEN: Again, that was sputum?

DR. ALDER: Correct. That was --

DR. BADEN: Sputum sample, local lab, microbiology?

DR. ALDER: Well, yes. The sputum sample was grown locally, but all of the micro results are confirmed centrally, and that's what we report as part of the trial results.

DR. BADEN: In your slide C-33 with the

technetium -- you don't need to show it -- what is interesting and I think intuitive is the stomach had a moderate amount of cipro. One would imagine that the GI tract would be exposed.

Any assessment of resistance in the GI tract?

DR. ALDER: For assessment of so-called innocent bystander, we did nasal swabs. And the rationale for doing nasal swabs is that's the area more likely to be exposed to cipro. So we cultured, and speciated, and then did MIC profiles on nasal swabs, and found no increase in resistance in those isolates.

The GI was not specifically cultured. We can say that a little less than 50 percent of the administered cipro would make its way into the gut with a 32-milligram dose that's quite a low concentration in the gut.

DR. BADEN: Then I will encourage others to join in. In the briefing you provided us on microbial resistance, it looked like about half the time in cipro recipients, a resistant isolate -- or

half the participants had a resistant isolate at some point during the course of treatment, and baseline resistance of Pseudomonas suggested less of a response, and those who had emergent resistance seemed to have subsequently less of a response, although it's all trending, given the small numbers.

Am I reading that correctly?

DR. ALDER: That was a lot to read. Give me Romeo Foxtrot 1, please.

The incidence of resistance through the trial was, as we said, approximately 20 percent at baseline. We see here the baseline numbers. Now, the middle row is what I believe you're talking about, development of resistance pre-treatment at any time, with 20.8 percent in both cipro treatment arms.

What that literally means is the isolate was present and susceptible at baseline and then present and resistant at some time point. They could have shown resistance at 3 months, never before, never after, and they're still tabulated in

this, so that's exactly correct. The overall incidence rates is approximately 20, 25 percent at any given time point, so there's a constant flux.

DR. BADEN: About half of the participants have resistance detected at some point during the course of treatment.

DR. ALDER: At some, yes. About 20 percent of that would be baseline, and about another 30 at some point. And it's important to note that that's transitory.

DR. BADEN: The determination of the absence of persistence of resistant organism was through the local microbiology lab determination of absence of culture at the end of study?

DR. ALDER: Correct. All microbiology was first done locally but confirmed centrally, absolutely.

DR. BADEN: Thank you very much.

MS. NAPOLITANO: Mr. Chairman, I will ask Dr. McShane to offer her experience from her practice on the issue of resistance.

DR. McSHANE: Slide 1 up, please. I'd like

to show you a snapshot of my patient, Anwar's sputum culture results over the last year. As you can see, it's 2017 there.These are his Pseudomonas strains presumably different each month when I've checked them. So this is not some fancy techniques. This is the usual microbiology lab that we send his sputum to when I see him in clinic.

I want to be clear, this is a patient who has severe disease. His FEV1 is below 40 percent. He has copious sputum production. And for the better part of the last decade, he's been on nebulized antibiotics and intermittent IV antibiotics. And the point that I want to present to you is that his resistance comes and goes.

I don't think the one resistant organism or strain necessarily commits the patient to having that same resistance in the future. And the other important point that I want to tell you is that after I treat him, he feels better. The exacerbation is treated, and he has a resolution of his exacerbation symptoms.

DR. BADEN: Dr. Green, you had a follow-on question?

DR. GREEN: Yes. First is a clarifying question on the timing -- it's a follow-on to Lindsay's question -- the timing of obtaining the cultures. There's obviously lots of times that are just after or on therapy, and then there's periods of time when there's a trough.

So I'm wondering if there are culture data that were specifically per protocol obtained either at the end of a treatment cycle or while on a treatment cycle, and also the same question to being off of a treatment cycle.

I have follow-ons after that.

MS. NAPOLITANO: I will ask Dr. Alder.

DR. ALDER: Sure. As part of the per protocol, samples were obtained both following on cycles and off cycles, and that was done regularly. We did then examine -- or I think you're going for patterns of resistance and were they higher or lower following an on versus following an off. And we found absolutely no pattern as far as resistance

rates for either treatment arm or following on and off cycles.

DR. GREEN: This is true for Pseudomonas as well as the other bacteria in question?

DR. ALDER: We can state most conclusively it's true for Pseudomonas because that's where the majority of the resistance was. For most of the other species, the resistance numbers were so low, it's difficult to make a conclusion.

DR. GREEN: I noted I think in the prep information that was provided to us that you guys even went to the trouble of doing pulse field work and demonstrated that it was emergent resistant within strains as opposed to acquisition of new strains. Correct?

DR. ALDER: We did genotyping. We didn't genotype everything, but what we did was genotype the baseline isolate and the first proximal resistant isolate. We found about 70 percent of relatedness, meaning about 30 percent of the resistance that you've seen in the tables was either present but silent at baseline or was

acquired environmentally by the patient, so about 70 percent confirmed.

DR. GREEN: Per study protocol, no selective media looking specifically to screen for the presence of resistant strains to cipro was used, that is to say you didn't plant them on plates that had cipro as part of the media.

MS. NAPOLITANO: Dr. Alder?

DR. ALDER: Yes, that's correct. There wasn't any selective, like a cipro plate containing 4 or 8 micrograms per mL. That was the standard hospital procedure.

DR. GREEN: Then the last question -- and I'm not sure you answered this question, if Lindsey specifically asked it. But again, in the individual patients who had emergence of resistant strain with Pseudomonas, did you notice any change in their pattern of responsiveness after that event?

So I'm looking at the durability of impact that you have because we've only done a 12-month trial, and you're seeing emergence in approximately

20 percent of patients of resistance. And I wondered what happens if you do this for a longer period of time.

DR. ALDER: To clarify, are you asking for impact on treatment efficacy or are you asking about durability of resistance?

DR. GREEN: I'm asking about treatment efficacy, therefore the durability of treatment efficacy in a population, that is, one-fifth of which require resistance in the first year of using the available cipro study drug.

DR. ALDER: Thank you. Tiff, Romeo Echo 2, please. So efficacy, as you noted in the book, was certainly tracked, and we also looked at efficacy by baseline-resistant patients who detected resistance first post-baseline or the never resistant. What we're going to show you is the proportion of patients who suffered one or more event.

We're looking here at the bottom the baseline resistance, self-evident. The middle count grouping are those that first had a resistant

isolate post-baseline and then the never-resistant through the whole trial to the far right.

Now, starting at the far right, we see the differential is greatest or amplified in those who have never shown a resistant isolate. That effect is narrowed somewhat in those that show a resistant isolate post-baseline. And this analysis is somewhat simplistic in that we're not looking at the relationship of the event to the detection of resistance, but for this purpose is post-baseline resistant and you see the effect.

Now, the baseline resistant, there is still positive effect, but that is narrowed 3 to 6 percentage points, and you see the differential for the never resistant. So treatment effect is maintained with baseline resistance. It certainly narrows compared to the never resistance.

DR. BADEN: Dr. Corbett, you had a follow-on?

DR. CORBETT: Yes. Amanda Corbett. For curiosity along the same lines, did you have a breakdown? I know you said you looked at this and

there was no correlation with RESPIRE 1 and 2 related to several outcomes or demographics. But did you see any, even though not statistically, differences in baseline and acquired resistance between the two trials, RESPIRE 1 and RESPIRE 2?

MS. NAPOLITANO: I'll ask Dr. Alder.

DR. ALDER: Tiff, Romeo Foxtrot 4 and 5, please. The resistance that occurred both at baseline and was present at the end of the cycle was primarily a Pseudomonas issue. We did not see major differences between RESPIRE 1 and 2.

We'll give you a flavor. Slide 1 up, please. This will show both baseline resistance rates and then at cycle 12 at the end of the trial. So we see, at both baseline and post-baseline, resistance rates are primarily a Pseudomonas issue.

You see the percent resistance numbers by genus and species, and in Pseudomonas, the numbers proportionally appear to increase, but of course the number of isolates has decreased over the course of the trial.

So it is a complicated interaction when

looking for a patient who is present, has sputum, grows something, and then we evaluate for resistance. This is the most conservative way to look at it, i.e., the patients who can't produce sputum for a culture are counted one way or the other in this tabulation. So we're showing potentially the worst case here.

There was basically no difference between RESPIRE 1 and RESPIRE 2.

DR. BADEN: Dr. Gripshover, you have a follow-on?

DR. GRIPSHOVER: Yes. So instead of trying to get at the impacts of developing resistance, and it's a little bit of a mix because it's actually a safety question, I didn't see hospitalizations or the need for IV antibiotics to treat their exacerbation because we're going to be losing oral therapy for the Pseudomonas.

Was the safety data broken down to include that at all?

MS. NAPOLITANO: Dr. Alder?

DR. ALDER: There was a difference in

hospitalization rates as a direct result of exacerbation. In the pooled placebo groups across RESPIRE 1 and 2, there were a total of 49 hospitalizations. The Cipro 14 and Cipro 28 across both trials had 38 hospitalizations in relation to an exacerbation, so 49 for the pooled placebo, 38 for each of the 2 DPI arms.

It's interesting that, overall, with 248 total exacerbations in pooled placebo, that's roughly 1 out of 5 resulted in a hospitalization. The reduction in hospitalization is about 22 percent for each of the cipro arms, very similar to the overall reduction in frequency of exacerbations.

DR. BADEN: It is now 10:40. I think we should take a break that's been well earned. We have many more questions and clarifications. We will, after the agency's presentation, have more Q&A and clarification to better understand these data. I again would like to thank the applicant for extremely well-done studies, terrific data, complex data, and we appreciate your working with

us to clarify their meaning.

MS. NAPOLITANO: Thank you.

DR. BADEN: We'll take a break for 10 minutes and resume at 10:50. Thank you.

(Whereupon, at 10:39 a.m., a recess was taken.)

DR. BADEN: It is now 8:50 [sic]. We will proceed with the FDA's introductory remarks from Dr. Smith. We'll now proceed with the FDA presentations, and I think Dr. Kadri [ph] --

DR. KADOORIE: Kadoorie.

DR. BADEN: -- Kadoorie. We can begin with your presentation.

FDA Presentation - Christopher Kadoorie

DR. KADOORIE: Good morning. I'm Chris Kadoorie, and I'll be discussing efficacy findings for Cipro DPI. After a brief overview, I'll go into the study design, touch on demographics, and then discuss efficacy findings in detail. I'll also provide some additional analyses to better understand the data, mention some points to consider, and conclude with a summary.

The applicant's development plan included two phase 2 and 2 phase 3 trials. The first phase 2 was in cystic fibrosis patients. It compared 2 doses of Cipro DPI to 32.5 milligram and 48.75 milligram against matching placebo. This trial failed to show significant improvement in FEV1 at 4 weeks for either Cipro dose. From this trial, the applicant also determined that 32.5 milligrams was the more optimal dose.

The second phase 2 trial was in patients with non-CF bronchiectasis. It compared Cipro DPI 32.5 milligrams BID therapy against matched placebo. This trial met its primary endpoint of showing a reduction in total bacterial load at 4 weeks.

I will be focusing on the larger phase 3 trials you see here, RESPIRE 1 and 2. As you can see from the timeframes of the trials, RESPIRE 2 was ongoing when RESPIRE 1 was unblinded, so the applicant was able to make changes in their analysis plan based on RESPIRE 1 findings, and I'll point out some of those changes.

RESPIRE 1 and RESPIRE 2 are phase 3 randomized, double-blind, placebo-controlled, multicenter trials with nearly identical designs. These trials included patients 18 and above diagnosed with non-CF bronchiectasis using a CT scan. These patients had to have a positive culture for a predefined pathogen, some loss of lung function, and a history of at least 2 exacerbations in the previous year. They also had to be on a stable regimen of standard treatment or macrolides.

The RESPIRE trials included four study arms, 2 cipro and 2 placebo arms. Randomization was 2 to 1 for cipro versus placebo, so there was approximately twice as many subjects on active therapy.

The four study arms were Cipro 28, placebo 28, Cipro 14, and placebo 14. Patients in the Cipro 28 arms received repeated cycles of 28 days on Cipro DPI therapy followed by 20 days off Cipro therapy over a 336-day study period. Placebo 28 differed from Cipro 28 in that patients

received matching placebo instead of Cipro DPI during the on-therapy phase.

Cipro 14 and placebo 14 differed by Cipro 28 and placebo 28 in that the on- and off-therapy periods were 14 days instead of 28 days.

Randomization was also stratified by presence of Pseudomonas aeruginosa, geographical region, and macrolide use at baseline. The applicant planned to pull the placebo 28 and placebo 14 arms provided a pretest showed no significant differences.

This is a graphical depiction of the study design. After screening, the 28-day arms start the randomized period with 28 days of Cipro or matching placebo therapy followed by 28 days off therapy, which completes the first cycle. This 56-day cycle is repeated again and again for a total of 6 cycles to complete the randomized period.

The 14-day arm start the randomized period with 14 days of cipro or matching placebo followed by 14 days off therapy to complete the first cycle. The cycles for the 14-day arms are half as long as

the cycles for the 28-day arms, so 2 cycles for the 14-day arms correspond to 1 cycle of the 28-day arms. This 28-day cycle is repeated for a total of 12 cycles to complete the randomized period.

From the follow-up period, we also note that the 28-day arms have a 28-day off period following the randomized period, while the 14-day arms have a 42-day off period after the randomized period.

The 28-day arms and 14-day arms are also observed to have different number and timing of visits. The 28-day arms have 15 visits, while the 14-day arms have 11 visits. The 28-day arms also have their end-of-therapy and end-of-study visits at weeks 46 and 54, while the 14-day arms have them at weeks 44 and 52.

Due to these differences, there may be different placebo effects associated with the 14-day and 28-day arms. This can affect comparisons involving pooling across the regimens such as Cipro 28 versus pooled placebo or Cipro 14 versus pooled placebo. Although patients are blinded to the therapy they receive, they're not

blinded to the regimen they receive, 14-day or 28-day.

The primary endpoint in these trials was time to first exacerbation, abbreviated TFE, over the 48-week study period with an exacerbation defined by worsening of at least 3 signs or symptoms plus fever, malaise, plus an intervention with systemic antibiotics. The key secondary endpoint of the trial was frequency of exacerbations, or FOE, over 48 weeks using the same definition for exacerbation.

The next secondary endpoint tested was FOE with an exacerbation defined as worsening of at least one sign or symptom plus an intervention with systemic antibiotics. There was no requirement for fever or malaise.

There are also several other secondary endpoints tested which focused on changes or differences from baseline to EOT. These endpoints included the SGRQ, the presence of new pathogens not present at baseline, pathogen eradication, QOL-B, the symptoms domain, and changes in FEV1.

The applicant prespecified a hierarchical testing strategy in the RESPIRE trials. Cipro 28 and Cipro 14 were each statistically tested against pooled placebo under separate hierarchies in each trial. Hierarchies were identical except for alpha levels used for testing.

Under each hierarchy, the primary endpoint, TFE, is tested first. Then the secondary endpoints are tested sequentially using the order shown previously, and statistical testing stops after the first nonsignificant findings. All other testing becomes exploratory.

There are four separate hierarchies, as I mentioned, and these hierarchies are independent, so the results in 1 hierarchy don't affect the results in the other hierarchy. The hierarchies are identical, only differing in how the alpha was allocated, so the statistical testing of the two different cipro arms in each study could be performed without inflating the overall type 1 error.

In RESPIRE 1, the available alpha of 0.05

was split equally across Cipro 28 and Cipro 14 at 0.025 for each testing hierarchy. Originally, RESPIRE 2 also used a 0.025/0.025 split, however, the applicant knew the results from RESPIRE 1 prior to finalizing an alpha for RESPIRE 2. And since Cipro 14 was more promising, more alpha was allocated for testing Cipro 14 at 0.049 and less for testing Cipro 28 at 0.001. All these hierarchies are tested similarly except for the difference of alpha.

This slide shows the results of the testing strategy. We can see for Cipro 28 versus pooled placebo, which was tested at alpha, equals 0.025. TFE was not significant, so therefore, no further statistical testing could be performed on any of the endpoints in that hierarchy.

Cipro 14 versus pooled placebo was tested at alpha equals 0.025. It was significant for TFE, but it was not significant for the next endpoint, which was FOE, so further testing of all other endpoints down the hierarchy could not be performed.

Moving to RESPIRE 2 and Cipro 28 versus pooled placebo, it was tested at alpha equals 0.001. TFE was not significant at that level, so there was no further testing. Going to Cipro 14 versus pooled placebo, it was tested at alpha equals 0.049. TFE was not significant, so there's no further statistical testing. In all these hierarchies, you really only have one statistical test.

This slide briefly describes the statistical methods used for testing the primary and secondary endpoints in the hierarchical testing. Analyses of these endpoints were performed among all randomized subjects. Analyses were also adjusted for the presence of pseudomonas, geographic region, and macrolide use at baseline.

TFE was tested using a Cox proportional hazards model where subjects who discontinued the study were censored. FOE was tested using Poisson regression, and there were different primary approaches used for accounting for early dropouts in RESPIRE 1 and 2. In RESPIRE 1, extrapolation

was used to estimate the number of exacerbations among dropouts. In RESPIRE 2, log of the time in study was used as an offset variable in the Poisson regression. Other secondary analyses used a Cochran-Mantel-Haenszel, or ANCOVA test, without imputation from missing data.

Before I discuss the efficacy findings, I'll present the demographic and baseline characteristics. Overall, treatments were generally well balanced within each of the studies. There were a few differences between the study populations in RESPIRE 1 and 2.

RESPIRE 1 included slightly older subjects, approximately 5 years older on average. RESPIRE 1 also included more female subjects, fewer Asian subjects since it had no Asian sites. There was also greater chronic macrolide use in RESPIRE 1, and subjects in RESPIRE 1 also had a greater proportion of patients with FEV1 percent -- less than 50 percent.

This slide includes the results of the primary endpoint of TFE. For Cipro 28 versus

pooled placebo, or C28 versus P, we see that the hazard ratio estimate is consistent across RESPIRE 1 and 2 with estimates of 0.73 and 0.71. Therefore, patients taking Cipro 28 versus pooled placebo are estimated as being about 73 percent and 71 percent as likely to have an exacerbation event over any given time period in the trial.

In RESPIRE 1, we see a 97.5 percent confidence interval for hazard ratio, which ranges from 0.50 to 1.07, and a p-value of 0.065, which is not significant since it's greater than 0.25. Recall that we used a 97.5 percent confidence interval since the alpha is 0.25.

Since the hazard ratio is a relative measure, dimensionless, we cannot quantify the absolute risk reduction that a patient will achieve over time. For this, we can look at the percent of patients with the first exacerbation.

In RESPIRE 1, 47.5 percent of patients on Cipro 28 versus 57.2 percent on placebo had an exacerbation, and in RESPIRE 2, it was 32.7 percent on Cipro 28 versus 42.0 percent on placebo.

Median time to first exacerbation is another measure that can be considered. However, in these studies, it was usually not estimable because less than 50 percent of patients had an exacerbation in at least one of the treatment arms compared.

In RESPIRE 2, the confidence intervals used were much wider at 99.9 percent since the alpha was 0.001, and the hazard ratio estimates ranged from 0.039 to 1.27. The p-value was 0.051, which is above 0.001, and is therefore not significant. 32.7 percent on Cipro 28 and 42.0 percent on placebo had an event.

Turning our focus to the C14 versus P comparison, we see that the hazard ratio is estimated to be 0.53 with a 97.5 percent confidence interval of 0.36 to 0.80 and a p-value of 0.0005, which shows a strong degree of significance. However, when we go to RESPIRE 2, we see a hazard ratio estimate of 0.87 and 95.1 confidence interval of 0.62 to 1.21, a p-value of 0.397, which is above 0.049, which is not significant.

If we look at the Kaplan-Meier plots, in

RESPIRE 1 on the top panel, we see the blue line, Cipro 14, doing the best in RESPIRE 1 and pooled placebo, the red line, doing clearly worse. In RESPIRE 2, the bottom panel, we see the survival curves are much closer together with Cipro 28, the black dotted line, doing the best.

As a reminder, there were 2 FOE endpoints tested. FOE on the left side of the table is the key secondary endpoint with exacerbations defined by worsening of at least three signs or symptoms, fever and/or malaise, and systemic antibiotics. FOE on the right has a more inclusive definition of exacerbations of at least one sign or symptom plus systemic antibiotic therapy. Keep in mind that these endpoints are highly correlated.

If we look at incidence rate ratios, or IRRs, for Cipro 28 versus placebo, incidence rate ratios have a similar interpretation as the hazard ratio we saw earlier for TFE. We see that patients on Cipro 28, rather than pooled placebo, are about 86 percent as likely to have an exacerbation over any period of time in RESPIRE 1 and 56 percent as

likely in RESPIRE 2.

Turning our attention to C14 versus P, we see for RESPIRE 1 an incidence rate ratio of 0.73 with a 97.5 percent confidence interval of 0.52 to 1.03. The p-value of 0.038 is not significant at the alpha equals 0.025 level. Of all the p-values in the table, the p-value of 0.038 is the only one that we can clearly interpret because it is based on a statistical test. Since TFE was not significant in its testing hierarchy, which was not the case for all the other comparisons in this table, that's the case.

In RESPIRE 2 for Cipro 14 versus pooled placebo, we see an IRR estimate of 0.81, which also trended in favor of Cipro 14. It was less pronounced than in RESPIRE 1.

