FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Thursday, January 11, 2018

8:30 a.m. to 4:14 p.m.

College Park Marriott Hotel and Conference Center

General Vessey Ballroom

3501 University Boulevard East

Hyattsville, 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

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Theresa Eisenman.

Are you here? She's in the back, left corner.

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

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

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

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

DR. BADEN: I'm not hearing well over here.

DR. SMITH: Sorry. Okay. Tom Smith, clinical team leader in the Division of Anti-Infective Products, CDER FDA.

DR. ALLENDE: Good morning. I'm Maria Allende, medical officer in the Division of Anti-Infective Products, CDER FDA.

CDR TRACY: Hello, I'm LaRee Tracy. I'm the statistical reviewer in the Office of Biostatistics, CDER FDA.

DR. HARKINS: Michelle Harkins, University of New Mexico, adult pulmonary and critical care.

DR. SCHAENMAN: Joanna Schaenman, infectious diseases, UCLA, David Geffen School of Medicine.

DR. DASKALAKIS: Demetre Daskalakis, infectious diseases, New York City Department of Health and Mental Hygiene.

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DR. M. GREEN: Michael Green, pediatric infectious disease, Children's Hospital, Pittsburg, University of Pittsburg.

DR. GRIPSHOVER: Barb Gripshover, adult infectious disease at Case Western Reserve University in Cleveland.

DR. FOLLMANN: I'm Dean Follmann, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

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

DR. HAWKINS: Randy Hawkins, private practice, internal medicine, pulmonary medicine,

Inglewood, California.

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

DR. CARVALHO: Good morning. I'm Paula Carvalho, University of Washington, adult pulmonary and critical care medicine.

DR. J. GREEN: Jonathan Green, adult pulmonary and critical care medicine at Washington University School of Medicine in St. Louis.

DR. HILTON: Joan Hilton, professor of biostatistics, University of California, San Francisco.

MR. KARTSONIS: Nick Kartsonis, vice-president clinical research of infectious diseases at Merck Research Labs.

DR. BADEN: I will ask that if we all can only have our mic on when we're talking; otherwise, I think there is feedback and it interferes. Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, a gentle reminder, individuals will be allowed to speak into the record only of recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that 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 discussion of 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.

I'll pass it to Dr. Lauren Tesh who will read the conflict of interest statement.

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 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 this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the 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 210693 ciprofloxacin dispersion for inhalation sponsored by Aradigm Corporation for the proposed indication of treatment of non-cystic fibrosis bronchiectasis patients with chronic lung infections with Pseudomonas aeruginosa.

Based on the today's agenda, all financial interest reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this session.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product 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 & Company.

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

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

DR. BADEN: We will now proceed with the FDA's introductory remarks. Dr. Smith?

FDA Opening Remarks - Thomas Smith

DR. SMITH: Good morning. I'd like to welcome the committee members and Aradigm to this advisory committee meeting.

By way of introduction, we'll be discussing ciprofloxacin dispersion for inhalation this

morning. We refer to this as cipro DI in our briefing document, although it's more properly referred to as ciprofloxacin dispersion for inhalation or ciprofloxacin DI, which is how we will be referring to it during our presentations today. The applicant uses the proposed name, Linhaliq.

Just so you know, we were notified on Monday of a few minor discrepancies between information that was in the applicant's briefing document and ours. We've made the necessary corrections where needed in the slides that you'll be seeing today, and our presenters will point these out during their talks.

As I mentioned, this product is ciprofloxacin dispersion for inhalation. The proposed indication is the treatment of non-cystic fibrosis bronchiectasis patients with chronic lung infections with Pseudomonas aeruginosa.

The proposed dosage form and strength are vials that contain ciprofloxacin liposome inhalation suspension and ciprofloxacin inhalation

solution. These are co-packaged for oral inhalation use with a nebulizer. The proposed dosing regimen is 189 milligrams once daily in 28-day on/off cycles.

The development program for this product contained one phase 2 trials and two phase 3 trials in patients with non-CF bronchiectasis. There were reasons that we wanted to have two phase 3 trials to support this indication, and those are listed here.

There currently are no approved therapies for the prevention or management of non-CF bronchiectasis exacerbations. Studies of other inhaled antibacterial drugs, including tobramycin, gentamicin, astreonam, colistin, and ciprofloxacin for the prevention of non-CF bronchiectasis exacerbations have yielded mixed results, and these publications are referred to in our briefing document.

There are uncertainties regarding the duration of treatment, the frequency of administration, and the appropriate endpoints for

this use with a lack of prior successful trials. There are no relevant animal models to explore dosing regimens, the duration of therapy, or to provide other supportive information.

This is a new indication and route of administration for ciprofloxacin, and we believe that two independent trials would provide replicative evidence of efficacy. And finally, there's a need for an adequate safety assessment.

The phase 2 trial, ORBIT-2, was a randomized, double-blind, multicenter trial comparing treatment with ciprofloxacin DI once daily versus placebo in 42 patients for three 28-day on/off cycles.

The primary efficacy variable was a change in sputum Pseudomonas aeruginosa load measured as a log colony forming units per gram from baseline to day 28. The results of this study showed that there was a mean log reduction, at day 28, of 4 logs for the ciprofloxacin product and no change for placebo.

Phase 3 trials were ORBIT-3 and ORBIT-4.

These were randomized, double-blind, placebo-controlled trials in patients with non-CF bronchiectasis, who had a history of two or more pulmonary exacerbations that were treated with antibacterials in the preceding 12 months and who had positive sputum or deep throat cultures for Pseudomonas aeruginosa.

Patients were randomized in a 2 to 1 ratio to receive either ciprofloxacin DI, 189 milligrams once daily, or placebo which was control liposomes in saline in 28-day on/off cycles. There was a 48-week double-blind period, so there were six 28-day on/off cycles with a 28-day open label extension. Patients were stratified by sex, number of exacerbations prior to screening, and current smoking status.

The primary endpoint in these studies was time to first exacerbation by week 48, where exacerbation was defined as a change in 4 or more of 9 signs and symptoms of a pulmonary exacerbation, and these had to occur concurrently.

The first secondary endpoint was the

frequency of exacerbation by week 48, and there were additional secondary endpoints, which included frequency of severe exacerbations, which were defined as dose requiring either IV, antibacterials, or hospitalization; and a change from baseline to week 48 in the quality of life bronchiectasis respiratory symptom scale.

You should note that there was a pulmonary exacerbation adjudication committee that was available to review cases of discrepancies between protocol-defined criteria for an exacerbation and an investigators' report.

The statistical analysis was a hierarchical stepdown approach in each trial, and these were done separately. If the primary endpoint of time to first exacerbation at week 48 was statistically significant at a two-sided 0.05 alpha level, then the frequency of exacerbations was tested at a 0.05 two-sided alpha level.

If this was significant, then there was another stepdown procedure that was used to test the frequency of severe pulmonary exacerbations in

the Qol-B respiratory symptoms scale secondary endpoints.

After the trials were done, there was an unplanned data re-review after database lock for both trials and after the data were unblinded and analyzed. The reasons for this re-review are unclear. The applicant identified programming errors that affected the primary outcome status of 4 patients, 2 in each trial.

They performed a comprehensive audit of all electronic case report form entry for signs, symptoms, or laboratory abnormalities as entered into the pulmonary exacerbation worksheets for all patients, and this led to a blinded re-adjudication of 10 pulmonary exacerbations -- there's 7 in ORBIT-3 and 3 in ORBIT-4 -- that had previously been reviewed by the adjudication committee. These changes affected the total number of primary endpoint events.

These are the results based on after the data re-review. If you look at ORBIT-3, there were 59 percent of the patients in the ciprofloxacin arm

who experienced at least 1 pulmonary exacerbation versus 57 percent of patients in the placebo arm. The median time to first pulmonary exacerbation had a hazard ratio of 0.99, which gave a p-value of 0.974, suggesting there is no difference between treatment arms.

The results of ORBIT-4 were somewhat different. There were 55 percent of patients versus 65 percent of patients in the ciprofloxacin and placebo arms, respectively, who experienced exacerbations, so there was about a 10-percent difference. The hazard ratio for the median time to first pulmonary exacerbation was 0.71, which did result in a statistically significant p-value.

I mentioned about the reassessment of outcomes. These programming errors and the re-adjudication of exacerbations resulted in a change in the primary outcome for 2 patients in ORBIT-3, both in the ciprofloxacin arm, and 2 patients in ORBIT-4, both in the placebo arm.

For ORBIT-3, the addition of 2 patients raised the p-value from what was in the original

data, 0.826, to the 0.974. In ORBIT-4, the addition of 2 patients to the placebo arm resulted in a change in the p-value from 0.058 to 0.032.

This is the frequency of exacerbations which was a secondary endpoint. Since ORBIT-3 failed in the primary endpoint analysis, these additional analyses are considered exploratory. What you see here is that the mean number of pulmonary exacerbations was 1.1 roughly in the ciprofloxacin arm versus 1.3 in the placebo arm.

The p-value for the incidence rate ratio is listed there. Findings for the frequency of severe pulmonary exacerbations were similar with a mean number of exacerbations of 0.22 in the ciprofloxacin arm and 0.28 in the placebo arm.

Results in ORBIT-4 were different. There was a difference of approximately 0.5 in the mean frequency of pulmonary exacerbations between the study arms. This resulted in a statistically significant finding for the frequency of exacerbations and a similar finding for the frequency of the severe pulmonary exacerbations.

In summary, I mentioned there was an unplanned re-review after data-locking and unblinding that led to changes in the primary outcome. ORBIT-3 failed to demonstrate a difference between arms across all endpoints and analyses. There were slightly more patients in the ciprofloxacin DI arm who experienced a pulmonary exacerbation compared to placebo.

ORBIT-4 had a marginal effect on reducing the time to first pulmonary exacerbation based on the re-review and re-adjudicated data. There was a significant reduction in the frequency of pulmonary exacerbations and of severe pulmonary exacerbations which favored ciprofloxacin DI. There was no demonstrated treatment effect on the Qol-B respiratory symptom scale, pulmonary function, or duration of exacerbations with ciprofloxacin DI.

We lack a clear explanation for the discordant findings between these trials and have no information about the durability of these efficacy findings over time.

Safety assessment included 583 patients in

the pooled phase 3 safety population. There were 389 patients who received at least one dose of ciprofloxacin DI, and 193 patients who received at least one dose of placebo liposomes in saline.

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 local effects of the drug product. These would include things like dyspnea, bronchospasm, hemoptysis, cough, and taste disorders.

Patients who were treated with ciprofloxacin DI were more likely to have treatment-emergent ciprofloxacin-resistant Pseudomonas aeruginosa cultured at any point post baseline.

It is unknown whether exposure beyond one year may lead to additional safety concerns, further increase in resistance to fluoroquinolones, or to a reduced treatment effect.

The outline for today, I'll be followed by

presentations by the applicant. There will then be presentations by the FDA. LaRee Tracy will present the efficacy data, Maria Allende will present the safety data, and then I'll be back with a brief summary.

This will be followed by lunch, open public hearing, and then the question for the committee, which as you listen to the presentations, we ask you to keep in mind: Has the applicant provided substantial evidence for the safety and efficacy of ciprofloxacin dispersion for inhalation in delaying the time to first exacerbation, after starting treatment, in non-CF bronchiectasis patients with chronic lung infections with Pseudomonas aeruginosa?

If yes, we ask that you please provide any recommendations concerning labeling. And if no, comment on what additional studies and analyses would be needed, including a discussion of appropriate endpoints, drug regimens, and trial duration. Thank you.

DR. BADEN: Thank you, Dr. Smith.

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 relationships that they may have with applicant, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon 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 the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Aradigm's

presentations. Dr. Gonda?

Applicant Presentation – Juergen Froehlich

DR. FROEHLICH: Good morning. Dr. Baden and committee, my name is Juergen Froehlich, and I'm the chief medical officer at Aradigm. Before we begin, all of us at Aradigm would like to thank the hundreds of patients, investigators, and staff who participated in our clinical trials. We'd also like to thank our colleagues at the FDA for their close collaboration. We are deeply grateful for all of you.

Here is the proposed indication for Linhaliq that we will be discussing today. We will present data we believe support the approval of our proposed indication in bronchiectasis patients who suffer from frequent pulmonary exacerbations.

We will make four key points. First, the bronchiectasis with pseudomonas is a chronic, debilitating condition with no known cure.

Second, while not a cure, Linhaliq offers for the first time a well-tolerated inhaled antibacterial that can reduce exacerbations, making

patients' lives more tolerable.

Third, our evidence comes from one phase 2 trial and two phase 3 trials, ORBITs 3 and 4. And while ORBIT-4 is clearly positive, ORBIT-3 did not meet its primary endpoint. Having said that, you will see that the majority of exacerbation endpoints in ORBIT-3 do trend in the positive direction.

You will hear that the frequency of exacerbations is recognized as the most clinically meaningful outcome, and PE analysis we have conducted explained most of the difference between the trials.

Finally, and importantly, we saw that increased in MICs do not result in loss of efficacy, emergence of super organisms, or difficult-to-treat infections. In particular, systemic use of fluoroquinolones remains an effective therapy for these patients.

Bronchiectasis represents an urgent unmet medical need. It is a severe rare disease with increasing prevalence, marked by irreversible

damage of the bronchi, airway inflammation, and recurrent respiratory infections.

When bronchiectasis patients are chronically infected with pseudomonas, their condition takes a turn for the worse, and they face much higher rates of morbidity and mortality.

With frequent exacerbations, these patients suffer from strong predictors not only of future exacerbations but also of increased hospitalizations and diminished quality of life. To-date, there is no approved treatment to prevent or reduce the number of exacerbations in these patients.

As a result, healthcare providers must turn to off-label use of antibacterials drugs with efficacies unproven and whose safety and tolerability is poor.

Linhaliq is a fluoroquinolone antibacterial drug with high activity against pseudomonas. It consists of a unique mixture of liposome encapsulated aqueous dispersion, or CFI, and an unencapsulated aqueous solution of free

ciprofloxacin or FCI. This combines the slow release of ciprofloxacin from the liposomal component with the benefits of an instant peak of free ciprofloxacin.

Because tolerability is important, we designed small liposomes, similar to lung surfactant, to deliver the ciprofloxacin. The delivery of liposomal ciprofloxacin is not limited by drug solubility, which results in higher-peak concentrations than its dry powder.

Linhaliq is delivered using a commercially-available jet nebulizer and compressor. The recommended dose of Linhaliq is 6 milliliters delivered through one vial each of 3 mL CFI and FCI. Because inhaling Linhaliq results in high sustained sputum concentrations of ciprofloxacin, only once daily administration is required. Systemic exposure is low. The dosing regimen is repeated cycles of 28-days on treatment, followed by 28-days off treatment for chronic use.

As you can see here, Linhaliq has received several prominent regulatory designations. These

reflect the FDA's recognition of this urgent unmet medical need.

The clinical development of Linhaliq began with phase 1 and phase 2A clinical trials with liposome encapsulated ciprofloxacin and Linhaliq prototype in both healthy volunteers and bronchiectasis patients. We then conducted our phase 2B trial, 0902, or ORBIT-2, and our phase 3 trials, ORBITs 3 and 4, in bronchiectasis patients with chronic lung infections with pseudomonas.

We recognize that the data before you today is challenging; so is the disease. Bronchiectasis with pseudomonas is a complex condition, and our understanding of it has been evolving. For example, while time to first exacerbation has been used traditionally as a primary endpoint, the patients in our trials experienced frequent exacerbations known to result in irreversible morbidity, and clinicians are now finding that reduction in the frequency of exacerbations, especially those requiring interventions with antibacterials, to be the most meaningful endpoint.

Therefore, we ask you to evaluate the totality of evidence as you consider the following overarching questions: Are the data in front of you adequate to support the safety and efficacy of Linhaliq in the proposed indication?

As you weigh the evidence before you today, please consider the following: Linhaliq reaches concentrations that are very high in sputum but low in plasma and consistently reduces pseudomonas load in all clinical trials.

ORBIT-4 met the prespecified primary and secondary exacerbation endpoints at levels that were robust, clinically meaningful and statistically significant. Studies ORBIT-3 and ORBIT-2 further support these positive outcomes. Linhaliq has been well-tolerated, without short or long term local and systemic side effects, unlike many off-label antibacterial therapies.

Finally, we believe the totality of evidence demonstrates a favorable benefit-risk profile of Linhaliq and for bronchiectasis patients who currently have no appropriate treatment options.

Dr. Gregory Tino will first discuss the unmet medical need and disease background. Dr. Igor Gonda will then present our efficacy data. Dr. Janet Wittes will provide the statistical perspective. I will return to present the safety data. And finally, Dr. Sanjay Sethi and Professor James Chalmers will provide the clinical perspective on the development of microbiological resistance and the overall benefit-risk of Linhaliq. We also have a number of additional expert advisors available to take your questions.

Dr. Tino?

Applicant Presentation – Gregory Tino

DR. TINO: Thank you, Dr. Froehlich.

Good morning. My name is Dr. Greg Tino. I'm a pulmonary and critical care physician at the University of Pennsylvania, and I'm also a principal investigator of the U.S. Bronchiectasis Research Registry and have more than 15 years of experience in the care of bronchiectasis patients.

I'm also a paid consultant to Aradigm in preparation for this meeting but have no direct

financial interest in the outcome of the meeting today.

It's a privilege for me to be here. My goal is to give you an overview of bronchiectasis as a clinical entity, with a specific focus on the urgent unmet medical needs and challenges faced by our patients.

I think it's always helpful to start with a definition of what bronchiectasis actually is. At its most basic level, bronchiectasis is a pathologic entity characterized by airway inflammation and permanent bronchial dilatation. The results in a clinical syndrome characterized by productive cough and recurrent respiratory tract infections.

The differential diagnosis of specific causes of bronchiectasis is quite extensive. An important goal of the clinician, once a diagnosis of bronchiectasis is made, is to try to identify specific etiologies which can impact therapy in a small number of patients. Some of these etiologies are listed here. In a fair number of cases,

despite an extensive workup, no specific cause is identified, and we term this, idiopathic bronchiectasis.

The pathogenesis of bronchiectasis is quite complex. What I've illustrated here is a simple conceptual framework that was proposed by Dr. Peter Cole in the mid-1980s. It's called the vicious cycle or vicious circle hypothesis.

I find this hypothesis useful when I think about the sequence of steps and the important pathologic changes that happen in this disease. The cycle starts with an inciting event, typically an infection, which causes neutrophilic inflammation and activation of a number of proteases, which in genetically-susceptible patients results in bronchiectasis; that is airway distortion and destruction.

Because of these pathologic changes, as well as a ciliary dysfunction that also goes along with them, mucus clearance is impaired, and this sets up a scenario of chronic bacterial infection which, in turn, further propagates inflammation. Of note,

these changes occur regardless of the underlying bronchiectasis etiology.

The clinical course of bronchiectasis is also punctuated by acute respiratory infections or pulmonary exacerbations that can also further contribute to this vicious cycle disease pathogenesis. The most important concept to remember here are inflammation and recurrent infection that dominate the pathogenesis of bronchiectasis.

Now, this is what bronchiectasis looks like from a gross pathologic perspective. Here, you see massive bronchial dilatation with this horrible-looking, hemorrhagic material within the airway, a massively dilated airway with mucoid impaction, and far advanced bronchiectasis.

This is an image from a high-resolution CT scan of the chest, which is the gold standard imaging technique for bronchiectasis, which illustrates some of the important findings, including bronchial dilatation and bronchial wall thickening. You can also see that the CT scan

images nicely mimic what one sees on gross pathology.

The exact prevalence of bronchiectasis in the United States remains elusive, but it's been estimated that there are more than 110,000 patients with bronchiectasis in this country. Just to put that in a perspective, there are about 33,000 patients in the U.S. to have cystic fibrosis.

The prevalence clearly increased with age, and more recent studies have shown that the rate of bronchiectasis has been increasing by about 9 percent annually in the United States, and this has been reported in Europe as well.

As I mentioned earlier, one of the clinical hallmarks of bronchiectasis is recurrent respiratory infection. The microbiology of these infections and the microbiology of bronchiectasis in general are quite complex.

One of the important themes here is that Pseudomonas aeruginosa is among the most common pathogens. In fact, one-third of our patients develop chronic pulmonary infection with

Pseudomonas aeruginosa. An infection with this particular pathogen really poses vexing clinical challenges and is associated with significant morbidity and mortality.

This slide illustrates some of these pointes. Chronic pseudomonas infection and bronchiectasis, regardless of underlying etiology, results in more hospitalizations and higher mortality rates than other pathogens.

This data is from a study by Dr. Chalmers, who looked at a large cohort of patients over a period of four years. You can see on the left side of the slide that in patients who have chronic pseudomonas infection, in contradistinction to other pathogens listed, that the rate of hospitalization is significantly higher. When compared to those who don't have a dominant pathogen, the risk of hospitalization is 7-fold higher.

On the right side, you'll see the impact of chronic pseudomonas infection on mortality. Mortality over a four-year period of time is 3-fold

higher in patients with pseudomonas as compared to other pathogens and those without a dominant pathogen identified.

Bronchiectasis in general and bronchiectasis associated with chronic pseudomonas infection also results in poor quality of life for our patients. This slide uses the St. George's respiratory questionnaire, which is a quality of life assessment tool that's been widely applied in a number of lung diseases. I would remind you that as you can see on the vertical axis, a higher score indicates worse quality of life.

If you compare bronchiectasis, regardless of underlying etiology to other more common severe airways diseases like COPD and asthma, as well as cystic fibrosis, and idiopathic pulmonary fibrosis, you'll see that the impairment of quality of life is akin to and as severe as what has been reported with these other conditions.

If you look more specifically at patients with bronchiectasis and chronic pseudomonas infections, as shown here in yellow, you'll see

that the quality of life is even worse than from bronchiectasis alone or the other conditions included.

In short, pseudomonas is a common pathogen, it's a bad pathogen, and it truly portends significant morbidity and mortality for our patients.

I'd like to return to the theme of recurrent respiratory tract infections that characterize the clinical course of bronchiectasis. Again, we call these pulmonary exacerbations. The definition of a pulmonary exacerbation continues to evolve, but this slide indicates some of the common symptoms, both respiratory and systematic, that occur with these episodes.

Exacerbations are characterized primarily by increased cough and importantly by changes in sputum characteristics. In addition, patients note increased dyspnea and chest congestion.