Also reported on this slide are the mean PEs per subject for Cipro 28 in RESPIRE 1. Subjects had an average of 0.82 PEs compared to 0.91 on placebo. Looking at the more inclusive FOE endpoint, we see similar findings but with higher estimates of mean PEs, as would be expected.

This slide here is the percent of patients with each frequency of exacerbation, 0, 1, 2, 3, or 4 or more. One thing we noticed in RESPIRE 1 on the top panel is the large difference between Cipro 14 in red and pooled placebo in green in the percentage of patients who have zero exacerbations. This difference is much smaller in RESPIRE 2.

I will now summarize some of the findings that were observed in the other secondary endpoints. The analyses were all exploratory, so I will focus on the point estimates of the secondary findings.

There's a general trend favoring the cipro arms with the exception of FEV1. However, as in the primary and key secondary endpoints, we are not seeing much consistency. So if we look at pathogen eradication at EOT, the eradication rates are much higher in the Cipro 28 and Cipro 14 arms versus pooled placebo at 24.1 percent versus 16.7 percent and 28.5 percent versus 16.7 percent. Looking at the same comparisons in RESPIRE 2, we see higher rates of pathogen eradication, but the differences

between cipro and placebo are less pronounced.

For changes in SGRQ, we see that patients in Cipro 28 and Cipro 14 had at least a square mean difference of minus 5.21 points and minus 7.59 points, respectively, and negative changes are better. Looking at the same comparisons in RESPIRE 2, we see much smaller changes in SGRQ, around minus 1.4 points.

We also observe that differences in SGRQ scores are less favorable for Cipro 28 in RESPIRE 2 compared to RESPIRE 1. This is not what we would expect because we saw a much larger reduction in FOE for Cipro 28 versus pooled placebo in RESPIRE 2, and we would expect improved quality of life to move together with the reduction in exacerbations.

Looking at new pathogens not present at baseline, comparisons tended to favor the cipro arms. For changes in QOL-B, we are seeing very minimal treatment effects in the cipro arms, but again moving in the right direction.

Going to FEV1, we are seeing somewhat

different findings. This was the one endpoint which moved in the wrong direction. Cipro 28 versus pooled placebo went in the wrong direction in both trials, and Cipro 28 versus pooled placebo comparison went in the wrong direction in RESPIRE 1 only.

We're seeing that in both trials, patients in the Cipro 14 arms lost approximately 0.04 liters in FEV1 relative to placebo, however, these differences were not significant.

We also conducted further analyses of changes in FEV1 over the course of the study, for example, graphical changes in AUC analyses. These analyses also suggested no meaningful changes in FEV1 with the use of Cipro.

In this presentation, I will discuss the following additional analyses. Since the two trials are identically designed, I will present some exploratory analyses of the first two endpoints for the two trials pooled. I'll consider some results without pooling the two different placebos, and I'll look briefly at the duration of

the exacerbations, which can impact the FOE endpoint.

If you looked at the combined trial data of time to first exacerbation, we see a remarkable consistency of findings between Cipro 28 and Cipro 14 with hazard ratio estimates of 0.72 and 0.69 with p-values under 0.01.

Results were also consistent across C28 and C14 when looking at the combined trial data for the frequency of exacerbations using both the restricted and more inclusive definition of exacerbations. The mean reduction of PE is approximately 0.2 exacerbations per patient over the 48 weeks in all of these analyses.

This slide shows the results of the applicant's pretest, which was used to determine whether or not to pool placebo 28 with placebo 14 in the mean study analyses. We see the estimated hazard ratios in RESPIRE 1 and 2 are not significant, and therefore, pooling of placebo arms was done in both trials.

We see that the survival for placebo 28

patients, as shown by the blue line, is greater than survival for placebo 14 patients, shown by the black line.

Although the placebo arms were not pooled in the analyses based on a nonsignificant pretest, we can't rule out the possible difference in these placebo arms. So we conducted analyses of Cipro 28 versus placebo 28 and Cipro 14 versus placebo 14. Additionally, this was important to explore due to difference in study design in terms of number and timing of visits and different cycle length and lack of blinding between the 28- and 14-day arms.

Similar analyses were conducted for TFE and FOE, and the overall conclusions remain the same. TFE was significant only in RESPIRE 1 for the 14-day arm, and TFE was not significant for the 28-day cycle in either trial.

Possible differences in the duration of exacerbations between the Cipro groups and pooled placebo could potentially affect the interpretation of TFE and FOE findings. We note that longer durations may indicate more severe exacerbations

and can also decrease the patient's risk interval for FOE.

In the RESPIRE trials, one limitation was that the resolution date of exacerbations was not recorded. Therefore, the duration of exacerbations could not be estimated. However, durations of exacerbations classified as serious adverse events were recorded. There were 133 of these exacerbations, which was about 21 percent of the total number of exacerbations.

The number of exacerbations classified as SAEs was different across the treatment arms. In RESPIRE 1, there were 21 exacerbations in Cipro 28, 9 in Cipro 14, 18 in pooled placebo. The mean duration of those exacerbations was 10.4 days for Cipro 28 versus 7.7 days for Cipro 14 and 18.8 days for pooled placebo.

In RESPIRE 2, there were 20 exacerbations in Cipro 28, 30 in Cipro 24, and 35 in pooled placebo. The mean duration of these exacerbations was 14.4 days for Cipro 28 versus 12.4 days for Cipro 14 and 14.7 days for pooled placebo.

Before I summarize the results, I would like to mention a few important points to consider in the overall interpretation of the findings. First, there are limitations in the endpoints that were used in the RESPIRE trials. In particular, the time to first exacerbation may not be an appropriate measure of efficacy since it does not consider information following the first exacerbation, which is important in a chronic setting.

In addition, frequency of exacerbations can be influenced by small subsets of patients, and also, risk intervals can differ because they depend on the duration of the exacerbation. The clinical relevance of the other secondary endpoints is also not clear.

A second point to consider is how clinically meaningful is the magnitude of the treatment effect. This consideration becomes more difficult because the true placebo effect is unknown. There were limited treatment effects in the non-exacerbation-related endpoints such as FEV1, which

showed no differences. And finally, the durability of effect over time is unknown and can change due to other factors such as resistance.

In summary, we note the following points regarding the observed efficacy findings: Findings generally trended towards a cipro benefit but lacked consistency. That was consistency among common endpoints between trials, among related endpoints within the same trial, and between the Cipro 28 and Cipro 14 within the same trial.

Combined analyses, though exploratory, showed consistency in treatment effects for Cipro 28 and Cipro 14 for both TFE and FOE. This was considered as mutually supportive evidence because we see a low p-value in one Cipro arm and it gives us confidence to see the same low p-value on the other one.

Type 1 error concerns with these findings were also mitigated by the small observed p-values that we saw. However, the size and clinical relevance of the treatment effect should be considered.

So just because you're getting these low p-values when you combine the data, you can't confuse that with having a stronger effect.

DR. BADEN: Thank you, Dr. Kadoorie. We'll do questions after the presentations.

Dr. Kim will present the clinical safety evaluation.

FDA Presentation – Peter Kim

DR. KIM: Good morning. My name is Peter Kim, and I will giving the presentation of clinical safety for NDA 209367 from FDA's perspective. The outline for this presentation consists of a discussion of safety assessments from phases 1 through 3 followed by conclusions.

Phase 1. The phase 1 studies included in the applicant's summary of clinical safety included 195 participants of which 18 were healthy subjects and 177 were patients with cystic fibrosis, chronic obstructive pulmonary disease, and non-cystic fibrosis bronchiectasis. Out of the 195 participants, 164 healthy subjects and patients received at least 1 dose of cipro dry powder for

inhalation or Cipro DPI ranging from 1 to 13 days.

Common treatment-emergent adverse events included product taste abnormal, dysgeusia, headache, bronchospasm, dyspnea, cough, and nasopharyngitis.

Phase 2. There were two phase 2 studies. The first, study 12429, was in cystic fibrosis patients. Ninety-three patients were exposed to Cipro DPI at a dose of 32.5 milligrams twice a day for 28 days. An additional 93 patients were exposed to Cipro DPI at a higher dose of 48.75 milligrams twice a day for 28 days, and 100 received matching placebo powder.

Based on the higher incidence of adverse events, serious adverse events, and adverse events leading to withdrawal in the 48.75 milligram regimen and comparable bacterial load reductions in sputum, Bayer chose to continue development with a 32.5 milligram regimen.

The second phase 2 study was study 12965 in non-cystic fibrosis bronchiectasis patients. Sixty received Cipro DPI at a dose of 32.5 milligrams

twice a day for 28 days, and 64 received matching placebo powder. Similar numbers in each group experienced treatment-emergent adverse events, serious adverse events, and adverse events leading to withdrawal. Common treatment-emergent adverse events in the Cipro DPI group included product taste abnormal, bronchiectasis, dysgeusia, headache, nausea, and bronchospasm.

Phase 3. There were two phase 3 trials named RESPIRE 1 and RESPIRE 2. 933 subjects were included in the pooled phase 3 safety population. Out of the 933, 622 subjects received at least 1 dose of Cipro DPI 32.5 milligrams. Out of the 622, 310 received the 14-day Cipro DPI regimen, and 312 received the 28-day Cipro DPI regimen. An additional 311 subjects received at least 1 dose of placebo powder. 156 received the 14-day placebo regimen, and 155 received the 28-day placebo regimen.

This table displays a summary of the pooled phase 3 safety data. As you can see, there are rows for treatment-emergent adverse events, serious

adverse events, both non-fatal and fatal. In general, the incidence of treatment-emergent adverse events were fairly similar across the four treatment groups. We do note that the incidence of serious adverse events was higher in the placebo 14-day on/off group.

This table displays the phase 3 treatment-emergent adverse events leading to premature treatment discontinuation. In general, the incidence of treatment-emergent adverse events and serious adverse events leading to premature treatment discontinuation was similar across the four treatment groups. We do note a slightly higher incidence in the placebo 14-day group.

Examples of treatment-emergent adverse events leading to treatment discontinuation possibly related to Cipro DPI, based on review of case report forms and narratives, included dyspnea, dysgeusia, ageusia, headache, bronchospasm, hemoptysis, cough, et cetera.

This table displays the serious nonfatal treatment-emergent adverse events that occurred in

at least 3 subjects in the Cipro DPI group in the phase 3 trials. As you can see, the top five adverse events were all of respiratory origin. In general, the incidence of these adverse events was similar across the different treatment groups.

This table displays the treatment-emergent deaths that occurred in the phase 3 trials. A treatment-emergent death was defined as any death that occurred during the period from study drug administration first dose through to 30 days after the last dose of study drug administration.

In RESPIRE 1, there were 6 deaths, and the deaths were distributed as follows: In the cipro 14-day group, there was 1 death attributed to aspiration pneumonia. In the cipro 28-day group, there were 2 deaths attributed to pneumonia and cor pulmonale. In the pooled placebo group, there were 3 deaths attributed to pneumonia, pulmonary hemorrhage, and complications of transplant surgery.

In RESPIRE 2, there were 9 deaths, and the deaths were distributed as follows. In the Cipro

14-day group, there were 3 deaths, one due to bronchiectasis, one to gastrointestinal hemorrhage, and one to esophageal carcinoma. In the Cipro 28-day group, there were 4 deaths. Two were attributed to bronchiectasis, one to cor pulmonale, and one to congestive cardiomyopathy. In the pooled placebo group, 2 deaths were attributed to bronchiectasis.

This slide provides a list of the phase 3 treatment-emergent adverse events that occurred with a higher incidence in the pooled Cipro DPI group versus pooled placebo. They include taste disorders, dyspnea, headache, fatigue, malaise, oral candidiasis, dizziness, et cetera.

The following adverse events occurred at similar rates in both the Cipro DPI and placebo groups. However, it is plausible that inhaling the dry powder caused irritation of the respiratory tract, resulting in these adverse events, namely, hemoptysis, cough, and bronchospasm. Without a comparator arm that did not receive any dry powder, it is difficult to ascertain the incidence of

adverse reactions due solely to inhaling the dry powder.

Systemic exposure to Cipro DPI is at least tenfold lower than following orally or intravenously administered ciprofloxacin at approved doses. Adverse events associated with quinolone class effects were not observed to a significant extent in the phase 3 trials. For example, the overall incidence of tendon disorders was similar between the treatment groups and ranged between 1 and 1.6 percent among the Cipro DPI groups and pooled placebo.

Of note, a subject in RESPIRE 1 who received the 14-day regimen and who had no prior history of tendon disorder experienced left Achilles heel tendinopathy of moderate intensity which the study investigator deemed related to study therapy.

This table displays the number of subjects with treatment-emergent ciprofloxacin-resistant pathogens at any point post baseline in RESPIRE 1 and RESPIRE 2. For this analysis, the numerator is the number of subjects with the indicated pathogen

susceptible at baseline who then had a resistant isolate cultured at any point post baseline. The denominator is the number of subjects with the indicated pathogen susceptible at baseline.

As you can see, in RESPIRE 1, there was approximately a twofold difference in the percentage of subjects who had a susceptible isolate at baseline followed by a resistant isolate obtained any time post baseline between the Cipro groups and the pooled placebo group. In RESPIRE 2, the difference was greater, approximately a four- to fivefold difference between the cipro groups and pooled placebo.

This table displays the number of subjects with treatment-emergent ciprofloxacin-resistant Pseudomonas aeruginosa at the end of study visit in RESPIRE 1 and RESPIRE 2. We note that the end-of-study visit occurred 8 weeks after the last dose of study medication.

The numerator in this analysis is the number of subjects with Pseudomonas aeruginosa susceptible at baseline who then had a resistant Pseudomonas

aeruginosa at the end of the study. The denominator is the number of subjects with Pseudomonas aeruginosa susceptible at baseline.

As you can see, in RESPIRE 1 and RESPIRE 2, there was a difference in the number of subjects or percentage that had a resistant Pseudomonas aeruginosa at the end-of-study visit that was susceptible at baseline. In RESPIRE 1, the difference was approximately twofold. In RESPIRE 2, the difference was approximately three- to fourfold, almost fivefold.

This slide serves two purposes. First, it's to provide a revision to table 17 in the FDA briefing packet. Please note the revisions in yellow highlight.

Secondly, this slide provides another analysis of the number of subjects with treatment-emergent development of ciprofloxacin-resistant pathogens in RESPIRE 1 and RESPIRE 2. The difference between this analysis and the prior two analyses is that the denominator is the full analysis set population for each treatment group.

So for the Cipro DPI 28 RESPIRE 1, the denominator would be 141.

We do note that the difference in the number of subjects who had a resistant isolate obtained at any point post baseline after having a susceptible isolate at baseline is higher in the Cipro groups compared to the placebo groups in both trials.

Conclusions. In the phase 3 trials, there were similar rates of treatment-emergent adverse events resulting in death and adverse events leading to premature treatment discontinuation and nonfatal serious adverse events, and common treatment-emergent adverse events in the Cipro DPI and placebo groups.

The majority of treatment-emergent adverse events appeared to be related to local effects of Cipro DPI such as taste disorders, dyspnea, bronchospasm, hemoptysis, and cough.

There was a low incidence of systemic effects. Two- to fourfold more subjects treated with Cipro DPI versus pooled placebo had treatment-emergent ciprofloxacin-resistant Pseudomonas

aeruginosa cultured at any point post baseline, and notably 2 months after the last dose of study medication.

It is unknown whether exposure beyond 1 year may lead to additional safety concerns, increased resistance to fluoroquinolones or result in reduced treatment effect. Without a comparator arm that did not receive any dry powder, it is difficult to ascertain the incidence of adverse reactions due solely to inhaling the dry powder. Thank you.

DR. BADEN: Thank you very much, Dr. Kim, for a comprehensive analysis of these data.

Dr. Smith will present some summary thoughts from the agency.

FDA Presentations – Thomas Smith

DR. SMITH: Just a few summary comments. First of all, regarding non-CF bronchiectasis in clinical trials for this condition, as you've heard, there are no approved therapies for prevention or management of non-CF bronchiectasis exacerbations.

We certainly recognize the need for safe and

effective therapies for patients with this disease. Studies of other inhaled antibacterial drugs, including tobramycin, gentamicin, aztreonam, and colistin, for the prevention of non-CF bronchiectasis exacerbations have yielded mixed results, and none are approved for this indication. There are uncertainties regarding the duration of treatment, frequency of administration, and appropriate endpoints to use in clinical trials for this condition.

The overall observations from these two studies are as follows. In RESPIRE 1, only the ciprofloxacin 14-day regimen had a statistically significant finding for the primary endpoint of time to first exacerbation. This treatment effect was not replicated in RESPIRE 2. The ciprofloxacin 28-day regimen did not meet the prespecified primary endpoint in either trial.

Pooled analyses of the primary and secondary endpoints are considered exploratory. There was a lack of consistency of findings within trials and across trials. There are limitations of endpoints,

particularly with time to first exacerbation, which may not be the most appropriate endpoint for assessing the long-term success of a therapy which potentially will be used lifelong.

Safety of ciprofloxacin DPI appears to be similar to that of pooled placebo powder. Patients treated with Cipro DPI are more likely to have treatment-emergent ciprofloxacin-resistant Pseudomonas aeruginosa cultured at any point post baseline.

Some remaining uncertainties. The clinical relevance of the observed treatment effects when risks such as adverse reactions and the development of resistance are considered; the durability of the efficacy and safety findings over time, and by this I mean beyond 1 year. This includes the development of additional resistance, the potential loss of treatment effect, and whether there are any additional safety concerns,

The long-term use of inhaled ciprofloxacin could limit the utility of systemic fluoroquinolones for the treatment of severe

bacterial exacerbations and pneumonia in patients with non-CF bronchiectasis.

These are the questions that we'd like to committee to discuss. Keep in mind that the proposed indication is for the reduction of exacerbations in non-CF bronchiectasis adult patients with respiratory bacterial pathogens. The clinical studies were done using an endpoint of delay in time to first exacerbation, and that's why we've phrased the questions the way we have.

The first question is, has the applicant provided substantial evidence of the safety and effectiveness of ciprofloxacin DPI, the 14-day regimen, in delaying time to first exacerbation after starting treatment?

If yes, please provide any recommendations concerning labeling. If no, what additional studies and analyses are needed? And we'd like you to discuss appropriate endpoints, drug regimens, and trial duration.

Same questions for the ciprofloxacin DPI 28-day regimen, has the applicant provided

substantial evidence of safety and effectiveness in delaying the time to first exacerbation after starting treatment? If yes, please provide additional recommendations regarding labeling, and if not, what additional studies and analyses would be needed? Thank you.

Clarifying Questions

DR. BADEN: Thank you very much. We will not be discussing these questions right now. The issue right now are clarifying questions to the agency regarding their presentations and understanding these data. If there is time before lunch, we will then, if the applicant is available, come back to discussing some of the questions remaining from the prior session. But right now, it's questions for the agency regarding their presentation of these data.

Dr. Ellenberg?

DR. ELLENBERG: I will ask these questions. I don't know whether the FDA can answer all of them, but I did not get a chance to ask the company before.

Looks like about 15 to 20 percent of the patients on each arm were not available for final analysis. Either they discontinued or they dropped out. I'm not sure how many discontinued treatment and how many dropped out. I would like to know whether there was follow-up information on those who discontinued treatment for the remainder of the course, and if so, were their outcomes included in the primary analysis? If not, I guess I would like to understand why they weren't followed.

I would like to understand what kind of sensitivity analyses were done. We heard about some kind of extrapolation analysis, which sounds like a single-imputation approach that would not account for the variability inherent when data are estimated. So I'd like to know if any additional sensitivity analysis based on some kind of multiple imputation procedure that would account for that variability were done.

I'd like to know if those participants were given the option of continuing treatment after their course, and if so, were they followed?

Those are specific questions that I have about the follow-up and the dropouts and the treatment discontinuations. I have another question that I think the FDA can answer about the integrated analysis.

DR. BADEN: Well, let's do one set of questions at a time. We will discuss further with the applicant their considerations around these issues, but this is for the agency.

I don't know if, Dr. Kadoorie, you have thoughts on the question.

DR. KADOORIE: That was a lot of questions. I think with time to first exacerbation, I think missing data is not as much of an issue because you have an exacerbation, and even if you drop out after that, it doesn't really matter. You've fulfilled the requirements for the endpoint.

As far as time to first exacerbation is concerned, we didn't think the missing data was such an issue mainly because any difference in missing data we thought would actually favor -- the missing data actually favored placebo that we saw.

So if we actually correct for missing data, it would make the results look better.

DR. ELLENBERG: (Inaudible – off mic.)

DR. KADOORIE: Yes, but from what we saw, it seemed that way.

So we're not overly concerned with the missing data. For time to first exacerbation, we did some other methods where we assumed patients who are dropping out were counted as having an event at the time of censoring.

This analysis, if I recall, didn't affect the -- I think it mainly affected the Cipro 28. It mainly made the Cipro 28 results look better in RESPIRE 1, and the other results from the analyses, I didn't see too much of a change.

DR. ELLENBERG: So you're saying that there were no other kinds of -- you were just happy to ignore. What about the people who -- if people discontinued treatment, were they continued to follow if somebody had an event after they discontinued treatment, but within the 48 weeks, were those events counted?

DR. KADOORIE: Excuse me. Say that again.

DR. ELLENBERG: If someone discontinued treatment before the 48 weeks or whatever the treatment course -- I know it differed in the two studies -- if they discontinued treatment, did they continue follow-up? If they had an event, if they had an exacerbation after that during that study, were those captured, and were those included in the primary analysis?

DR. KADOORIE: I think every effort was made to follow up with these patients.