One of the things that I'd been impressed with is the degree of systemic symptoms that these folks have, including malaise, which patients

complain about bitterly, fatigue and lethargy, and decreased exercise tolerance. These are oftentimes accompanied by increased wheezing as well, and in general, people feel awful during these episodes.

Pulmonary exacerbations adversely affect quality of life and result in irreversible morbidity and mortality. That's why we, as clinicians, focus on these exacerbations, both on their prevention and in the reduction of their frequency.

The mean duration of exacerbations is about 16 days. Importantly, symptoms can persist for several weeks. In fact, in one study, 16 percent had not returned even a month after the onset of the symptoms -- had not recovered, I'm sorry. Frankly, many patients do not ever return to their previous baseline.

Another critical point is that patients who have a history of exacerbations are clearly more likely to have future events as well, and you'll hear more about this later. Preventing and reducing exacerbations that require interventions

with antibacterial agents or hospitalization are the highest priority for clinicians, and certainly for our patients.

How do we reduce pulmonary exacerbations? The relationship between bacterial load expressed by colony forming units and pulmonary exacerbations is outlined on this slide.

In this study, higher bacterial load was associated with increased risk of exacerbations, hospitalizations, and markers of inflammation. Long term inhaled antibacterial therapy was associated with reduction of bacterial load and markers of inflammation and therefore can positively impact pulmonary exacerbations.

Now, clinicians and patients certainly have other goals of treatment, but these have really been difficult to assess subjectively in clinical trials. In general, FEV1 does not improve with antibiotic therapy in non-CF bronchiectasis. Our aim, therefore, is to stabilize lung function. With regard to quality of life, there is no fully validated assessment tool, but reducing point of

exacerbations would be expected to have major impact.

Finally, reduction in mortality would obviously be quite desirable, but impact of therapy has not been formally studied as it would require a very large long-term clinical trial.

Now, we often refer in discussion about treatment options by referring to unmet clinical needs. When you talk about bronchiectasis, the question is: What do we have to offer these patients? What are, what I call, the met needs?

Well, I've listed those met needs on this slide, and there are none. This really underscores the dilemma that our patients face when diagnosed with this condition and that we face when caring for them.

I'd like to briefly present a patient that I've been taking care of for many years and whom I think illustrates a common clinical course and the challenges that patients like him face.

He's a 77-year-old man who was diagnosed with bronchiectasis after having pneumonia. You

can see his CT scan in the lower panels with extensive, very extensive bronchiectasis involved in the entire left lung, as well as bronchiectasis in the right middle lobe.

He did well in repeated years and has managed for many years with rotating oral antibiotics and chest physiotherapy. He later developed chronic pseudomonas infection, and that really changed his life.

His daily sputum production is now 40 mLs of sputum. Importantly, he typically has 2 to 3 acute exacerbations per year, sometimes requiring hospitalization and oftentimes requiring intravenous antibiotics. His treatment options are quite limited, including the fact that he is intolerant of macrolides. We are in desperate need of safe, efficacious therapies for individuals like him.

As I mentioned before, there are no approved treatments for bronchiectasis patients, including for preventing or reducing the frequency of exacerbations. What we've learned over time is

that there is extensive but variable off-label use of antibacterial agents in the United States.

The data presented here is from the first paper of the United States Bronchiectasis Research Registry, reporting our experience in the first 1800 patients enrolled. You can see that antibiotics in this cohort were used for exacerbations only in about 41 percent patients. Suppressive antibacterials were quite often in about 39 percent of patients. Fourteen percent of macrolides, 10 percent were on inhaled antibiotics, and 7 percent were on a rotating systemic antibiotic regimen.

Now, importantly, unlikely in cystic fibrosis where inhaled antibiotics have long been the standard of care and associated with improving in symptoms, reduction of pulmonary exacerbations may lead to lung function and reduced morality, inhaled antibiotics in non-CF-related bronchiectasis are commonly used without evidence of efficacy and are often poorly tolerated.

This slide illustrates the poor tolerability

of inhaled antibiotics studied at clinical trials for bronchiectasis, specifically in patients who have chronic pseudomonas infection. You'll see that there have been several trials using aminoglycosides, both tobramycin and gentamicin, and two large trials of inhaled aztreonam.

Respiratory adverse effects are very common. In fact, they were reported in all clinical trials, except for a very small clinical trial with tobramycin. Bronchospasm when looked for is also commonly reported.

What you can also see here is that there's a high rate of drug withdrawal when using these inhaled antibiotics relative to placebo. Unfortunately, the efficacy of inhaled antibiotics in bronchiectasis has also not been proven, except in a 2001 study of inhaled gentamicin, which is a small single-blinded study of 27 patients.

One of the reasons why efficacy has not been established in bronchiectasis is that tolerability issues have precluded longer-term trials. Again, unlike cystic fibrosis, inhaled antibiotics haven't

been proven to work and poor tolerability dominates the story.

In summary, I'll like to leave you with several points. I hope that I've convinced you that bronchiectasis is a disease with increasing prevalence that results in significant morbidity and mortality.

Secondly, that Pseudomonas aeruginosa is a particularly challenging pathogen associated with poor quality of life, high rates of hospitalization, and higher morality; that the prevention and reduction of exacerbations are absolutely key goals.

Please remember that all current therapies are off-label and have safety and efficacy concerns, so that a safe and tolerable inhaled antibiotic that prevents and reduces exacerbation is a critical and unmet need. I thank you for your attention. I'll turn things over to Dr. Igor Gonda, CEO of Aradigm who will discuss efficacy.

Applicant Presentation – Igor Gonda

DR. GONDA: Thank you, Dr. Tino. Good

morning. I'm Igor Gonda, the CEO and former chief scientific officer of Aradigm. I've been involved in the development of Linhaliq over the last 11 years.

As Dr. Tino mentioned, the challenge in bronchiectasis has been combining efficacy with respiratory safety and tolerability of inhaled antibacterials. To overcome that challenge, we encapsulated a potent anti-pseudomonas antibacterial, ciprofloxacin, in material similar to what is found in the human lung to minimize both airway irritation and the potential for long-term toxicity.

I'll begin with our dosing regimen and rationale. As you have heard, the dose is 6 milliliters, 3 of the liposomal component and 3 of the aqueous solution. The long half-life of this formulation makes it possible for once daily dosing that promotes good adherence. Finally, we follow the same 28-days on, 28-days off-treatment paradigm that has been used successfully for decades with other inhaled antibiotics in cystic

fibrosis.

With oral or intravenous ciprofloxacin, the maximum plasma and sputum levels are about 4 micrograms per milliliter. Pseudomonas aeruginosa with MICs higher than 4 micrograms per milliliter are therefore deemed to be resistant to all our intravenous ciprofloxacin.

Let me now show you the pharmacokinetics following inhalation of Linhaliq. This graph depicts a single-dosing interval at steady state achieved after about 4 days of dosing. The solid blue line shows the very high sputum concentrations of ciprofloxacin with Linhaliq.

As you can see, these are sustained throughout the whole 24-hour dosing interval, still over 1700 times higher than the maximum concentrations in sputum for all ciprofloxacin at the end of 24 hours.

The situation is reversed when it comes to plasma concentrations. The solid orange line shows far low plasma concentration of ciprofloxacin resulting from Linhaliq compared to all

ciprofloxacin. The sputum concentration of ciprofloxacin from Linhaliq are over 10,000 times higher than the plasma concentrations.

This pharmacokinetic profile was measured during the open label extension at the end of one of the phase 3 trials. It helps explain the efficacy and the systemic safety that we see for Linhaliq in the phase 2 and phase 3 studies.

Our most detailed microbiology results also come from the phase 3 studies. This figure shows the change in the density of pseudomonas in the sputum of patients on placebo, the gray lines, and of the Linhaliq patients, the blues line in the ORBIT-3 and ORBIT-4 clinical trials.

These reductions demonstrate Linhaliq's anti-pseudomonas effect throughout the 48 weeks during every on-treatment period. Based on this, we expect that the dosage regimen of Linhaliq, it will retain this characteristics beyond the 48 weeks.

Let me now turn to our phase 2 and phase 3 clinical trials. I'll be referring to them as

ORBIT-2, 3, and 4. The evidence of efficacy, as well as the safety database, comes from these three randomized, placebo-controlled, double-blind studies. They included over 600 patients.

In each study, we focused on patients recurrently infected with pseudomonas with at least 2 pulmonary exacerbations in the prior year, requiring interventions with antibiotics. These are the most severe bronchiectasis with the highest risk of increasing morbidity and mortality.

ORBIT-2 was a six-month study whose primary endpoint was the reduction of sputum density of pseudomonas at 28 days. The study met its primary endpoint with a mean change in sputum pseudomonas of minus 4.2, again, it's for Linhaliq, versus minus 0.8, again, it's for placebo, with a p-value of 0.002.

Knowing that reduction of exacerbation was the most meaningful outcome for these patients, we included the time to first exacerbation as a prespecified secondary endpoint. There result was a hazard ratio of 0.53 in favor of Linhaliq.

We found this compelling as an indicator of Linhaliq's ability to prolong the time to subsequent pulmonary exacerbations and therefore reduce the number of exacerbations in a chronic setting of this disease.

We observe very good respiratory tolerability and safety in this study, and together with the efficacy results, this prompted us to design the phase 3 studies based on this trial.

Let me now turn to this phase 3 results. The inclusion criteria for these studies were essentially the same as for ORBIT-2. Patients needed to have two or more exacerbations treated with antibiotics in the prior year, including infections with pseudomonas.

Nor did we enroll patients with resistance isolates of pseudomonas in the sputum during the screening as long as they had at least one non-resistant isolate. The key exclusion criteria were patients with diagnoses of cystic fibrosis, COPD related to smoking, and non-TB mycobacterial infections that required active treatment.

We also excluded patients who took anti-pseudomonas therapy, received 28 days prior to the first dose of the study drug. We didn't allow patients who are on stable chronic macrolide therapy.

As Dr. Tino discussed, the primarily goal of bronchiectasis therapy is to prevent and reduce exacerbations. This is reflected in the primary endpoint, as well as the most important secondary endpoints, the reduction of the number of all exacerbations, as well as the number of severe exacerbations.

The European Agency, EMEA, further prespecified the reduction of those exacerbations that require interventions with antibiotics. In our trial, all moderate and severe exacerbations were treated with antibiotics.

We made sure that exacerbations were rigorously defined. We used the older definition, which had been used in the largest previous clinical trial for this patient population.

A patient was considered to be experiencing

an exacerbation with a minimum of 4 of non-concurrent signs or symptoms were present. In our phase 3 studies, the symptoms you see in blue were observed in more than 85 percent of the exacerbations: sputum changes, dyspnea, cough, and general signs of fatigue.

Severity of exacerbations was also strictly defined based on the nature of the intervention. The mild exacerbations were those that did not require treatment with antibacterials. The moderate exacerbations require treatment with oral or inhaled antibacterials or increased doses of macrolides. Finally, the severe exacerbations required intravenous antibacterials or hospitalization.

The duration of the exacerbations was also rigorously defined in order to ascertain, in a consistent manner, the difference between one long exacerbation versus a number of distinct smaller, shorter exacerbations.

The duration of mild exacerbations was based solely on the investigator's judgment. The end of

a moderate or a severe exacerbation was based on the investigator's judgment or the conclusion of treatment with antibiotics, whichever occurred later. Mix exacerbation was defined if the next course of antibiotics was given 14 days or more after the resolution of the prior exacerbation.

Any discrepancies between an investigator's assessment and the definition of an exacerbation were adjudicated by a blinded committee feedback that was managed by a clinical research organization without the sponsor's involvement. Feedback strictly adhere to the per protocol definitions in their decision-making.

Our study design reflected our wish to build a robust efficacy and safety database, 48 weeks of double-blind, followed by a 28-day open label extension with Linhaliq, and finally a 30-day follow-up period.

The randomization is 2 to 1, Linhaliq to placebo, and the duration of a full year and the fact that we ran the trials concurrently in both hemispheres minimized any effects from seasonal

variations.

Baseline patient demography was similar between the Linhaliq and placebo, representative of the bronchiectasis population with chronic pseudomonas infections in the United States. The median age is about 65 years, and the disease affects more women than men.

The most notable features are very small number of current smokers and the prior history of pulmonary exacerbations. The only discernable difference in baseline characteristics was an imbalance in the use of baseline macrolides, an observation that we'll return to later.

In ORBIT-4, the number of dropouts was modest and the rates of premature discontinuations or treatment were low considering the nature of the populations. These are relatively old and quite sick people, and a quite onerous nature of the study, 14 visits with numerous tests. Note also, please, that the patients who discontinued the treatment, either in the placebo or in the active group, were encouraged to stay in the trial and

complete all study visits.

It was very gratifying, particularly to see, that about 90 percent of patients who completed the double-blind treatment with Linhaliq also decided to continue into the open label extension.

We saw a similar pattern in ORBIT-3. We had an almost 90 percent completion rate in both arms in the double-blind period. And again, we are gratified that 97 and 96 percent, respectively, in the Linhaliq and placebo groups went into the open label study.

Let me now present the efficacy results for ORBIT-3 and ORBIT-4. In the Linhaliq groups, the median times to first exacerbation was similar between the two trials, 230 and 240 days, respectively. While in the placebo groups, there were 158 and 136 days, respectively.

In ORBIT-4, Linhaliq met the primary endpoint with a favor of a hazard ratio of 0.72 versus placebo. In ORBIT-3, Linhaliq did not meet the primary endpoint. Since the primary endpoint result for ORBIT-3 was not significant, all

additional analysis for this study are considered exploratory. Sensitivity analysis for this primary endpoint in ORBIT-4 and ORBIT-3 were consistent with these results.

We believe that the most meaningful endpoint for subjects with this chronic disease is reduction in the frequency of pulmonary exacerbations. In ORBIT-4, Linhaliq demonstrated a statistically and clinically significant reduction in the risk of all exacerbations with a risk ratio of 0.663 or a 37 percent reduction in risk compared to placebo. In ORBIT-3, the risk reduction was 15 percent without reaching nominal statistical significance.

Looking now at the severe pulmonary exacerbations, those requiring intravenous antibiotics or hospitalizations, in ORBIT-4, Linhaliq demonstrated a clinically and statistically significant reduction of 60 percent compared to placebo. In ORBIT-3, the risk reduction was 30 percent without reaching the nominal statistical significance.

The European Agency also requested

prespecified analysis of those exacerbations that required interventions with antibiotics as they are more burdensome for patients and the healthcare system. Additionally, moderate to severe exacerbations requiring drug interventions had been the primary efficacy outcomes for trials in COPD or asthma.

In our phase 3 studies, all moderate and severe exacerbations required interventions with antibiotics. In ORBIT-4, we observed a risk reduction of 0.58 or a 42 percent reduction of these exacerbations that required interventions with antibiotics. In ORBIT-3, the point estimate for the risk reduction was 0.78, just missing nominal statistical significance.

Let me summarize the results of the prespecified analysis for all exacerbations endpoints. ORBIT-4 met all these endpoints, and ORBIT-3 trended in positive direction for the pulmonary exacerbations frequency endpoints. As the FDA noted, there were 10 exacerbation cases that were readjudicated post data lock. These had

very little bearing on the analysis of the frequency of exacerbations.

It was important for us to know if elevated minimum inhibitory concentrations would impact efficacy. As you may recall, we also enrolled patients with MICs greater than 4 micrograms per milliliter.

Furthermore, we saw shifts toward high MICs at the end of the on-treatment periods in the Linhaliq group. We see such pattern stabilize after the 1st cycle, that is there was no further trend in the elevation of MICs due to Linhaliq.

We measured the relative risk of exacerbations for these two groups. First, those patients with MICs, about 4 micrograms per milliliter at baseline, who would be deemed to be resistant to oral or IV ciprofloxacin. And second, we looked at those who had MICs emerging above this breakpoint at any visit.

These results show that the efficacy of Linhaliq as an ongoing treatment for reducing exacerbations is not diminished in the presence of

resistant pseudomonas. We attribute this result to the sustained high levels of ciprofloxacin in the lung throughout all 24 hours of all 28 days of the on-treatment cycles.

We have been, of course, very interested to understand the differences in the results between ORBIT-3 and ORBIT-4. The agency also asked us to provide a rationale for the difference.

We first looked at pre-randomization factors that could affect the results. This included the demography, as well as other baseline characteristics. We looked particularly at those factors that could be clinically and biologically plausible.

As I mentioned before, the only imbalance observed at baseline was the proportion of subjects on baseline macrolides. This was lower in the Linhaliq group in the ORBIT-4 study but higher in the ORBIT-3 study. Dr. Wittes will address this baseline imbalance in more detail.

We also extensively analyzed post-randomization factors using a variety of

prespecified analysis. In particular, there was no difference in dosing compliance, nor difference in pharmacokinetics, or the microbiology.

In sensitivity analysis, we had only two factors that were of note. One related to the subgroups used for stratification by the history of the number of exacerbations in the prior year and another related to the frequency of respiratory events requiring interventions with antibacterials.

Let me describe the first. We see that there is a difference between the two trials in the subgroups of subjects with a prior history of the prior year of 2 to 3 exacerbations. The results for patients with 4 or more pulmonary exacerbations in the prior year are remarkably similar across the two trials.

What is really reassuring for us are the strengths of the efficacy data in the severe, difficult-to-treat group of patients who frequently exacerbates. In those trials, these patients see a very similar benefit in the reduction of exacerbations by Linhaliq compared to placebo.

When we look at the Kaplan-Meier plots, this is Kaplan-Meier plots for the first exacerbation, we see, again, a remarkable difference between ORBIT-3 and ORBIT-4 in the strata of patients with 2 to 3 exacerbations in the prior year.

When we looked at the Kaplan-Meier plots for the subjects who had 4 or more pulmonary exacerbations in the prior year, they are similar. So the key difference between the two trials is the odd behavior of the low frequency exacerbators in the ORBIT-3 placebo group.

The important point for us is that we see impact of the reduction of all pulmonary exacerbations in ORBIT-4 in all subjects and a similar impact in ORBIT-3 in the patients with the highest need, the most frequent exacerbators.

As you just saw, there appears to be a difference between frequent and less frequent exacerbators. New clinical research that was published during our phase 3 clinical trials showed that one of the strongest predictors of future exacerbations are past exacerbations.

In other words, exacerbations are not independent random events. They are interdependent. Reducing the number of exacerbations is the most meaningful way to measure the long-term impact of Linhaliq. Therefore, it is very important how frequency of exacerbations are analyzed given this interdependence.

I would now like to invite Dr. Janet Wittes to present an alternative method to analyze our phase 3 results that takes into account this new knowledge.

Applicant Presentation – Janet Wittes

DR. WITTES: Good morning. I'm a biostatistician. I'm president of Statistics Collaborative in Washington, D.C., just down the road, and I've been involved in clinical trials for more than four decades, as some of you know.

I am a paid consultant for Aradigm. We, at Statistics Collaborative, have performed a number of analyses on the phase 2/3 trials, and we've been paid for those analyses. I'm being paid for being here today, but neither nor Statistics

Collaborative has any direct financial interest in the outcome of the meeting today.

What I'd like to do is talk about the frequency of pulmonary exacerbations. As Dr. Gonda and Dr. Tino have pointed out, this is the most important endpoint in the study. The prespecified method for assessing the frequency of PE's was a negative binomial model. That model assumes that each pulmonary exacerbation is independent of the previous ones. As Dr. Gonda has pointed out, that assumption is not biologically plausible.

The negative binomial model also assumes that the hazard function, that is the risk of the PE, is constant over time; and that is also not plausible. Therefore, post hoc, we did an analysis, or a set of analyses, that I think is more appropriate.

The model we used, a counting process, generalizes the model used for the primary analysis. Importantly, the counting process is not dependent on the assumptions underlying the negative binomial. Had I been involved in writing

the statistical plan, I'm pretty sure I would've recommended the counting process.

The counting process is an old model that was introduced in 1982 by Andersen and Gill, and it does not assume independence of serial PEs. In other words, it understands that having one PE can predispose a patient to having another.

Further, it allows the hazard to be non-constant over time; that is, the risk of having a pulmonary exacerbation can vary over the course of the disease.

Also, unlike the prespecified negative binomial model, although not all negative binomial models, the counting process that we use understood that a person cannot have a new exacerbation during the period while he is having another exacerbation. It subtracts out the time of having the exacerbation.

Dr. Bruce Thompson, who performed these analyses, and I both felt that the counting process more closely reflected the underlying biology of the disease.

In my opinion, one should base one's inferences on the effect of Linhaliq from the counting process and also from the frequency of exacerbations. These graphs show the cumulative number of PEs over time in each study. The tables below the graphs show the negative binomial model and the counting process.

The graphs show that in both studies, the cumulative event rate was higher in the placebo group than in the Linhaliq group. Now, look at the two tables below the graphs. They show that the two methods yield essentially the same degree of risk reduction.

As you'll see as the estimates for the negative binomial, the relative risk is 0.63, the hazard ratio for counting process is 0.61, and you'll see in the ORBIT-3, the numbers are 0.85 and 0.84. However, compared to the negative binomial, the confidence intervals for the counting process, they get squeezed a little bit, and the calculated p-values are smaller.

In ORBIT-4, the two models give the same

inference, a convincingly large effect of Linhaliq on the cumulative PE events. In ORBIT-3, however, the counting process, by narrowing the confidence interval for the estimated effect, is now more consistent with the data from ORBIT-4 than it had been under models that considered only the time to first event or when one used a negative binomial model.

Now, let's go more admittedly post hoc step. As Dr. Gonda pointed out, in ORBIT-4, a higher proportion of patients randomized to placebo were taking macrolides at baseline, and in ORBIT-3, the opposite was true.

Thus, by chance -- and although we believe that randomize on average balances every variable measured and invariable, measured and unmeasured, sometimes it yields dirty tricks -- it looks as if the placebo patients in ORBIT-4 had more severe disease on average than on Linhaliq patients, and vice versa for ORBIT-3. That led to the question of whether our counting process analyses overestimated the benefit in ORBIT-4 and

underestimated the benefit in ORBIT-3.

What is the effect of adjusting for baseline macrolides? Let's look at ORBIT-4. This figure is restricted in the counting process, but the results are essentially the same for the negative binomial.

As expected, when one adjusts for the use of baseline macrolides, all of the ORBIT-4 estimates are slightly attenuated; they're pushed slightly toward the line of 1, but the p-values remain less than 0.001.