DR. BADEN: Some of these questions we can direct to the applicant for clarification.

DR. ELLENBERG: All right. Then can I ask a question about the integrated analysis? How was that done? Was that done stratifying for the study and for the other important baseline factors, or was everything just thrown together in a pooling without that kind of stratification?

DR. KADOORIE: You have to consider the integrative analysis is a purely exploratory analysis. It's not something we even consider as

part of the evidence. We did use methods that were an extension of the primary analysis method, I would say. So we used the same stratification factors that were used in the primary analyses, and we also added an adjustment for the study.

DR. ELLENBERG: So it was basically the comparison within study and then aggregated overall.

DR. KADOORIE: Yes.

DR. BADEN: Dr. Kartsonis?

DR. KARTSONIS: I had two questions for Dr. Kim. On one of your slides you mentioned that treatment in the conclusion slide that you saw more bronchiectasis, hemoptysis, and cough with cipro. That didn't appear to be the case in the data. So I just wanted to clarify that issue.

DR. KIM: It was actually the case that there were similar incidences. If we go back to that slide, I note that there were similar incidences between the cipro groups and the placebo group, but we couldn't necessarily exclude causality from the cipro drug powder --

DR. KARTSONIS: Got it.

DR. KIM: -- versus the placebo powder.

DR. KARTSONIS: Then the second question I had with regard to the resistance data that you presented, clearly you're showing a difference in terms of the resistance with regard to cipro-related resistance.

Did you do any analysis that also accounted for the fact that there were also more newer infections that occurred on the patients in the placebo versus the ones that had received the active agent, i.e., accounting for both resistance or new infections as a combined analysis?

DR. KIM: Not that I'm aware of. I'll ask the microbiology colleague to see if she has any additional comments.

DR. BADEN: Please just state your name for the record.

DR. SUVARNA: This is Kalavati Suvarna, clinical microbiology reviewer for this product. Yes, we did do that analysis, too. Overall, also, there was a trend for higher resistance within the

cipro, and this I believe is in the briefing document that was provided.

DR. BADEN: Do you have a follow-on?

DR. KARTSONIS: No.

DR. BADEN: If not, the Dr. Swenson is next.

DR. SWENSON: Twice in the FDA's presentation, you've raised this issue of the primary endpoint being time to first exacerbation as possibly not being fully relevant to a disease of chronicity like chronic bronchiectasis. If that was the case, was that a reservation that you had from the very start, and what was the decision-making between you and the Sponsor as to that endpoint?

DR. BADEN: I don't know if someone from the agency wants to comment on how the endpoint was determined a priori.

DR. NAMBIAR: This is Sumathi. I can try to retrieve information from my memory. I think going into the design of this trial, there was a lot of uncertainty, as was discussed in Tom's presentation. I think what we were working off is

a few clinical trials that had been done with inhaled antibacterials, none of which actually showed demonstrable efficacy.

The endpoints used in those trials were also quite variable. Some of them used a microbiologic endpoint. I think the inhaled aztreonam trials, if I remember correctly, used a quality-of-life QLB endpoint.

I think it was working a little bit in the dark in that we didn't know which would be the most appropriate endpoint. So our hope was if we picked the time to first exacerbation with some of its shortcomings, but we would look at all the other endpoints, particularly the frequency of exacerbations, the hope was that between the two regimens and between the two trials, it would all align.

I think what we're struggling with right now is that we have so much variability within a trial, between trials and between regimens.

DR. BADEN: Follow-on?

(No response.)

DR. BADEN: We'll continue with the list. Dr. Ofotokun?

DR. OFOTOKUN: Actually, that was the question that I wanted to ask. It's been addressed, yes.

DR. BADEN: Okay. Then I'm next. To Dr. Kadoorie, in looking at the signal of efficacy, given the design with hierarchical testing, my understanding is that the Cipro 14 in RESPIRE 1 met the prespecified endpoint. The other three groups did not. And therefore, the interpretation of all of the other analyses is nominal.

How do we weigh the subsequent interpretations with confidence intervals that are now having failed the initial analyses? Help me weigh that.

DR. KADOORIE: I think it's a big challenge to try to weigh that. I believe that you have to be able to be flexible in trying to look at some of these analyses. For instance, frequency of exacerbations is not a farfetched endpoint. It's an endpoint we look at probably, the one we

consider to be extremely important.

We saw that, for instance, Cipro 28 had a p-value of 0.0003 in the RESPIRE 2 trial. Now, that kind of finding, yes, it's exploratory, but it's an endpoint we look at, and it's a very low p-value. I don't know how much the exploratory label would detract from that finding, but I think it's still a very meaningful finding.

DR. BADEN: So it gets back to the totality of the data?

DR. KADOORIE: Yes.

DR. BADEN: Though a clear hierarchical testing algorithm to minimize the play of chance was decided upfront.

DR. KADOORIE: Yes.

DR. BADEN: Thank you.

Dr. Brittain?

DR. BRITTAIN: Following on to that, would you think at all this way, that one trial -- I'm sorry. If you were hoping to get two trials at 0.05, that if you got a single trial at .05 squared, which is .0025, would you regard that as similar statistical evidence? I know

it doesn't have the same replication that the two independent trials have, but in a sense it's the same level of statistical evidence, and I wonder what your thoughts are about that.

DR. KADOORIE: I think there's danger in looking at very low p-value and saying, okay, the probability would -- the likelihood of that kind of p-value is just the same as getting a significant result in two studies because single factors, design issues and conduct issues, could affect that p-value. I think it's a little bit weaker than actually seeking two low p-values in two studies, but I think we can't always see that kind of consistency across trials.

DR. BADEN: Dr. Cox?

DR. COX: So maybe I'll just add to. The issue of one trial versus two trials, you can in some circumstances do one trial. If it's highly statistically significant, it can provide strong evidence. Our evidence document talks about this, the weight of statistical evidence for one trial versus two. But I think if we look at the situation that we have here, it's actually perhaps a little bit different than

one trial versus the two-trial question.

We actually do have two trials here, and the issue that makes this challenging and where we're looking for input from the advisory committee deals with the issue of we've got the two trials, we've got two dose groups in each of the two trials, and we've got results in one trial that are not necessarily the same as what we see in the other trial.

So it goes a little bit beyond just the one-trial issue and gets to this issue of you've got a couple of trials, you've got a couple of dose groups, and the findings are not necessarily consistent was you move across, as you've seen in the presentation. So that I think is the challenge here.

So yes, we can take one trial. We do it sometimes. One trial can provide statistically strong evidence depending upon the design of the trial and the nature of the endpoint. Here, we've got two trials, but the results aren't all lining up, and that's what's making this one challenging.

DR. BRITTAIN: I do have one just very quick follow-up. It's related to Dr. Ellenberg's question.

And I'm not sure I got the answer, or she got the answer to it, which was when the integrated study was done, was it done like a meta-analysis or were the data all just lumped together? And maybe you did answer it, but I didn't get it.

DR. KADOORIE: I think the data were just lumped altogether. I looked at all the results, and I said, "Oh, well. It looks a lot better when you combine it," and I think that's something to consider. So it wasn't really a formal analysis that I had at least planned.

DR. BADEN: Dr. Cox, to your comment, we have two trials. We have four primary endpoints. We have one significant primary endpoint. In the reciprocal group in the other trial, that primary endpoint was the weakest and showed no effect; yet together, they showed an effect, while the two 28-day showed a consistent but not yet significant. I agree this is different than one trial that shows a clean result of benefit, which can advance care; here it's a very mixed result.

DR. COX: I appreciate your clarity on the issue of the consistency in the 28-day but not achieving

statistical significance, yes. Thanks.

DR. BADEN: Dr. Clark?

DR. CLARK: Nina Clark. I just had a question about the implications of just pooling the data versus meta-analysis.

DR. BRITTAIN: It might not make much difference in this case because they have the -- both studies have the same allocation of patients. If they didn't have that, then there would definitely be a problem in just lumping them together. But there might be -- I mean, normally a meta-analysis, which is combining two studies -- not just lump the patients together; there's stratifying. It's like getting the result in one study and the result in the other study and mixing them together, and can sometimes lead to a somewhat different result.

DR. BADEN: Do you have a follow-on, Dr. Clark?

DR. CLARK: Just for the FDA, is there a precedent for approving drugs for rare diseases where there was more than one study with conflicting data, where most of the primary endpoints were not met?

DR. COX: Okay. So that's a hard question.

Let me just try and maybe give some background that might be helpful.

There are probably precedents isolated here and there for just about anything. When we think about rare diseases and evidence in rare diseases, when we're looking at an application, we can take risk-benefit into consideration, but the standard is the same, even for some rare diseases. If you look at some of the rare diseases that are out there, some of the findings statistically are actually quite strong, and that may be a product of the effect of the particular drug, the particular endpoint that's being measured.

So the standard that we're looking at, even for infrequently occurring diseases, is the same standard, but we can in the process of looking at that data take into consideration the risks and the benefits and the unmet need.

DR. BADEN: Dr. Green, you had a follow-on question?

DR. GREEN: Yes. This would be for the FDA, probably for Dr. Kadoorie. A long time ago, I got a masters in public health and epidemiology, and the

world's statistics has gotten much more complicated from when I had that degree, and my memory of what I learned from that degree has faded a great deal.

But I'm confused as to the process and the implications of how the p-value allocation is done for RESPIRE 2, and what that does in terms of my simplistic thinking. Because, you know, I'm sort of a classic-thinking guy, and I get a p less than 0.05, and that's a 1 in 20 chance that that's by chance alone. That means something to me.

Yes, in RESPIRE 2, presumably -- or at least a statement was made -- because they had results from RESPIRE 1, they're trying to make it, I guess, easier for them to get to the endpoint. So they say we're going to allocate a higher -- or you are going to meet a primary endpoint, instead of 0.2 and 0.25, at 0.01 and 0.049. And I just don't understand how that manipulation gets to work when what we're looking for is both a biologic and statistical assessment of what's supposed to be meaningful.

Maybe you can explain how that works and why that's allowed.

DR. KADOORIE: It's allowed because we're really concerned with the type 1 error rate, in controlling the type 1 error.

Now, you can control the type 1 error when you're testing two treatments many different ways. One way is to control the type 1 error with an 0.25/0.25 split. Another way to control the type 1 error, with multiple testing of two arms, is 0.01/0.49. As long as it's controlled, controlling the type 1 error, that's what we look for. We want to make sure the type 1 error is controlled.

The sponsor, they were convinced, the RESPIRE 1, that the 14-day was the treatment they wanted to go forward with. So obviously, they're going to want to have as much power to detect a difference. They try to replicate the RESPIRE 1 finding. So it's a reasonable change, and I think we allowed it mainly because it controls the type 1 error.

DR. BADEN: Dr. Carvalho?

DR. CARVALHO: Thank you. Paula Carvalho. I have a question for the FDA, and also perhaps the sponsor can speak to this a little later. But this is a

very heterogeneous population of patients that we're talking about, and the results were variable. And I just wonder if either the agency or the sponsor looked at each patient as their own control.

DR. BADEN: It sounds like we may have to revisit that question when we talk with the applicant.

Dr. Ofotokun?

DR. OFOTOKUN: Yes. I have a question and then a follow-up to that question also. Just looking at the heterogenicity [ph] of the patient population -- I mean, studies were done in different countries where the practices are different. I was wondering whether -- I know a lot of secondary treatments were allowed.

Did you control for the use of macrolide? I know it's a randomized controlled trial, but because it's done in different settings and practices are different, you would expect that the use of macrolides and other secondary treatments for non-CF bronchiectasis were different because of the heterogenicity of the population, and whether that was factored in, and that could account for some of the differences we see between the two studies.

DR. KADOORIE: Macrolide use was one of the adjustment factors that was in the model, along with geographical region and presence of Pseudomonas aeruginosa at baseline.

DR. BADEN: And it was stratified for macrolide use.

DR. KADOORIE: Yes.

DR. BADEN: So that was carefully considered patients

DR. KADOORIE: Stratified and the analysis stratified.

DR. OFOTOKUN: So if you don't mind, my real question that really bothers me is still on the issue of resistance. Although the dry powder is concentrated significantly in the lung, there was systemic exposure to cipro. There was a question that was raised earlier on about resistance in the lung and also resistance in the GI tract. And this is an older population of patients.

Did we look for evidence of resistance outside of the pulmonary system, GI system, and other systems, like urinary tract for instance? The emergence of

resistance to cipro, even subtherapeutic exposure to cipro, systemic subtherapeutic exposure to cipro, could also encourage the development of resistance in other parts of the body.

I'm wondering whether FDA routinely required that in advising or guiding the sponsor in the design of the study, whether that is some of the additional information that is required or requested from the sponsor.

DR. KIM: I'd like to call on the microbiology colleague to respond.

DR. SUVARNA: This is Kalavati Suvarna, clinical microbiology reviewer. The applicant actually did not submit any information related to specimens from other sites, just sputum and nasal swabs. Thank you.

DR. BADEN: Dr. Green, J.

DR. J. GREEN: Jonathan Green. This also relates to just the heterogeneity of the disease. I would point out that one of the entry criteria into the study was a history of two or more exacerbations over the prior year, yet over 50 percent, or around 50 percent, of the patients in the placebo group in both

of the studies didn't have any exacerbation, if I recall the data correctly, which makes me wonder if all of this -- so there's both inter-subject and intra-subject variability in the frequency of their disease exacerbations.

So the question is -- and again, the sponsor may be better able to answer this. But did FDA look at any subgroup analysis looking at the baseline severity of disease perhaps by the frequency of exacerbations in the prior year and whether or not there was a signal for those who had greater numbers of prior exacerbations as opposed to fewer on entry to the trial.

DR. KADOORIE: Yes, that is one of the analyses we did. We did a lot of subgroup analyses. The applicant did a lot of subgroup analyses, too. We did those subgroups and even more subgroups. One of them was the number of exacerbations -- subgroup based on the number of exacerbations in the previous 12 months.

(Pause.)

DR. KADOORIE: The history of let's say a number of acute exacerbations in the previous months was 56 percent -- it was roughly between -- of course,

patients with 2 exacerbations or more was a little bit over 50 percent in RESPIRE 1; RESPIRE 2, it was much higher. It was close to -- just under 80 percent. So RESPIRE 2 had a very big difference in exacerbations than the previous two ones.

But I think your question is how did they actually perform, the subgroup, right? I have to pull that up.

DR. BADEN: Thank you. We can come back to that.

DR. KADOORIE: Okay.

DR. BADEN: Do you have a follow-on? Dr. Gripshover?

DR. GRIPSHOVER: Getting to that, it sort of looks -- and maybe I can ask if you guys think that the RESPIRE 2 group might have been a little sicker. One, they had more frequent exacerbations, and their FEV1, I think they had more people with a lower FEV1 in that group. And you would hope that that's where the drug was going to help more, and unfortunately RESPIRE 2 is the one where we didn't meet an endpoint.

Is that correct?

DR. KIM: So as far as severity of disease, probably the applicant will be able to describe it more. But yes, there were a number of factors that would go one way or another way, depending on how you looked at it, between RESPIRE 1 and RESPIRE 2. It is the case, as you said, that in RESPIRE 2, there were more subjects who had a lower FEV1.

There was also the case in RESPIRE 2 that more subjects had I believe hospitalization for an exacerbation in the prior year as well. But I don't know if that's related to the severity of disease or the practice of treatment of non-cystic fibrosis bronchiectasis in those regions of the world.

DR. BADEN: Dr. Clark?

DR. CLARK: I had a question for Dr. Kim regarding the resistance data. Is it known whether any of the respiratory outcomes like pneumonia or bronchiectasis exacerbations, or deaths from pneumonia, were related to resistant organisms?

DR. KIM: Okay. So thank you for that question. That is something that we tried to look at and perhaps the sponsor has additional information on.

I can have the microbiology colleague provide additional comment.

When we did try and look at it, we didn't necessarily have culture results at the time of the pneumonia per se. And if we did have culture results, we didn't necessarily know the susceptibility pattern of those pathogens. But I'll let the microbiology colleague also answer.

DR. SUVARNA: This is Kalavati Suvarna again. So we did look at the pneumonia patients and looked at the culture results provided at the time of when they had the adverse events. For most of the patients, there was no culture information, but as in this study, samples were collected at various visits.

We do have information, basically sputum results, for samples that may have been collected either initially or at some of the site visits that were collected routinely. And in those cases, they were either the same pathogen that we observed for the non-cystic fibrosis bronchiectasis pathogens.

DR. BADEN: Dr. Hawkins, did you have a question?

(Dr. Hawkins gestures no.)

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: I just need some clarifications from the statistician regarding the magnitude of the impact of this intervention. If we assume that this intervention is effective, assuming, my understanding from looking at the inclusion and exclusion criteria, about 20 percent of people that have non-cystic fibrosis bronchiectasis will fall into the category that will benefit from this treatment; that is people that have at least 2 or more exacerbations per year. That will present about 20 to 40 percent of the population, the entire population; correct?

Then the second question is, even if we assume from the RESPIRE 1 study that this treatment is effective among those populations -- so the pooled analysis indicates that only about 20 percent of those who were intervened, who were treated, actually had some marginal benefit based on time to first exacerbation.

I'm trying to look at the total population of people that are affected by this rare disorder, how many of them are really benefitting from -- how many of them,

first of all, will be eligible for this treatment based on the conclusion and exclusion criteria? And then if the intervention is effective, what is the effect size? How many people have been affected by this?

DR. KIM: We were interested in that question as well, and we tried to do a back-of-an-envelope analysis. And at least prior to -- today's the first -- we hadn't really thought about necessarily just patients with at least 2 exacerbations, but that was the including criteria. But among the patients treated in the trial, it was our thought that one way of interpreting the results would be that, approximately, if you treated or put 5 non-cystic fibrosis bronchiectasis patients on this therapy over the course of about a year, roughly you would prevent one exacerbation among those 5 patients during that one-year period. What we don't know is what happens beyond that year, and these are sort of back-of-the-envelope calculations.

DR. BADEN: Thank you. Dr. Harkins?

DR. HARKINS: Thanks. This gets to some of the resistance questions that were brought up by Dr. Clark

and Dr. Green, because I wonder how it relates to their treatment for their exacerbations or hospitalizations. The sputum obviously is higher for Pseudomonas resistance at any time point in RESPIRE 1 and 2, but at the end of the treatment, it's still higher but still less than it was -- I think that goes to the variability of the sputum being positive/negative for resistance organisms.

But do you have any data -- and maybe the sponsor has more of the data. But do you have any data, for these patients that had the resistance, how many systemic antibiotics they received at the time that might influence some of this information, or their hospitalizations?

DR. KIM: We don't have that information right in front of us. The sponsor might be able to answer that question.

DR. BADEN: Dr. Green, G. [sic]?

DR. M. GREEN: This is just a quick follow-up on the question, and it's a clarification. We heard earlier that someone else on the committee came to the interpretation that the second group, the second study,

might have had sicker patients. But I think we said earlier -- and I'm just looking at the figure. That may not be -- because the second group also had less events during the study period; right?

So I don't know if they were really sicker or not before the study, but during the study time in the placebo arm, there's less total events, a lot less. So you have 60 percent -- roughly 60 percent -- of placebo patients in RESPIRE 2 that had zero events as opposed to 40 percent having zero events in RESPIRE 1, which is paradoxical to thinking that there are more sick patients in RESPIRE 2.

DR. KIM: We agree that there are paradoxes here, and it all depends on what parameter you look at to try and determine severity or level of sickness. But yes, in RESPIRE 2, there were fewer exacerbations.

DR. M. GREEN: And then just one more question. We heard from the sponsor that they did a gazillion efforts to try to understand the difference in populations between RESPIRE 2 and RESPIRE 1 to potentially explain the difference in results.

Did you guys try to look for differences in the

population in variables in RESPIRE 2 and RESPIRE 1? And did you also fail to come up with any explanation between the two studies that might explain the variable results that are seen?

DR. KADOORIE: Yes, we also looked at some of the variable results, and we also requested that the sponsor run analyses, too. We looked at it. There are a lot of factors, but nothing really strong.

I believe that one reason you're seeing all this variability, that's a frequency of exacerbations with this 0.0003 p-value is because if you look at the distributions, there can be very small subsets of patients with very high numbers of exacerbations, 3, 4, 5 exacerbations. And if those subjects kind of swing just a little bit in one direction, it can result in very erratic p-values. So I think that sort of explains that.

DR. M. GREEN: But not on the primary endpoint, right?

DR. KADOORIE: That's the secondary.

DR. M. GREEN: The primary endpoint is just going to be first events.

DR. KADOORIE: Yes. The primary endpoint is more difficult. Obviously, we see that the patients did not get as many -- their exacerbation rate was just very different over time. They just did not get the exacerbations that we're seeing in RESPIRE 1.

DR. OFOTOKUN: Shouldn't randomization take care of that?

DR. KADOORIE: Take care of what now?

DR. OFOTOKUN: The differences you're talking about.

I was saying shouldn't randomization have taken care of that? You said there were differences in the pattern of disease in individual patients and some people may have more frequent -- but this is a live sample size and they were randomized.

DR. KADOORIE: That wasn't at baseline. I'm talking post-baseline. Post-baseline, if you look at the survival curve, you see in one study, the survival curve completely separates from the other one.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: I just have one quick -- just thinking about the primary endpoint and trying to figure

the difference. So people who do appear of sicker baseline, who have less exacerbations during the trial, some of that could be in how they're treated on the trial and how we read an endpoint.

Does the FDA put that -- you had to get antibiotics. Wouldn't the Western world have a higher threshold for treating and treat faster? Could that make a difference? Do you feel like the endpoint was consistent across both studies or implemented equally?

DR. KIM: This is something that we've been wrestling with for a while. That's why we have an issue with this endpoint, and we're asking you potentially what other endpoints you might think might be more relevant to this patient population who are going to be taking this drug for a prolonged period of time, potentially lifelong. But yet, we have questions related to this endpoint, and we're learning as these trials are being done.

Just to respond back to I think Dr. Green's point regarding -- as far as the heterogeneity between RESPIRE 1 and RESPIRE 2, I think we all can acknowledge that the placebo group in the 14-day regimen for RESPIRE

1 seemed to do particularly worse than in RESPIRE 2.

I mean, once again, this is an issue of did that placebo group do particularly worse or did the placebo groups in RESPIRE 2 do particularly better? We don't know the answer to that either, and perhaps another trial would help to answer some of these additional questions. We just have a lot of questions.

DR. BADEN: Thank you. Dr. Ellenberg?

DR. ELLENBERG: Yes. We've heard a couple of times that when you're looking at the number of exacerbations in a given period, which I actually find a more compelling outcome than the time to the first one, that it can be very much affected by a few patients here or there. But that's a general statement.

Did you find that here, in this particular example, that this was really driven by a very small number of patients with a large number of exacerbations? How did this affect your analysis?

DR. KADOORIE: I looked at the distributions, and I did see that in RESPIRE 1/RESPIRE 2, you look at the frequency of exacerbations and you're seeing zero exacerbations, one exacerbation, not too much

difference. But you really see a difference in 3, 4, 5 -- a very small subset of patients is actually affecting that difference.

DR. ELLENBERG: I just wonder then how robust is this analysis, if it's really just depending on a few patients.

DR. KADOORIE: I think it's not that robust of an analysis. I think that's why you have to look at other analyses such as truncating the number of events that occur so you place a maximum on how many events a patient can have so there's less influence from these patients with high numbers of events.

I've done those analyses, and they actually pretty much tell the same story. You're still getting -- you're not seeing too much different trends. You still get a highly significant -- that 0.0003 is now only like a 0.001 or something like that. It's not as -- but then I think the other p-value actually got lower. So you saw a little bit more consistency across the studies when you start looking at that truncation.

DR. BADEN: Thank you. Dr. Brittain?

DR. BRITTAIN: Hi. I think this is a quick

question. Can you tell us what the study was powered on in terms of the hazard ratio and what -- maybe that would help give us some context to what hazard ratio they expected to see and what power it was, and if they also powered it -- justified the sample size in terms of the secondary endpoint as well.

DR. KADOORIE: I believe they powered the study to show -- I think they assumed a 67 percent reduction. I don't think they got the kind of numbers maybe they were searching for or expecting. That's why some of these -- that's why the point estimates were not quite -- so convincing. I don't think -- I think in RESPIRE 2, they had increased the sample size quite substantially, I think from 416 patients to 521 patients. And it's because the -- I think they're not seeing the exacerbation rates quite as high as expected.

DR. BADEN: Dr. Kartsonis?

DR. KARTSONIS: One of the things I found very interesting this morning when sponsor presented was that when you actually looked at the integrated data, it was highly consistent, between 14 and 28 days, in terms of number of exacerbations and time to exacerbation.

With that in mind, did the agency then go back and say, okay, look in each individual study to look at those patients who got intervention irrespective of whatever it was, 14 or 28 days, versus placebo and see if it had any -- would that help you make each individual study stand on its own?

DR. KADOORIE: I'm not quite sure what you're saying.

DR. KARTSONIS: What I'm saying is you have essentially two different active arms in each study. And frankly, they're the same dose, really, when you look at it over a 12-month period, if I'm not mistaken, based on the way that the case --

DR. KADOORIE: Yes, same overall dose, yes.

DR. KARTSONIS: And when you look at the integrated data of 14 days versus 28 days, it's spot-on almost in terms of the consistency. Does that then afford you the opportunity to go back and look at each individual study, and then combine the 14 and 28 within each study versus placebo so that each study could then stand alone on its own?

DR. KADOORIE: I don't like the idea of, let's

say, combining Cipro 14 with Cipro 28.

DR. KARTSONIS: Active versus placebo.

DR. KADOORIE: Yes. I don't like that idea.

DR. KARTSONIS: Why is that? I'm just curious.

DR. KADOORIE: It's two different products. It's how we view it.

DR. KARTSONIS: Okay.

DR. KADOORIE: We don't mind so much to pool the same product across studies, but pooling like Cipro 14 is a little bit -- it's just not easy to interpret. How would you label something like that?

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: This is just a simple follow-up question to the statisticians. Do you think that this is an issue of sample size or duration of follow-up? Do you think if the sample size was to be more and the duration of follow-up was to be longer, do you think that -- it looks like there's a trend, but the trend is not just quite enough. It's not statistically significant. Is than an issue of design?

DR. KADOORIE: I believe it's an issue with the design. I think by testing two different cipro arms,

that really limits your power. Not only do you have fewer subjects spread across -- now you have to spread all your subjects across four arms instead of two, and on top of that, you have to use all this alpha adjustment. So it's a lot of -- I think design will greatly limit their chances. If it tested one against another, then you'd probably see much clearer evidence, but we have to go by what we see.

DR. BADEN: Dr. Carvalho?

DR. CARVALHO: Thank you. Just to follow up on Dr. Kartsonis' question, on page 23 of the FDA's document, is that not what we did over here with the RESPIRE 1 and 2, combined 14- and 28-day versus placebo pooled?

DR. BADEN: Which -- there is more than one slide 14.

DR. CARVALHO: No, it's page 23 on the FDA's document.

DR. BADEN: Oh, page 23 of the briefing --

DR. CARVALHO: Yes.

DR. BADEN: -- the pre-meeting material.

DR. CARVALHO: The sponsor also showed that

data.

DR. KADOORIE: Yes, that's just a Kaplan-Meier plot. I think the top panel is RESPIRE 1 looking at the Cipro 28, Cipro 14 and pooled placebo, and then the second panel is RESPIRE 2, and then the third panel is RESPIRE 1 and 2 combined, a combined analysis.

DR. COX: Chairman, if I may?

DR. BADEN: Yes, Dr. Cox?

DR. COX: So I think Dr. Kartsonis' suggestion was to pool the 14 and the 28 in RESPIRE 1.

DR. BADEN: Yes.

DR. COX: And I think what this figure shows is RESPIRE 1 14 and 28, and then pooled placebo; RESPIRE 2 14 and 28, and then pooled placebo. Then the pooled figure is the 14 from RESPIRE 1 and RESPIRE 2 pooled and the 28 from RESPIRE 1 and RESPIRE 2 pooled.

I think that may be the difference between what Dr. Kartsonis was suggesting and I think what you're asking about for this figure. I hope that provides a little bit of clarification.

DR. CARVALHO: Thank you. It does. I do have a second question, though.

The patients in RESPIRE 1 and RESPIRE 2, as we've mentioned before, they seemed to be a different population in terms of treatment as well. And I believe that Dr. Kadoorie had already commented on adjusting for macrolide use. But there's also -- according to my notes, RESPIRE 1 was also -- there were more patients on long- and short-acting beta agonists. Some had had more prednisone somewhere along the way, more inhaled corticosteroids, and of course macrolides.

I just wonder if analysis was done looking at all of this, which is more conventional management than perhaps patients of RESPIRE 2.

DR. KADOORIE: I think we looked at a lot of different factors to see how the results would change, and I don't think we got much of a substantial change.

DR. BADEN: Dr. Weina?

COL WEINA: I have one quick question for the agency. When we think about -- or at least when I think about unmet medical need or we kind of weigh the evidence a whole lot differently than when you have something that is adding something to the toolbox -- and they brought up the fact that this -- given FDA multiple

designations like breakthrough therapy, fast track, orphan drug, qualified infection, I am trying to understand the unmet medical need here when -- I mean, I understand that there is no specific designation for preventing exacerbations in this population, but it's not like there are no treatments that are available. And I'm trying to understand that designation and how to weigh the evidence based upon all of these multiple designations.

DR. BADEN: Dr. Nambiar?

DR. NAMBIAR: Sumathi. So in terms of the various designations, the criteria you use for each one of them is a little different. It's not necessarily based on an unmet medical need. The requirements under the law for a QID pure qualified infectious disease product designation is you have to be an anti-bacterial/ anti-fungal product that can treat serious infection. So that's a different issue.

Breakthrough designation is when you have preliminary clinical evidence that the product can offer some benefit over currently available therapies. So when you have results of RESPIRE 1 on their own, at

least for the 14-day regimen, it seems to have provided a benefit. So that's the designation that was given based on the results of the RESPIRE 1 trial.

COL WEINA: But the RESPIRE 1 was data over doing nothing because it was a placebo, as opposed to maybe using the current suppressive antibiotic therapy that 40 percent of the population is using already.

DR. NAMBIAR: So it's over nothing, but it's all standard of care. So that's what you look at, and you see if it's over currently available therapies, and you see if there's any available approved product. And if there is an approved product, then does it provide a benefit over that? If there is no approved product, then you seek relative to standard of care. So it's not that these patients were getting nothing. They were getting the standard of care.

But having said all of that, even if one decides there is an unmet medical need, the standard, the evidence standards do not change. And I think that was the point that was made earlier. So even for unmet need programs, rare diseases, you still meet the statutory requirement for substantial evidence of

efficacy. I just wanted to make that clear.

DR. BADEN: Thank you. We will break for lunch. We'll reconvene again in this room at 1:30 sharp. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch, amongst yourselves, with the press, or with any member of the audience.

When we come back at 1:30, we'll have the open public hearing segment, then we will go back to clarifying questions to the applicant before we go to further discussion. So thank you all. See you back here at 1:30 sharp.

(Whereupon, at 12:35 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:30. We'll bring the meeting back to session. We'll have the open public hearing element, and then we'll go back to clarifying questions to the applicant from this morning, continue that discussion.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's

payment of your travel, lodging, or other expenses in connection with your attendance of the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium,

introduce yourself? Please state your name and any organization you are representing for the record.

MS. WARDEN: Good afternoon. My name is Christa Warden, age 69 from Reston, Virginia. I have non-cystic fibrosis bronchiectasis, and I have been under treatment for 9 years. My transportation today has been subsidized by the sponsor, but I am not receiving any other form of compensation for speaking here.

I am here to share my experience in the hope that I can provide insight into the life of a patient with bronchiectasis and the need for a better treatment and management protocol.

I am the mother of three and a grandmother. I was a military wife, educator, school counselor, and middle school administrator for 28 years. My professional goal was to retire after 30 years. Disappointingly, my career ended abruptly after a two-year series of repeated and debilitating bouts of pneumonia and worsening asthma.

My recurring respiratory infections fell into a cycle of a new infection every 3 to 4

months. This went on for 2 years. I rarely saw my primary care physician as my pneumonia would begin abruptly -- it still does -- and urgent care through my medical group was referred to the nurse practitioner or one of the physicians assistants.

In retrospect, I feel that this lack of continuity of care and the lack of knowledge of non-tuberculosis bronchiectasis led to missing the pattern of my infections and exploring the cause.

In 2009, I had a chest CT scan indicating the bronchiectasis. I had no idea what this diagnosis would mean. A few pulmonary physicians were familiar with the impact that this would have on my lungs and health. I felt that I had to be my own advocate to find a physician willing to explore the cause of my repeated infections.

Discovering that there is no FDA-approved treatment protocol for non-cystic fibrosis bronchiectasis was devastating. My life has been and continues to be highly impacted by this disease. I have life-changing fatigue and limited stamina. I live what I call an every-other-day

life.

When I undertake a physical activity, social activity, or even caring for my grandchildren, I must spend the following day, or more in my case. I must spend the day recovering, or I will develop infection. And it can develop suddenly and become serious without warning.

My forced retirement is not what I dreamed about. I hesitate to make travel plans. My health is unpredictable. My family and friends understand that making social plans too far in advance always with the understanding that I cannot predict how I will feel that day.

If I try to push through the fatigue and ignore my body, I can become seriously ill, requiring hospitalizations and IV antibiotics. One night recently, I was tucking my precocious 9-year-old granddaughter into bed and she asked me if I'd be alive in 20 years. I was caught off guard. I reassured her that I was doing everything possible to be strong and healthy. Her question went straight to my heart.

The truth is, I really do worry. Will the next pneumonia or infection be the end of me? The unpredictable nature of my illness fills me with sadness. I have always been an optimistic and social individual. Now, I struggle with a big secret of anxiety and depression surrounding chronic illness. I fear that, even with doing everything suggested, it might not be enough.

Controlling or managing my disease requires time and consistency with medications, inhalers, nebulizing treatments, and general lung hygiene. It also requires getting an hour of strenuous physical activity, building strength, and doing cardio every other day if I'm up to it.

Managing non-cystic fibrosis bronchiectasis is my part-time job. After a long and bumpy search, I had been extraordinarily fortunate to find my current physician at Georgetown University Hospital. In addition to the kind and attentive care she provides, she participates in drug trials.

When I qualified to enter a trial, I felt hopeful for the first time. I felt the possibility

that these trials might directly impact me. Of course, I prayed that I would not get the placebo. It turns out that I received the actual medication, inhaled cipro, and there was an immediate break in my 3-month cycle of exacerbations. I participated in the 28-day-on and 28-day-off cycle of the study. During the year-long trial, while taking the inhaled cipro, my previous cycle of exacerbations and pneumonia was broken.

Since the end of the trial, I have suffered several serious exacerbations and pneumonia and have had to be hospitalized for days on IV antibiotics with debilitating side effects. While on the inhaled cipro, I did not suffer any known side effects from the medication.

I would like to speak for every individual affected by this disease by asking you to please approve the inhaled cipro. It could provide for a more successful management and treatment for non-cystic fibrosis bronchiectasis. My help and quality of life was dramatically improved during the trial. Inhaled cipro made a difference for me

and it provided significantly better control of my disease and allowed me to live a more normal life free from life-threatening lung infections. Thank you.

DR. BADEN: Thank you very much for those comments.

Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WEISS: My name is Robert Weiss. I am a professor of medicine at Johns Hopkins University School of Medicine. As chair of the Medical and Scientific Advisory Committee, I am here today on behalf of the COPD Foundation, which represents more than 15 million Americans with chronic obstructive pulmonary disease and the 100,000 or so patients in the United States who suffer from non-CF bronchiectasis. I have no conflicts interest, and I have paid for my own travel to this meeting.

The COPD foundation has not taken any

position on the drug that is under consideration today. My purpose today is to describe the toll of this disease as well as to emphasize the important unmet needs of patients with non-CF bronchiectasis and the physicians who care for them.

Non-CF bronchiectasis is an orphan disease that is associated with other orphan diseases, including alpha 1 antitrypsin deficiency, primary ciliary dyskinesia, and immunodeficiencies. In many patients, the underlying susceptibility is not known.

As a practicing pulmonary physician, I care for patients with this disease and have been able to witness firsthand the struggles that these patients have and the challenges to the physicians who care for them.

The disease causes progressive destruction of airways with dilatation and thickening of the airway walls that impairs the clearance of mucus. This leads to mucus plugging and inability to clear noxious and infectious agents. Patients may enter into a cycle of repeated respiratory infections

that leads to progression of the disease and susceptibility to resistant bacterial organisms.

Patients suffer from frequent exacerbations manifested by worsening cough and phlegm associated with shortness of breath and frequent pneumonias. These exacerbations, if severe, may lead to hospitalization, respiratory failure, and death.

As the disease progresses, the bacterial organisms become more resistant. And when oral antibiotics are not effective, patients may need to have intravenous antibiotics or intensive respiratory therapy in the hospital.

In order to minimize these exacerbations, patients often undertake a very exhaustive program of airway clearance, including inhalation of multiple bronchodilators and hypertonic saline. They need to use physical devices to promote mechanical airway clearance.

Patients with advanced disease may spend several hours per day engaged in these treatments, which disrupt their ability to engage in meaningful school or work activities. Moreover, the constant

cycle of infectious exacerbations causes uncertainty in life that precludes planning of family vacations, social gatherings, or scheduling travel.

The frequent coughing leads to social isolation such that patients may be unable to attend public events such as movies, sports events, or public transportation for fear that their seatmates will be bothered or worried that they are seated next to someone with a communicable disease.

Currently, there are no drugs licensed in the United States for non-CF bronchiectasis. Physicians generally rely on mechanical airway clearance treatments and culture-guided antibiotics.

The long-term course of bronchiectasis associated with cystic fibrosis has been markedly improved by aggressive combinations of therapies, including inhaled antibiotics. However, some inhaled antibiotics that have been effective for cystic fibrosis have been disappointing in non-CF bronchiectasis.

In particular, when resistant bacteria such as Pseudomonas persist in the sputum, the course of the disease accelerates and the treatment options become limited. Long-term treatment with oral fluoroquinolone antibiotics are limited by adverse effects such as tendonitis and concentrations in the mucus layer may be suboptimal.

Accordingly, the availability of a safe and effective inhaled antibiotic that has coverage for these organisms is sorely needed. Our patients need new treatments that can simplify their lives, reduce exacerbations, limit the progressive destruction of lung, and improve their quality of life.

I want to thank the members of the panel for listening to my comments.

DR. BADEN: Dr. Weiss, thank you for those comments.

Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. MAYER: My name is Mike Mayer, and I am here today because I utilized my personal resources for travel from Philadelphia to help provide a perspective on a disease that most Americans know little about, called bronchiectasis.

I would submit that if you were to ask the common person on the street what this disease is, you would get answers that range from a rare reptile in the Amazon jungle to a newly released microbrew or perhaps something in between. For me and my family, bronchiectasis is scarier than cancer or a heart attack.

My experience with bronchiectasis began shortly after I met my father-in-law, Richard Scarborough, nearly 40 years ago. He had recently been diagnosed with a lung condition, which was the beginning of a multitude of frantic trips to the hospital and a lifetime of labored breathing.

The day of Richard's or Dick , as most of us knew him, funeral, there were 400 people jammed into a small New Hampshire church, deeply saddened that they lost a husband, father, grandfather,

uncle, boss, and friend to a disease that slowly took his life away quite literally breath by breath.

During his working life, Dick was able to travel internationally as a successful marketing executive in a large technology company. Over time, he had to cancel appointments, postpone or cancel trips, or significantly curtail his working or travel activity due to the more frequent episodes he had with his breathing.

There was not a person that knew Dick Scarborough that didn't experience his inability to stop coughing and clear his lungs of the massive amounts of phlegm that seem to work overtime to decrease his lung capacity and rob him of precious oxygen.

Our family took turns making sure that his oxygen tank was operating properly and that his concentrator was situated in the right spot in the house for him. At the end, he didn't speak because he didn't have enough breath to. It was too hard.

As much as he traveled the globe during the

early experience of this disease, at the end of his life, he was unable to travel from his bed to the bathroom without great effort. His wife, my mother-in-law, Pat, courageously cared for him throughout most of his life by helping him clear mucus from his lungs and being his advocate in seeking medical help.

Shortly after Dick died in 2005, his brother Collin and I work together as we start to find a way to either cure or at least treat the disease that killed Dick at the age of 68. In researching organizations that might be able to help us, we found the COPD Foundation and established the Richard H. Scarborough Bronchiectasis Research Fund. In early meetings with experts in the medical community and through a meeting held with the sponsorship of the NIH, we convened a group of very committed physicians and pulmonologists who began to take some first steps.

With this information in hand, we built a consortium of eight medical centers -- it was expanded to 14 -- as a means of gathering patients'

data with bronchiectasis and getting a better understanding of this life-robbing disease.

Today, we have nearly 2400 patients in the database. Data from these patients indicate that they each average nearly 2 exacerbations every year, average. This history is important because, as I understand it, until this bold step was facilitated and assembling the kind of knowledge that we have, there was not much awareness about bronchiectasis and the cost to human life that it inflicts on America today.

For our family, there were many events that Dick could not attend. He was invited to my son's first Little League game as a starting pitcher and accepted the invitation to travel to Philadelphia to be with us. Because of one of perhaps 100 or more exacerbations and episodes that he experienced in his life, he had to cancel and disappoint his grandchildren and family. This same scenario occurred a multitude of times, school plays, church activities. The list goes on. "Dick won't be able to make it. Sorry."

As part of my commitment to make certain that other patients and loved ones may live a better life than we did with our bronchiectasis patient, I became actively involved with the COPD Foundation. The foundation believes that everyone has a right to breathe. For Dick, this was a right that he frequently was not able to enjoy. In fact, it eventually took his life.

I wear this lapel pin, which is the logo of the foundations attributed to Dick and the tens of millions of people in the United States who have chronic obstructive pulmonary disease.

When asked about it and about COPD, I commonly hear, "Yes, COPD is for people who have emphysema and smoke. They know that they shouldn't be smoking, so they kind of get what they deserve." For me, I find this to be particularly troublesome on two fronts.

First, Dick never smoked, never worked in a shipyard, never in the chemical industry or near smoke, yet he was diagnosed with and died from this seemingly obscure disease. Second, while people

who smoked most likely knew or know of the consequences of their reactions, they still have a right to breathe.

The drug you are considering for approval is the first drug introduced to help treat, not cure, treat bronchiectasis since Dick Scarborough died nearly 13 years ago. My hope is that this drug is approved. My hope is that for those for whom it is appropriately prescribed, they are able to avoid the terrible path that Dick and our family endured.

As a footnote, most children don't grow up wondering if their grandfather will attend grandparents' day at their elementary school or their annual holiday concert, their dance recital, soccer games, Eagle Scout ceremony, or senior day at the high school or graduation.