Now, look at ORBIT-3. As expected the estimate of hazard ratio becomes smaller, i.e., more evidence of benefit after adjustment of baseline macrolides, and the nominal p-values also become somewhat smaller. Thus, after adjusting for the unfortunate imbalance of macrolides at baseline, which can be viewed as a proxy for severity of disease, the differences between ORBIT-4 and ORBIT-3 become less pronounced. Both seem to be trying to tell us a similar story with respect to frequency of PEs. For reference, the pooled estimates are shown to the right. Thank

you.

Applicant Presentation – Igor Gonda

DR. GONDA: Thank you very much, Dr. Wittes.

In addition to measuring the exacerbations, we measured several other prespecified endpoints that I'd now like to discuss. The agency advised us to us the Qol-B instrument to assess the changes in the quality of life.

The instrument was still in the development when we started the studies, and it was not previously tested in long-term clinical trials. The patients completed the questionnaire at every visit, recalling their quality of life over the last 7 days.

The agency also asked us to compare the changes in the colony forming units of pseudomonas to an efficacy measurement. The only efficacy measurement at every visit that we could compare to the colony forming units was the quality of life questionnaire.

On the vertical axis are the changes in the quality of life from visit to visit, and on the

horizontal axis are changes in the colony forming units from visit to visit. This is the placebo group. You can see there is no change in the colony forming units in the placebo group.

The response to the quality of life questionnaire is random; it does not depict whether the patients are responding to the questionnaire during the on-treatment period or during the off-treatment period. There is no placebo effect.

The situation is very different for the Linhaliq group. During every on-treatment period, this is what we are showing, the upper quadrangle. During the early on-treatment period, we see an improvement in the quality of life in both trials comparing the end of each on-treatment visit versus the previous off-treatment visit. This goes hand in hand with the reduction in colony forming units.

As you would expect, during the off-treatment periods, the right-hand side, lower quadrangle, there is an increase in the colony forming units. On average, patients are feeling worse compared to the way they felt during the

7 days of the previous on-treatment periods.

What I want to emphasize is that this quality of life instrument was validated against big drops in quality of life at the time of a pulmonary exacerbation. We'd see the same big drop in the quality of life of these patients. If you look at the changes, in the Qol-B, in our own trials, at the time when a patient experiences a pulmonary exacerbation, the drop is about 10 points, on average, in both trials.

Because we reduced the number of pulmonary exacerbations in the Linhaliq group compared to the placebo group, we believe that the Linhaliq would play an important role in reducing the number of these episodes in the lives of the patients and so reduce such precipitous drops in the quality of life.

Unfortunately, the prespecified endpoint compares the quality of life questionnaire from a 7-day recall at the end of the off-treatment period at the end of the trial versus the 7-day recall at the first visit before any treatment. With

hindsight, it is not surprising that neither study showed a significant benefit with the skill of the instrument and the way it was applied.

For patients with bronchiectasis and chronic infections with pseudomonas, quality of life can be understood also through such objective measures as hospitalizations and the use of intravenous antibacterials.

Comparing Linhaliq to placebo in our phase 3 trials, we saw relative reductions of 26 percent in the proportion of patients who were hospitalized for exacerbations and a 32 percent reduction in patients requiring intravenous antibiotics for an exacerbation. We also saw reductions of 23 percent in the number of exacerbations requiring hospitalization and 32 percent in the number of exacerbations requiring IV antibiotics.

As I mentioned earlier, one of the post hoc analyses we found particularly informative looked at all events requiring antibacterials to resolve respiratory symptoms. This approach is used to assess efficacy in cystic fibrosis and other

clinical trials. The events include not only the moderate and severe pulmonary exacerbations but any other respiratory events for which the principal investigator decided to intervene with antibiotics.

In ORBIT-4, we see a better profile for Linhaliq than placebo. We see the same trend in ORBIT-3. The pooled data that integrates both studies shows a clinically meaningful point estimate of reduction of these events. It is also consistent with the reduction of the use of systemic antibiotics in the Linhaliq group compared to placebo.

Let me finish with the key efficacy conclusions. We believe that the totality of the evidence shows that Linhaliq provides substantial efficacy benefits for patients with bronchiectasis who have frequent exacerbations associated with chronic lung infections with pseudomonas.

The mechanism of action in terms of the reduction of pseudomonas is well-documented throughout our preclinical and clinical development. What is most important for patients

is the reduction of the number of exacerbations and especially those that require interventions with oral antibiotics, IV antibiotics, and hospitalizations.

The results from ORBIT-4 made the primary endpoints and all secondary pulmonary exacerbations endpoints. The results from the ORBIT-3 trials also point in the same direction with point estimates consistently better than for the placebo.

We are also very pleased that Linhaliq's efficacy to reduce the number of exacerbations was not affected by the baseline MICs or MICs found during the trials. We can account for a significant part of the differences between the two trials by using the counting process, stratifying for macrolides, and analyzing the impact of antibiotic use for respiratory symptoms throughout the studies.

Moreover, the proportion of patients in the phase 3 studies on Linhaliq requiring hospitalization or IV antibiotics was lower than in the placebo group, and similarly, the frequency of

exacerbations requiring hospitalization, as well as the frequency of exacerbations requiring intravenous antibiotics was lower in patients on Linhaliq.

To conclude, we believe Linhaliq demonstrated many important efficacy attributes important for bronchiectasis patients, and in particular those who are the highest risk of increasing morbidity and mortality. Thank you.

Our chief medical officer, Dr. Froehlich, will now provide the results of our safety analysis.

Applicant Presentation – Juergen Froehlich

DR. FROEHLICH: Thank you, Dr. Gonda.

Let me begin our safety presentation with an overview of the pooled safety data of both phase 3 trials. Both trials had the same design which allowed us to pool the data. For both trials, the safety population is identical with the pooled analysis set population used for the efficacy analysis. Compliance was notably high in both trials with more than 85 percent of subjects

achieving more than 90 percent compliance.

While the safety data from the small phase 2B trial, ORBIT-2, are not shown in this presentation, they are consistent with the pooled phase 3 trials. Let me note that you can find them detailed in the briefing book.

With regard to selection of the placebo, our main concern was safety and tolerability. Therefore, we selected as placebo for FCI isotonic saline and the 5 percent dispersion of empty liposomes with a similar appearance to FCI.

You see here those comorbidities reported in more than 10 percent of patients. Both groups were generally balanced. About 25 percent had gastro-esophageal reflux disease. Notably, one-third of the study population had hypertension, and about 20 percent had asthma or were diagnosed with COPD, indicating that we were successful in selecting for a sicker bronchiectasis patient population. Let me add though that our protocol excluded primary COPD patients with a smoking history of 10 or more pack years.

You can see here that the concomitant administration of antibacterials was high in both treatment groups. Indeed, close to 50 percent of all trial subjects took fluoroquinolones on at least one occasion during the double-blind period, followed by penicillins in 20 to 24 percent and macrolides in 15 to 19 percent of subjects.

Please note that in general, there was less use of concomitant antibacterials with Linhaliq than placebo. This may in part be due to Linhaliq subjects having been on an Linhaliq-active antibacterial.

More than one-third of subjects took corticosteroids. Close to 30 percent used bronchodilators, and about 20 percent are given mucolytics. As with other respiratory drugs, these tended to have been used either at a similar or lower frequency in the Linhaliq group than with placebo.

Let me now turn to a discussion of adverse events. Almost all subjects in both groups experienced adverse events, with serious adverse

events reported in about 25 percent of patients. Because the signs and symptoms of a pulmonary exacerbation could be reported as adverse events, the observed rates were relatively high with slight more placebo subjects experiencing an event.

SAEs and fatal AEs were numerically lower, but in the same range for Linhaliq versus placebo. Study drug discontinuations were comparable between arms, but withdrawals from the study due to AEs were slightly more common with Linhaliq.

This table shows the most common respiratory AEs in 5 percent or more of subjects. These are the respiratory AEs captured in the study. They were common in part; we followed such events very carefully at each visit in order to accurately document exacerbations. The events were balanced within treatment arms. Other common adverse events were generally reported less frequently than respiratory adverse events. Overall, the rates are fairly balanced between groups.

Given the safety and tolerability issue with other inhaled antibiotics, we looked at a variety

of signs and symptoms indicating possible respiratory tract irritation that were prespecified prior to database log as adverse events of special interest.

As mentioned earlier, among the more frequently reported AESIs, 5 percent or more, the highest were for cough, dyspnea, and wheezing; all of which represent signs and symptoms of a pulmonary exacerbation.

Here, you see less frequent events, and the overall rates were similar in each group. The rate of bronchial spasm, laryngitis, and pharyngitis were low for Linhaliq and placebo, confirming the good tolerability of Linhaliq.

Here are the related adverse events reported in 2 percent or more subjects treated with Linhaliq that were numerically higher than those related to placebo. As shown here, the numbers were generally low in both groups.

Turning now to serious adverse events, they were reported in about 20 percent of subjects but numerically lower in the Linhaliq group.

Individual preferred terms reported by 2 percent or more of subjects were generally balanced across the treatment groups.

A low number of deaths were reported in both treatment groups. None were reported as related. The cause of each death is listed here for each group.

Let me now turn to spirometry assessments. We conducted serial spirometry at the beginning of the 1st and the 4th treatment cycle with values taken pre-dose, and at 15, 30, and 90 minutes post-dose. The mean values for every 1 percent predicted showed no changes in both groups at the post-dose time points.

We considered a decrease of 15 percent or more in FEV1 percent predicted as a threshold indicating potential bronchial constriction. Numerically, more subjects in the Linhaliq than in the placebo group showed a decrease at both visits, although overall, a very small number of patients were affected. Of note, 1.1 percent of patients in each group discontinued study drug due to

bronchospasm, and no subject discontinued study drug due to low spirometry values.

We assessed FEV1 and FVC over the course of the study as a potential safety indicator. The spirometry tests at these visits were overread by a central laboratory. As was expected in this population, there was a small decline in pulmonary function over a 48-week period. However, the decline was numerically lower in Linhaliq patients than with placebo.

We went beyond spirometry and also followed carbon monoxide diffusion capacity to assess any effects on the lung tissue. Data were also overread by a central laboratory. There were no differences in mean percent changes of absolute DLCO values in both groups.

We saw no clinically meaningful differences in laboratory parameters, including shift tables between baseline at the end of the double-blind phase in either the Linhaliq or placebo group.

This slide shows adverse events observed in both phase 3 studies that are known to be

fluoroquinolone class effects. We did not see any cases of treatment-emergent Clostridium difficile diarrhea. Of note is the lower rate of unspecified diarrhea in the Linhaliq group, suggesting that the GI tract was not affected by exposure to Linhaliq.

For tendonitis or tendon rupture, as well as peripheral neuropathy, event rates were low with no differences between groups. All other events had similar rates in both groups.

I will now move on to our data on the selection for resistant strengths. As Dr. Gonda reported, during each on-treatment period, we saw reduction of ciprofloxacin susceptibility in pseudomonas isolates with a partial recovery during each subsequent off period. We, thus, were motivated to look for any safety issues associated with resistance.

We did not see an increase in infections with ciprofloxacin resistant pathogens. Treatment courses and duration of systemic infections, including urinary tract infections, were comparable in Linhaliq and placebo.

We were concerned for the potential of pseudomonas isolates to become cross-resistant to other antimicrobials, so we looked at the change in MIC of the pseudomonas isolates for the list of antibacterial drugs.

For each antibacterial drug, the percentage of patients with isolates that had a greater than 2-fold increase in MIC is reported for both Linhaliq and placebo groups. There was no difference other than for ciprofloxacin.

In summary, the safety profile with Linhaliq was similar to the placebo group with no indication of increased airway irritation. The adverse events event profile did not indicate fluoroquinolone class effects. Linhaliq was associated with less use of antibacterial drugs and other respiratory adjunctive or anti-inflammatory therapy.

We did not see an increase of infections with ciprofloxacin-resistant pathogens or super infections. Other anti-pseudomonas antibiotics showed no trend of decreased susceptibility in pseudomonas.

Let me add that Aradigm is committed to continued microbiological surveillance post-approval in collaboration with the FDA.

Dr. Sanjay Sethi and Professor James Chalmers will now wrap up our presentation with their clinical perspective on development of resistance and overall benefit-risk.

Dr. Sethi?

Applicant Presentation – Sanjay Sethi

DR. SETHI: Good morning. I'm Dr. Sanjay Sethi. I'm a pulmonologist at the University of Buffalo, SUNY. My research interest in the last two decades has been respiratory infections and airway diseases. I was the chair of the Data Safety Monitoring Board for the ORBIT-3 and 4 studies.

I am a paid consultant to Aradigm in preparation for this meeting but do not have any direct financial interest in the outcome of the meeting today.

I would like to take this opportunity to address the risk-benefit of Linhaliq use in

bronchiectasis, focusing specifically on the question of antimicrobial resistance.

Emergence of antimicrobial resistance with chronic inhaled antibiotics was a major focus of the ORBIT DSMB. We carefully reviewed the microbiology data and serious adverse events related to infections.

We, indeed, did observe an increase in Pseudomonas aeruginosa MICs with Linhaliq. However, serious pulmonary or systemic infections specifically related to these bacteria, were not seen. In addition, we did not observe any super infections with other antibiotic-resistant bacteria or fungi that we could relate to Linhaliq use.

Now, these observations were as expected because we took them in the context of several decades of experience with inhaled antibiotics in a related disease, cystic fibrosis.

I think there are several important lessons to be learned from the effect of inhaled antibiotics on Pseudomonas aeruginosa in CF. As we saw in the ORBIT studies, an increase in

pseudomonas MICs is seen within 20 weeks of use of inhaled antibiotics in CF, as shown on this slide.

However, in spite of this increased MICs, suppression of pseudomonas bacteria load in the airways in these patients continues, as for example in this CF study where they looked at this over 56 weeks.

Furthermore, in spite of emergent of pseudomonas resistance, the clinical benefits of inhaled antibiotics persist in CF. The longest systematic observation, not a trial, but the longest systematic observation in the CF literature over two years is depicted over here. What it shows is a persistent reduction and hospitalization over both the first and second years of inhaled antibiotic use in these patients.

Another concern with inhaled antibiotic use is the loss of efficacy of that particular antibiotic when used systemically to treat exacerbations. There are two intriguing observations in CF that address this concern. In spite of decades of use, antibiotics delivered by

the inhaled route, for example, aminoglycosides, still retain their efficacy when used systemically to treat CF exacerbations.

Furthermore, interestingly, antimicrobial susceptibility of sputum bacteria in these chronically-treated CF patients does not predict systemic antibiotic efficacy. Therefore, per current guidelines and clinical practice, a CF patient on inhaled tobramycin who experiences an exacerbation and has tobramycin-resistance pseudomonas in the sputum can be still treated with systemic tobramycin.

In summary, the increase in pseudomonas MICs in CF with chronic inhaled antibiotics does not have significant negative consequences.

Let us now turn back to the ORBIT-3 and 4 studies and look at systemic antibiotic use in these studies. An important observation that Dr. Froehlich has already shared is that Linhaliq led to reduced use of all classes of systemic antibiotics in these studies. This implies that the selection question on bacteria of chronic

inhaled antibiotics is mitigated by less systemic antibiotics exposure.

Interestingly, in the ORBIT-3 and 4 studies, the most common systemically used antibiotics for PEs were the fluoroquinolones. When we looked at the data more closely, the number of antibiotic courses used per PE were comparable between the two arms throughout the two studies as shown on this slide. This is consistent with no apparent loss of efficacy in spite of inhaled fluoroquinolone exposure of systemic fluoroquinolones.

If I command this with the DSMB safety observations, in my mind, the data from the ORBIT studies strongly suggest that over 48 weeks, the clinical implications of increased pseudomonas MICs to fluoroquinolones follow the pattern seen in CF.

Now, antibiotics are unique drugs, as they are societal implications to the use because of the concerns of associated emergence of resistance and spread of resistant bacteria.

We did a calculation. Bronchiectasis is an orphan disease, and even if every patient with

bronchiectasis who met the criteria for Linhaliq were to be treated with Linhaliq, it would still only account for 0.5 percent of the overall fluoroquinolone use in the United States.

This estimate, combined with study showing that the patient-to-patient transmission of fluoroquinolone-resistant strains is extremely rare in bronchiectasis, strongly suggests that Linhaliq will not cause an epidemic of fluoroquinolone-resistant strengths.

In summary, as detailed in the slide, you can see that the risk-benefit ratio in terms of antimicrobial resistance clearly favors Linhaliq in severe bronchiectasis patients. Thank you.

Dr. Chalmers?

Applicant Presentation – James Chalmers

DR. CHALMERS: Thank you very much. My name is Professor James Chalmers, and I'm the British Lung Foundation chair of respiratory research at the University of Dundee in Scotland.

I've been working in international clinical trials in bronchiectasis for over 10 years and work

very closely in collaboration with colleagues, such as Dr. Tino in the U.S. COPD Foundation bronchiectasis group to further bronchiectasis research internationally. I also care for nearly 800 patients with bronchiectasis at one of the largest specialist clinics for this disease in Europe.

I am a paid consultant to Aradigm in preparation for this meeting but have no direct financial interest in the outcome of the meeting.

I want to give a clinical view of risk-benefit profile for Linhaliq, particularly focusing on the importance of preventing pulmonary exacerbations. Although bronchiectasis can be caused by a number of different underlying disorders, once patients become chronically infected with pseudomonas, their outcomes is universally poor, regardless of the underlying condition. When making a decision about how to treat these patients, the frequency of pulmonary exacerbations is the key factor that we take into consideration.

Dr. Tino has previously mentioned what a major impact exacerbations have on patients, which in some cases leads to irreversible loss of lung function and quality of life. For this reason, all of the guidelines that have ever been written internationally for bronchiectasis recommend basing treatment decisions on the frequency of pulmonary exacerbations.

Time to first exacerbation is commonly used in trials but is not considered to be important for clinical decision-making because we regard it as a surrogate for exacerbation frequency.

In clinical practice, we particularly focus on the moderate and severe exacerbations. These are the events that require antibiotics, and they're also the key clinical outcome in trials in areas like COPD. So what I'm looking for and what my patients are looking for is to identify a safe therapy that can reduce the frequency of moderate and severe pulmonary exacerbations.

The reason this is traditionally not been the primary outcome in bronchiectasis trials was a

concern that it would be very hard to show reduction in frequency of exacerbations over a 48-week study because patients in placebo arms tend to take a large amount of antibiotics for exacerbations and other reasons and because, as we've heard today, the treatment of the first exacerbation can impact on the risk of a subsequently exacerbation.

For this reason, it has been felt that it would take a highly effective therapy to be able to demonstrate a reduction in the overall frequency of exacerbations.

This is part of the reason why I'm so persuaded by the efficacy data of the two Linhaliq trials. ORBIT-4 demonstrated a statistically significant reduction in the frequency of all PE endpoints, and it's particularly important to observe the 42 percent reduction in the frequency of moderate and severe PEs, and the striking 60 percent reduction in the frequency of severe PEs.

ORBIT-3 demonstrated a reduction of

22 percent in the frequency of moderate and severe PEs and a 20-percent reduction in severe PEs, neither of which reached statistical significance.

You've heard today that there were baseline imbalances in the two trials, which may have led to patients with a greater risk of exacerbation being allocated unevenly between the arms of the trials. For this reason, I believe the pooled data gives us the closest approximation of truth with regard to the efficacy of Linhaliq. And the pooled data shows a clear 33-percent reduction in the frequency of moderate and severe PEs and a 42-percent reduction in the frequency of severe PEs.

In spirometry medicine, when we're looking at conditions like COPD, inhaled corticosteroids are improved and recommended when they achieve a 15 to 20-percent reduction in moderate and severe exacerbations, even when there's multiple other therapies available for COPD. For bronchiectasis where we really have no other alternatives, a reduction of more than 30 percent in the frequency of exacerbations would represent a major benefit.

It's really important to remember that we're not talking about a novel treatment approach here. We know that antibiotics benefit patients with bronchiectasis, and we have performed extensive clinical studies showing that patients with high CFUs in sputum have more exacerbations and that FCU reduction results in reduced lung inflammation and a lower risk of pulmonary exacerbations.

What's novel here is that this formulation allows for a very high sputum concentration far above the MIC with low systemic exposure, providing that optimal balance between airway bacterial killing and the systemic adverse effects or effects on the gut. And we have decades of experience in cystic fibrosis to validate this approach to therapy.

I see a large number of patients with pseudomonas infection who have frequent exacerbations, and these patients could really benefit from Linhaliq, so I have to ask myself what my alternative is for these patients. There's no other approved therapy with the result that most of

these patients simply receive repeated courses of oral and intravenous fluoroquinolones.

Off-label use of inhaled antibiotics is common. We heard today that 10 percent of patients in the U.S. Bronchiectasis Registry receive off-label inhaled antibiotics. It's actually 30 percent of patients that have two or more exacerbations per year.

None of these drugs have proven efficacy in bronchiectasis, and many patients can't access the therapy because of lack of approval. Those that can, find it very difficult to adhere to the therapies because of the poor tolerability. We really have to provide better options for our patients.

Compared to previous inhaled antibiotic studies, the safety data from Linhaliq was very reassuring for me as a physician. There was no significant increase in the respiratory-related adverse events compared to placebo.

I believe that Linhaliq has stronger evidence, both for efficacy and safety, than any of

our previous alternatives currently available for bronchiectasis patients. It's clear that these trial results weren't perfect, so let me try and tackle head on some of the problems that we've seen and explain why I think despite the limitations of the data, Linhaliq represents our best option for bronchiectasis patients at this point in time.

Firstly, in terms of the primary outcome, we have one positive and one negative trial, and there's no getting away from that. Baseline imbalances in the two studies were clearly a problem, but that's why clinical guidelines and also physicians, in general, will tend to evaluate drugs on the totality of their evidence rather than taking a single endpoint in a single trial.

I've already made the point that the frequency of exacerbations is the endpoint I consider most clinically meaningful. Time to first exacerbation is a surrogate, and if you hit the really hard endpoint, which is frequency, the surrogate does become less important. For this reason, I really believe our question for today

should be very simply: Does Linhaliq reduce exacerbations, rather than specifically focusing on the time to event.

I'm going to use this drug in sickest, highest risk patient population, and so I find the evidence the effect is more consistent between the two trials in patients with more than three exacerbations very important.

Regarding whether this exacerbation reduction is clinically meaningful, for me, this is beyond doubt. I've already pointed out that this level of exacerbation reduction is far greater using the pooled data and effect sizes we've seen in bronchiectasis before or effect sizes that have been used to approve drugs in COPD, asthma, or other respiratory diseases.

I want to make one other important point about the effect that we've seen in these studies. No single treatment is going to cure a disease as severe and complex as bronchiectasis, and Linhaliq is very clearly not a cure. But we've learned from cystic fibrosis is just how powerful incremental

benefits can be.

This graph shows the improvement in survival we've seen in cystic fibrosis over the 20th and early 21st century, with the survival in years on the Y-axis. No one intervention achieved this dramatic improvement in survival, but the slide shows that the drug treatments on the right and the non-drug treatments on the left, together, achieved this.

The arrows on the right show the approval of the different inhaled antibiotics, but individually showed modest benefits on endpoints like FEV1 or exacerbations, but when put together have produced one of the greatest healthcare success stories of the past half century.

Returning to the quality of life data, I would have liked to have seen evidence that this drug improves patients' quality of life. Unfortunately, the Qol-B questionnaire was a new tool when this trial was designed, and we've learnt that it's not really adapted to measure treatment responses in this way in a clinical trial. It was

designed to measure short-term treatment responses.

Nevertheless, we've seen evidence today presented that patients felt better when they were on the drug, and there's no question that patients' overall quality of life is improved by exacerbation reduction.

Finally, am I concerned about antibiotic resistance? Empathically, yes, but this drug is targeted at only the most severe patients with bronchiectasis that already have a very high rate of fluoroquinolone use. This is definitely not a drug for everybody with bronchiectasis.

We have longstanding experience with other inhaled antibiotics that suggest that the resistance implications will be modest. And I'm reassured that we saw no loss of efficacy over time.

For the population as a whole, Linhaliq is a drop in the ocean in terms of overall U.S. quinolone use, and the alternative for most of these patients is further courses of oral quinolones. I believe the impact of our decision

today will not have any meaningful impact on quinolone resistance in the United States generally but will have an important impact on these patients.

I'm evaluating our question today on the totality of the data just as we do in clinical guidelines. Across the key safety endpoints, we see remarkable safety with low rates of bronchospasms, better than any prior inhaled antibiotic studies in bronchiectasis.

For resistance, we expect to see increases in MIC with therapy, but I'm reassured not only that patients with high MCIs continue to respond to Linhaliq but that quinolones remain an effective therapy for exacerbations during the study.

For efficacy, the overall picture is of substantial patient benefit, reduced exacerbations, including those most clinically meaningful endpoints, the exacerbations that require antibiotics and hospitalization. The reduced healthcare utilization, including total antibiotics use, speaks to both efficacy but also the potential

to reduce systemic antibiotics exposure, which is very important.

Finally, as I would expect, patients do feel better when they're on the drug and reducing exacerbations is the best way to improve their overall quality of life. This is an antibiotic, and it does exactly what I would expect from an inhaled antibiotic.

It's quite clear to me that if the only question we have to address today is whether both ORBIT-3 and 4 met their primary endpoint, we wouldn't need to have an advisory committee, but I think there's a recognition that bronchiectasis trials are very challenging.

The management of patients worldwide is very heterogeneous, and this is an orphan condition, so studies have to be done across a large number of sites, which means a large amount of variabilities introduced. This is part of the reason why so many bronchiectasis trials have been negative and why we still don't have a licensed therapy.

The picture on the right of this slide is

from a meeting of an international consensus panel between bronchiectasis patients and physicians that was held in 2017. These wonderful people have been struggling and waiting for an effective therapy for more than 10 years, and now we finally have something that I believe works. I feel an obligation to stand here on their behalf and express to you the urgency of giving patients the opportunity to try this therapy.

Not approving this drug would be devastating. It means potentially another decade of trials, while patients continue to use unproven, off-label drugs. We have the power today to transform the field of bronchiectasis, as well as the lives of some very sick and desperate patients. Thank you very much for your attention.

Clarifying Questions

DR. BADEN: We have about 15, 20 minutes to ask clarifying questions. We'll have a break. If we're not able to clarify all issues, we will then bundle the questions for after the agency's presentation. I will start with the first

clarifying question while others on the panel gear up.

I would like to thank, Aradigm, Dr. Gonda and your team for a fabulous presentation, a tremendous amount of data that has been shared very efficiently, and we appreciate that. However, with complex data, there are lots of issues to make sure we understand. And at least three or four issues emerged that I'd like to better understand the process, and that has to do with changes in the study design, and understand what triggered them.

It appears that the endpoint was changed, or "changed" is the wrong word, was re-evaluated as to the value of the endpoint. What went into that re-assessment? What went into the re-assessment of the 10 subjects or participants who were reclassified? Why did that occur?

What went into the post hoc macrolide and post hoc 2, 3 versus 4 exacerbations? Because those all appeared to have occurred, at least from what I see, after unblinding, in which case, it raises many other issues. So if you can help us

understand those design feature.

DR. GONDA: Thank you. Let me start off with the issue of baseline macrolides. That was a post hoc analysis, and it was done because we realized that there was an imbalance.

During the time, while we were doing the studies, macrolides became more widely used, so we were wondering whether the use of macrolides and the imbalance between the placebo and active in the two trials could have helped us to understand the differences between the two trials.

We did note that knowledge was not available before we started the trial. Had we known that the macrolides would be an independent risk factor, we would have stratified to macrolides at baseline.

As I said, unfortunately, this was quite a few years ago. This was almost eight years ago now when we started the phase 3 trials. In the light of that knowledge, we did the post hoc stratification for macrolides, and Dr. Janet Wittes did that. That's the macrolide story.

With respect to the analysis for the prior

number of pulmonary exacerbations, there was a prespecified subgroup analysis by FDA. We did that analysis as prespecified in the statistical analysis plan, and it was very interesting to observe these differences that the people who exacerbated frequently. The prior strata of 4 exacerbations or more behaved very similarly in the two trials. It was the strata of the 2 to 3 exacerbations, the lower frequency exacerbators, they looked different.

DR. BADEN: It was prespecified at 2, 3 versus more? Was that specifically prespecified?

DR. GONDA: The original stratification for randomization was 2 to 3, 4 to 7, and 7 and more. Then we agreed with FDA that because there are very, very few patients with 7 or more exacerbations, they were lumped together.

I'd now like to invite Dr. Froehlich, our chief medical officer, to speak to your first question, if I recall correctly all three of them.

Did I correctly recall the three questions? The macrolides --

DR. BADEN: It was the issue of the evolution of the endpoint from time to exacerbation versus number of exacerbation, which has a strong rationale, but that appears to have emerged after unblinding, correct?

DR. GONDA: Well, no, not actually. The question between the choice of the endpoint was -- we had many discussions with FDA about this endpoint. Again, we have to go back to seven or almost eight years ago now.

There's a lot of discussion whether we should use the time to the frequency or both of them. In fact, the original design was using both of them as primary in one and secondary in the other, and vice versa, and then do some collective analysis of all of those p-values.

I think that in the end, the agency advised us to use the time to the first exacerbation based on precedence at the time in COPD. The opinion was that the time to was the better endpoint, but I think that that has changed over the years as well. And I think that the COPD guidelines is also now

moving towards frequency of exacerbations as being the more important endpoints.

That's the evolution of the endpoint. It was not a new idea. We knew from the patients and the key opinion leaders that what they really cared about was the frequency of the number of exacerbations.

DR. BADEN: Thank you. For members of the panel, please signal to myself or Lauren. We have a list, and we'll go down the list as far as we can. Jasan Zimmerman?

MR. ZIMMERMAN: I think this is more of a question for Lindsey or Lauren. Is the question that we're evaluating today the one that Dr. Chalmers posted at the end about the safety and efficacy, or are we looking at time to first exacerbation?

DR. BADEN: The question before the panel is the question that the agency has asked us, which is the overall safety and efficacy, which is a totality question. The applicant is giving us as much information as they can to make that

evaluation.

Part of what I hear is the field evolves, and the study begins eight years ago, and our understanding of the disease evolves, and therefore, their analyses of the data try to incorporate that. But it's the totality of the data for the agency's question.

Dr. Igho?

DR. OFOTOKUN: I also want to thank the sponsor or the applicant for such a thorough presentation in a clear manner. I just have a couple of questions that will help me understand the design and the conduct of the study.

One, how was adherence measured? Was it different between ORBIT-3 and ORBIT-4? Do we have those data?

Second is just to help me understand the pathology of the disease. Are there seasonal variation in pulmonary exacerbation? If there are, would that affect, influence the time to first exacerbation?

Then the other thing is that the study was

conducted in three or four different countries. Were there differences? Did you look at regional differences in outcome of your results?

DR. GONDA: Thank you very much. I think that I got the first and the last question. One of them was about adherence, and the other one was about country differences. I don't think that I quite got your third question. Could you please repeat it for me?

One of them was about adherence. Adherence was mentioned. The other one was the differences between countries.

DR. OFOTOKUN: One was if there were differences in adherence --

DR. GONDA: Yes.

DR. OFOTOKUN: -- to the use of study product during the study. The second question was whether there were differences in outcome in different countries where the study was conducted.

DR. GONDA: Thank you.

DR. OFOTOKUN: Lastly is does season affect pulmonary exacerbation?

DR. GONDA: Thank you very much.

DR. OFOTOKUN: Would that account for some of the differences we see in time to exacerbation?

DR. GONDA: Okay. Let me start off with the seasonal differences. The study design was deliberately -- I think it was very good advice from the agency that we should do a running [indiscernible] study because we run it two hemispheres. The studies were run approximately 18 to 24 months.

We didn't see any seasonal variations. They were basically neutralized by the fact that we were running the study in both hemispheres concurrently over about 18 to 24 months. We don't think that there is any seasonal variation.

Dr. Froehlich will address the issue of the adherence. Could you please come up?

DR. FROEHLICH: The way that we measure adherence is by the amount of vials that were returned. We had two methods. One is the return of old vials that were distributed versus the other method was the return of used vials. Both vials

were pretty consistent, and it showed us that in about more than 90 percent of -- in 80 to 87 percent of cases, we had 90 percent or more adherence to the therapy.

DR. OFOTOKUN: No, I was just saying in both ORBIT-3 and ORBIT-4 trials?

DR. FROEHLICH: I'm sorry. Could you --

DR. OFOTOKUN: In both studies?

DR. FROEHLICH: In both studies.

DR. OFOTOKUN: Yes.

DR. FROEHLICH: We had consistent adherence in both studies. There was no difference in adherence that could explain any difference in the two studies.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: My question was addressed. Thank you.

DR. BADEN: Dr. Green?

DR. M. GREEN: Thank you. As I pose this question, I recognize randomization might have controlled for it, but I just want comments if there's data on it.

Clearly, if you're using time to event as your primary measure, patients are enrolled sometimes after a short period of time, I presume, if they have just had a previous event, and sometimes it may have been many months after previous event.

If the time clock is ticking differently, or if you had different places on that time clock at the point that you're enrolled, it could predispose you to an earlier event just because it's been long enough, and there's going to be breakthroughs in both populations.

I wonder if you have any data on that and whether you looked to see whether randomization controlled for, potential differences in the time between, last event prior to enrollment, and enrollment between all the different groups.

DR. GONDA: The short answer is we did look at it, and we really didn't see any differences either between the trials or between the placebo actually, so there really wasn't any discerning pattern.

What I also want to add is that anybody who had used anti-pseudomonas therapy, we've seen 28 days of the first dose, would have been excluded from the trial.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Thank you. I'd also like to thank the sponsor for a very thorough analysis of the data. I have a couple of questions. The first one has to do with the duration of the PEs. I was wondering what the median duration was and whether it differed between the two groups.

DR. GONDA: The median durations ran about three weeks.

DR. FOLLMANN: About three weeks?

DR. GONDA: About three weeks.

DR. FOLLMANN: And similar for the two groups?

DR. GONDA: Yes, I believe they were, yes.

DR. FOLLMANN: During that time, I guess when you have exacerbation, you get additional antibiotics and treatment, which would tend to make the two groups similar in terms of duration?

DR. GONDA: Sorry. Can you please repeat it?

DR. FOLLMANN: When you have a PE, you treat it. I would imagine both groups would get similar treatments, which would tend to make the duration similar in my mind.

DR. GONDA: Yes, that is correct. Particularly, I just want to emphasize that about 80 percent of the exacerbations in the trials were those that were treated with antibiotics. Yes, the duration of the treatment of antibiotics would essentially determine the lengths of the exacerbation.

DR. FOLLMANN: My second question has to get to resistance. As was pointed out in the FDA document, for example, this is a one-year study and the therapy might continue on for more than a year. You addressed this to some extent in your slide, CE-29, which looks at, I think, exacerbation rate by MIC.

I think there is actually a better way to do this. If we look at the bottom part, it gives you

the highest cipro MIC at any visit. Hypothetically, you could have someone who had an MIC of the lowest value, say, 1 until the very final visit when he goes up to 50 or so. Effectively, that person had a very low MIC and that he's, in my mind, misclassified as being a high MIC, which will tend to, in my mind, might not be the best analysis.

I think a better way to do this would be to use the machinery Dr. Wittes had where you would take an MIC at a particular time when you measure it, and then say what's the risk of a PE going forward. So you measure MIC, say, at the end of March, and then you say, okay, this is going to determine my risk of a PE in April and so on.

I think resistance is a potential issue, especially because it's long-term therapy. I think this is not the best analysis to get at that. I think you have the machinery and the data to look at it in another way to address it, in my mind, a better way.

DR. GONDA: Thank you. We're obviously very

interested in this phenomenon as well. If I understand you correctly, you are asking whether we looked at the association of elevation of MICs with pulmonary exacerbations. And I'd like to invite Dr. VanDevanter to speak to the topic, who's in microbiology.

DR. VanDEVANTER: Hello, my name is Donald VanDevanter. I'm an adjunct professor of pediatrics at Case Western Reserve University. As a paid consultant, I helped Aradigm put together their integrated summary of microbiology, but I have no direct financial interest in the outcome of this meeting.

It's a very great question about the relationship between MICs and pulmonary exacerbations. There's a lot of microdata that was not obviously presented in the sponsor's presentation. If I could have the slide up, please.

The analysis that we did that I think is as close as we can get to what you're describing is one where we looked at respiratory specimens

collected within 28 days of a pulmonary exacerbation, and asked the question, for any given MIC, again, the highest MIC in patients that often will have multiple pseudomonas isolates, what proportion of those isolates were associated with a pulmonary exacerbation?

What we see is that the sample sizes are obviously much higher in the lower MICs, so the confidence intervals are tighter. We really don't see any relationship where as MICs increase, and that does tend to happen later in the study, that there's a greater association of those isolates with MICs relative to visits where patients have those MICs and no pulmonary exacerbation occurred.

DR. FOLLMANN: So that I understand this, this is where you would identify a pulmonary exacerbation and then try to get the MIC just prior to it. Is that what that table was doing?

DR. VanDEVANTER: I'm sorry if I wasn't clear. First of all, that was an analysis of all highest MICs taken at all visits from all patients. The question was, when that MIC occurred, what was

the proportion of the times that when that MIC occurred, there had been an exacerbation within 28 days after that MIC?

I agree that it's not as elegant as the design that you propose, but it certainly suggests there's no association where as MICs increase, the probability of a PE associated with that MIC increased.

DR. FOLLMANN: Thank you.

DR. BADEN: A follow-on question, how were isolates selected? How well does that represent the microbiome of the respiratory tract being sampled?

DR. GONDA: Dr. VanDevanter will give you an answer to this question.

DR. VanDEVANTER: First of all, these were traditional selective culture methods, so there was no microbiome analyses. Traditionally, plating of specimens, then plucking colonies based on morphology.

The protocol was designed to pick as many different morphotypes as could be identified in an

individual specimen, then each one of those morphotypes was worked up for study. In the instance where a patient had a single morphotype, the technician was allowed/instructed to pull multiple isolates of the same morphotype.

DR. BADEN: Done centrally or at a local micro lab?

DR. VanDEVANTER: Kind of a hybrid. There were three central laboratories that were spaced geographically so that shipment of samples could be achieved over night. Slide up, please.

There was a lab in New York, a lab in Dublin, and a lab in Singapore that handled regional isolates for North America and South America, respectively, Europe, South Africa, and Israel, and Eastern Europe. And then finally, for Oceania, those samples went to Singapore.

DR. BADEN: Thank you.

DR. GONDA: I also want to point out that the central lab was run by a single organization with the same SOPs, the same training, and so on. It was one central lab with multiple locations.

DR. BADEN: It is now 10:40. We'll take a 10-minute break. We will resume further clarification for the sponsor after the agency's presentation as we've done in the past.

Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:50.

(Whereupon, at 10:40 a.m., a recess was taken.)

DR. BADEN: We shall resume the meeting. We'll now proceed with the FDA's presentations. Dr. Tracy will present on the agency's efficacy evaluation.

FDA Presentation – LaRee Tracy

CDR TRACY: Good morning, committee, Aradigm. My name is LaRee Tracy, and I'm the statistical reviewer for this NDA.

This morning, I will present on the efficacy evaluation for ciprofloxacin dispersion, which I will refer to as ciprofloxacin DI, for the inhalation indication of treatment of non-cystic

fibrosis bronchiectasis with chronic infections with Pseudomonas aeruginosa.

This is my outline for today. First, I would like to begin to discuss the overall cipro DI clinical development program. As was previously discussed, this program comprised of phase 2 study, which was a proof of concept trial named ORBIT-2. This trial was randomized and double-blind in design. It was conducted among 42 patients who are 18 to 80 years of age. Twenty were randomized to the treatment arm and 22 to placebo.

All patients have had a diagnosis of non-cystic fibrosis bronchiectasis confirmed by computed tomography, evidence of P. aeruginosa colonization in the sputum, and at least two pulmonary exacerbations in the past 12 months of screening.

This trial was performed solely in Australia and New Zealand, and the duration of the trial was 6 months, comprising three on and three off-treatment periods. The primary endpoint in this trial was the change in the P. aeruginosa in

the sputum collection after 28 days of treatment, which was statistically significant with the p-value of 0.0002.

The trial did include several secondary endpoints, including the time to first pulmonary exacerbation, or PE, which was numerically longer in the ciprofloxacin DI arm compared to placebo. However, this endpoint was exploratory in nature only. The frequency of pulmonary exacerbations endpoint was not assessed in this trial. For the remainder of my presentation, I will focus on the results of the confirmatory phase 3 trials, ORBIT-3 and ORBIT-4.

Both phase 3 trials were multinational, multicenter, randomized, double-blind, and placebo-controlled with 48 weeks of double-blind treatment followed by 28 days of an open label period during which all participants received ciprofloxacin DI.

Aside from a PK substudy performed during the extension phase of ORBIT-3, all trials were identical in design and conducted almost concurrently. The key inclusion criteria are

stated here. Patients had to be male or female, at least 18 years of age with confirmed non-cystic fibrosis bronchiectasis per CT showing bronchial wall dilatation with or without bronchial wall thickening.

They had to have a documented history of at least two pulmonary exacerbations treated with antibiotics in the past 12 months, an FEV1 percent predicted of at least 25 percent, and a positive sputum or deep throat culture for P. aeruginosa.

Patients were randomized in a 2 to 1 design to either ciprofloxacin DI or matching placebo, which comprised a solution of placebo liposomes and saline.

Randomization was stratified by sex. The smoking status is screening where a smoker was defined as a patient who had never smoked or who had quit smoking in one year or more prior to the time of screening, and the number of PEs in the past 12 months prior to screening, which were categorized in the randomization as 2 to 3, 4 to 7, or more than 7.

Each trial was powered to demonstrate a difference between treatment arms in the time to first pulmonary exacerbation at week 48, assuming an 80-percent and a 60-percent failure rate in the placebo and ciprofloxacin DI arms, respectively.

This figure illustrates the general trial design, which you have seen already in the applicant's presentation. It essentially illustrates that following randomization, patients were randomized to the 1st cycle of treatment on day 1 and received treatment for 28 days, followed by 28 days of no treatment.

This process of 28 days on and off lasted for a total of 6 cycles. Following the final 28-day off treatment double-blind period, patients who had successfully completed the visit 14, which represents the end of the double-blind phase, were allowed to enter into an open label period for another 28 days on and off treatment.

The primary endpoint in both trials was the time to first pulmonary exacerbation measured at week 48. A PE was defined as the occurrence of at

least 4 signs or symptoms associated with exacerbations, which had to occur concurrently but did not have to start at the same time.

The signs and symptoms included the change in sputum production, dyspnea, cough, wheezing, a fever defined as a temperature at or above 30 degree Celsius, a decrease in exercise tolerance, malaise, fatigue, lethargy, or decrease in FEV1 or FVC of at least 10 percent from the past value, finally, radiographic changes. I will note that several of these signs and symptoms are subjective in nature.

Now, the first secondary endpoint was defined as the frequency of total number of pulmonary exacerbations by week 48. Then additional secondary endpoints included the frequency of severe pulmonary exacerbations, again defined as a pulmonary exacerbation requiring use of an IV antibiotic or hospitalization, as well as a change from baseline at week 48 in the quality of life bronchiectasis respiratory symptoms score, Qol-B.

Now, both trials included a pulmonary exacerbation adjudication committee, or a PEBAC, which functioned to adjudicate any PEs for which there was a discrepancy between that what was reported by the investigator and the definition of a PE as per the protocol. Note that the PEBAC did not review all PEs, only those for which there was a discrepancy.

The time to first PE was analyzed using a Cox proportional hazards model that included patients' sex and the prior number of PEs. Please note that these models did not include the third randomization stratum of smoking because too few patients had entered the trials who were smokers at the time of screening. And additionally, the categories of prior PEs was collapsed down to 2 to 3, or 4 or more due to the fact that there were too few patients enrolled into the trial with 7 or more PEs.

The survival curves were compared using the log-rank test statistic. The frequency of exacerbations endpoint was analyzed using a

negative binomial regression model that included the patients' sex and prior PEs as covariates as well. These models also included time, which was transformed on the log-scale as an offset variable; time, being the time in trial. This is an approach to attempt to address for time in trial as an indirect approach to account for patients' at-risk time for suffering from a PE.

Now, the quality of life measure was analyzed using a mixed effects model that included patients' sex, the prior number of PEs, baseline quality of life score, visit and treatment, and an interaction term for the two.

Finally, the full analysis set comprised all randomized patients who received at least one dose of medication, and this population served as the primary and secondary analysis population.