For any of Dick's children and grandchildren, the question of whether you thought Granddaddy would or would not make a particular event was the most commonly asked question. In addition, most children haven't experienced the horrors of seeing a loved one slowly losing life by

not being able to complete the simple act of drawing a breath. My children have. I hope they will be the last generation to have this experience.

In closing, I think it's important for you to know that Dick Scarborough never complained about any of the challenges he had with his lungs as a result of bronchiectasis. We did know that he was keenly aware towards the end of his life that as each treatment failed to treat the ever-present and growing Pseudomonas in his lungs, his time was limited.

There were no promising drugs in the pipeline, in development, or even in the initial phases of research. I can only imagine that if a drug like the one that's being proposed were to have been available in his time, it may have been able to prolong the life of Richard Scarborough and allowed us to have him for just a bit longer.

I'm not a medical expert, but I do believe that this drug can slow down the life-deteriorating exacerbations that my father-in-law experienced and

should be available widely on the market, assuming there's an acceptable risk to the patient. Thank you for your time.

DR. BADEN: Mr. Mayer, thank you for those comments.

Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin, and I'm a senior fellow at the National Center for Health Research. I trained at Johns Hopkins before joining our research center, which analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from the pharmaceutical or medical device industries, so I have no conflicts of interest.

We strongly support efforts to improve antibiotic use and drug safety. We also recognize the need for safe and effective treatments for

patients with non-cystic fibrosis bronchiectasis. However, we have serious concerns about the efficacy, safety, and potential for antibiotic resistance of this drug.

Based on available clinical data, this drug has not been shown to be effective. Across both studies and treatment regimens, researchers only found a significant treatment effect in one instance. The ciprofloxacin DPI 14-day regimen achieved a statistically significant improvement in the time to the first pulmonary exacerbation, the primary endpoint, in the RESPIRE 1 clinical trial.

However, in the RESPIRE 2 trial, the cipro 14-day regimen did not achieve a statistically significant improvement in TFE. The 28-day regimen did not demonstrate improvement in either study. These results indicate that the first finding may have been due to chance.

In addition, we have methodological concerns about the clinical trials. We agree with the FDA that it is unclear whether the chosen primary endpoint studied for over 48 weeks translates into

a clinically meaningful benefit for patients who could take this drug for life.

Patients care about lung function and being able to perform activities of daily living. They care about staying out of the hospital due to respiratory failure or bleeding. For example, shortness of breath, rather than just sputum color, is a more well-defined and reliable patient-reported outcome.

We also urge caution with the comparison to the inhaled placebo. As the FDA noted, it is quite possible that the inhaled placebo exacerbated symptoms, which could make symptoms work for patients. This comparison also makes it difficult to evaluate risks due solely to inhaling the dry powder.

Regarding safety, we know fluoroquinolones can have dangerous side effects, including arrhythmias, tendon ruptures, kidney problems, changes in blood sugar levels, and nerve issues. Though likely due to inhaling dry powder, we are concerned about this drug's adverse events,

including hemoptysis and bronchospasm.

Older adults, particularly those 75 and older, have a higher incidence of NCFB and experienced more adverse events. This population should be adequately represented and assessed for side effects, including kidney issues, neuropathy, and tendinopathy. Unfortunately, these studies do not provide enough data to generalize to this group.

Given serious risks without evidence of efficacy, how can we approve this drug for patients? While fluoroquinolones can be life-saving drugs for certain types of infections, we must be extremely cautious about their safety and efficacy to ensure that benefits outweigh harms for any new indication or any new version. We need to promote safe and appropriate antibiotic use, especially for those with more potential to harm patients.

For example, in May 2016, the FDA encouraged physicians and other healthcare providers to avoid prescription of quinolones for respiratory and

urinary tract infections unless other antibiotics have been tried and were unsuccessful.

We applaud the FDA for recommending that two adequate and well-controlled trials be conducted to support this drug's NCFB proposed indication, particularly as this is a new treatment indication and route of administration for ciprofloxacin. The sponsor provided the recommended data, but unfortunately, the data indicate that this drug's benefits do not outweigh its potential risks.

Finally, we are concerned that the potential antibiotic resistance is high for any patients taking it for a long period of time. The two clinical trials provided by the sponsors show that this concern is valid.

In both trials, a higher proportion of participants taking the active treatment had resistant Pseudomonas compared to those taking placebo. Thus, we cannot roll out the prolonged use of this drug will result in increased resistance. Lifelong exposure is likely to make matters worse and creating resistant Pseudomonas

will have devastating consequences for the most vulnerable patients.

Will there be additional safety issues and a decrease in efficacy due to bacterial resistance over time? None of us know the answer to this question. The question for you today is, do we know enough to approve this drug for people who really need it?

We respectfully urge you to consider the serious limitations of the current data. We recommend further study of this drug with clinically meaningful primary endpoints such as severity of exacerbation, overall lung function, and patient-reported outcomes to directly assess symptoms such as cough, wheezing, and sputum production. We also recommend comparing the drug to a non-powder to ensure that the method of use does not worsen symptoms and including more patients 75 and older.

Thank you for the opportunity to share our views.

DR. BADEN: Dr. Polanin, thank you for those

comments.

Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. WEINER: Hello. My name is Marcy Weiner. I am very grateful to be here. It is unusual for us to have an opportunity to tell our story. I'd also like to say I've been sponsored by the COPD Foundation. They've been extremely generous in providing the travel expenses and really invaluable assistance.

On top of that, I can bring a little bit extra perspective because I'm a group leader and support leader for NTM patients in the Boston area, and I see quite a variety of patients with bronchiectasis and complications.

I was diagnosed with bronchiectasis and MAC, mycobacterium avium complex, 10 and a half years ago following a business trip to a trade show in Shanghai. A trip to the local ER with pneumonia and a CAT scan revealed the underlying disease in

my lungs. I was very fortunate because it was found very quickly.

I spent the next several weeks at the computer researching the disease until night sweats or fatigue forced me to stop. It quickly became evident that this was likely incurable. I had done medical research as a young woman.

This sensitivity test for my particular specimen of M. intracellulare showed only 1 drug is effective against it. Symptoms vary from time to time. When there is a MAC attack, or an exacerbation, there may be night chills, night sweats, sudden deep fatigue, weight loss, abruptly falling asleep, even when driving, and increase in the change or color of the sputum, coughing, sometimes violent, but low energy levels, thinking through a fog, sometimes constant phlegm moving up and down the throat.

These MAC attacks, as I call them, may be shallow and last for weeks as my last one did from September to mid-October. I was still functional, but I was not well; or just a few days to a week a

few times a year.

This disease, as you have heard, impacts every aspect of life, work. That trip to Shanghai, China, was my last. Work of any kind stopped for six months. I could no longer be the reliable worker I once was, and I never knew when another attack would come on as you've heard. Fatigue was my constant companion.

Time. An average day consists of 2 to 4 hours or more dedicated to stimulating, oxygenating, and clearing my lungs, and maintaining my health. It begins with an hour of Luo-Han Gong airway clearance, which is very effective; deep breathing exercises; self-percussion; strength training; Tai Chi classes; daily walks; stretching; flexibility exercises; doctor visits, generally in Boston, about an hour away; pulmonary therapy; allergy shots; et cetera.

Home life. I have a very loving and accommodating husband. I'm very fortunate. He's now 81 in Germany as we speak, cooks gourmet omelets to help me keep my strength up, drives me

to doctors and to train stations when I'm tired or not safe to do so, does most of the grocery shopping and all those things, schedule changes, events, activities curtailed. The greatest impact perhaps is emotional, and I can tell you this as a support group leader, the constant concern for people's health and well-being and of the family immediate around them.

Water issues, a major fact, especially for NTM patients, is it resides in water, drinking, showers, hot water heaters. Only warm baths and an occasional lukewarm dribble shower is permitted. All drinking, cooking, toothbrushing water is boiled or Poland Spring only.

My showerhead recently tested positive for M. abscessus, a far more virulent and drug-resistant species than the one I have now, or at least maybe I have two. M. intracellulare is my other one.

We now drain the hot water heater every six months, sterilize showerhead and kitchen faucets in vinegar monthly, remove aerosolizers in the

bathroom faucets to reduce the build-up of biofilms and mycobacteria. The drip coffee pot was tossed out in favor of a glass pour-over pot, no reservoirs. Water is continuously boiled in a glass teapot, no ice, no water in restaurants unless boiled or Poland Spring. The reason is that Poland Spring uses 0.2 micron for filters, so it screens out the bacteria.

Driving in travel. I cannot drive the long distances anymore due to fatigue or suddenly falling into a deep, deep sleep; not a problem on short errand runs except during an exacerbation. Hotel rooms must be extra clean, no room fresheners, deodorizers, no pets, no mold in the bathrooms, high floor, clean air vents, hopefully windows that open. Clean air circulation is imperative.

Airplane travel means preferred seating such as bulkhead, aisle, or whenever possible on a very long flight in business class. I carry face masks, nasal gels, sprays, life straws, and Poland Spring water, and Clorox wipes.

The cost can be enormous at times, frequent changing of special furnace filters, ultraviolet lights, air duct cleaning -- a thousand dollars a pitch -- changing auto-cabin air filters, built-in vacuum cleaner system, and household cleaning as MAC has now been found on common surfaces and dust and bedrooms in patients.

The cost of antibiotics to treat MAC for a month cost me over $900. OTCs can be expensive, too. Mucinex, Align, vitamin B complexes are necessary as antibiotics affect the absorption of vitamin B.

Complications. My complications are reaction to mold, pollen, dust, pets that cause post-nasal drip, mucus production in the nose and the lungs, often triggering a MAC attack, especially mold.

Secondary infections such as C. difficile, other bacterial infections, pneumonia, bronchitis, et cetera are all a risk. GERD is a significant issue. I have it along with most MAC bronchiectasis patients. Acid reflux has created

ulcers and inflammation in my stomach and in my esophagus. It affects my diet and my weight. Maintaining a healthy weight is very difficult with reduced carbs to help the GERD and intestinal bacterial overgrowth.

Lung cancer. There is a slightly higher risk of lung cancer for MAC patients. I was diagnosed and successfully treated for lung cancer in February 2015 by a lobectomy of my right middle lobe. That was followed by a resistant bout of C. difficile that was eventually cured with a fecal transplant.

So I want to thank you again. The new drug under review would provide this new tool for patients and doctors. Its ease of use and immediate action would be very welcome to so many. The present drug treatment regimen, as you've heard, is 3 or more drugs for 18 months to two years and, often when the patients are off that, very shortly they're back on it again. They're lucky if they get 2 years.

Reluctant to do so, patients delay going to

the doctor or getting on medication, as I do. Many stopped the drugs due to the side effects of hearing loss and vision impairment. This one antibiotic needing only a few weeks delivered directly to the lungs, bypassing the GI tract, may reduce or together avoid side effects that are caused by the present drug regimen, which is very difficult.

Lastly, by reducing fatigue and illness, it would allow us to work, travel, and lead a more productive life. I'm grateful to know that there's the possibility of something out there.

I want you to know I have a light case, and I'm still able to remain productive at 78 years old, but it's with a great deal of vigilance, and constant alertness, and modifying, and watching my behavior every single day. I can tell you I walk a tightrope.

So thank you for taking the time to listen, and I hope that you will undertake this and give this drug a chance because I think the ultimate test will really be when patients are on it. Thank

you very much.

DR. BADEN: Thank you, Ms. Weiner, for those comments.

Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. KITLOWSKI: Hi. My name is Mary Rose Kitlowski, and I'm from Loch Hill, Maryland. I have not been compensated to be here, and I don't represent any organization. I have bronchiectasis as a result of a rare disease called primary ciliary dyskinesia or PCD. I have a sister who is four years younger. She also has PCD and had bronchiectasis. She had a double lung transplant in 2014.

I was diagnosed with bronchiectasis from my first chest x-ray when I was 17. From there, further testing was done to find the cause of the bronchiectasis. Exacerbation started in my 20s. I had one hospital stay that was about 3 weeks long because of hemoptysis. I had quite a few more

hospitalizations in my 20s and 30s. None were as long, and most were to put in a peripherally inserted central catheter or PICC line.

I've had at least 1 exacerbation requiring IV antibiotics a year for at least the last 20 years. The past two years, I've had 2 exacerbations each year requiring IV antibiotics. During these exacerbations, I'm on IV antibiotics for 3 to 6 weeks.

I am standing in front of you today actually with a PICC line, and I have two medications I'll be doing as soon as I finish my comments. I've been taking these since October 20th.

Most common IVs require changing every 3 to 5 days. Because most of the veins in my arms are now too small, I require a PICC line for IV treatments. I'm lucky that despite over 30 PICC lines, they still work for me. My sister had to get a port-a-cath because her veins could no longer support PICC lines due to scarring.

PICC lines are surgically placed in the radiology department. As I stated above earlier, I

used to get PICC lines while I was a patient in the hospital. Now the process is done as an outpatient. While this is much more convenient, I still have to take at least half a day off work to have the PICC line placed. They also require dressing changes. A nurse comes out to my house once a week.

The treatment schedule can be pretty exhausting. Currently, I'm on two antibiotics every 8 hours. This means that, if I start my nighttime dose at 9:00 p.m., I am finished around 10:00. I then have to get up at 5:00 a.m. to do the next dose. Some antibiotics are every 6 hours and some are every 12 hours.

I've also had to start taking antidiarrhea medication because of the problems that antibiotics have been causing. When you take antibiotics as often as I do, you can develop resistances and reactions. While I can take cipro, I can't take the required doses of the oral form because of the severe nausea and vomiting it causes.

There are several IV antibiotics I can't

take. One is because my body reacted with the fever after taking it. Another includes a whole class of antibiotics because I developed ototoxicity from one of the antibiotic family members.

I was unable to drive a car or even walk a straight line for 4 months. Luckily, my brain was able to rewire itself. I still have some lingering effects, though. My balance is not quite what it used to be. And when I'm walking, if I'm tired, I weave more. It is heartening to know more research is being done in the field of inhaled antibiotics. I can no longer take TOBI. It's in that family that I reacted to.

Having more inhaled antibiotic options that could help prevent exacerbations or even shorten an exacerbation requiring IV antibiotics would be huge for me. Reducing the time of one exacerbation may not sound like that much to you, but less time with a PICC line in my arm means I can return to a normal schedule.

It also means I don't have to spend as much

money. Right now, I am paying $31.57 a day for the two antibiotics I'm on, plus 16.50 for the nursing visits. That means I'm paying $221 each week. This is my out-of-pocket cost. While the price varies based on the antibiotics, this is not an inexpensive treatment. There is also the expense of the lab work, and the PICC line this time around was $179. So I'm looking at around $1,300 for this round of treatment.

I'm a federal employee with decent health benefits. My out-of-pocket expenses for bronchiectasis have been between $3,000 and $5,000 a year for at least the last 10 years. Bronchiectasis is a daily battle for me and has been since even before I was diagnosed with it at 17. I do daily nebulizer treatments to help open my airways, prevent bronchospasms, and to loosen the mucus in my airways. I do a sinus rinse to keep the mucus in my nasal passages from dripping into my lungs. I also take a few oral medications to, again, open up my airways and loosen the mucus.

I have a chronic cough and a runny nose.

There are times when I'll have bronchospasms and go on uncontrollable fits of coughing. I cough when my head changes positions. This means I cough when I first go to bed. Most of the time, I just cough stuff up, and I'm able to go to sleep. Some nights, though, I wake up coughing so much that I have to go downstairs so as not to keep my husband up. I probably spend an average of five nights a month not sleeping in my bed for some period of time. Sometimes it is just a few hours and sometimes it is all night.

When I work out, I have to have tissues with me. I try to be discreet when I have to cough stuff up. I cough it into the tissue and put it into a bag to dispose of later. Some days, my airways are fairly clear, and I use just one or two tissues. Other days, I go through 10 or more, and that's just at the gym for an hour or two.

My last pulmonary function test was on July 25th and showed my FEV1 to be 34 percent, a decline from 40 percent last December. Up until about May of this year, I only needed supplemental

oxygen when I exercise. Now I need it when I sleep and leave the house. I still work full time. I am able to work from home. If this wasn't an option, I'm sure I would be on disability.

Having inhaled antibiotic treatments like cipro available will make a big difference for me. Having another inhaled antibiotic option would reduce the burden and invasiveness of IV antibiotics.

Being able to reduce the time of an exacerbation or even prevent an exacerbation would have a big impact for me, both on the quality of my life and the quantity of my bank account. Thank you for giving me the opportunity to share about my experience with bronchiectasis and the impact it has had on my life.

DR. BADEN: Ms. Kitlowski, thank you for those comments.

Will speaker number 7 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SULLIVAN: Good afternoon. My name is Jamie Sullivan, but I am reading a statement on behalf of a patient that could not be here today, Barbara McGuirk.

"Good afternoon. My name is Barbara McGuirk, and I reside in northern New Jersey. I would like to share with you my journey with damaged lungs caused by bronchiectasis. I don't know exactly how or when this damage occurred, but I do know that it was discovered in 1997, after I experienced two bouts of pneumonia.

"My doctor informed me that because of this condition, I would need to take an antibiotic whenever I caught a cold. This, I thought was a simple and easy solution to my new problem. I went on with life completely unaware of the dangers that awaited me.

"In the years that followed my diagnosis, I developed a constant cough. I was given medications used for asthma because there were no treatments specifically targeted for bronchiectasis, but I still coughed. Every day,

despite being concerned with this persistent cough, I was assured that my bronchiectasis was stable. Again, I trusted this medical device that I was given.

"In the summer of 2013, while enjoying a swim across our local pool, I became so short of breath that I could not sustain the activity. Frightened, I floated on my back to the pool's edge, moved to shallow water, and climbed out to dry land.

"I was now more convinced than ever that I needed to be seen by a pulmonologist. A CT scan indicated a lung infection. A bronchoscopy, which removed much of the mucus I had collected in my damaged lungs, provided samples of infected material that was cultured.

"I remember so clearly how much easier it was to breathe after that procedure. Six weeks later, the culprit was identified. Mycobacterium avian complex had taken up residence in my damage lungs. I had NTM.

"I was given some scary facts about my

future with bronchiectasis and NTM from my original pulmonologist. She mailed me prescriptions for three different antibiotics with a combined daily dosage of 1700 milligrams. The only instructions I received were written on the medicine vials.

"I was overwhelmed. Surely my body could not tolerate taking such a large antibiotic load all at once. I called her office to inquire how I should space these drugs throughout my day. Did I need to take a probiotic? I was told to take my own decisions about these issues.

"The three-week period following the beginning of my treatment was the lowest point in my journey with damaged lungs. I experienced exhaustion that I never knew was possible. I thought about individuals undergoing chemotherapy. Was this how they felt? It was during this time that I decided to become more proactive in learning about bronchiectasis and NTM. I scoured the web for sites that could provide well-documented information. This is how I discovered the New York City Support Group and a new pulmonologist at NYU

who specialized in treating my lung condition.

"My new physician informed me that to be effective, all my meds had to be taken at the same time. They should not be spaced across a 12-hour period of time, as I had been doing. She also agreed that a probiotic would be valuable.

"I had a cardiac pulmonary stress test, and an exercise regimen was recommended. A nutritionist suggested better approaches to my diet and advocated maintaining a healthy weight even though the medication I was on left me with little appetite. A lung clearance therapist instructed me on the correct way to use several devices like the a cappella and lung flute to help rid my lungs of mucus.

"The 1 or 2 exacerbations per year that I developed retreated. After two years on the NTM medications, I had to stop taking them, and now I am routinely monitored for the possibility of worsening bronchiectasis and new infection.

"Bronchiectasis has changed the structure of my lungs forever. It has also changed my daily

routine. Every day, weather permitting, I walk 2 to 3 miles and set aside time for clearing the mucus from my lungs. I fight fatigue. When on meds, I have many more doctor's appointments to check my hearing, my heart, and the optic nerve in my eyes because drugs can have adverse side effects. And I have lost the ability to engage in activities that I once enjoyed, like swimming and gardening.

"I have become very cautious about being around large numbers of people, especially during the winter months when there is more sickness, because I have learned that if I come in close contact with someone who is coughing and getting over an infection, the chances are great that I will become ill.

"I am wiser now and know so much more than I did when my journey began, but some of the knowledge I have gained is quite sobering. Statistics indicate that I will most likely develop another NTM infection, and it will probably be caused by a different strain of mycobacteria.

"I can no longer use one of the three antibiotics routinely included as part of the cocktail since starting my last round of treatment, my platelets dropped to a very low level. What if I have also developed sensitivity to other drugs that were used in my initial protocol?

"I am very aware that there is an extremely limited number of drugs that physicians can select from to treat bronchiectasis-related infections and exacerbations. I know that there has never been a drug approved specifically for treating bronchiectasis. I see new drug commercials for all sorts of problems and wonder when there will be one approved for the condition that makes me ill.

"I implore you to consider the struggles of patients with bronchiectasis and recommend approval of the drug that is currently before you. But please don't stop there. The need for specifically targeted medications is great in the bronchiectasis community.

"We need industry and the FDA to develop a process that can get those drugs to us more

quickly. I strongly believe that the approval of more drugs for this condition will also highlight to the medical community that bronchiectasis-related symptoms need to be explored further, not brushed aside.

"I suffered and waited 16 years for a correct diagnosis and proper treatment because the medical implications of having bronchiectasis were not recognized. Many others have experienced the same wait.

"A desire for my future is to continue an active and vital lifestyle for many years to come. Industry and the FDA have the power to help me stay well by recognizing the needs of patients with bronchiectasis.