Now, to control for the overall type 1 error, a hierarchical stepdown approach was utilized separately in each trial. If the p-value for the test for the primary endpoint of time to first PE was equal to or less than 0.05 two-sided,

then testing of the first secondary endpoint of frequency of PEs was performed at a two-sided 0.05 level as well.

If statistically significant, then testing of the frequency of severe PEs and the change in the quality of life B endpoints were tested using a Holm-Bonferroni approach, which essentially ranks the p-values from highest to lowest and then applies a factor of 2, corresponding to the two endpoints being tested, to the lowest p-value. If that value was below 0.05, then it is considered statistically significant.

Now, pooling of data between the two trials for purposes of inferential testing was not part of the final statistical analysis plan. Pooling was only part of the integrated efficacy analysis, which is an analysis included in many NDAs for which when there are multiple clinical trials. This is an approach to use to assess and quantify the totality of evidence. Again, as I have noted, each trial was designed as a standalone trial.

Now, as discussed, the trials were designed

with a 48-week double-blind period after which the primary endpoint was to be assessed. The last study visit during the double-blind period occurred on August 17th of 2016 in ORBIT-3; on August 11th of 2016, in ORBIT-4, after which point the databases were essentially cleaned and locked.

After the double-blind databases were locked and after unblinding and analyses of these data by the applicant's CRO, which occurred between September and October of 2016, the applicant performed an unplanned re-review of both trial databases. This led to findings of programming errors that, once corrected, led to a change primary outcome status for two cipro patients in ORBIT-3 and two patients in ORBIT-4.

The applicant then performed a comprehensive audit of all electronic case report form entries for signs and symptoms or laboratory abnormalities as had been entered into the pulmonary exacerbation worksheets for all patients.

This audit led to an identification of 10 potential pulmonary exacerbations that had

previously been reviewed by the PEBAC and for which findings were potentially incorrect as per the applicant. Then these PEs were sent to the blinded PEBAC for re-adjudication.

The reasons provided as to why these 10 PEs were sent for re-adjudication included, A, that the clinical site had provided updated information to the electronic case report form after the initial PEBAC review, this occurred for two PEs;

B, incorrect information was supplied to the PEBAC during the initial adjudication process, this pertained to 2 pulmonary exacerbations;

Finally, C, inconsistencies between visit dates in reported signs and symptoms. This corresponded to 6 PEs or potential PEs. Due to the re-reviews, there were changes made to the final status of some patients in both trials, which I will discuss shortly.

Now, I'll discuss the results of the phase 3 program by first providing an overall of the patient dispositions. In ORBIT-3, 193 and 97 patients were randomized to ciprofloxacin DI and

placebo, respectively. However, 5.2 percent and 2.1 percent, for ciprofloxacin DI and placebo, respectively, failed to receive study drug. The most common reason for that was that those patients had suffered an exacerbation between the point of screening and randomization.

The full analysis population, therefore, in ORBIT-3 included 278 patients, of which 22.4 percent in the ciprofloxacin DI arm and 18.9 percent in the placebo prematurely discontinued from the trial. The prevailing reasons for failing to complete the trial were patient withdrawal followed by an adverse event. Overall, 78 percent of all randomized and treated patients in ORBIT-3 completed the double-blind period.

The total number of patients enrolled in ORBIT-4 were slightly larger, specifically 207 and 101 patients in the ciprofloxacin DI and placebo arms respectively. Few patients, only 1.3 percent failed to receive trial drug.

15 percent of patients in the full analysis

population prematurely discontinued from the trial largely due to patient withdrawal and adverse events, such that overall, 86 percent of randomized and treated patients completed the double-blind period, slightly more in the ciprofloxacin DI arm, which is 86 percent versus the placebo of 83 percent.

Now, as we would expect in randomization, treatment arms were generally balanced across the measured baseline characteristics and demographics. Specifically, among patients in the full analysis population, the majority of patients were female, approximately 70 percent in ORBIT-3 and 65 percent in ORBIT-4.

The average age at randomization was 65 and 63 years, respectively, in ORBIT-3 and 4, and 61 percent of patients in ORBIT-3 were 65 years of age or older of which the proportion was slightly lower in ORBIT-4, which was 54 percent.

In both trials, the average number of prior PEs in the past 12 months of enrollment was 3. In both trials, most patients were of white race.

However, in ORBIT-4, 8 percent of enrolled patients were with a reported race of either American Indian or Alaskan Native. None of this population was enrolled in ORBIT-3. Few patients were current smokers at baseline, only 1.4 percent and 0.6 percent in ORBIT-3 and ORBIT-4, respectively.

As has been discussed, the proportion of patients receiving macrolide treatment at baseline was higher in the ciprofloxacin DI arm, 24 percent, compared to the placebo arm, 14 percent in ORBIT-3. However, in ORBIT-3, the reverse was shown. There were 24 percent of patients on baseline macrolides in the placebo arm versus 16 percent in the ciprofloxacin arm. This factor imbalance was assessed by myself in various sensitivity analyses, which I will discuss shortly.

Finally, these trials were conducted across multiple regions, which were generally similar between the two trials with the exception of in ORBIT-3, patients enrolled in Central and Eastern Europe comprised approximately 12 percent of the population compared to 24 percent in ORBIT-4. And

in addition, more patients, specifically 25 percent were enrolled at sites located in Australia or New Zealand in ORBIT-3, compared to only 14 percent in ORBIT-4.

Finally, data on the overall duration of the disease prior to screening or randomization, as well as the number of effective lobes, the subjects enrolled were not collected.

Now, I will discuss the results of the primary efficacy analyses, and these are results based on the data after the applicant's re-review of the data.

In ORBIT-3, 59 percent and 57 percent of ciprofloxacin DI and placebo-treated patients in the full analysis population experienced at least one pulmonary exacerbation by week 48. This results in a difference in the proportion of approximately 2.2 percent.

The difference in median time to the first exacerbation was 78 days, and the overall hazard ratio, cipro to placebo, in the stratified model was 0.99, yielding a 95 percent confidence interval

0.71 to 1.38, and a large p-value of 0.974, suggesting no overall difference between treatment arms in time to the first pulmonary exacerbation.

Now, the results were similar in an unstratified model and in a model including the sex and prior PEs as randomized. Results of the primary endpoint analysis in ORBIT-4 differed slightly from those ORBIT-3. Specifically, fewer patients, 55 percent, in the ciprofloxacin DI arm, suffered a PE by week 48 compared to the placebo arm which was 65 percent.

This yielded a difference in the proportion of approximately minus 10 percent favoring ciprofloxacin DI. Overall, the difference in the median time to first pulmonary exacerbation was 72 days, with a hazard ratio of 0.71, and a p-value of 0.032. Again, this is in the corrected data.

These results suggested 29 percent reduction in the hazard in the ciprofloxacin arm compared to the placebo arm when assuming a constant to proportional hazard over the 48 weeks.

Finally, results were similar when

considering pulmonary exacerbations based on the investigators' assessment only. Specifically, the hazard ratio in ORBIT-3 was 0.92, with a p-value of 0.61. And in ORBIT-4, the hazard ratio was 0.73, with a p-value of 0.05.

The Kaplan-Meier survival are illustrated here and are consistent with the measured hazard ratios just presented. ORBIT-3, shown on the left, and ORBIT-4, on the right, and in both figures, the ciprofloxacin DI arm is shown in the dashed red curve.

Overall, the figure on the left illustrates no overall difference between treatment arms in the survival function. The figure on the right illustrates a constant and proportional hazard between arms favoring ciprofloxacin DI.

In ORBIT-3, the proportion of patients censored due to prematurely discontinuing the trial before suffering a pulmonary exacerbation was 11.5 percent in the cipro arm and 12.6 percent in the placebo arm. The median days when patients were censored was 84 and 88.5, respectively.

In ORBIT-4, the proportion of patients censored prior to experiencing a pulmonary exacerbation was 5.3 percent in the ciprofloxacin arm and 7.1 percent in the placebo arm. The median days of censoring among these patients was 151 days in the ciprofloxacin DI arm and 56 days in the placebo arm.

As introduced previously, an unplanned re-review of data after the database were locked, and unblinded, and analyzed, led to changes in the finally primary outcome for some patients. This table highlights those changes that affected the primarily outcome only.

As shown in blue, there were 2 patients, both in the ciprofloxacin DI arm, denoted as C in the table, with a PE added after the re-review, and no changes in the placebo arm. These changes resulted in a minor change in the p-value from 0.826 to 0.974. In contrast, in ORBIT-4, there were two added PEs, both in the placebo arm, leading to a change in the p-value from 0.058 to 0.032.

Please note that there were other changes to the pulmonary exacerbations as a function of this re-review that affected the frequency of PEs endpoint, but there are not shown here because the overall changes and the impact on the endpoint are considered nominal.

Now, we'll discuss findings from the analysis of the secondary endpoints. Although ORBIT-3 failed to demonstrate a statistically significant difference between treatment arms on the primary endpoint of time to first event, I assessed the frequency of events secondary endpoint for exploratory purposes only, and the rationale being that the overall number of events is as important as the time to event. In addition, these two endpoints are highly correlated, so we would expect to see consistency between them.

As shown here in the left-hand side of the table, in ORBIT-3, the mean number of PEs by week 48 was 1.09 in the ciprofloxacin DI arm and 1.3 in the placebo arm, leading to an estimated incidence rate ratio, or IRR, of 0.852 and a

confidence interval ranging from 0.647 to 1.123, showing a lack of sufficient evidence of any difference between treatment arms. Results of the exploratory analysis of severe PEs was also similar to that of the frequency of overall PE, showing no overall difference.

In ORBIT-4, the mean frequency of exacerbations at week 48 was 0.98 and 1.47 in the ciprofloxacin DI and placebo arms, respectively. This corresponds to a reduction of approximately one-half of one PE over one year. The estimated IRR was 0.631, suggesting a 37-percent reduction in the frequency of PEs, an associated p-value of 0.0006. The results suggest a significant decrease in the overall frequency of PEs by week 48 in the ciprofloxacin arm compared to placebo.

Please note in this table that the confidence interval for the IRR for frequency of severe PEs is correct, however, it's incorrect in your briefing document.

Now, the hierarchical testing approach that was prespecified in the analysis plan for testing

of the frequencies PE secondary endpoint was such that if the primary endpoint was statistically significant, then those endpoints would be subsequently tested.

For ORBIT-3, since the primary endpoint did reach the value of less than 0.05, testing of the frequency of the pulmonary exacerbations was performed, and that yielded a p-value of 0.0006, as I just showed, thereby allowing testing of the frequency of the severe exacerbations endpoint, which showed a p-value of 0.0027. The Holm-Bonferroni adjusted p-value therefore is 0.0014, which is less than 0.05.

Keep in mind that the frequency of the overall and severe PEs endpoints are highly correlated. Also, I would like to point out here on this footnote on this particular slide that the corrected p-value should be 0.0054, not 0.0014 as I just stated.

The distribution of patients by a total number of exacerbations is shown in this slide. In ORBIT-3, slightly more patients in the placebo arm

did not experience a pulmonary exacerbation compared to the ciprofloxacin DI arm, and the reverse was observed in ORBIT-4.

Also, in ORBIT-4, one patient in the ciprofloxacin DI arm experienced 6 PEs, one patient experienced 7, and another experienced 8 PEs. No patients in ORBIT-3 experienced more than 5 PEs during the 48 weeks.

Therefore, I had conducted a sensitivity analysis to see if these extreme number of pulmonary exacerbation events overly impacted the results of the trial and found that they did not. Analyses of events that were truncated at 4, 3, and 2 yielded findings similar to those presented on the prior slide.

Results of the analysis of the additional secondary endpoints of change in quality of life bronchiectasis at week 48 on the respiratory domain is shown at the top of this table. Neither trial demonstrated a difference between treatment arms on this quality of life measure over the course of the 48-week period. Again, analysis of this endpoint

for ORBIT-3 was for exploratory purposes only.

The results show that the overall least squares mean difference between treatment arms was negative 1.62 in ORBIT-3 and 0.84 in ORBIT-4, where a positive difference favors cipro as it suggests an increase over time in the measure. Nevertheless, neither difference was of any meaningful magnitude, which would be close to 8 or 9 based on several estimates.

The bottom half of this table presents findings from an analysis of the FEV1 percent predicted change from baseline at week 48, which is an additional endpoint but not one part of the hierarchical testing. As shown, all arms had a slight drop in the FEV1 percent predicted, which is unfavorable. The differences between treatment arms were negligible and not statistically significant.

Here, I am presenting results of subgroups analyses on the primary endpoint to time to first pulmonary exacerbation by sex, prior PEs, age, baseline macrolide use, FEV1 percent predicted, at

or below 50, which is viewed as a clinically relevant value, and region.

While trials were not powered to show a statistically significant difference between treatment arms on any specific characteristic at baseline, these analyses are performed in an attempt to identify any factors for which there could be an imbalance in treatment effect.

As shown here, there was no evidence of any interaction. The overall point estimates in ORBIT-3 hover around 1, again suggested a no difference between treatment arms. In ORBIT-4, the estimates are generally consistent, all falling to the left of 1, against consistent with the overall results.

As previously noted, the proportion of patients receiving macrolide treatment at baseline in the ciprofloxacin DI and placebo arms was 23.5 percent and 13.7 percent in ORBIT-3 and 68.5 percent and 24.5 percent in ORBIT-4, respectively.

Therefore, a sensitivity analysis was

performed, including baseline macrolide use as an additional factor in the primary and secondary analyses models to assess that these imbalances between arms might help to explain the observed discordance in efficacy between trials.

Findings from these analyses shown here suggest that, overall, there was a slight decrease in the hazard ratio from 0.99 to 0.93 and a decreased p-value, from 0.974 to 0.731 in ORBIT-3, and a slight increase in the hazard ratio of 0.71 to 0.74, and an associated increase in p-value from 0.032 to 0.057 in ORBIT-4. However, I would say these overall results resemble those from the primary efficacy analysis.

The lower half of this table provides the sensitivity analysis, including baseline macrolide for the frequency endpoint. Overall, the results remain unchanged, but including baseline macrolide use.

Therefore, the discordant findings in efficacy between ORBIT-3 and 4 do not appear to be associated with numerical imbalances between

treatment arms and baseline macrolide use. This is somewhat to be expected given that while the use of baseline macrolides was imbalanced between arms, the overall use was approximately 20 percent in both trials.

Finally, I performed a sensitivity analysis considering the prior number of pulmonary exacerbation events before screening as a continuous factor in both the primary and the secondary analyses models rather than treating that as a categorical factor, as was done in the planned analysis.

The results are shown here for both the primary and the secondary endpoint of frequency of PEs, and overall, the results do not change greatly from those presented already.

There are some issues and limitations in the findings from ORBIT-3 and ORBIT-4. With respect to the time to the first pulmonary exacerbation, the issue is that this endpoint only captures the first exacerbations and the time to, ignoring subsequent events.

For a chronic disease such as non-cystic fibrosis bronchiectasis, understanding how long between treatment initiation and the first pulmonary exacerbation is certainly important. However, understanding subsequent exacerbations is important as well.

The applicant did provide results of post hoc analyses using a counting process approach, which considers all events using a time to event approach; though again, results were similar to those shown in this presentation and do not alter the negative results of ORBIT-3.

That brings me to the secondary endpoint of frequency of PEs, which certainly captures all exacerbations. However, from an analytical perspective, it is challenging it of an endpoint to model.

The modeling approach used by myself and the applicant included the patients' time in trial as an approach to indirectly measure the patients' at-risk time. However, this fails to account for the times during which a patient is experiencing

exacerbations is therefore not at risk.

The applicant performed several other analyses, including post hoc counting process analyses to attempt to address this, but again, overall, the findings are similar to those presented today. Additionally, I considered other modeling approaches, including a Poisson regression approach, again leading to results that are similar to those when using a negative binomial model.

Now, also, findings from an analysis comparing the total duration of exacerbations between treatment arms yielded differences that were not statistically significant in either trial. Specifically, when accounting for total time in trial, the mean difference between treatment arms in ORBIT-3 was 3 and a half days, favoring placebo, and a p-value of 0.65. And it was 10.2 days favoring ciprofloxacin DI in ORBIT-4 with a p-value of 0.22.

Finally, both trials were designed with a 48-week double-blind treatment period, comprising 6 cycles, on and off, as I've discussed. Given the

chronic nature of this disease, these trials were likely too short to fully assess if treatment effect would wane over time, which may likely occur with increasing drug resistance.

In summary, there are concerns regarding the cause and the rationale behind the applicant's re-review of data after database locking, unblinding, and analysis. As highlighted, these unplanned steps led to slight changes in the overall results in both trials, but mostly affected results in ORBIT-4.

Review of these changes is ongoing, which is why I presented the results using the prior data and the data after the re-review. As for ORBIT-3, more patients prematurely withdrew from the trial in the ciprofloxacin DI arm compared to the placebo arm. The trial failed to demonstrate a difference between treatment arms across all planned endpoints and analyses, and slightly more patients on the ciprofloxacin DI arm suffered at least 1 PE compared to the placebo arm.

In contrast, more patients in ORBIT-4 on

ciprofloxacin DI completed the trial compared to placebo. The trial demonstrated a marginal effect favoring ciprofloxacin DI on time to first pulmonary exacerbation in the data after the data re-review and re-adjudication.

Results were statistically significant in favor of ciprofloxacin DI for the frequency endpoints, however, no meaningful difference was observed on the quality of life or on the pulmonary measures.

Despite numerous analyses, including those controlling for baseline macrolide use, assessing region, and other baseline factor, no clear explanation can be identified to explain the discordant findings in efficacy between ORBIT-3.

Finally, these trials may be too short in duration to fully characterize the potential for drug resistance due to the chronic antibiotic exposure. Further details regarding the resistance patterns observed in these trials will now follow in the clinical presentation. Thank you for your attention.

DR. BADEN: Thank you, Dr. Tracy. I'd like to ask Dr. Allende to please present the evaluation of the clinical safety.

FDA Presentation – Maria Allende

DR. ALLENDE: Good morning. My name is Maria Allende, and I am the medical reviewer for the NDA 210693, and I will be presenting the clinical safety of ciprofloxacin dispersion for inhalation in non-cystic fibrosis bronchiectasis patients.

This is my outline. I will review the safety assessments of the to-be marketed product in phase 2 and phase 3 trials. The differences noted between treatment arms in the two phase 3 trials, the spirometry assessments for safety, the evaluation of resistance of Pseudomonas aeruginosa isolates during follow-up, and will end with my conclusion.

This is the goal of the safety review, is to explore and assess systemic and local adverse events related to the inhaled route of administration, and the difficulties in assessment

of the causality are that there's an overlap of adverse events and disease outcomes that are comorbidities and concomitant medications.

The safety database admitted in support of the indication consist of one phase 2 trial of a total of 42 patients randomized in a 1 to 1 ratio to ciprofloxacin DI or placebo, and two phase 3 trials with a 2 to 1 randomization in which a total of 582 patients received at least one dose of study drug or placebo.

Therefore, the total safety database consists of 409 patients who received at least one dose of ciprofloxacin DI and 215 patients who received at least one dose of placebo.

The earlier phase 1 and phase 2A studies, as Dr. Froehlich referred in his presentation and Dr. Gonda also, evaluated prototype formulations and the liposomal formulation of ciprofloxacin in healthy subjects and in non-CF bronchiectasis patients who were treated with the liposomal ciprofloxacin for inhalation, the patients, listed as CFI in this slide, for 28 days for one cycle

only.

The phase 2 trial was the first one to test the to-be marketed product, which was the same formulation and dose used later in the phase 3 trials. It included 42 patients, 20 treated, and 22 placebo controls, and the primary endpoint was the microbiological efficacy in reducing the Pseudomonas aeruginosa sputum density. The treatment phase included three 28 days on and three 28 days off cycles for a total of 6 months with a 28 days follow-up period.

Because of the different endpoints, the fewer number of cycles, and shorter follow-up, this trial was reviewed separately without pooling it with the phase 3 trials.

Here is the phase 2 trial safety review. There were no deaths reported. Three patients in each arm, which represented 15 percent of the treatment arm and 13.6 percent of the placebo arm, experienced a serious adverse events of lung disorder; that was the preferred term in the dictionary, and this term included verbatim terms

of pulmonary exacerbations and respiratory infections.

Lung disorder, wheezing, hemoptysis, dyspnea, and abnormal product taste were the most common adverse events observed at comparable rates in the placebo and treatment arms.

The main safety database consists of two identical phase 3 trials, ORBIT-3 and ORBIT-4. The only difference between them is that a pharmacokinetics and safety substudy was conducted in the open label phase of ORBIT-3 only. As you heard from LaRee and other's presentations, these trials randomized a total of 582 patient in a 2 to 1 ratio of whom 389 received at least one dose of ciprofloxacin DI and 193 received at least one dose of placebo.

The treatment phase included 6 treatment cycles, each one composed of 28 days on treatment, followed by 28 days off treatment, for a total duration of 48 weeks. Following this double-blind phase, an open label extension of voluntary enrollment followed in which patients received

28 days of treatment with an active drug only to increase the number of exposed subjects. The safety review here presented includes only data from the double-blind phase.

This table is an overview of the safety summary showing the proportions of patients with any treatment adverse events and their distribution shown on the first column in blue by severity and seriousness, including those leading to death and those leading to permanent study drug discontinuation. That's the last row.

Data from ORBIT-3 and ORBIT-4 shows some differences, and I want to draw your attention to the proportions of patients with serious adverse events and adverse events leading to study drug discontinuation, the third and the fifth rows.

In ORBIT-3, there was a higher proportion of serious adverse events and of adverse events leading to permanent study drug discontinuation in the treatment arm as compared to the placebo arm. In ORBIT-4, the opposite is observed, with higher proportions of SAEs and study drug discontinuations

occurring in the placebo arm. The last column on the right shows data from the pooled studies where most of the differences appear to even out.

The adverse events leading to deaths mostly represented common pulmonary complications of the underlying disease and were proportionately higher in the placebo arm of each study.

The top row shows the rates in the pooled studies, the two middle rows, those of ORBIT-3, and the bottom two rows, those of ORBIT-4. The most common fatal adverse events were pneumonia and respiratory failure. Overall, there were 1 percent more deaths on the whole study population in ORBIT-3 than in ORBIT-4, with a narrower difference of 0.5 percent between treatment and placebo arm observed in ORBIT-3 as compared to that of ORBIT-4 which was wider, 3 percent.

This table shows respiratory serious adverse events that occurred in two or more patients in the ciprofloxacin DI arm. The assessment of causality is difficult, again, because these represent the most common manifestations of the underlying

disease. However, a contribution of the study drug by means of irritation, inflammation, or lack of efficacy cannot be ruled out.

Again, some differences are noted in ORBIT-3 and ORBIT-4. The rate of hemoptysis and bronchospasm in SAEs in ORBIT-3 are more than double in the treatment arm as compared to placebo. In ORBIT-4, pneumonia is observed only in the treatment arm. And in the pooled study, the rate of hemoptysis is still higher in the treatment arm, mainly driven by the ORBIT-3 outcomes. Most of the other differences appear balanced in the pooled study.

Because of the fact that pneumonias occurred only in the treatment arm of ORBIT-4, we took a closer look at all cases of pneumonia reported in similar preferred terms across the study. In this table, only the pneumonia classified as SAEs are shown.

We have some demographic and sputum culture data on all patients with any event, AE or SAE, of pneumonia which total in amount of 30 patients, and

22 of those in the treatment arm and 8 in the placebo arm. All of these patients were treated with antimicrobial agents.

The frequency was higher in patients older than 65 years of age and higher rates of colonization within 28 days of the event of pneumonia. Colonization by Pseudomonas aeruginosa resistant to ciprofloxacin was observed in subjects in the treatment arm in this population.

The rates of adverse events leading to premature treatment discontinuation show, as mentioned before, higher rates in the treatment arm of ORBIT-3 as compared to placebo. A slightly higher rate of serious adverse events leading to discontinuation was also observed in the treatment arm of ORBIT-3 as compared to placebo.

This, however, was not observed in ORBIT-4, and in the pooled study, there is a slightly higher rate of adverse events leading to discontinuation in the treatment arm and mainly driven by the ORBIT-3 outcomes.

This table shows the most common adverse

events which are pulmonary events frequently observed in this patient population, and there was active surveillance for this, as Dr. Froehlich explained.

The asterisk indicates where terms of similar clinical significance had been pooled by individual patient identifiers, so we only counted one subject. The terms included in each group are listed in the footnote.

Wheezing and forced expiratory volume decreased are included in the group termed bronchospasm, which is the top row. And the two rows below that are indented mean that they belong to that group termed above.

I present them below separately because these were the two most common terms in that group. I have to clarify that all terms included also belong to the standardized MedDra query called asthma-bronchospasm. Patients have been counted only once in each row, but a subject may have contributed to events in more than one row. Again, we see that rates are higher in the treatment arm

of ORBIT-3 than placebo, and the opposite in ORBIT-4 is occurring.

In the pooled study, forced vital capacity decrease and forced expiratory volume decrease reported as an AE when it was at least a 10-percent decrease or higher, where the events with highest risk differences between treatment and placebo arms -- I mean, forced expiratory volume decreased only. This was mainly driven by the ORBIT-3 outcomes.

Then upper respiratory tract infection was 3 percent higher in the treatment arm, and most of the other events were reported at similar rates of 1 to 2 percent higher in the treatment arm.

These are the adverse events most likely due to the inhaled route of administration by means of irritation or inflammation of the respiratory tract, and are cough, hemoptysis, and bronchospasm. In addition to this, there were 7 cases of epistaxis reported only in the treatment arm at a rate of 1.8 percent total. Even though confounding factors were present, a contribution of the study

drug by means of irritation cannot be ruled out.

The effect of the drug administration was evaluated with serial spirometry measurement at selected visits, which were visit 1 and visit 8. Measurements were done at 4 time points, 30 to 60 minutes before treatments, administration, and then at 15, 30, and 90 minutes post-treatment.

A decrease at FEV1 percent predicted of 15 percent or higher was protocol defined as clinically significant. This slide shows the proportion of patients for the pooled study who had a decrease of 15 percent or higher in the FEV1 percent predicted at any time point during these assessments post-treatment.

A higher proportion of subjects in the treatment arm was observed at both visits. Even though this shows the pooled data, similar trends were observed in each of the studies.

Regarding the evaluation of adverse events associated with the fluoroquinolone class, two points to consider are that the systemic exposure of ciprofloxacin DI is 10-fold lower than following

orally or intravenously administered ciprofloxacin DI at approved doses.

The confounding factor is that approximately 50 percent of subjects, as Dr. Froehlich mentioned in his presentation, received oral or intravenous ciprofloxacin during the study. However, adverse events associated with fluoroquinolones were not increased to a significant extent in the treatment arm as compared to the placebo arm in any of the studies.

This slide serves as an introduction to the next four slides that I will present. Throughout the study, emerging resistance to ciprofloxacin was evaluated by sputum cultures that were to be taken from all subjects at baseline and at all follow-up visits.

Isolates were classified in these three categories, sensitive, intermediate, and resistant, based on these MIC cutoffs. Frequently, patients had more than one Pseudomonas aeruginosa isolate present in the sputum.

The evaluations include these three

assessments: the distribution of Pseudomonas aeruginosa isolates by treatment arm at baseline and after treatment; the number of subjects who acquired resistance to Pseudomonas aeruginosa isolate during follow-up by treatment arm; and the effect of intermittent exposure to ciprofloxacin DI throughout the study reflecting in the proportion of isolates with highest ciprofloxacin MIC by treatment group and study visits.

I have to clarify that no genomic testing was conducted in this study, and no other cultures from any other body site was obtained prospectively.

This slide shows the distribution of isolates by MIC categories in each of the studies by selected visits at baseline, visit 1, at the start and end of the 6th treatment cycle which are visits 12 and 13, respectively, and at visit 14, the last study visit, which occurred at the end of the 6 off-treatment cycle.

I want to draw your attention to the proportions of sensitive and resistant isolates in

the treatment groups of ORBIT-3 and ORBIT-4, particularly at baseline and at visit 4, the last visit.

In the treatment arm, there's a consistent decrease of 15 percent or more in the proportion of sensitive isolates and an increase of 10 percent or higher in the proportion of resistant isolates. However, in the placebo arm, represented in blue, the proportion of sensitive isolates at these same time points remain comparable, and the proportion of resistant isolates decreases by 5 percent and 3 percent in ORBIT-3 and ORBIT-4, respectively.

These are the numbers of patients who acquired one or more resistant isolates during the study follow-up in ORBIT-3 and ORBIT-4, the results presented from the same selected visits as in the previous slide.

In the treatment arm, there was a consistent increase in the proportion of patients who acquired resistant isolates in the treatment arm of both ORBIT-3 and ORBIT-4, a 9 percent increase in ORBIT-3 and a 16 percent increase in ORBIT-4. In

the placebo arm, the proportion of patients with resistant isolates in both studies remain stable throughout.

This graph represents the same information of the previous slide, however, this is for all the follow-up visits to show that the rates were consistently higher in the treatment arm in all of the study follow-up visits.

This figure was submitted by the applicant and presented, I believe it's the same as Dr. Gonda presented, also shows a consistent pattern among the highest ciprofloxacin MIC Pseudomonas aeruginosa isolates from the treatment arm where ciprofloxacin MICs, represented in the red bars, tended to increase and decrease, depending on study visit.

The horizontal line crossing the bars represents the MIC value of 4, above which all the isolates were considered resistant. The crosses on the vertical lines represent the mean MIC values, and the whiskers are the ranges.

After 28 days on treatment, for example,

after the first treatment, visit 3, on treatment, the proportion of patients in the treatment arm had an MIC above 4, numbers that were higher in proportion, 37.8 percent as compared to the proportion of placebo recipients, which was 21 percent.

At visit 4, which occurred following the 28 days off treatment, the percentage of highest MIC isolates decreased in the treatment arm. By the end of the last 6th off treatment, which is visit 14, on the top right, was the last study visit of the double-blind phase, the proportion of highest MIC isolates do not appear to return to baseline. On the contrary, proportions in the placebo arm, represented in the blue bars, show a consistently stable pattern throughout the whole study follow-up.

Here are my safety conclusions. Although differences were observed in the safety profile of ORBIT-3 and ORBIT-4, most were balanced in the pooled analysis. A higher proportion of patients with worsening of lung function, as manifested by

FEV1 percent predicted decreases, was observed with study drug administration.

Increased ciprofloxacin resistance from baseline to follow-up was seen in the treatment arm as compared to placebo. It is unknown whether exposure beyond one year may lead to additional safety concerns, increased resistance to fluoroquinolones, or result in reduced treatment effect.

Thank you so much for your attention.

DR. BADEN: Thank you, Dr. Allende. I'd like to invite Dr. Smith to provide us with a summary presentation of the agency's evaluation.

FDA Presentation – Thomas Smith

DR. SMITH: Thank you. Just in consideration of trials in non-cystic fibrosis bronchiectasis in general, as you've heard, there are no approved therapies for prevention or management of exacerbations. We do recognize the need for safe and effective therapies for patients with this condition.

Studies of other inhaled antibacterial

drugs, which include tobramycin, gentamicin, aztreonam, colistin, and ciprofloxacin for the prevention of non-cystic fibrosis bronchiectasis exacerbations have yield mixed results, and none are approved for this indication. Once again, these publications are referenced in your document.

There are uncertainties regarding the duration of treatment, the frequency of administration, and the appropriate endpoints to use in clinical trials of this condition.

What we have observed from the data presented by the applicant are that there was an unplanned review after data-locking and unblinding that led to changes in the primary outcome.

ORBIT-3 failed to demonstrate a difference between arms across on all endpoints and analyses. There were slightly more patients in the ciprofloxacin DI arm who experienced a pulmonary exacerbation compared to placebo patients.

ORBIT-4 demonstrated a marginal effect on reducing the time to first pulmonary exacerbation based on the re-review and re-adjudicated data.

There was a significant reduction in the frequency of pulmonary exacerbations and of severe pulmonary exacerbations that favored ciprofloxacin DI.

There was no demonstrated treatment effect on the Qol-B respiratory symptoms scale, pulmonary function, and duration of pulmonary exacerbations with ciprofloxacin DI. We lack a clear explanation for the discordant findings between these trials.

From a safety standpoint, 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. Patients treated with ciprofloxacin DI were more likely to have treatment-emergent ciprofloxacin-resistant Pseudomonas aeruginosa cultured at any point post-baseline.

There remain several uncertainties. The clinical relevance of the observe treatment effects when risks such as adverse reactions and the development of resistance are considered; the durability of the efficacy and safety findings beyond one year of use, for example with the

development of resistance; and there are uncertainties as to whether the long-term use of inhaled ciprofloxacin could limit the utility of systemic fluoroquinolones for treatment of severe bacterial and exacerbations and pneumonia in non-CF bronchiectasis patients.

We'll be having some clarifying questions, and open public hearing, and additional discussion, but I would like to remind the committee that the question before it is whether the applicant has provided substantial evidence of the safety and efficacy of ciprofloxacin dispersion for inhalation in delaying the time to first exacerbation after starting treatment in non-CF bronchiectasis patients with chronic lung infections with Pseudomonas aeruginosa.

If yes, we'd appreciate any recommendations concerning labeling, and if no, we would like a discussion of what additional studies and analyses are needed, including discussion of appropriate endpoints, drug regimen, and trial duration. Thank you.

Clarifying Questions

DR. BADEN: Thank you, Dr. Smith.

If members of the committee have clarifying questions for the agency's presentation, please let Lauren or myself know, and we will facilitate an orderly discussion. I will start with the first question to Dr. Tracy.

The applicant in the earlier presentation discussed the count method. What is your evaluation of that statistical approach versus what was initially proposed?

CDR TRACY: That's correct. I view them as exploratory at this point. They weren't planned. They weren't part of the initial analysis plan for analyses of the frequency or the time to. They have their value in exploratory uses at this point, but beyond that, they're not conclusive in my opinion.

DR. BADEN: Thank you. Dr. Green?

DR. J. GREEN: This is also for Dr. Tracy, and perhaps maybe the applicant needs to respond, too. There seems to be a discrepancy in the

subgroup analysis between the FDA's analysis and the applicant's analysis, specifically in looking at the population that, at baseline, had greater than 4 pulmonary exacerbations.

The applicant's presentation would suggest that, at least in ORBIT-4, there was a significant reduction in frequency of PEs in that group, and time, whereas in FDA's, I think that wasn't shown.

CDR TRACY: My analysis of subgroups was presented for only the time to first event. Their results that they show were for frequency endpoint.

My results in the frequency endpoint by subgroups resemble theirs. I didn't present them because at that point, I didn't put much value into them. We typically focus on subgroup analyses for the primary endpoint. I'm happy to show you my results, but they do mirror the sponsor's for that particular endpoint.

DR. BADEN: There are many more questions for the applicant, so where time allows, we'll have more discussion with the applicant before lunch or after lunch.

If there are key aspects of questions to the agency where the applicant can provide critical information, we'll encourage that, but I want the focus right now to be clarifying the agency's presentation.

DR. GONDA: Thank you.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: This is a question again for the FDA, Dr. Tracy. Since the question before us deals with the primary endpoint of time to first event, looking at that a little bit more, did you have a pooled analysis of both trials looking at the efficacy to prevent the first PE, and perhaps in all of that incorporates macrolide use and a number of prior PEs?

CDR TRACY: I'm not showing results of a pooled analysis of the time to the pulmonary exacerbation endpoint. I see no value in pooling those data between trials because one failed; one did not. It wasn't part of the analysis plan.

Certainly, I provided results of stratified analyses using baseline for each trial

independently. I will say that the pooled results of the time to are provided in the sponsor's documentation, and as you note there, when pooling, again, I don't support it, but when pooling it, the overall p-value still is above 0.05 for the time to.

DR. BADEN: Dr. Green?

DR. M. GREEN: This really is a follow-up to the previous question. From a statistical perspective, what error would we make by accepting the pooled data? As a caveat, those of us who practice clinical medicine frequently look at meta-analyses where they combine studies.

In this particular case, we have the beauty of two studies whose design are identical with the exception of, I think in one study, something was done during the last 28 days when they were no longer on randomization.

I would just ask your opinion as a statistician, what errors would we make by combining these, particularly given the design is so similar or, in fact, identical?

CDR TRACY: I don't know if you're making an error per se. I think that you would have to have a different standard, a different value for what you're going to deem the pooled result to be statistically significant.

Would it be 0.05 two-sided alpha level as your criterion at that point? Perhaps not, perhaps something lower. Again, that wasn't part of the analysis plan, and at this point, to me, it's post hoc, it's exploratory.

I don't know what the criterion is at this point. I've already seen the results of the two trials. One is positive; one is negative. It hovers at around 1 for a p-value, frankly.

Let me step back. Typically, when I pool data, it's when I have studies that lean in the same direction; perhaps they're underpowered to detect a difference, but collectively, you're gaining more power by pooling them and accounting for the trial size accordingly in a way to approach. But here you have one study that's trending in favor of the treatment arm and one that

isn't showing that at all, so, to me, it's inappropriate to pool the data.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: The question of pooling was the pressing question in my mind, which you have addressed. The other question I have was with the microbiology data, in particular in relationship with the occurrence of pneumonia in ORBIT-4.

There were 10 cases of pneumonia. Do we know what pathogens were responsible for those pneumonia? Were they resistant pseudomonas or were they other pathogens different from pseudomonas that were resistant to cipro?

DR. ALLENDE: Not all of the patients were worked up for the diagnosis, so we can't say that the pathogens isolated were responsible for the pneumonia. We have data collected within 28 days before and after the diagnosis of the episode.

I have a backup slide that I can show. The slide number is 35; 35 in the total set, not in the backup set.

There were 30 patients with pneumonia, and 6

of them in the ciprofloxacin arm were below 65 years of age, 3.5 percent, and 3.9 percent at that age group in the placebo arm. 7.3 percent were in the group of older than 65 years of age, and 4.3 percent in the placebo.

Sixty-eight percent were serious adverse events and 87 percent in the placebo group. Two resulted in death in the treatment arm, and one in the placebo arm, basically no differences.

There were seven more colonizations -- the percentage of pseudomonas-resistant colonization was 36.3 percent in the treatment arm versus 25 percent in the placebo arm of these subgroups of 30 patients. And there was a slightly higher increase in the colonization by Staphylococcus aureus also. There were 7 in the ciprofloxacin arm and only 1 in the placebo arm.

DR. OFOTOKUN: [Inaudible – off mic].

DR. ALLENDE: No strep pneumo was found. Although I think the company has more data about Haemophilus influenzae occurring at a higher rate in the placebo arm, not in these 30 patients,

though. This is data only from the 30 patients with pneumonia. Pneumonia was reported as pneumonia only, pneumonia bacterial, and pneumonia viral, but all of the patients had no infiltrates and received antimicrobial therapy for a long time.

We can't say that that is the etiology. The colonization is the only data we have.

DR. BADEN: Just a follow-on, how confident are you in their assessment of other pathogens being present?

DR. ALLENDE: Well, I think that's a limitation from the data because we only have sputum cultures. The other emergent pathogens were not tested for resistance to ciprofloxacin, so there's a limitation. Maybe the applicant wants to talk more about that?

DR. BADEN: What I would like the applicant to do is keep track of these questions, and then when we move to the more general clarifications, we'll ask for you to clarify.

DR. GONDA: Thank you very much.

DR. BADEN: That will be very helpful.

DR. GONDA: Thank you.

DR. ALLENDE: Okay.

DR. BADEN: Thank you. Dr. Hawkins?

DR. HAWKINS: Thank you. The participants in the studies did not include any African-American or Latino members. I realize that particularly with rare diseases such as this disorder, it's going to be hard to get some population to participate. Is there a requirement to try to get those groups in all studies? That's it.

CDR TRACY: I didn't go into that level of detail, but there were approximately 1 percent of patients in either trial of black or African-American reported race.

DR. HAWKINS: I thought there weren't any, but maybe that was just the one trial. That's fine. Thank you.

DR. BADEN: Dr. Clark?

DR. CLARK: Thanks. Two questions for Dr. Tracy. One may be a minor point. On slide 11, the patient characteristics, the prior PEs range includes 1 in the placebo groups. Weren't all

patients supposed to have at least 2 higher exacerbations?

CDR TRACY: Yes, ma'am. There was one patient in the placebo arm who was randomized and subsequently found that he -- I think it was a he; it doesn't matter -- only had had one PE prior to screening, but it was after randomization.

DR. CLARK: Okay. Then I had one other question. The company had submitted an analysis, a per protocol analysis in the ORBIT-4 study that showed a loss of significance for the primary endpoint. That seems kind of curious, and I was wondering if you had any thoughts on that.

CDR TRACY: Yes, so I found the same thing. Granted, that's the subset of the overall, and it represents those subjects who successfully completed trial without any major protocol deviations or violations and stayed on treatment.

Beyond that, I don't have any final thoughts other than to suggest that the overall results in the full analysis population, as I've said in my conclusions, at least in the time to endpoint

analysis, just weren't strong. They were marginal, so I wouldn't necessarily expect to see a real strong finding in a subset of subjects.

I believe in that per protocol population, I have to pull up my data, but it represents about 70 or so percent of patients randomized. As you know, you're losing power at that point to detect a difference. I'll allow the applicant to comment further on that later.

DR. BADEN: Dr. Tracy, you're still needed. The applicant has argued, and we're all aware that the field has changed over the last 5, 10 years, from when the study inception, to execution, to now, results, the understanding that perhaps frequency of event may be more informative than time to event.

How do you advise us in weighing the data, given that the field has evolved during the course of this study?

CDR TRACY: I certainly acknowledge the importance of the frequency endpoint, as I noted in my conclusion slides. This is a challenging

application for us me as well, largely because I can't really understand the discordance between the two trials given the exact designs.

Putting weight on that frequency endpoint, I would have expected to have seen something stronger for ORBIT-3 than I saw, or we saw, a very strong finding in ORBIT-4 for the frequency's endpoint, but not in ORBIT-3 at all, and to me, that suggests something.

With that said, the primary and the secondary endpoint are of importance. I'm not suggesting one is more important than the other. Again, my concern in overall evaluation of these data is the lack of consistency.

DR. BADEN: In terms of from a design standpoint, are there things that could have been done at the time of unblinding or prior unblinding that may have mitigated the change in how we weigh the endpoints?

I'm harping on the issue of post hoc versus a priori. Our statistical techniques are geared to the a priori powering of studies versus post hoc

once one has seen the data, then things make a lot more sense, and are there things that can be done to mitigate this concern as the field changes during the course of a study?

CDR TRACY: I'm sorry. Going forward or in terms of interpreting these data?

DR. BADEN: Could things have been done here to have made this an easier discussion for us?

CDR TRACY: Well, I can't speak to all the nuance because I wasn't part of the IND review process or discussions, I should say, for this particular product.

Now, given the post hoc and post-analyses changes, I think it is reassuring to know that it doesn't affect the frequency of pulmonary exacerbations finding because it is strong in ORBIT-4, that finding.

Clearly, there are concerns about the time to first event results given the changes in the data, as I've outlined. If I was to be a, statistically-speaking, strict person, I wouldn't even be looking at the frequency's endpoint because

the primary failed. I'm looking at everything given the challenges that have been discussed, and the fact that the endpoint has evolved, et cetera.

However, that said, whatever is stated in the analysis plan is what I go with because changes after that, after unblinding and analyses of an analysis plan, lend to a lot of concern for me.

DR. BADEN: Thank you.

As we as a committee have done before, if there are follow-on questions, I'm going to have them follow on. I think Dr. Ofotokun has a follow-on.

DR. OFOTOKUN: Yes. In relationship to the design of the study, I think one thing that keeps coming up in the FDA's presentation is the duration of the study is too short to assess emergence of resistance.

What duration will be adequate? If this were to be used, it's going to be a lifelong therapy, where do we make the cot [ph] to help us access the current data?

DR. NAMBIAR: Yes. This is Sumathi Nambiar

from the FDA. I'm not sure if we have an exact number or duration of follow-up. I think you've seen the data and our concerns.

At the time these studies were designed, one, you've seen like a realistic goal because it's hard to do these studies much longer because of difficulties in following up these patients. But I think it has become apparent that 48 weeks may be short; it needs to be longer.

How much longer, I think we have to take into consideration the practical aspects of doing such a study and at the same time getting data on slightly longer follow-up. During the course of the discussion, we are looking to the committee to see if they might have any recommendations for us if, in fact, one year is good enough or we need to go beyond one year as we work towards developing trial designs for future studies.