"By developing and improving drugs designed specifically to treat bronchiectasis, they can take a significant step in aiding physician ns to treat patients like me. Thank you for listening, Barbara McGuirk."

Clarifying Questions (continued)

DR. BADEN: Thank you, Ms. Sullivan.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We will now resume our clarifying questions related to the applicant's presentation.

I think the applicant has a few comments to make regarding some of the questions that we had right before lunch that was relevant to clarifications of their data.

Ms. Napolitano, please?

MS. NAPOLITANO: Thank you, Mr. Chairman. So we heard the committee ask several questions that we would also like to offer some of our data and some of our perspective to help you in your deliberations.

I would like to start with the comment on some other instances where the totality of evidence was used that may be useful in today's consideration. For instance, in 2010, this

committee actually voted 15 to 1 to approve Cayston for treatment of patients with cystic fibrosis, and it was based on imperfect evidence and it did consider totality of data.

There were two studies for efficacy. One had an endpoint of time to first antibiotic use, kind of like an exacerbation, and that study did not meet its primary objective primarily due to having heterogeneity in their placebo arms. The 3-times-daily placebo outperformed the twice-daily active.

The second study was using PROs as a primary efficacy measure and was designed to show improvement in cystic fibrosis symptoms. That study actually met its primary objective. Then there was an open-label safety study.

The committee considered the very highly unmet medical need. They considered the totality of evidence, which included the fact that aztreonam was previously approved in a systemic setting for lower respiratory tract infections. So the committee considered the unmet need, the totality

of the data, and the fact that it's not a new molecular entity; similar to our case today, where we have obviously different studies, but we have a high unmet medical need and we are dealing with a drug that has no bactericidal effect.

I would like to also now hand it -- we have a couple of points that we would like to make. I would like to ask Dr. McShane to speak to you about the clinical relevance of magnitude of the treatment effect that was discussed, because I think that you were asking about actually what that effect means, is it clinically meaningful.

Following Dr. McShane, we will have a comment on the trial endpoint selection meta-analysis. Then we wanted to address the question about quinolone excessive exacerbations. That was actually a question that was asked towards us, and we felt we may not have maybe answered it completely. And then a couple of other statistical points, and that will be it.

Dr. McShane?

DR. BADEN: Ms. Napolitano, since you are

addressing different questions raised earlier by committee members, perhaps after each topic is discussed, the committee members who need to get their questions answered can actually have a back and forth to make sure that the question is answered.

MS. NAPOLITANO: Absolutely.

DR. McSHANE: Thank you. I think those on the panel who just spoke probably can say it, have said it, even better than I can, especially Ms. Warden. I'd like to echo her sentiment.

I'm not a statistician. However, I do have boots on the ground with these patients every day. And I go through life with them. And many of these patients, I've known longer than a decade, and I take care of them day in and day out with their exacerbations.

It's my experience that they feel better on an inhaled antibiotic. I presented you with examples of patients who were on inhaled antibiotic, and I don't want you to get the impression that those are easily prescribed.

They're off label. They don't have safety follow-up. They have me following the patients, but they don't have the support of the sponsor. And they're very difficult to cobble together, and they often delay the patient's therapy by months.

I have to write 3 to 5 appeal letters for every 1 patient who I write this prescription for, and they are costly. So I really find that there is a strong potential clinical benefit here.

DR. BADEN: May I have a follow-up question? The benefit of preventing an exacerbation is what's being put forward. If patients are on fluoroquinolones 50 percent of the time, so 180 days out of the year, when they have their exacerbation, how do you then treat them? And what are the implications to the fluoroquinolone class used in that setting, getting back to one of the comments earlier about PICC lines and IV therapy.

Are you forcing that issue?

MS. NAPOLITANO: I will actually ask Dr. Alder because we have our own data to show you on that.

DR. ALDER: Tiff, x-ray 11 followed by x-ray 15, please.

In the trial, with the exacerbations, about 30 percent overall were treated with the fluoroquinolone. That's across the board. The trial was not designed to measure success of treatment of exacerbations, but we do have a couple ways to get at that.

What we did is looked at the antibiotic therapy, and if the patient needed either a second antibiotic or piggybacked a second one concurrent with the first, it was considered or tabulated as a failure. Otherwise, the single course of therapy was the end that was tabulated as a success.

So here, we're pooling. Now, bear in mind, with the 2 to 1 randomization, there's twice as many patients in the pooled cipro than the pooled placebo. So there's 7,597 exacerbations. Success as defined by not needing a second antibiotic, or a second script of the same antibiotic was roughly 75, 80 percent across the board.

Also, there was a subgroup of those that had

resistance at least at baseline, cipro resistance, and were still treated with the quinolone. And the success rates were about the same. The numbers get much, much smaller and of course are not statistical. So overall, we're looking at, by this measure, about a 75 to 80 percent success rate.

One more thing. There was a comment about we're losing cipro and obviously there's concern. Obviously, we're very aware of cipro resistance. We've had the drug since 1987.

Slide 3 up, please. A portion of this was presented this morning. We want to make this clear. Baseline resistance in this patient population is basically 20 percent. With a 20 percent resistance rate, most ID docs will tell you you've not likely to reach for that drug for treatment.

By the end of the trial, again, patients that are present, have a culture, grew something that was evaluated, were still t about 20 percent. The proportion of patients that show a resistant isolate are certainly higher in the Cipro

DPI-treated arms than the pooled placebo. That's not a surprise. That resistance appears to be transitory or at least it'll appear at month 3, gone for months 4, 5, and 6, perhaps back at 7, gone 8, 9, et cetera. So at any given time point, we're looking at more or less a stable resistance rate.

DR. BADEN: Mr. Zimmerman, do you have a question?

MR. ZIMMERMAN: Do you have any data regarding other antibiotics that are treated along with the cipro, how that affects resistance?

DR. ALDER: To clarify, you're talking about for treatment of exacerbation, other drug groups? We do have that demographically. We don't have it for success or what have you.

Or you're talking about multi-resistance now? Okay. Yes. We have done analysis of the isolates from RESPIRE 1 in resistance, or did biograms in each one, found no multi-drug resistance as defined by 3 or more drug classes, including TOBI, a beta lactam, and cipro. We did

find 1 MRSA, and that's among all three groups, the pooled placebo, the Cipro 14, and the Cipro 28.

DR. BADEN: Dr. Hawkins, you had a question?

DR. HAWKINS: Just a quick reminder, quality-of-life outcome, each of the studies, what was the result of that?

DR. ALDER: In pure statistical terms, Cipro 14 and the SGRQ in RESPIRE 1 achieved statistical significance across both trials, both PROs. The point estimates were consistently favorable for the DPI groups.

Papa, Quebec 8, Tiff, please. Now, one point that we tried to bring up this morning, you've seen before. We call it the sawtooth graph within Bayer. This is the differential in DPI minus placebo scores in the quality of life following the on cycle, which is the purpose dot, and the forest green or the light blue dots are following the off cycle.

This was also a potential follow-up to the question about trying to use a patient as a their own control, which was asked earlier this morning.

This is perhaps the best way I can think of, of using a patient as their own control. They're on drug and they're off drug. What are they failing when they're on drug? That's represented by the purple dots. What do they feel like after a period of being off drug? And that's represented by the forest green dots for Cipro 14, and the lighter blue for Cipro 28.

Obviously, more favorable effects when they're on drug and less favorable following the off cycle.

DR. BADEN: Dr. Green?

DR. GREEN: So this goes back to the resistance questions. Rather than asking about multi-drug resistance with three classes, there is an association between loss of quinolone susceptibility and loss of carbapenem susceptibility due to an efflux pump.

So I wonder if you can speak specifically to carbapenem resistance, not multi-drug resistance.

DR. ALDER: The biograms that were done were limited at this point to RESPIRE 1. We're still

working through. But the multi-drug resistance testing was for quinolone, beta lactam, and tobramycin, and amino glycosides. I haven't seen any carbapenem. I know obviously the mechanism you're talking about. It might be a fact of the number of isolates that we have.

DR. GREEN: Just to clarify, I think earlier there were comments made that cultures were done at the local centers, and then at a central lab, something was done.

Was there something done on isolates so the local labs recovered isolates of pseudomonas, and pneumococcus, and what have you, and then they sent those to you, or did they send you the actual sputum?

DR. ALDER: All sputum samples were processed locally at the local hospital, and the local hospital then collected the isolates. They went to a central lab; not to us, to a central lab for then confirmation, MIC testing, and profiling.

So by the rules of clinical trials, all of our microbiology data is from central lab analysis,

not from the different local labs.

DR. GREEN: By microbiology, you mean you verified the name of the germ, but you only looked at the germs that they sent you. You didn't look at isolates that they didn't send you, and you only looked at the examples of the isolates that they sent you, because polymicrobial and polyclone infection is probably the rule in these patients and not the exception.

DR. BADEN: Do you want to respond?

DR. ALDER:Exactly. Yes. The hospital would isolate and then send to the central lab. We've done a study once in phase 2 that involved mailing sputum to a central lab, and it becomes a study in how efficient you are getting the mail out within 24 hours. For the more liable bugs, H. flu and M. cat, we'd achieve great eradication. It was a function of the slow male service.

DR. BADEN: For the record, Dr. Kartsonis had to leave for an emergency. I think, Dr. Kim, you had a comment?

DR. KIM: Would it be okay for us to provide

interpretation of the quality-of-life measures slide that was just up from our perspective?

DR. BADEN: Yes. That would be useful.

DR. KIM: Dr. Alder, would you be willing to put up that slide again, please?

DR. ALDER: That was Papa, Quebec 8.

DR. KIM: Thank you.

DR. ALDER: Slide up.

DR. CHEN: This plot showing that the on drug and on treatment and off treatment, sometimes you can see that the patient, because they know they are on treatment, that the self-expectations and self-efficacy, what we call a respondent bias, they will say, because I'm on treatment, I feel much better.

What this plot doesn't show is the placebo, where the placebo has also these kind of patterns. So if you have a placebo plot, that will be actually helpful to have more context of interpreting these plots, because this could be just because of those kind of biases that are causing that drug, in that small amount of

differences in that.

DR. ALDER: To clarify, the placebo is included in every data point in this graph. The purple dots are active minus placebo for quality of life. So the Cipro 14 minus placebo 14, and the resulting differential in RESPIRE 1 Cipro 14, first time point is 7 points. The green dot is active minus placebo following the off-cycle, so placebo is incorporated into every data point.

What we're showing here is the difference between active and placebo following the on cycle and following the off cycle. So it's the best way I can think of to address the question about patient as their own control.

DR. BADEN: Thank you. Dr. Brittain?

DR. BRITTAIN: Can we go back to that slide? So I was wondering exactly the same thing about the placebo. Can we just go very carefully through, first, the upper left quadrant? Just so I understand what the first pink dot is and what the first green dot is.

DR. ALDER: Okay. You see pink, and I see

purple, but we'll work with it. That's the Cipro 14 RESPIRE 1 data. So the first pink dot -- we'll do it your way -- is showing a plus 7. What that is, is the quality-of-life respiratory, the symptom components score for the Cipro 14 minus the placebo 14.

So the resulting differential is a plus 7, and then the quality-of-life plus scores are good and minus scores are bad.

DR. BRITTAIN: The means in the two groups; is that what you're saying?

DR. ALDER: In what?

DR. BRITTAIN: Are you talking about the means?

DR. ALDER: Yes. I'm sorry. Yes, that's right.

DR. BRITTAIN: It's not really within a person, then. It's the means in the two groups.

DR. ALDER: Correct.

DR. BADEN: The clinically meaningful delta is 1, 3, 15?

DR. ALDER: There's not an

established -- when we did this trial, numeric score is clinically meaningful, especially when we're down to a symptom subcomponent score of the quality of life.

Depending on different literature that has come out since then, differences that are considered medically important, 6 points, 7 points, 8 points, somewhere in that range, there's clearly more work needed on PROs as far as their use in NCFB. And there's no established point score for what is or is not medically meaningful.

DR. BADEN: Dr. Ellenberg?

DR. ELLENBERG: In the briefing document, it's stated that the results of the PRO outcomes are not different between placebo and treatment, that one of them actually shifts slightly in favor of placebo, and one of them shifts slightly in favor of the drug.

So I'm having a hard time understanding what analysis tells us that the other one doesn't. What's in the briefing document seems to suggest that there really isn't much of an impact, if any,

on quality of life.

DR. ALDER: The prespecified analysis was from the baseline to the end of treatment, simply looking at differentials from those two, not looking at the data points in between.

Tiff, Papa, Quebec 1, and then have Papa, Sierra 1 behind that, please. Slide 1 up.

So this is the quality-of-life data. This is the formal preplanned testing that's part of the hierarchy. And in this case to the right, a positive score indicates it nominally favors Cipro DPI.

You can see that the point differences are quite close to the line, but a plus 1, plus 2, i.e., so these do not favor placebo. They slightly favor Cipro DPI. But the point was that the analysis, looking just at the beginning and the end of treatment, is not capturing all the waxing and waning during the trial. That's a much more complicated analysis.

DR. BADEN: So another follow-on to what you've recently discussed, you note that a

particular patient may have a resistant isolate at baseline or at testing second month, not have it at month 3, 4, have it at month 6, not have it at end of treatment.

When they have it at month 6, two-thirds of the time, by genetic analysis, it's the same as the earlier isolate; is that correct? Approximately?

DR. ALDER: Approximately, I just want to clarify, the genotyping was done just for the isolate that was closest in time to the baseline. We didn't genotype all of them, but the first one, about 70 percent.

DR. BADEN: But there will be intermittent positive in a given patient, and the majority of isolates you genotyped related to the earlier isolate. But you genotyped a minority.

DR. ALDER: Yes, about 70 percent related baseline to the first resistant; 30 percent did not.

DR. BADEN: So therefore, if the early isolate is assessed and the subsequent isolate is at the fifth testing episode, then they're

eradicated at testing episode 2, 3, 4, and at episode 5, it's a new infection or it's persistent of the infection and therefore, at episodes 2, 3, 4, it was just a detection issue rather than eradication issue.

I'm trying to understand this aspect of the data.

DR. ALDER: That's getting into deep microbiome questions as far as is the bug eradicated, or is it there but not detected, or perhaps overgrown by susceptible isolates. One bit we can offer is that based on the MIC patterns and MIC shifts, once a patient has a resistant isolate, say pseudomonas at MIC 8, and that isolate appears to be gone and then is rediscovered later, the MIC is stable. In other words, we don't see an 8 to 6 progressive march-up. Once there is a resistant MIC, it's pretty stable for us.

DR. BADEN: No. I just wanted to make sure. Your term was "eradication," because at the end of study, you say "eradicated."

DR. ALDER: Yes.

DR. BADEN: And that term is a powerful term in my view. What you're really saying is not detected.

DR. ALDER: Yes. We've made that clear.

DR. BADEN: So that's a clarification of terms. It's detection at different times, but I'm not sure you're ever eradicated.

DR. ALDER: Yes. We're making that clear. What we've called eradication is sputum-negative culture. They produced adequate sputum and grew nothing. That's why you'll see some eradications in the placebo arm as well.

DR. BADEN: Thank you. Other follow-on questions? Dr. Green?

DR. GREEN: Just a follow-on with the microbiology. You've talked to us about patients who started out with an organism and lose that organism. I wonder if you have data that you're able to share with the committee about what fills the niche.

So you start with haemophilus. You lose haemophilus, so that's good. There's no more

haemophilus. But what then did the patient get to fill the niche in the absence of haemophilus? Because I suspect they didn't have a negative sputum, but maybe they did.

DR. ALDER: In the trial, it was extremely rare for a patient who was, in your example, positive for haemophilus at baseline to become positive for something else later. It was either haemophilus, yes or no. So when there's a negative sputum culture, we can't speculate if there's something else there or if there's true eradication.

DR. BADEN: Given the time, I would ask to continue with your clarification, but if we all can be as succinct as possible both on the clarifying and also on our questioning side.

MS. NAPOLITANO: Will do. Thank you. So the next clarification for you is the trial and point selection.

DR. ALDER: I will be brief. We negotiated with the FDA for trial endpoint. It was clear it was going to be an exacerbation endpoint.

Basically, the medical people, both on the agency side, I think, and at Bayer, preferred frequency of exacerbations; and the statisticians at the agency and at Bayer preferred time to event.

So I think in the end, we compromised, and we did it the statistician's way. So we did time to event, and that has some power in that frequency can be influenced by downstream events. So a patient has an exacerbation, they're treated with something. Now we've introduced potentially a variability in the trial.

So it was felt time to event was a more pure way to look at drug efficacy within the context of the trial.

MS. NAPOLITANO: I will ask Dr. Friede --

DR. BADEN: Dr. Swenson has a follow-on question.

DR. SWENSON: Something of a follow-on just to that point was a question I'd hoped to raise earlier. It was a randomized trial, and I'm sure things broke out pretty evenly on both sides. But I couldn't find anywhere a discussion of when the

patient's last exacerbation was relative to the start of their treatment.

Do you have any data to suggest that something like that could in fact alter this primary endpoint that you focused on?

MS. NAPOLITANO: We'll ask Dr. Roth to answer that question.

DR. ROTH: Good afternoon. My name is Catherine Roth. I am lead statistician at Bayer responsible for this project. We performed an analysis looking at the time from the last reported previous exacerbations to randomization.

In RESPIRE 1, this time was at a median of about 90 days in each of the treatment groups. In RESPIRE 2, this time was slightly higher, reflecting that there were fewer historic exacerbations in the trial. But there were no differences between the treatment groups, so this cannot be considered a source of bias.

MS. NAPOLITANO: Thank you. Then I will ask Dr. Friede to comment on the meta-analysis.

DR. FRIEDE: Good afternoon. I am Tim

Friede, professor of biostatistics at the University Medical Center, Gottingen, in Germany. I am compensated by the sponsor for time spent in preparing and attending the meeting today, but otherwise do not have any interests in the outcome of today's meeting.

On the matter of the integrated analysis, Dr. Brittain and Dr. Ellenberg, you both asked about the statistical model, and I can clarify here that what the analyses that were presented as integrated analysis by the sponsor were in fact individual patient data meta-analysis.

So the model that was used was a stratified Cox regression, stratified by the SPICE study and also adjusting for the randomization factors. So this is very close to what we usually do in meta-analysis by some aggregated data, and we have checked the results. It's again very similar.

I think also for the reasons that you, Dr. Brittain, mentioned earlier, the results are very similar to the results presented by the FDA, where a study was included not as a stratum, but as

a factor.

DR. BADEN: Dr. Kadoorie has a follow-on comment.

DR. KADOORIE: I just wanted to say the model we used on study, as an additional stratification factor -- I'm sorry, as an additional covariate in the model.

DR. BADEN: Thank you.

MS. NAPOLITANO: Thank you. Then we covered the quinolone success in exacerbation, so we'll proceed to -- I'll ask Dr. Roth to come back and talk about the hazard ratio, the power consideration, and handling of the missing data, which was one of the questions before lunch.

DR. ROTH: To clarify an earlier question, when planning the studies, we were assuming a hazard ratio of 0.6 for each of the active treatment groups, and the studies were powered on that at a power of 90 percent.

We adjusted the sample size for RESPIRE 2 based on the blinded exacerbation rate that we observed, which were lower than expected.

Therefore, we increased the sample size to achieve the required number of events.

Regarding the question of missing data, I would like to first comment that patients who discontinued treatment were followed up if they agreed to follow up, and exacerbations occurring after the end of treatment were included in the analysis if they occurred within the 48 time window.

Overall, about 12 percent of the patients were censored before the end of study and were not fully evaluable for the primary endpoint. We did a number of analyses to assess the impact of missing data. Among others, we used a tipping point analysis based on multiple imputations.

With that tipping point analysis, we inflated the hazard after drop-out in the active treatment group to 2.5-fold of the original hazard. That is way beyond the placebo hazard. And even with that inflation factor, it remained significant for RESPIRE 1 in the 14-day regimen.

MS. NAPOLITANO: Thank you. Then our last

point was to comment on the lack of effect of small number of high exacerbations on overall treatment effect, and I'll ask Dr. Alder to comment on that.

DR. ALDER: Tiff, Charlie 25, please. Slide up.

The question, to recap was, could a small number of patients with a large number of exacerbations be causing undue influence within the trial. So this slide was presented earlier this morning as part of the totality of data, i.e., Cipro 14 and Cipro 28, about the same dose, and they give you about the same treatment effect, 188, 184 total exacerbations.

The top part, though, may address this question about whether there are few patients at undue cause/undue influence. Looking at the right side, from the right of the dotted red line, we see the proportion of patients that had 1, 2, 3, 4, or more exacerbations. It's clearly a trailing endpoint. There's not a big bolus or a bolus at all of the 4 or more or the 3 or more. In effect, it's a decreasing function looking at proportions

of 1, 2, 3, 4, or more.

Within each grouping, the Cipro DPI groups are at or typically below the proportion of patients in corresponding placebo group as far as having multiple exacerbations.

Analysis by truncating it to 2, 3, or some other number become very complicated, but basically show the same overall pattern that we're showing here as far as the treatment effect of Cipro 14 and Cipro 28 within the trial.

So this can give you an idea of the real numbers of patients that had 3 or 4 more exacerbations. They certainly are part of the analysis, but did not have undue impact in the overall picture of efficacy.

MS. NAPOLITANO: Mr. Chairman, this concludes the points we wanted to clarify.

DR. BADEN: We have several panel members who had questions pending from this morning. We also have an hour and 8 minutes to conclude our business. Would the group like an 8-minute break or shall we just continue through? Continue

through, good.

I'm sorry? I've just been informed we have to break.

DR. BADEN: Do you need a 10-minute break? So we can continue?

(Transcriptionist gestures no.)

DR. BADEN: We're back on.

(Laughter.)

DR. BADEN: We need to listen to each other, so thank you for facilitating that. Dr. Weina?

COL WEINA: I have two seemingly unrelated questions, but I think they're linked somewhat. On your CC-33 slide, you show a technetium scan, and this is actually in a healthy volunteer.

I'm curious if you did the technetium scan in an affected individual because, of course, the architecture is completely different. And with the mucus plugging, you're not going to be delivering -- I'm just wondering where that additional medication goes, et cetera, if you've done that scan or not.

MS. NAPOLITANO: So we'll ask Dr. Stass to

address your question.

DR. STASS: Good afternoon, ladies and gentlemen. My name is Heino Stass. I'm the clin pharm representative of this project for Bayer, and I'm located in Wuppertal, Germany. We did indeed study also patient groups, and it's in the graphic study, and if I could have slide 1 up, please.

This shows a summary of the patient types that we studied, first of all NCFB patients in the middle scan and COPD patients on the right scan. We were able to show in this study that for all patients that ventilate, part of the lung is covered by Cipro DPI powder. We did this by comparing the contrast scans of the lung done with krypton gas and to the powder scans.

The data were quantified -- slide 2, please, up -- and the result of this quantification is shown in slide 2. In the various groups, we did some graphic quantification. The intrapulmonary deposition was quite effective [indiscernible] wise. The total amount of drug deposited was in about 53 percent with a low variability. And we

speak here of patients which cover the whole range of lung function impairment, down from as low as 20 up to normal lung function.

Extrathoracic deposition drug, which is swallowed down, amounted to about 40 percent roughly. Less than 10 percent remained in the device, and about 1 percent of the drug is getting exhaled again.

COL WEINA: Then actually, what I think a related question was, at least in my mind, the question about time to exacerbation is not as much Cipro DPI versus placebo, but Cipro DPI with what we're already doing. And that is that you've got 40 percent of the population that is getting suppressive antibiotic, and what is that population's time to exacerbation versus Cipro DPI?

I would assume you've asked yourself that question. You may not have presented it, but you certainly asked yourself that.

MS. NAPOLITANO: I will ask Dr. Alder.

DR. ALDER: You're asking, I think, about macrolide therapy and how did the time to event

look?

COL WEINA: Not necessarily just macrolide, but it depends upon what the practitioner and what the local practice is. In fact, it could be ciprofloxacin for an exacerbation.

DR. ALDER: Okay. Got it. Under the trial, they were not non-systemic antibiotics, other than macrolides, during the trial for enrollment.

Tiff, Echo, Tango 1 and 2, please. So we did do subgroup break-outs. We'll show you the RESPIRE 1 time to event. There are a number of groups on the forest plot. We'll direct you to the right spot.

Slide 1 up, please. So this is the Cipro 14. The macrolide is the next to the last row, the penultimate line. The yes/no is basically did they have macrolide on board at baseline. If they did, they were allowed to stay on macrolides, of course.

So the preponderance of patients were not on macrolide, but of the 46 that did, you see the point estimate in RESPIRE 1 Cipro 14 is actually a

little bit better than the no group.

COL WEINA: I understand, but that's actually a very different question than what I was asking. And that was that -- right now, based upon the data you showed in slide CC-23, you have a pretty good idea about what NCFB is doing out there; that you have 40 percent of individuals that are on any kind of suppressive antibiotic, do we have any kind of idea as to how much them being on that suppressive antibiotic is delaying time to exacerbation versus doing absolutely nothing at all? Which is what you're comparing Cipro DPI to in the clinical trial.

MS. NAPOLITANO: We'll ask Dr. Aksamit to try to address that question.

DR. AKSAMIT: So the short answer is we don't know. I would have that same slide up, CC-23, please. This was taken at baseline data from the registry data, so this is going into it. And that's in contrast to enrollment into the study, where patients were not on suppressive therapy.

I might also add that this 40 percent that did not include chronic macrolide use. This is a bit of a moving mark, as you know, just because at the beginning of this study, much like the beginning of the registry data collection, macrolides were not such a part of incorporation in the clinical practice, so it is a bit of a moving market.

This 40 percent really reflects, as Dr. McShane said, a lot of people are on a lot of antibiotics already on a regular basis, systemically, is the point that we see in the clinic every day.

DR. BADEN: So I'm going to continue to proceed.

DR. AKSAMIT: Mr. Chairman, may I just maybe expand on that? So then there was the issue -- slide 1 up -- and this is taken from retrospective data published in our blue journal last year. And what this really looked at is the experience at one academic center retrospectively, non-controlled setting, looking at exacerbation shift before and

after the start of inhaled antibiotics.

So what this group did was just take just the individuals they placed, they felt were important to receive antibiotics inhaled. And this was in the hands of what we would consider a specialized center, people that took care of a lot of bronchiectasis patients and looked at before and after the start of antibiotics and what happened to their exacerbations.

This was over a period of time, and it was a statistically significant decrease, good p-value, and the number of exacerbations went down from an average of 2.3 per year to 1.3 per year. And this was, again in the hands -- and granted, retrospective data -- of presumably experienced clinicians at one center that deal with a lot of bronchiectasis patients.

I don't know if this helps scratch at your question about do inhaled antibiotics really work. To a large extent, many of us who use those, we use because we think they work. And they're used off label and unapproved with all the trappings then of

authorizations, and a lack of data safety monitoring, and all the other really important issues that have been emphasized by the committee.

DR. BADEN: Thank you. I am going to continue with the list we have from this morning. If I call to one of the committee members, and your question is no longer relevant, it's been answered, we can keep moving. Dr. Swenson?

DR. SWENSON: My questions were answered.

DR. BADEN: Dr. Corbett?

DR. CORBETT: I have a couple of pharmacology questions, and then one pharmacology question related to the case of tendinopathy. So that's sort of what I'm going with here.

Related to slide CC-34 -- and I think I understand, but I just want to clarify -- this was built around a variety of populations; is that true? So healthy volunteers, COPD as well as CF, or is that not the case?

MS. NAPOLITANO: We'll ask Dr. Stass to address that question.

DR. STASS: The data that you see here in

this graph were generated from phase 2 and phase 3 NCFB patients using population pharmacokinetic methods that determined the Cmax and sputum in plasma.

DR. CORBETT: So this is your phase 2 and phase 3 data?

DR. STASS: Correct.

DR. CORBETT: Excellent. So the variability around the sputum, I understand the upper limit, but do you know the lower range of that sputum exposure for Cmax? I don't know if that's a min/max or if that's an IQR or 95?

DR. STASS: That's 95 percent. The variability of the sputum concentrations -- unbound sputum concentrations were quite tremendous and did allow in-depth analysis of variability.

DR. CORBETT: I'm guessing that's somewhat based on the not 100 percent delivery to the lung that we've already talked about, I'm guessing, is the case.

Just looking at the plasma exposures as well, is that 95 percent interval fairly

representative of the range as well? I would assume so. So I'm trying to get at, are there some outliers where perhaps the systemic exposures might be higher?

DR. STASS: No. The variability that you see here is in the same range, as you know, from oral or IV treatment. There are no outliers there.

DR. CORBETT: So based around that, looking at your two phase 3 trials, because you said some of this was based on those patients -- and I know you guys looked at exposures. I think you did. Did you see any differences in exposures in RESPIRE 2 and RESPIRE 1, not suggesting it would be statistically different, but giving some sort of suggestion that, that may have contributed to the differences in those two trials?

DR. STASS: Simple answer, no, we did not see something.

DR. CORBETT: You did not?

DR. STASS: No, correct.

DR. CORBETT: No differences?

DR. STASS: Yes.

DR. CORBETT: Last question is about -- and I'm not sure if you can answer it -- the case of tendinopathy that was in the FDA briefing. Is there any pharmacokinetic data or systemic concentrations of cipro for that particular patient?

MS. NAPOLITANO: I will ask Dr. Schomakers to address the question regarding that.

DR. SCHOMAKERS: The case you're addressing is a non-serious case that occurred in RESPIRE 1 that was a tendinopathy of the Achilles heel that was non-serious and considered drug related by investigator. And we do not have the exact concentration for this patient.

DR. CORBETT: As far as you know, that was one case that was reported from both RESPIRE 1 and 2?

DR. SCHOMAKERS: As was shown in the core presentation, there were several cases of more unspecific tendon disorders. This was the only case in which the Achilles heel was specifically mentioned.

DR. CORBETT: Has there been any speculation or question -- and maybe this is an unfair question -- around why that particular patient may have developed tendinopathy and others did not?

DR. SCHOMAKERS: So from this specific patient, we know that the patient had a wound on the same leg 2 weeks earlier. So if or if not that's a drug-related effect is a matter of speculation. But of course, we cannot exclude it due to the known class effects of ciprofloxacin.

DR. CORBETT: Thank you.

DR. BADEN: Thank you. Dr. Ellenberg, any residual questions from this morning?

(Dr. Ellenberg gestures no.)

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: None. My questions have been addressed.

DR. BADEN: Dr. Clark?

DR. CLARK: Yes. Were total systemic antibiotic days collected, and were there differences between the six arms?

MS. NAPOLITANO: I will ask Dr. Bandel to

address that question.

DR. BANDEL: I'm Tiemo Bandel, clinical development, Bayer. No. Total systemic antibiotic dates were not counted. What we have, though, is data on how many exacerbations have been treated. Antibiotics might be also of interest and how many were treated with quinolones.

DR. CLARK: Yes. I was just getting at, as a possible future endpoint, are systemic antibiotics reduced, or were there any confounders in terms of giving systemic antibiotics for other indications that didn't meet an exacerbation criterion, and could that have affected the results.

DR. BANDEL: I can only answer that about 90 percent of all of our exacerbations, all exacerbations observed in this study were treated with antibiotics. And as Dr. Alder already said, about 35 percent were treated with quinolones.

There are a variety of other antibiotics that were used, but we did not specifically count the days on antibiotics per group, but I would

expect those would not differ.

We have, though, data -- slide 2 up -- that was shown before. Slide 1, please. This is data that was shown already by Dr. Alder. We do have data, however, on follow-up prescription in multiple therapies that indicate that if you look at the follow-up prescriptions with multiple therapies across the groups, there's no difference.

So that would indicate that also an exacerbation can be treated successfully with antibiotics, and there's no difference whether the patient is pre-treated with Cipro DPI or with placebo.

DR. BADEN: Dr. Baden. In the briefing document on page 56, you have the forest plot for RESPIRE 1. And in that forest plot, you show the baseline culture for pseudomonas positive/negative, as well as the cipro resistance of the pathogen at baseline, yes/no. And my read of this is that the for benefit, pseudomonas needs to be there and not be resistant.

Is that the correct interpretation of this

forest plot, which is the strongest result of the study?

MS. NAPOLITANO: Just for clarification, you mean the sponsor briefing book; correct?

DR. BADEN: Sponsor briefing book, and you show that, with cipro-resistant pathogen at baseline, yes/no, and then crossing 1 or not. And in that, it looks like, if cipro-resistant pathogen at baseline is present, then the benefit is unclear.

MS. NAPOLITANO: I will ask Dr. Alder to address your question, and I will pass the -- it's figure number 5-4 from our briefing book.

DR. BADEN: Correct.

DR. ALDER: Or it could be Echo, Tango 1, either way. It's the same thing.

DR. BADEN: I was going to say that.

(Laughter.)

DR. BADEN: Your knowledge of your slide nomenclature is very impressive, and assuming that there is a systematic order to it, you have a lot of slides, so congratulations on knowing your data

so well.

DR. ALDER: Thank you. One of the people with the headset is a lot younger than me. The only thing we can communicate on is the military alphabet, so that allows us to get slides up quickly for you. Slide 2 up, please.

I think this is what you're after. It's the Cipro 14 RESPIRE 1. The top half is baseline culture, pseudomonas yes or positive negative. And the very bottom row is resistant, yes/no.

Now, of course, any of these subgroup analyses -- we start paring down to groups of 100 or 200 -- are not intended to stand alone as a statistically significant test. So as we look through these forest plots, we can certainly see cases where the positive pseudomonas subgroup might be a little better or a little worse than the pseudomonas negative, meaning they had 1 of the other 6 pathogens.

Same thing for resistance at baseline, although there the effect is a bit more consistent. It was always better to not have a resistant

isolated baseline than to have a resistant, although as you can see here, the treatment effect is preserved, even in those with resistance at baseline.

So, no. I would not start parsing groups down to pseudomonas this or that or hospitalization with an FEV of this or that. This is all meant to be informative, but not statistical.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: Just a quick follow-up. Can we have this slide back?

MS. NAPOLITANO: Slide back, please.

DR. ALDER: Echo, Tango 1.

DR. BRITTAIN: Did you test for interaction in these?

MS. NAPOLITANO: We'll ask Dr. Roth to address that.

DR. ROTH: In the preplanned analysis, we did not test for interactions. These were just plain splits of the overall population and the effect in the population.

In a post hoc analysis, we tested for

interaction. However, we detected across the number of tests we did a few significant values, but there was no consistent trend across treatment groups and across studies.

DR. BADEN: I have one last question. We've heard comments about NTMs. Patients with bronchiectasis become colonized with a variety of organisms. What might the implications be of aerosolized quinolone on NTMs, and then the impact on potential future treatment?

This gets at the issue that Dr. Green raised earlier about the niches because one of the subsites -- I think you mentioned galactomannan testing, although you said aspergillus antigen.

Will the flora rotate and be modified outside of the seven indicator pathogens, where you may perhaps have more NTMs or you have NTMs that are resistant to fluoroquinolones? And you may develop more colonization with aspergillus, which you suggested, although the data seem quite uneven, so it's hard to know how to interpret. But I'm interested in your thoughts on those two issues.

MS. NAPOLITANO: I will ask Dr. Winthrop to address that question.

DR. WINTHROP: Great. Thanks. I'm Kevin Winthrop. Thanks for allowing me to be here. I'm from University of Oregon Health Sciences University in Portland. I'm in the infectious disease division there, and I run a chronic chest infection, clinical program, and research program.

I have received honorarium and grants from my spouse -- I mean, sponsor, sorry --

(Laughter.)

DR. WINTHROP: -- and that's for research in this area, both clinical and safety research. And I have no financial stake as to the outcome of this meeting like my colleagues. I also work with Tim and several folks here. I was one of the co-PIs in the national bronchiectasis registry that's been mentioned several times today.

So we see lots of NTM patients and certainly patients with NCFB, lifetime. Probably it's a 5 or 10 percent chance that they'll become colonized with NTM at some point. That's the best data we

have. And not all those people becomes diseased; it can just be airway colonization, as you know.

Most NTM in the U.S. is MAC, 90 plus percent of it. And MAC, by and large, almost uniformly is resistant to fluoroquinolones at baseline. I find fluoroquinolones not useful in the treatment of MAC, and I almost never use them.

I am intrigued by the idea that this drug might help prevent acquisition of MAC simply because of the high achievable concentrations in airway, or maybe it would eventually be something to study in the context of treating MAC because, again, of those high levels. But at baseline, systemic fluoroquinolones really don't have any role in the treatment of NTM.

DR. BADEN: Thank you. Dr. Gripshover, you had a question?

DR. GRIPSHOVER: Sorry. Yes. Just a quick one. When you had these scatter plots up, the low FEV1 were less likely to respond. Right? Yes, less likely to respond. So I was wondering actually, do you know about drug delivery and

people with lower FEV 1's?

MS. NAPOLITANO: You mean in our setting for our product?

DR. GRIPSHOVER: Yes.

MS. NAPOLITANO: Yes. You want to see that we tested for the low FEV --

DR. GRIPSHOVER: Yes. I just wondered if you checked for drug delivery in the lungs in people with low FEV1. Does it get in as well as people with higher since it seems like they didn't --

MS. NAPOLITANO: I will ask Dr. Stass to address that question.

DR. STASS: Yes. In the scintographic study, we checked with the patients were able to inhale even if every one were very low. In slide number 2, you see this result presented a minute ago.

This represents the different groups in here and both patient groups, COPD patients, in orange and the NCFB group in purple, had across all ranges of lung function as low as 20 up to normal, the

same deposition pattern with high and effective deposition. And all of them were also able to operate the device in a way that is guaranteed that the drug is aerosolized and taken up by the lung.

DR. BADEN: I think the last question goes to Dr. Swenson.

DR. SWENSON: Again, it was answered. While I have the speaker, I did want to ask just one question. We do use steroids and often oral steroids in the exacerbations. Did you present any data to the extent that this chronic toll or chronic steroids might have that might have been ameliorated by inhaled cipro?

MS. NAPOLITANO: We did not present any such data, but I can ask Dr. O'Donnell to comment.

DR. O'DONNELL: I'm Anne O'Donnell from Georgetown University, pulmonary critical care medicine, receiving an honorarium from the sponsor to be here, but I have no stake in this outcome.

We don't have data on steroid use and the study population that's analyzable, but in clinical practice, I think oral steroids are relatively

uncommonly used in exacerbation, but certainly occasionally. The other issue is inhaled corticosteroids, which we do have some information on, but I don't think it's of any difference in the groups.

DR. BADEN: I think Dr. Green has a question.

DR. GREEN: Jonathan Green. I guess this is a more general question. I would like to understand how representative do you think the population of NCF patients that were present or enrolled in the study are really of the greater population in which the drug will be used should it be approved?

The reason I am thinking about this is, is it strikes me, if you look at the table that shows the frequency of exacerbations, 80 percent of the patients, in any group, have only zero or 1 exacerbation over the course of the study of a year. Certainly, the descriptions by patients and the descriptions by the physicians presenting would seem to be a much more severe condition.

So I guess I'd like to understand, was the population studied truly representative of the population it will be used in. This frequency of exacerbations during the study was less than the year prior because to be enrolled, you had to have 2 more.

Was there some change in the standard of care that might have accounted for that shift or that period, or is it just by chance a less ill population during that year they were in the study?

MS. NAPOLITANO: I will ask Dr. Aksamit to address your question.

DR. AKSAMIT: Thank you for that question. That's a fantastic question and actually really focuses on why we're here today. I think what I would leave you with is about the heterogeneity. And I think exactly the study helps us confirm that ciprofloxacin DPI would not be intended for everybody.

As we heard from our patients, the individuals most likely to benefit are the people truly having additional exacerbations, 2 or more

with a specified pathogen present. We feel, I feel as a clinician, that those are the people most likely to benefit, as is asked on the label.

I think the heterogeneity issues that have been covered greatly here this morning, and now this afternoon, really emphasize and I think help us understand the importance of that; and that if we're going to advance the science of bronchiectasis, this is a first step in that direction.

I think if we're consistent and have some fidelity to exactly what we're intending to do, 2 or more exacerbations, specified pathogens, in addition to all those other measures that our patients had told us about and we're asked about by the committee, I think that that's in fact exactly why we can make a compelling argument that this is something that really is important for the unmet need to move forward.

DR. BADEN: I think we have succeeded in exhausting the questions.

MS. NAPOLITANO: Thank you.

Questions to Committee and Discussion

DR. BADEN: So thank you very much for running the marathon with us and for clarifying these many issues.

We will now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote.

If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the

screen. The DFO will read the vote on the screen into the record. Next, we will go around the room and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in this same manner until all questions have been answered or discussed.

Any questions about the process?

(No response.)

DR. BADEN: If there are no questions or comments concerning the wording of the question, we'll open the question up to discussion. Does Dr. Nambiar wish to pose the question to the group or any other comments?

DR. NAMBIAR: Thank you, Dr. Baden.

At today's meeting, we have discussed the benefits and risks of ciprofloxacin dry powder for inhalation for the proposed indication of reduction of exacerbations in non-CF bronchiectasis adult patients with respiratory bacterial pathogens.

The proposed dosing regimen in the new drug application is the 14-days on/off regimen. You

heard about the efficacy and safety findings from each of the two phase 3 trials, RESPIRE 1 and 2. Some key discussion points we have heard today relate to the differences in the efficacy outcomes between the two trials and between the two regimens, the 14 days on/off versus the 28 days on/off, and for the different endpoints in each of the two RESPIRE trials, and the magnitude of the treatment effect that was demonstrated in these trials.

You have heard presentations from the FDA and the applicant and comments from speakers at the open public hearing. Based on the information provided to you in the briefing documents, the presentations, and discussions today, we seek your input on two voting questions.

As always, in addition to your yes/no vote, your rationale and any recommendations you have are extremely valuable to us, and we look forward to hearing your perspectives.

The first question is, has the applicant provided substantial evidence of the safety and

efficacy for ciprofloxacin dry-powder inhalation 14-day regimen in delaying the time to first exacerbation after starting treatment?

If yes, please provide any recommendations concerning labeling. If no, what additional studies or analyses are needed? Please discuss appropriate endpoints, drug regimens, and trial durations for future trials.

May I have the next question, please?

The second question is has the applicant provided substantial evidence of the safety and efficacy for the ciprofloxacin DPI 28-day regimen in delaying the time to first exacerbation after starting treatment?

If yes, please provide any recommendations concerning labeling. If no, what additional studies or analyses are needed? Please discuss endpoints, drug regimens, and trial duration. Thank you.

DR. BADEN: Are there questions regarding the question?

DR. OFOTOKUN: Are these two questions

combined? Can we vote separately each question or is the vote representative of both questions?

DR. NAMBIAR: Two separate questions.