DR. BADEN: Dr. Weina, you had a follow-on to the prior question?

DR. WEINA: I did, and this is for Dr. Tracy. It kind of follows on with Dr. Baden's

question.

I know for myself, if I'm looking at a study, you do it per protocol, and you've got your committee that basically looks at it and says, hey, yes, you're going to do your study this way; you're going to analyze it this way; this is your primary endpoint. But I know for myself, if prior to unblinding, somebody says, well, you know, the art has changed, so maybe we ought to be analyzing it this way instead of this way, I know for myself that would have an influence on whether or not, like I said prior to unblinding, that they changed what their primary endpoint is.

Would that have an influence, though, on how the agency looks at it, I guess is the question I'm asking.

DR. NAMBIAR: Yes. This is Sumathi. I think certainly, there are instances when we've made changes, but it's always been before we have been unblinded and we know the results of the studies. Sometimes once the trials are designed and they complete, that science changes, we think

other endpoints might be better.

So I think we can certainly come up with examples where we've done it. It's not perfect, but then we would look at the new endpoint. We'll also certainly look at the way it was supposed to have been looked at. But it all depends on why the endpoint is being changed. Is it really based on science? Or is it just that you're picking another endpoint because you had other suspicion that that might be a better endpoint?

DR. BADEN: Dr. Tracy, I understand your answer to my question. If the analysis plan is set, you consider it set prior to unblinding. So if there was an analysis plan from eight years ago, five years ago, two years ago and unblinding is today, the analysis plan from two years ago you would still consider as a guiding principle versus the analysis plan tomorrow after today's unblinding, in terms of what you mean by the statistical analysis plan that you consider more robust.

CDR TRACY: No, I understand your question.

Yes, we review what was finalized insofar as the statistical analysis plan is concerned, prior to the databases being unblinded and especially before the analysis because sometimes we have trials that aren't blinded, but we always tell them it has to be final before the analysis.

In this case, it wasn't as if there was an analysis plan from two years ago; it was finalized. I didn't provide this level of detail, but it was finalized. There was a second version submitted that was finalized after the last patients were enrolled.

As I said a second ago, it wasn't at the beginning of the trials, which by the way, as the applicant noted, 18 months' total duration to conduct these trials roughly.

I want to add something on the interpretation of that frequency of exacerbations endpoint that I put to you, if I can, to think about, is that as I discussed in ORBIT-4, you were looking at a delta or a difference in the mean frequency of pulmonary exacerbations of about 0.5,

translating to about a half a PE in one year. Noting that these patients came in with, on average, 3 PEs in one year, is that a value of importance? Certainly is statistically significant.

DR. BADEN: We accept the challenge that there are statistical parameters to mitigate the play of chance, and then we have to decide, as a committee and as a community, what is the value of the difference observed, with the statistics helping us mitigate the play of chance. That is the point of our discussion.

Dr. Schaenman?

DR. SCHAENMAN: Thank you. I think like many of us, the struggle is with interpreting ORBIT-3 and ORBIT-4 together. As I think Dr. Green mentioned earlier, it's really a unique opportunity to see two co-eval [ph] trials with identical designs and then try to puzzle over how they end up differently.

I have a question for Dr. Tracy. I don't know if it's possible to see the slides or not, a

question regarding your slide 12. I ask this perhaps somewhat naively as an infectious disease expert and an immunologist, not as a statistician, and trying to understand why the trials ended up so differently.

Could it be, looking at your slide 12 and 13, that the statistical significance seen in ORBIT-4 --

DR. BADEN: Which slide again?

DR. SCHAENMAN: Number 12 from Dr. Tracy.

DR. BADEN: From Dr. Tracy's presentation, 12.

DR. SCHAENMAN: Yes.

DR. BADEN: Tracy, 12.

DR. SCHAENMAN: Tracy, 12. Could it be possible that the statistical significance observed in ORBIT-4 was driven by the higher frequency of events in the placebo group in ORBIT-4?

I know the primary endpoint was time to PE, but if you look at that first line of yours, you can see, at least, again to the naïve eye, it looks to me like the cipro placebo and cipro were

somewhat similar, but the placebo in ORBIT-4 was higher. I just wonder if that could've driven the statistical significance.

If you advance to slide 13, similarly, looking at the Kaplan-Meier curves and trying to superimpose them, at least mentally, it seems to me that the ORBIT-4 placebo begins to have PEs early and often -- well, I guess not often here -- early and that that curve is separating.

However, I think if I try to superimpose the cipro DI from ORBIT-4 with the ORBIT-3 cipro DI and placebo, they're more similar.

CDR TRACY: I agree with your observations. The challenge is going from a proportion of events to a hazard curve, and they're not always 1 to 1 in terms of the relationship because that's the function of when the event occurs, as you know, versus just the overall count of events.

I'm sorry. What was your question specifically?

DR. SCHAENMAN: I'm saying, is that a possible explanation of the differences observed

between the two trials, a higher event rate in the placebo group in ORBIT-4?

CDR TRACY: Noted, there were approximately 9 percent more events in ORBIT-4's placebo versus ORBIT-3's placebo with the similar, about 4 percent delta in the cipro arms between the two trials.

Certainly, I mean there were certainly more events, yes, noted in the placebo arm in ORBIT-4 than the placebo arm in ORBIT-3. As I said I my presentation, the overall number of subjects prematurely discontinued trial before having a PE was similar between treatment groups. We don't feel that those data are influenced by that alone. That's one observation, absolutely, but again, there's no factor that's coming out of the analysis to explain why that would be.

As shown with the analysis before and after the data were re-adjudicated and the programming errors were identified, the fact that two subjects can change the findings, if you really want to be at 0.05, sort of using that as your criterion, that suggests, again, the fact that the data, from the

time to analysis that is, simply just aren't that robust, and the curves illustrate that. It's not that much of a separation. It is proportional, but it's not as large as you would want to see, I would think.

DR. BADEN: Thank you. Dr. Hilton?

DR. HILTON: Thank you. I have a few questions. First, the high rate of treatment with concomitant medicines during the trial concerns me, and I think it might have influenced the findings. It seems like a confounder.

We saw the sponsor's slide, CS-4, which showed concomitant med use by arm but didn't split it between the two trials. I think it would be helpful if we could see that for the two trials.

Shall I just move on to my next point and allow that to come up later?

DR. BADEN: Yes. I assume that those data are from the sponsor, so I would ask the sponsor to keep a list of questions that you can clarify because we would very much want you to clarify after lunch.

DR. HILTON: The next couple of questions have to do with outcomes. The phase 2 trial used colony forming unit mean levels on the log scale. I wonder if we could see that for the two trials as well. I think that that would be quite an interesting outcome.

Also, the rationale for the trial for focusing on pulmonary exacerbations, I'm thinking of them as kind of a surrogate marker for longer term outcomes, which are rare enough that we would have trouble quantifying. I think the closest we can get to those would be a Kaplan-Meier time to event analysis of severe pulmonary infections, which required systemic antibiotics or hospitalizations. I wonder if we could see that by arm and by trial.

My last point is that if I caught these data correctly, it was on a fly, I didn't see it written, I believe that the median time to censoring in the ORBIT-3 was quite similar in the two arms and quite different for ORBIT-4.

For ORBIT-3, it was roughly 2 cycles, and

for ORBIT-4, it was maybe 3 cycles in the active arm and one cycle in the placebo arm. I'm thinking that that very level of censoring, a very high level of censoring relatively early on makes me have some doubt in the frequency analysis of the pulmonary exacerbations because differential dropout by arm and discontinuation over the course of the study is going to throw those mean levels off quite a bit. Those are my thoughts.

DR. BADEN: I don't know if the agency has specific responses. I would ask the sponsor to think about responses to these, and we will have you re-ask these questions to the sponsor after lunch, the ones that are relevant to their providing data.

CDR TRACY: Yes, Dr. Hilton. As I said on slide 13 in my talk, in ORBIT-3, the median days from point of randomization to when a patient was censored for prematurely discontinuation from trial without having suffered a PE was approximately the same between 84 and 85.5 days.

In ORBIT-4, as you correctly noted, the

times were different. In the ciprofloxacin DI arm, the median days was 151 versus 56 days in the placebo arm.

DR. BADEN: Very interesting.

Dr. Daskalakis?

DR. DASKALAKIS: I've been scooped again. My question has been asked.

DR. BADEN: Dr. Carvalho?

DR. CARVALHO: Thank you. We're all struggling a little bit with this issue of resistance. I would like to see if perhaps Dr. Allende could make a couple of comments here and maybe also leave the question as follow-up for the applicant afterwards.

Resistance, on our briefing AMDAC document, on figure 4 on page 18, it indicates the higher MICs on study did not impact the benefits of study drug to reduce the risk of PEs. I would wonder if the FDA could comment on that in view of a little bit of discrepancy between the FDA's analysis, as well as the applicant's analysis.

DR. NAMBIAR: Are you referring to figure 4

from the applicant's briefing book or from the FDA briefing book?

DR. CARVALHO: Applicant and then also with the FDA comment based on the applicant's briefing. This is the AMDAC briefing document page 18, figure 4.

DR. NAMBIAR: Just to make sure, so you're referring to the figure with higher MICs at baseline and on study did not impact. Is that the correct one we have?

DR. CARVALHO: That's correct.

DR. NAMBIAR: Okay. Could you clarify your question? Is it our thoughts on these analyses?

DR. CARVALHO: We're giving quite a bit of importance to the length of the study and the emergence of resistance and what may happen with these patients after a lengthy treatment with the study drug. There is, as I said, a little bit of interpretation difference also between the FDA's analysis, as well as the applicant's analysis, specifically slide CS-20 on the applicant's briefing and Dr. Allende's --

DR. NAMBIAR: I think what Dr. Allende presented were two sets of slides. Maybe we can pull those slides up. They are both by patient and by isolates, and it shows what the change was from baseline to visit 14. We don't have it by every visit, but I think it was at visit 14. I think that's a slightly different way of presenting the data then --

DR. BADEN: Which slides of Dr. Allende's presentation?

DR. CARVALHO: For Dr. Allende's presentation, it would be slides 17 and 18.

DR. ALLENDE: Slide 18, yes, those --

DR. NAMBIAR: 17 and 18.

DR. ALLENDE: Starting in slide 17 and on, so there was a trend of increased resistance over time with more exposure to the drug. The concern is that in the chronic use of this drug, in cyclic mode, the resistance could even increase; we don't know, so more surveillance for a more prolonged period of time would give us an answer of what would happen with safety outcomes and resistance

outcomes. That was the comment. I only show selected visits here, but the trend of increased resistance is observed throughout the visits of the study.

DR. CARVALHO: Perhaps we could leave that as a question that perhaps the applicant could also comment on a little later this afternoon and explain figure 4.

DR. ALLENDE: Yes. Thank you.

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

DR. G. GREEN: Yes. I mean figure 4 in the AMDAC briefing, I presume, is FDA's analysis, but maybe I'm wrong. And just to clarify, my interpretation of figure 4, at least I want FDA's interpretation of figure 4 that they gave us in their briefing, is that they saw an ongoing impact despite the fact -- at least when you look at highest MIC at any visit, it looks like there is a significant move to the left when the MIC is greater and equal to 4 such that implying that the product works even in the present of resistance.

That's at least how I was interpreting that figure, which I think has implications in how we think about the durability of this product over time.

Is this FDA analysis or the company's?

CDR TRACY: It is the applicant's analyses. It's the applicant's analyses. That's their document you're referring to, I believe, figure 4 page 18. Figure 4, that's the applicant's document.

DR. G. GREEN: Dr. Tracy, did you repeat that analysis yourself or do you think that curve is correct?

CDR TRACY: We're referring to the forest plots, not curves, right?

DR. GREEN: Yes, the forest plots. I'm sorry.

CDR TRACY: Okay. I've certainly looked at the data with respect to baseline MCI. I put little value in stratifying the data using a post-randomization factor, and that's what the lower half of that forest plot is providing.

Because I don't know exactly when that MIC

was measured with respect to when the event occurred. Again, post-randomization stratification is flooded with problems because you don't know if that stratification factor is influenced by treatment exposure.

DR. BADEN: Dr. Cox?

DR. COX: Just one other issue too with resistance and MICs, there's also for patients who might in a future point in time end up with an infection, the MIC and its relationship to successful outcomes when using systemic antimicrobials, in this case systemic fluoroquinolones or ciprofloxacin, is the other thing I think that's part of this equation.

There's the topical administration and the organism that you might be trying to eradicate with topical administration. The MICs here, and we're talking about an MIC of 4 is more relevant to the systemic. The topic that's been discussed around this has been the issue of the impact on the utility of fluoroquinolones in that setting should a patient end up with an infection.

DR. BADEN: Point is well taken about local concentration versus systemic issues.

Dr. Green?

DR. J. GREEN: Thanks. I wanted to get back just a minute to the clinical significance of the 0.5 reduction in pulmonary exacerbations. That number is of the overall group.

Is there any data to suggest that in the patients with more severe disease at baseline, as defined perhaps by more than 4 PEs prior to enrollment, that that number is different, that there's a higher reduction in PEs in that group?

(Pause.)

DR. COX: Dr. Tracy is looking at some information.

CDR TRACY: Sorry. As you know, I presented the subgroup analyses for the time to event endpoint only, but I've certainly looked at the subgroups for the frequency endpoint also, as did the applicant.

If you were to say among those who had 4 or more prior exacerbations at point of screening, the

delta between the mean frequency of PEs is approximately 1. Let me give you the specifics here.

The mean frequency in the ciprofloxacin arm is 1.27, and then placebo arm is 2.29, so approximately 1 is the difference there. This is for ORBIT-4. I don't have those data pooled.

For ORBIT-3, I suppose you want to know. Just a moment.

Not as large of a difference. In the ciprofloxacin DI arm, the mean frequency among patients with at least 4 prior PEs at time of randomization was 1.31, and the mean frequency in the placebo arm is 1.84, so approximately half a PE.

I will note, you're dealing with small groups at that point, subgroups, so this can have large standard deviations around them.

DR. OFOTOKUN: How small was it? Is it big enough for us to make sense of that? How small is that small group?

CDR TRACY: For ORBIT-3, 42 patients in the

ciprofloxacin DI arm and 25 in the placebo arm who had 4 or more PEs prior to randomization.

DR. BADEN: It is 12:36. We will break for lunch. I will ask the applicant to think about some of the questions raised because we will come back to them as we wish clarification. After lunch, we will resume with the open session, followed by further clarifications from the committee to the applicant.

We will now break for lunch. We'll reconvene again in this room in 45 minutes, approximately 1:30. 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, with any member of the audience. Thank you. We're now adjourned.

(Whereupon, at 12:37 p.m., a lunch recess was taken.)

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

(1:33 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:33, and we shall resume the session.

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, FDA believes that 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 the 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 at 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 the 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 insight 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 please step up to the podium and introduce yourself? Please state your name and any organization that you are representing for the record.

MS. KERR: Good afternoon. My name is Paula Kerr, and I have had non-cystic fibrosis bronchiectasis for more than 40 years. I have participated on patient advisory boards for Grifols in the past. The applicant has kindly covered my travel expenses, but I'm not being paid for my time. I hope that my story will enlighten and inspire not only bronchiectasis patients but also our medical community who provides care for their patients.

I began experiencing warning signs as early as age 2. Growing up, I was continually plagued with colds and multiple respiratory infections. As a result, I always sat out in sports activities throughout school. These conditions continued into my teens with frequent recurrences, especially with prolonged coughing episodes at nights. As I got older, my condition worsened, and by age 19, I started spitting up blood with each coughing incident. By then it was clear to me that I needed a diagnosis, but that took some time.

Initial visits to my family physician were

unsuccessful. I also made multiple trips to the ER only to be told on one occasion that the blood was coming from nose bleeds that had settled in the back of my throat. I wasn't convinced, so I returned to my family physician, and he referred me to a pulmonary disease specialist. After undergoing a series of tests, I was told that I had bronchiectasis.

At age 22, my pulmonologist performed a right upper lobectomy, however, in the years following surgery, I continued to develop colds and infections. My doctor would prescribe oral antibiotics such as cipro, amoxicillin, and Bactrim. I would take 500 milligrams a day to clear up the infections. This has been my standard of care since then. I also use these antibiotics on the onset of colds in order to prevent infections because the virus would advance to my lungs within the first 24 hours.

From time to time, I would alternate between these medicines, a regimen that's been very effective. As soon as I realized that this disease

was chronic, I began taking control of my health. Through regular visits and conversations with my healthcare professionals, I discovered various ways to manage the disease.

I ask a lot of questions and I do my own research. I've engaged in physical activities including pulmonary rehab, and I have used the Vest system. I eat healthy, I exercise regularly, and believe it or not, I am a soloist, worship leader, as well as a choir director in my church. These activities help strengthen my lungs while keeping my airway clear. In fact, my pulmonologist told me that singing is an effective therapy for the disease. Of course, there are times when I struggle to breathe, especially while walking up stairs or from the parking lot to my office building. When this happens, I will simply stop and catch my breath.

I would like to address the three particular groups in this forum; first, the fellow bronchiectasis patients. At times, living with the bronchiectasis can be debilitating, challenging,

and frustrating, making one feel helpless and perhaps even hopeless. I am blessed that I have been able to closely partner with my pulmonary care professional. I urge you to do the same. Be vocal about your situation, get second opinions, and be aggressive in demanding better care.

To our clinicians and the medical community, today I beseech you to place greater emphasis and effort on the diagnosis and treatment of this disease. Taking these steps for us will not only help to reduce misdiagnosis but will also minimize repeated exacerbations in patients like me and hopefully delay the progression of the disease over time.

Finally, my appeal to the FDA and committee. While I feel I am very much in touch with my overall health and in control of living with bronchiectasis, down the road, I know will be faced with decisions I will more than likely not be prepared to make. For instance, over time when my lung function declines and infections become more frequent, what then? What options will be

available to me? What about those patients that need this type of treatment now and cannot wait?

While there is no one-size-fits-all solution to health care, for those suffering patients who might have a chance with a treatment like Linhaliq, I urge you to consider the ramifications of your decision today. If your vote of yes will make a difference in the life of just one bronchiectasis patient, then I ask you, would that life be worth it? Thank you for your time.

DR. BADEN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. LEITMAN: Good afternoon, and thank you for this opportunity to address the members of the committee. My name is Amy Leitman, and I address you today not only as the daughter and caregiver of a patient, but also as the director of policy and advocacy for NTM Info & Research, a nonprofit patient advocacy organization for those with pulmonary nontuberculous mycobacterial infections,

or NTM, and related comorbidities, including bronchiectasis.

I would like to disclose that Aradigm supported our organization financially in 2017. I have no personal financial interest in their company, nor have they provided any compensation for any expenses related to my appearance here today. I'm here because it is a matter of life and death for bronchiectasis patients, many of whom are my constituents. It's estimated that up to 80 percent of NTM patients have or will develop bronchiectasis.

The drug we're here to discuss today, Aradigm's Linhaliq, represents a significant step forward in the potential to shorten the time and increase the efficacy and safety of treatment for pseudomonas. For patients with bronchiectasis and comorbid infections, this would represent welcomed relief and a potentially life-saving development in the fight against their diseases.

Inhaled liposomal medication takes advantage of a technology that has been around for decades.

Now this technology is finally being applied to drug development, and we owe it to our patients to explore its untapped potential.

My late step-mother, Fern Leitman, had pulmonary NTM disease. I wish I could tell you how many pseudomonas infections she got, but they were too numerous to count. I can tell you that her brother Nick named her Pseudomonas Sue, and I can tell you why she got those infections.

In 2012, Fern appeared at the FDA to speak at a meeting on Issues in the Design of Clinical Trials for Antibacterial Drugs for the Treatment of Non-CF Bronchiectasis. Because I have copies of her remarks and slide presentations, I can tell you in her own words what it was like for her to be a patient with bronchiectasis, quote.

"I was diagnosed with bronchiectasis at the age of 14 after a major hemoptysis. I've had multiple episodes of hemoptysis. I've learned to stay calm, and often antibiotics are needed. For most of my life, each cold became a major bacterial infection often resulting in hospitalization. One

of the most disturbing aspects of my illness is its unpredictable nature."

This is a slide Fern created, which in her own words, quote, "summarizes some of my challenges with bronchiectasis for over 50 years and NTM for more than 40 years." In describing her experience with pseudomonas and bronchiectasis, Fern said, "There are no vacations from bronchiectasis."

When talking about clinical trial design and drug development, Fern said, "The most important question is always, 'How are you feeling?' Treat the patient, not the test results. The lab tests and scans are very valuable but mostly in the context of patient functionality when making treatment decisions. Negative cultures and patient functionality are both important but do not always go hand in hand."

She started having serious exacerbations when she was 12 and that kept happening throughout her life. Imagine how much more time we could have had with her if better treatments had already existed. She said, "The infections associated with

bronchiectasis have largely relied upon product fallout from approved drugs for other indications. Some of the drugs I've taken have not been rigorously tested in clinical trials for my conditions or combination of comorbidities. What if the treatments stop working or my organs cannot tolerate them?"

Throughout her life, Fern dealt with many of the same side effects we hear about from so many patients who take antibiotics systemically for sustained periods. Though Fern's words have never faltered, she's no longer here to tell her story. In October of 2014, after 18 years of continuous treatment, which included more than 18,000 doses of IV medication and more than a quarter million pills, Fern died of kidney failure associated with the long-term use of systemic anti-infectives.

Organ failure is another devastating side effect patients face because their entire body is overloaded with antibiotics meant to treat a localized infection. Linhaliq treats the infection site with less absorption into the rest of the body

and fewer side effects than those patients have experienced. It's inhaled instead of systemic, so it may be more tolerable for patients and less harmful to them.

Fern had said there were no clinical trials, but now there are. We now have a clinical trial which demonstrates Linhaliq's safety and efficacy with strong support of data confirming. Nothing is approved for these patients. The benefit clearly outweighs the risk.

I'm here today to speak on behalf of patients, both living and the dead, with pulmonary NTM, and so many of them have bronchiectasis and are so vulnerable to co-infections like pseudomonas. It's time to give new hope in treatments. The only other option is to let them keep dying, and that's no option at all. Thank you.

DR. BADEN: Thank you. 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.

DR. COHEN: Good afternoon. My name is Dr. Keira Cohen, and I'm an attending pulmonologist and critical care medicine physician at the Johns Hopkins University School of Medicine in Baltimore, Maryland. I do not have a financial relationship with Aradigm to disclose.