DR. BADEN: We'll vote on one question, go around, have a discussion as to the rationale. And one of the important things is the agency, I think, appreciates our comments more than our actual vote.

We are time sensitive. They appreciate everything. But I think that the comments related to how we weigh the evidence, I think they will take quite seriously as well. But we'll deal with question 1. Each of us, if we wish, will make a brief comment as to rationale, and then question 2, and do the same.

Is there any discussion amongst the committee members before we vote about the question or the data for clarification without actually discussing how one's going to vote?

(No response.)

DR. BADEN: If there are no further discussions on this question, we'll being the voting process. Please press the button on your

microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light my continue to flash. If you're unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. TESH: The voting result for the record is 6 yes; 9 nos; zero abstentions; zero non-voting.

DR. BADEN: We will start on the right as to key aspects related to issues Dr. Nambiar raised and to the question at hand.

DR. BRITTAIN: I'm Erica Brittain. I voted yes, a very hard vote. I could have voted either way. Obviously, I'm very uncomfortable violating all the prespecified rules. I really want to follow the prespecified rules or why do we have them?

On the other hand, I felt when I looked at the combined trial, the integrated trial data, the results are pretty convincing of efficacy. If I

have a concern, it's more a concern about what happens after the first year. That's where I'm more concerned than about this first-year efficacy.

Also, in terms of the differing results in the different trials, maybe it's obvious that it would be this way. But if you consider the combined trial estimate of the hazard ratio is about 0.7 in both arms, all the confidence intervals in the individual trials all easily include 0.7.

So it seems very possible to me that that is the real treatment effect; and again, the fact that we see a strong result in both treatment arms. Although it is also true that they're sharing a control group, so that makes it a little less impressive that we're seeing it in both groups. But anyway, I could have voted either way, though.

DR. BADEN: Dr. Green?

DR. J. GREEN: Jonathan Green. I voted no. I want to first frame it and say that I am very sensitive to the needs of the patients as a critical care physician who takes care of patients

in their worse shape when they come to me in the ICU. But I am not convinced that this is the drug that is going to change that outcome.

I think that the inconsistency of the data between the trials was important. I also think that the time to first exacerbation is not the relevant endpoint here, clinically. If I'm a patient, I guess it matters the first time if it takes longer to get the exacerbation, but I'm much more interested in the durability of this effect over the long-term.

This is a drug patients will be on potentially for many years, and I want to understand is this going to help them after that first exacerbation, second exacerbation, and over time, and I'm not convinced that we're not going to, in the long run, cause more harm than good by removing what I think is a very important systemic antibiotic for treatment of this patient population and other patients in the future.

DR. BADEN: One comment. If you voted yes, please provide any recommendation concerning

labeling. If you voted no, what additional studies, analyses are needed? Please discuss appropriate endpoint, drug regimen, and trial duration; to the rest of the panel, as you present your comments to help give the FDA guidance on those corollary questions.

Dr. Ellenberg?

DR. ELLENBERG: I voted yes, but as with Dr. Brittain, I was right, smack on the margin, and went back and forth as the day progressed about how I was going to vote. I was troubled by the inconsistency of results in the two studies, but I was somewhat reassured by the fact that it was going in the same direction.

I'm troubled by the fact that there's no long-term data for treatment intended to be used long-term. I would have liked to have seen more frequent PRO outcomes during the treatment because from what I heard from the patients, their day-to-day quality of life is very important.

The wording of the question made it even more difficult because I think it was more clear if

you looked at the delay to the first exacerbation. I'm more comfortable with that, but overall, whether this is something that people should use, that's a different question.

If you say substantial evidence, well, I have to say I don't really think it's substantial evidence. And if I had voted no, I would have voted no because I don't think it's substantial, but I felt like it was enough.

DR. BADEN: Dr. Carvalho?

DR. CARVALHO: Paula Carvalho. I agree with some of the statements that the prior panel members have made. I voted yes, and also I was right on the line for this, for the 14-day. The way the question was also worded, it was asked about safety and efficacy in the same question. I didn't have safety concerns. I had a little more of efficacy concern, but I felt that, again, it was just over the line that it was enough.

In the future, I'd like to see a few extra things. I agree with PRO data. I would also like to see patients compare to themselves. This is a

tremendously heterogeneous disease, and I don't think we have a very good answer today as to how each patient did before and after treatment. So I would encourage better matching between patients or using them as themselves.

DR. BADEN: Mr. Zimmerman?

MR. ZIMMERMAN: Jasan Zimmerman. I voted no. I really appreciate the comment that this is not for every patient, but I have great concerns between the two studies, the variability of the results, and that's the main reason I voted no.

I'd like to see a longer study. I'm concerned about resistance in that I would like to see maybe twice the length or more. I'd like to see a dry-powder comparator arm as well to see if that's causing any issues with lungs. And I think the number of exacerbations would be interesting, but I'd also like to see specific exacerbations like hospitalizations, FEV, resistance, and those would be nice endpoints for me.

DR. BADEN: Dr. Hawkins?

DR. HAWKINS: Yes. I voted yes. Again,

difficult to decide, but in the end I thought that this group of patients does not have much available to them. And I take are of those patients in my private practice. I thought if the drug was approved, there would be an opportunity to figure out pretty soon, with well-crafted studies, to answer some of the questions that we have about the best way to do the study in the future.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. I voted no, and I really appreciate all the audience's stories and the need that we have to have better therapies for NCFB. But to me it wasn't clear -- these studies didn't show to me for sure that this is good therapy. I didn't think it showed clear benefit.

Even in the one study that did really just decreased the chance of an exacerbation about 18 percent in the first year, we saw in the time, there was already increasing resistance, so I'm not sure how long that benefit will last if it went longer.

So in regards to future trials, I think that

we need longer follow-up for a chronic disease. So I think that maybe we didn't have enough time to get to the exacerbations that it might stop, so that may still be a good endpoint. I think the population should be people who had more exacerbations at baseline.

I don't know. We said 2 or more, but clearly the majority of people didn't even have one in the year that they were followed on the study, whether they got treatment or not, so I don't know if that might help.

In terms of endpoints, I agree with Jasan that I thought hospitalizations or at least a need for IV antibiotic therapy might be stronger endpoints. FEV1, a decrease in FEV1 would be meaningful. I'm also -- maybe it's the ID doctor in me -- worried monitoring resistance and learning the development of aspergillus and nontuberculous mycobacteria, prospectively.

DR. BADEN: Dr. Green?

DR. M. GREEN: Michael Green, and I voted no. This was an exceptionally challenging question

for me, and I didn't know how I was going to answer until it was actually time to put my finger on the button. I think it's clear the need in this population, and there's a definite need for an effective and safe treatment.

The data that was presented are suggestive, particularly when they were combined. But they're not confirmatory of a potential benefit of the 14-day, which is what we're talking about now -- but I'll stay off of the 20th day and not say anything on the second vote -- on or off cycle of Cipro DPI treatment.

We only had 1 of 4 endpoints, primary endpoints, that were met, and I think the issue of resistance is truly a major concern. This is I think especially true with regard to the durability effect of this regimen, which many other people have mentioned as we're going around the table.

While I think there's not an apparent obvious safety signal from the medication itself -- and that might ease a decision to say yes -- we're really left with only trends. And we

actually don't know about the safety particularly of resistance if we go longer, and we have no real statistical evidence of impact.

I think we need to do a longer study. One might be able to do creative designs that at the end of the year, you could cross people over or maybe take the placebo group and put them on drug and let them be their own control from the year before. I think endpoints could be the number of events if you're going longer.

The comment that was made about days of antimicrobial therapy other than the quinolone would be good. And I think I might in fact put all patients on study on macrolide to eliminate that as a variable in the background. Thank you.

DR. BADEN: Dr. Weina?

COL WEINA: Pete Weina. I voted no. I guess I'm hung up on the term "substantial" as others have been, and because of this have to vote no, the idea of an unmet medical need not withstanding. Given that two or more of the documented exacerbations were needed for entry into

the trial, but the placebo group, at least 50 percent with no exacerbations at all suggests a couple of things.

Number one, that there's much greater heterogeneity in the population than we're taking into account, and maybe we need to be more selective in the population that enters; or the dry powder actually helped, and helped eliminate some of the exacerbations. And that's not so far off because certainly if that had been the treatment arm, we might be arguing that, hey, look-it, 50 percent of the people didn't have any exacerbations at all even though they had two or more when they entered.

The other thing is -- so I really think, regardless, that it's important to differentiate between the effects of the dry powder, so an arm without inhalation is really critical, even from the safety perspective, some of the things that we were seeing.

The NCFB is characterized as being a vicious cycle, and therefore I feel that really FEV is a

key endpoint. And just because it didn't work in the CF population, we abandoned that. And I think we're abandoning the exact argument that we're making, that we're breaking this vicious cycle by using this drug.

As an ID guy, of course, I also worry about resistance, especially given that while we're delivering super therapeutic levels into the lungs, we have a subtherapeutic level that's going to be floating throughout the blood and in the rest of the body for the rest of the year, and that's where resistance resides. That's where we train the bugs how to figure out how to kill our drugs and find their way around it, is at that subtherapeutic level.

So that really actually concerns me about the fact that we are actually delivering it in the difference between the technician that we're seeing for individuals that are healthy versus those that are ill.

DR. BADEN: Thank you. Dr. Baden. I voted no. Like others, this was a very close call and a

very challenging question. And I think that the sponsor's done a terrific job at trying to study a very complicated issue. The need for treatment here is self-evident and has been well articulated by many, including the open speakers.

The question here, as previously stated, is the evidence of substantial efficacy and safety and what are the data that support that level of proof. I think the population heterogeneity, the challenge of the endpoint has already been discussed.

The issue of resistance, I would argue resistance is best generated in the GI tract. That's where there are more bug cells than human cells.

The best way to generate resistance is some therapeutic antibiotic concentrations continuously. And if I were a betting man, my guess is there is a lot of that going on throughout the course of the year because of the mode of administration, and that the importance of safety is to really be able to understand what we are doing to the resist them. And that requires exquisite measurement, which is

not straight forward, but it requires exquisite measurement.

The implications of future treatment given that the quinolones are the oral class to treat Pseudomonas, which is a dominant organism in this setting, and the potential implications on oral treatment is not a trivial consideration, in my mind, for patients who need future treatment and may want to avoid intravenous therapy.

The durability of the effect, the emergence of resistance, and impact on efficacy, I think these are all issues that have previously been raised but resonate with me as well.

Dr. Okofutu [ph]?

DR. OFOTOKUN: Ofotokun.

DR. BADEN: Thank you.

DR. OFOTOKUN: I voted no as well, and like everybody else, it was a struggle. First, I want to thank the sponsor for doing a great job of providing the data in such a clear manner that it was easy to follow, and for addressing all the questions that we have, and also for all the

speakers.

This was a big struggle. What really drove my vote was the inconsistency in the body of evidence that was provided. The primary endpoint of time to exacerbation to me was a weak endpoint, and I think the frequency of event would have been a much better outcome to power this study after.

I was also very concerned about the issue of resistance, as everybody else has mentioned. Especially knowing the subtherapeutic level of drug systemically, I was worried about resistance not just in the lung but also in the GI tract, in the urinary tract, and in any other part of the body; for a drug that the quinolone, really, is heavily used in the treatment of multiple infection, different organisms at different sites within the body.

I think I see a number of issues to be addressed with the design of this type of study, and I think that going forward, like I said, the primary endpoint needs to be well designed, and acceptable effect sites need to be clearly

articulated prior to such study going forward. And I think detailed resistant profiling should be incorporated into the subsequent design. Thank you.

DR. BADEN: Thank you. Dr. Corbett?

DR. CORBETT: I also voted no, and consistent with I think everyone else, I voted no. I've done this for five years, and this was probably the most difficult vote I've had to make, for several reasons.

People have talked about efficacy, and I think it was just heterogeneity. It was really difficult to overcome. Also, I'm not convinced -- I think that's a word -- about the safety profile either. And that's what I was trying to get at, that with exposure systemically, I think we know there are some. Bayer has done a fantastic job.

First, thank you very much to both groups, FDA and Bayer, for undergoing this investigation. I think this drug could be effective, and likely is, and I'm very hopeful with that. But with the

data that we have right now, it's a little bit concerning.

To get back to the safety, I am concerned about systemic exposure in safety, obviously resistance of organisms. I was part of the panel in May 2016 that was mentioned earlier about the fluoroquinolone indications that we recommended to be removed, and I don't want to have to be in that situation again, and that was sort of unfortunate.

But I would recommend, moving forward, that there is a longer study, perhaps two-year study or longer if possible, obviously with an interim analysis and in some way providing a more active drug versus placebo to patients just so there can be more patients that are receiving active drug. And perhaps at some interval, which I think was mentioned already, that perhaps placebo patients could switch over to active drug would be very helpful.

Also, to try and perhaps focus on the RESPIRE 1 sites and population. To me, that study was a little bit easier to understand and to at

least support versus the RESPIRE 2 data and the sites. I'm not really sure why, but hopefully that would be the next step forward.

DR. BADEN: Dr. Clark?

DR. CLARK: Nina Clark. I voted no. Like others, I was not convinced there was substantial evidence of benefit of cipro and troubled by the inconsistency in the two studies, as well as what seemed to me to be a relatively small degree of benefit in those who did improve. And it was hard to predict which subgroups of patients might most benefit.

I was also concerned about resistance over time, especially if this is used more widely in off-label indications. And as far as endpoints, I would like to see a longer study with a focus on a number of events, the use of all systemic antibiotics, perhaps even healthcare utilization costs. I'm not sure if it's feasible, but perhaps eliminating those with baseline cipro resistance using careful methods to detect that, and also trying to make sure that all patients in the study

had maximized standard of care.

DR. BADEN: Dr. Harkins?

DR. HARKINS: I did share a lot of the concerns that the panel brings up, but I voted yes. And part of the reason I voted yes, while I am concerned about resistance, that does loom in my mind. I did feel that the 14-day trial, it probably would have been easier if both studies had the same results, and maybe we wouldn't be going back through this as much.

But I take care of these patients, and the more severe patients with bronchiectasis, I'm at a loss at times. I give them yet another course of oral or IV cipro, which I think honestly has a lot more problem than an inhaled, low-level dose that they may take on cycles.

I've used TOBI. I haven't used the other agents, but I've used TOBI in these patients. So I thought that this might be a novel opportunity to be able to use a dry-powder inhaler for patients with severe non-CF bronchiectasis to monitor in the future what happens to these patients.

I do like the idea of if this is not approved and things have to be looked at further, that the patient is their own control, where at some midpoint they would switch into either the active or the placebo arm.

DR. BADEN: Dr. Swenson?

DR. SWENSON: Well, I think, like most of us, we're either on one side of this 50 percent mark or the other. So I voted yes only because I think in totality there was a very, very strong suggestion of benefit. Certainly it's restricted to just a year's time in a disease that goes for quite some time.

I think that it will be extremely important then to follow on and continue monitoring these same patients. They are their controls a bit, so if over 2 to 3 to 5 years you see that their rate of exacerbation falls off significantly, that would be important information to know, and at the same time you'd be following for antibiotic resistance complications.

DR. BADEN: Thank you. Let me summarize the

comments, then we'll go to question 2. On comments from the yes camp, consistency of the combined data. Need better PRO data. Patients as their own controls can help in the future. Through approval, it would be easier to study, refine, and improve the use of this therapy. It's easier to study post-approval. The safety is clean. It's a desperate situation. We need options for this unmet need.

In the no camp, inconsistency of the data. Impact over time unclear. This is a lifelong illness. We need longer-term data. We don't know what the dry powder does on its own. The endpoint can be improved. A variety of suggestions were made for hospitalization, pulmonary function, FEV1, resistance, need for IV antibiotics.

A variety of parameters could be used as other markers of efficacy. Standardization of the macrolide therapy or standard of care to make sure that's equal. The population, heterogeneity, is there a better way to a more homogeneous or less heterogeneous population. Concerns about the

safety and systemic exposure. The risk of only oral class for pseudomonas treatment, and a relatively small benefit in those who have improved.

We can move now to question 2. Shall I read it? We've already read the question, so we can just go right to voting.

(Pause.)

DR. BADEN: We're missing one vote, so if everyone can just press their votes again to ensure everyone's counted.

(Voting.)

DR. TESH: For the record, we have 1 yes, 14 nos, zero abstentions, zero non-voting.

DR. BADEN: We will start with two panel members who have to leave sooner for plane issues. What I would say in comment here, if the comments are not different than the previous, they can be echoed from the previous and new amplifying comments can be made.

Dr Ofotokun, I think you go first because I think you have a plane, and then Dr. Swenson, and

we'll go around from the left.

DR. OFOTOKUN: This is Igho Ofotokun. It's kind of the same reason why I voted no for the firs question. The data for the second question was even less convincing, and I think all the suggestions about the first question still hold; the issue of endpoint, resistance, study design remains the same. Thank you.

DR. BADEN: Dr. Swenson?

DR. SWENSON: Well, I think the data were just a bit more favorable for the 14 and less so favorably on 28. I flipped sides on that just simply because I'm almost straddling the middle anyway.

DR. HARKINS: I voted no for the same reason. I thought 14 had a better signal.

DR. BADEN: Dr. Clark?

DR. CLARK: Nina Clark. I voted no for similar reasons as I stated previously.

DR. BADEN: Dr. Corbett?

DR. CORBETT: I voted no, also same reasons as last time. I just would emphasize that I do

support studying the 14-day on/off cycle in the future and perhaps not as much the 28-day.

DR. BADEN: I voted no. I think that the issue of the same total dose over the year to me suggests that the results from the 14- or the 28-day being inconsistent requires more explanation. A hint of the explanation was provided from the phase 2 study with a single dose showing the drop in the log, but those data needed to be more fully explained to understand the differences.

But the argument is that it's the same total dose over a year. Therefore, the consistency of the result should be through all four arms, and it came through as we all know. Dr. Baden, chair.

Dr. Weina?

COL WEINA: Pete Weina. I voted no pretty much all for the same reasons. I really don't hold -- at least in my mind -- that the 28-day shouldn't be studied. I think there's an interesting phenomenon there with the 28-day versus the 14-day that really needs to be teased out and not just abandon the longer arm.

DR. BADEN: DR. Green?

DR. M. GREEN: Michael Green. I voted no. My reasons are essentially the same as what I said for the 14-day. However, I also am not certain whether the 28-day should be abandoned or not.

DR. GRIPSHOVER: Hi. I voted no for the same reasons as the first time, and I agree I'm not sure that 14 and 28 are that different either.

DR. HAWKINS: I voted no. Hawkins. I was able to convince myself about the 14-day but not so with the 28 with the results.

DR. BADEN: Mr. Zimmerman?

MR. ZIMMERMAN: Jasan Zimmerman. I voted no. My comments for the 14-day regimen stand. I did fail to thank the FDA and the committee for having me here, and I also wanted to thank the sponsor. Please don't give up. You heard from the community how important this is, and based on my experience as well with bronchiectasis, this is a hugely important issue, so please don't give up.

DR. BADEN: Dr. Carvalho?

DR. CARVALHO: Paula Carvalho. I voted no

on this one again because the signal was less strong than the signal for the 14-day course. It would have been helpful to me to have had the questions asked in a way with the efficacy and then safety separately. Although I had less concern about the physical safety with these agents, I do share the committee's concern about emerging resistance, and that should be followed.

DR. BADEN: Dr. Ellenberg?

DR. ELLENBERG: I voted no for the easy reason that with the 28-day, it didn't meet the prespecified efficacy criterion in either study, although it was certainly suggested in both of them. I don't think the 14- and 28-day regimens are very different. I was intrigued by the fact that it was the 28-day regimen that showed the strongest benefit to reduction of the frequency of exacerbations, which to me is a more compelling endpoint than the time to exacerbations.

So if a further study is done, I would hope it be a longer study that would use frequency of exacerbations. And I would note that if we're

going to do a crossover type study with patient as their own control, if exacerbations is going to be the endpoint, then it's going to have to be done in a population at a much higher risk of exacerbations than we had here; otherwise, you're not going to see much when you cross over.

DR. BADEN: Dr. Green?

DR. J. GREEN: Jonathan Greed. I voted no, in large part for the same reasons as for the 14-day regimen, and in this case, both studies showed a negative result.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: I didn't know I'd be the soft one here on this. My first vote was very weak yes. This is a very, very weak yes. Again, I guess I was focusing on the combined results both looking strong and consistent with each other on the combined results. So I barely decided to vote yes.

Also, just in terms of the crossover design that I've been hearing about, I'm not sure that that's going to address the long-term follow-up that people are also interested in, so that's

something also to consider.

DR. BADEN: Thank you. In summary, the comments are largely similar to question 1. Some of the additional comments have to do with the consistency of the total dose or inconsistency of the data in relation to that; the don't abandon the 28-day; the 28-day data were less impressive than the 14 data. And for the yes, it was the combined result of the combined result. And therefore, that's the totality.

So that concludes the voting and discussion session. Before we adjourn, are there any last comments from the FDA?

Adjournment

DR. NAMBIAR: Thank you, Dr. Baden. We just wanted to express our sincere thanks to the committee for helping us think through this difficult application. Thanks to the sponsor for working with us over the years and developing this drug. We do appreciate your presentations and discussions today.

I also wanted to extend our thanks to the

speakers at the open public hearing for sharing their experiences and thoughts. That is very sincerely appreciated.

Safe travels, and we will take all the feedback we've received and work on it in the next few weeks. Thanks.

(Whereupon, at 4:05 p.m., the meeting was adjourned.)