I'm a physician scientist with particular expertise in microbacteria drug resistance in the care of people living with bronchiectasis. I'm here both as a clinician and a researcher to highlight the unique needs of individuals with non-cystic fibrosis bronchiectasis and to speak to the dire urgency for additional therapies to appropriately treat this condition. Together with my colleagues at Johns Hopkins, I'm in the process of founding the Johns Hopkins Center for Bronchiectasis and Nontuberculous Mycobacteria.

Patients with non-cystic fibrosis bronchiectasis have specialized medical needs relating to their lung disease. As recurrent respiratory infections are part of the vicious cycle of bronchiectasis, prudent antibiotic use is

key to providing proper care, however, antibiotics alone are not sufficient to maintain good lung health in the setting of moderate or severe disease. Airway clearance techniques are an essential part of the successful treatment regimen for these patients.

Accordingly, our clinic will be based on an interdisciplinary care model in which pulmonologists such as myself work side by side with infectious disease specialists and airway clearance specialists to provide more comprehensive care for these complex patients with pulmonary bronchiectasis and nontuberculous mycobacteria.

Heterogeneity is a word that I often use to describe patients with bronchiectasis. There are many different flavors of bronchiectasis. Patients vary with respect to the underlying etiology of their lung disease, the frequency and tenor of pulmonary exacerbations, and the degree to which respiratory symptoms affect their lives on a daily basis.

Some individuals with bronchiectasis appear

to have only minimal health problems related to their lung condition. In contrast, in other cases, despite our best efforts to provide optimal care, bronchiectasis can lead to end-stage lung disease and may require a lung transplant.

This diversity in heterogeneity means that patients seen in clinics do not always match those who were studied in clinical trials. In a recent study that was published by James Chalmers, who spoke earlier today, in Respiratory Medicine in 2016, up to 93 percent of patients with bronchiectasis who are enrolled in the European bronchiectasis registry would not have been eligible for the 8 main randomized clinical trials of bronchiectasis that have been performed to date. This means that we do not have clinical trial data to guide treatment for the vast majority of patients whom we are caring for in clinic.

As you are well aware, in the United States, there are currently no FDA-approved drugs that are specifically for the treatment or the prevention of exacerbations of non-cystic fibrosis

bronchiectasis. However, the in-clinic, on-the-ground reality is that multiple inhaled antibiotics are frequently used off label for certain patients with this disease.

There are many patients with bronchiectasis whom I have seen in clinic whose successful clinical outcome, stability, and longevity I attribute to judicious use of inhaled antibiotics. However, as a scientist and a clinician caring for people with bronchiectasis, I find this scenario troubling. I wish that I had at my disposal FDA-approved drugs that I could prescribe for my patients with bronchiectasis.

I wish there were drugs with proven safety and efficacy that I could use in this setting. We desperately need additional medicines and therapies for bronchiectasis, even if those therapies provide significant benefit only for a select subset of patients, especially if these are the people with more severe disease.

Please help my patients, my colleagues, and myself by striving to make available additional

tools with which to optimize the care of patients with non-cystic fibrosis bronchiectasis. Thank you.

DR. BADEN: Thank you, Dr. Cohen. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. KITLOWSKI: Hi. My name is Mary Rose Kitlowski, and I'm from Loch Hill, Maryland. I paid for my own travel today, and I have no financial interest in today's applicant or any competitors.

I have bronchiectasis as a result of a rare disease called primary ciliary dyskinesia, PCD. I spoke before this committee this past November regarding Bayer's application for inhaled cipro. I've returned to speak today because having studies that properly assess the efficacy of treatments and encourages research in treatments is very important to me.

First and foremost, I must say this. As a PCD bronchiectasis patient, it is frustrating to

have non-CF bronchiectasis studies continue to use endpoints that might not be realistic and could cause a study to be set up for failure. I question the use of time to first exacerbation as a realistic endpoint.

Personally, I always have an exacerbation in the fall. If I had participated in this study and started in August, then my time to first exacerbation would have been 1 to 2 months from the start. If I had started in January, my time to first exacerbation would have likely been 9 to 10 months. This hardly seems like a reliable measure.

As this committee noted when rendering its recommendation of the November hearing, NCFB is a heterogeneous disease. Its varied etiology is overlooked in the setup and endpoints of these studies. Some members mentioned looking at the patients individually and comparing results against each individual patient instead of comparing non-CF bronchiectasis as a whole. This would seem to be a better way of acknowledging the individualized and varied etiology of this disease and could be a true

indicator of whether these drugs are making a difference for the patients.

While I would regard not having an exacerbation in the fall as a true miracle, I would be thrilled at a treatment that would lessen the severity, reduce the length of an exacerbation, or reduce the number of exacerbations in a year. To have a possibility for an enhanced quality of life for myself and others would be wonderful. My concern is that with these continued failures and without adjustment to the setup and endpoints, patients will be deterred from enrolling in these studies, and more importantly, discourage companies from putting resources into bronchiectasis research.

Now, a little about by struggles with bronchiectasis. I was diagnosed with bronchiectasis for my first chest x-ray when I was 17. Bronchiectasis has been a daily battle for me. I do nebulizer treatments to help open my airways, prevent bronchospasms, and to loosen the mucous in my airways. I do a sinus rinse to keep the mucous

in my nasal passages from dripping into my lungs.

I have a chronic cough and a runny nose. There are times when I'll have bronchospasms and go into 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 5 nights a month not sleeping in my bed for some period of time.

Exacerbations started in my 20's. I've had at least one exacerbation requiring IV antibiotics a year for the last 20 years. The past two years, I've had 2 exacerbations, each requiring IV antibiotics. During these exacerbations, I'm on IV antibiotics for 3 to 6 weeks.

Reducing the time of one exacerbation means less time with a PICC line. It also means I don't have to spend as much money. My last round of IV antibiotics cost around $1300, out of pocket.

Having inhaled antibiotics treatments like cipro available will make a big difference for me. It 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.

One of the problems patients face with no FDA-approved treatments is insurance companies deny treatments all the time. This is especially discouraging to a patient who was part of a drug trial and you had a positive result during the trial. While I appreciate that the FDA has the onerous task in making sure drugs are safe, I'm not sure of the consequences and harm to patients is realized when these promising drugs fail to meet an unrealistic and too specific endpoint.

This morning, an FDA official stated, "It's not perfect." We don't expect this process to be perfect, but the lack of flexibility in considering endpoints can have serious consequences for patients. I'm asking the committee to consider what would make a difference for patients like me.

Thank you for your time and allowing me to speak today and for considering the needs for those of us with bronchiectasis that rely on antibiotics as we struggle every day to manage our worsening disease.

DR. BADEN: Thank you for your comments. Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. SNELLENBURG: Good afternoon. My name is Heidi Miller Snellenburg. I'm a bronchiectasis patient, and the applicant has covered my expenses to be here today. I participated in a Grifols' patient advisory panel in the past for which I received compensation for travel expenses and my time. Today I am here on my own time and have no financial interest in the company or the drug.

I was diagnosed with bronchiectasis and MAI at the same time, in 2002. I have no idea if I had the bronchiectasis before the MAI or if the MAI resulted from the bronchiectasis. But for at least seven years prior to my diagnosis, I had been

coughing up sputum for gradually increasing intervals on a daily basis.

Periodically I'd go to the doctor thinking I had a sinus infection and get an antibiotic that would clear up the sputum production for a month or two, but it wasn't until I started coughing up sputum heavily tinted with blood, and carried a bag of tissues with the evidence to my doctor, that I was finally sent to a pulmonologist.

Through a sputum sample, which I was able to easily produce, and CT scans, I received a diagnosis. Following the diagnosis, I began the usual MAI cocktail regimen of 3 oral antibiotics. After several months, I developed an allergy to one drug, which was replaced with another oral drug; developed a second allergy, received a replacement oral drug; developed a third allergy at which point the doctor had no replacement options, and I was off meds for a few years.

The bacteria in my sputum samples had also become resistant to all of the oral antibiotics which had previously cleared my sputum production

for brief periods, so I was left without drug treatment options. From 2012 to 2016, approximately 3 hours of my day, every day, was spent coughing up sputum. Sputum, purulent sputum. It's a great word, right? Sounds just like what it is.

Bronchiectasis produces a lot of sputum. It's impossible to keep coughing up sputum a secret. It's hard to suddenly expectorate into a tissue. Some people resort to swallowing this stuff when it comes up. You can't really carry a sample cup around with you to use as a spittoon in the presence of others.

Sputum production is noisy. It can sound violent and alarming to people around you. Sputum production is frankly disgusting. It's thick and green and brown, and it smells bad. It makes your breath smell bad. When you're coughing up sputum on public transportation, people move away from you. In business meetings, people apologize as they change seats if they don't want to catch what you have. You don't have the time to explain that

you're not contagious. And what's the likelihood of people believing you anyway?

Imagine being unable to attend concerts, theater, movies, your children's school events, client meetings, or a job interview that might advance your career for fear that you will start coughing up sputum. After age 50, it's hard enough as it is to be considered for a job without someone thinking you're a health risk.

Almost two years ago, unable to find relief through medication, I decided to have a lobectomy to remove the area of my lung that held most of the disease. The surgery brought relief to the daily coughing and sputum expectoration for about a year, but symptoms are gradually returning as my disease continues to spread, and there are no drug options currently available to me. I found myself wondering how long will it be until I look again for surgical relief, but also realize that I have only so much lung to remove since breathing seems to be a human necessity.

In recent years, I started a new cocktail,

which included an inhaled drug that I tolerated well. Unfortunately, my most recent health insurance won't cover the inhaled version of the drug, though they said they might consider covering an intravenous version. I'm not ready for a PICC line in my arm, nor the associated side effects and systemic toxicities. Without an approved inhaled antibiotic, our choices are extremely limited. For those of us who can only take one type of antibiotic, we're running out of options.

In summary, a non-invasive treatment for bronchiectasis is needed to allow people like me to live a life free from the symptoms that caused them to be societal pariahs. Bronchiectasis should not disable our ability to live full productive lives, lives that allow us to be engaged with others without fear of being shunned. Thank you for your consideration of this critical need to have access to a safe and effective treatment. Thank you.

DR. BADEN: Thank you for your comments. Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any

organization you're representing for the record.

MR. KEPHART: Good afternoon. My name is Craig Kephart. I am currently the CEO of the COPD Foundation, but I'm here today speaking on behalf of an individual with bronchiectasis by the name of George Philip Reynolds. Mr. Reynolds was scheduled to be here, but unfortunately was unable to come. So he asked me to read his statement. I have not been compensated for this, and to my knowledge, Mr. Reynolds has no financial interest in the sponsor.

"To the committee members, my name is George Philip Reynolds, and I have moderate to severe bronchiectasis. I participated in the Linhaliq trial for one year with a single exacerbation. My life prior to my diagnosis was full and rich with the ability to join friends at a moment's notice. I hiked and backpacked 1800 to 2000 miles a year for 15 years. I trained and led hundreds of Boy Scout outings, which was my avocation and enriched my life.

"Each year as my illness progressed, I lost

more and more of my ability to follow my dreams. In the year prior to being enrolled in the study, I had 7 to 10 exacerbations, each lasting 2 to 6 weeks. During that time, my pulmonologist followed all of the treatments that were available to her. TOBI and cipro were effective during this time, however, TOBI became less effective leaving cipro as the only treatment available to me.

"We discussed the possible need to use IV cipro as the only means to control my exacerbations, as they were becoming more and more frequent, if I did not meet the criteria for the study. Fortunately, I met the criteria for the study.

"During the trial, I was able to resume hiking 20 miles a week and between the cycles, 2 short backpacking trips of 50 miles in the desert at low elevation. I was also able to travel to Paris for 10 days without complications during a cycle while on study drug. These activities are more in line with a semi-normal lifestyle that I had hoped to continue after my retirement.

"After 7 months, I asked the research site to pursue compassionate use after completion of the study possibly to capture long-term safety data. I did not expect for that to happen, but if you don't ask, it's not likely that it would be granted. As you're aware, it was not granted. After the end of the study, my activities were again diminished and my quality of life was reduced to what it was prior to the study.

"I just can't emphasize enough how wonderful the year on the study was coming off of a bad year. The year before, I was coughing so much a nodule formed on my vocal cords that had to be removed. In the 6 months before the study, I could only talk for 10 minutes before losing my voice. I did a lot of training for the scouting program and had reduced my participation and eventually stopped completely.

"As you're aware, the treatment for this condition is very limited. I do not qualify nor would I contemplate a transplant, even if last resort, if offered. My hope is that this compound

will be released for manufacture. There is nothing to treat the colonization of pseudomonas available to me. Without this compound, I will continue with the diminished quality of life unable to spend time with my grandchildren, friends, or pursue the activities that enrich my life. I would love to have the year that I had during the year on the study again.

"I'm aware of the process involved with bringing a medication to market. Prior to retiring, I worked in the clinical trials arena for more than 30 years, the last 20 of which was the director of a small site supervising over 200 trials. During my career, I had compassion for our subjects, but that did not prepare me for meeting the criteria of this study, and after completion, not being able to have access.

"Thank you very much for your consideration and hopefully finding positively for this submission. Yours respectfully, George Philip Reynolds." Thank you.

DR. BADEN: Thank you. Will speaker

number 7 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. AKSAMIT: Good afternoon. Thank you for the opportunity to speak today. My name is Timothy Aksamit. I'm a pulmonary disease and critical care medicine physician, associate professor of medicine, and director of the Mayo Mycobacterial and Bronchiectasis Clinic at the Mayo Clinic in Rochester, Minnesota. I am here today representing my patients and non-CF bronchiectasis patients across the whole country. I have not received any support or monies from the applicant to be here today.

Over the past 20 years, I have participated in multiple clinical trials involving bronchiectasis. In addition, I chair the U.S. Bronchiectasis and NTM Research Registry, which currently captures data from almost 2500 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.

The conundrum facing NCFB patients today in 2018 is that there are no FDA-approved therapies despite a tremendous and longstanding unmet need being present. We are compelled to be keenly mindful of this need and should be careful not to dismiss this need today. I further judge that we are charged to embrace each of our roles as responsible stewards in advancing the science to make available therapies demonstrated to have efficacy and to consider the data that is available to date, including data presented today by the sponsor.

Inhaled antibiotics to treat airway infections in NCFB patients have been used for over 65 years in an unapproved and unmonitored fashion. Indeed, although the CF community has been using FDA-approved inhaled antibiotic therapies for nearly 20 years with great success, the best use of

inhaled antibiotics for NCFB patients has been elusive.

Let me share some data from the U.S. Bronchiectasis Research Registry. In an analysis of the NCFB patients with 2-year follow-up data and in the current hands of registry PIs and bronchiectasis experts, the use of off labeled and unapproved antibiotics varies between 1 in 6 and 1 in 3 NCFB patients.

Many of our NCFB patients currently need and receive unapproved inhaled antibiotics. And though there is an unmet need for all non-CF bronchiectasis patients, those that have more advanced disease, including the presence of pseudomonas, are in most need. These are in fact precisely the patients included in these phase 3 trials and arguably to benefit most from an effective approved therapy in the form of inhaled liposomal ciprofloxacin.

We understand that the association of pseudomonas is associated with more frequent exacerbations, accelerated loss of lung function,

and worse quality of life. In the same 2-year follow-up cohort from the U.S. registry, those NCFB patients with more frequent exacerbations had a 8-fold increase in hospitalizations.

As a clinician, educator, and clinical researcher, I would like to be clear that inhaled liposomal ciprofloxacin would not be indicated for all non-CF bronchiectasis, but what it does represent is a potential high impact on those that are desperately in most need. In fact, the positive impact of inhaled liposomal cipro, demonstrated by the data presented, including time to first exacerbation and frequency of exacerbation, is in fact meaningful.

So it is my opinion and my request today for a recommendation for approval for a safe and effective tool, inhaled liposomal cipro, for use in select patients with non-CF bronchiectasis and pseudomonas. For my patients and in my practice, this means less symptoms, less hospitalizations, less time away from family and work activities, which translates into a meaningful improvement in

patients' lives where none now exists.

The opportunity exists today, rather than waiting years for the completion of an additional study, for an effective, safe, and clinically meaningful treatment for select non-CF bronchiectasis patients. Having options in my clinical toolbox based on individualized patient needs for best clinical care cannot be overstated.

How might a recommendation for approval bring additional benefit? A recommendation for approval for inhaled liposomal ciprofloxacin will also allow a path forward from the decade's use of unapproved and unproven therapies and a chance to decrease systemic antibiotics exposures. The safety profile presented, including the low systemic exposures associated with its use assures me that this drug is safe and will be well tolerated.

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 approval and a new

beginning, a beginning for bringing much needed hope to select non-CF bronchiectasis patients with pseudomonas as well as making available an effective and safe tool to clinicians and a portal for advancing the science of bronchiectasis. I thank you for your time.

DR. BADEN: Thank you. Will speaker number 8 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

(No response.)

DR. BADEN: Will speaker number 9 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. HULNICK: Hi. I'm Lannie Hulnick. I'm speaking on behalf of my father, David Bickman, who could not be here today. When my father was diagnosed with bronchiectasis, it seemed as though he was always sick. Antibiotics became just another food group because he was constantly on them. When we were together, I would hear him up

through the night coughing, and I would worry that the next day he would be sick and tired and not be able to spend time with our family.

In 2013 and 2014, when my father was hospitalized, both times he spent several days in the ICU, and we were all afraid that this was going to be the end. I remember calling my rabbi asking him to pray for my dad. I was so worried and I felt so helpless.

Our family lives all over. I live in Philadelphia. My sister and her family are in Arizona, and my parents and brother's family live in Calgary Alberta, Canada. Due to this, we've all become accustomed to traveling in order to be together. Before my dad participated in the clinical trial, we were getting to a point where travel was an issue for my dad, and in order to be together, we would have to travel to him.

In addition to the times where my dad ended up in the hospital on IV antibiotics in Arizona, whenever he would come to Philadelphia, he would ultimately feel sick, have to go to the doctor, and

end up on antibiotics.

My father's quality of life improved dramatically after the clinical trial. He's been able to participate in day-to-day activities like golf that used to be a challenge, travel more, and spend quality time with his children and grandchildren. Thanks to the improvement in his health, this past summer we were able to take a trip of a lifetime as a family to Israel. While in Israel, my dad felt so good that he was able to participate in all of the daily activities, and we had many full days.

I promise this would not have been possible prior to September 2010 when he began treatment with a drug that is today up for FDA approval. I can attest that my father and our family have benefited from his participation in the clinical trial and taking this medication. I will now read his statement.

"I'm 70 years old, and I was diagnosed with bronchiectasis almost 11 years ago. Prior to that diagnosis, I had experienced several exacerbations

that culminated in pneumonia and other lung infections. After my diagnosis, I was treated with oral and IV antibiotics, including cipro, whenever I experienced an exacerbation.

"Between 2007 and 2013, to the best of my memory, there were three occasions where I suffered lung infections that were serious enough to require treatment with IV antibiotics. I also commenced to use a hand-held device called the Flutter to help with mucous clearance.

"All of this of course helped me to live with my chronic lung condition, but I continue to experience exacerbations to the point where in each of 2013 and 2014 I was hospitalized, the first time for 4 days and the second time for 5 days. On both of those occasions, I was treated with, among other drugs, IV antibiotics. In 2013, the IV antibiotic treatments were 3 times a day for 2 weeks, 4 days in the hospital, and then another 11 days as an outpatient. In 2014, the IV antibiotics were 3 times a day for 5 days and then again with outpatient treatment.

"There were side effects from the IV antibiotics. In spite of the fact that I took probiotics at the time, I suffered stomach aches and constipation, mainly. In addition of course, my veins were collapsing, complicating the treatment. Until 2015, I was quite discouraged about my prognosis. I had been told by my medical specialist that bronchiectasis was a progressive condition and that I would gradually get worse over time. Given how poorly I already felt, I took this news quite badly.

"My specialist in respiratory medicine, Dr. Julia Jarand, recommended to me that in the late spring of 2015, that among other things, I enter a clinical trial for nebulized cipro. I'd been taking cipro orally from time to time as in when it was needed, and it was proving reasonably effective in managing the pseudomonas that was infecting my lungs and causing my pneumonia and serious flu-like symptoms. At that time, the drug being studied and which I was to take if I participated was called Pulmaquin.

"I entered the clinical study in September 2015 and continued in the program for the required 12 months. I took the medication for 28 days at a time, and then did not take it for 28 days at a time throughout the 12 months. This meant, I believe, that I was on the drug being studied for a total of 7 periods for 28 days.

"I very rigorously followed the protocols for the study. It was explained to me in the documents given to me by the study's local coordinator, Linda Knox [ph]. In addition to participating in this clinical trial, I also began to use, on the advice of my respiratory physiotherapist, a device called POWERbreathe to expand my lung capacity. I have since the spring of 2015 been using this device religiously as instructed.

"Between the effects of the medication I took in the clinical trial and the lung physiotherapy that I continue to follow strictly, using both the Flutter and POWERbreathe devices, I can tell you that I've not had an exacerbation of

any kind since I was hospitalized in the spring of 2014. I have not had to resort to the use of even oral antibiotics since early 2015, which for me is truly unbelievable when compared to the previous years. Only in the past 6 month have my sputum analysis revealed that I once again am growing pseudomonas in my lungs, and my general health has been considerably better these past three years or so. For example, I'm much better able to walk uphill and climb stairs without getting unreasonably winded. I'm generally enjoying life much more now these past three years.

"Since I completed the clinical trial, I've inquired on a regular basis regarding the availability of inhaled cipro and an ongoing basis for my continued good health. I've been advised that this medication is not available because it has not yet been approved for use by the authorities like the FDA.

"I am becoming increasingly concerned about not being able to access this medication because my lungs are once again growing pseudomonas, and

without access to the medication, I expect that my condition will over time deteriorate and revert to those exacerbations I previously experienced, resulting in a necessity for oral and IV antibiotics treatments and severely reducing the overall quality of my life.

"In summary then, I can attest to the facts that I benefited greatly from being in the clinical study and taking this medication, want it to be approved for use by patients like me, and I urge the FDA to approve it as soon as possible. Thank you for your consideration and hopefully a favorable consideration of Aradigm's application. Yours truly, David M. Bickman."

DR. BADEN: Thank you for your comments. Will speaker number 10 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. FOX-RAWLINGS: Thank you for the opportunity to speak on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-Rawlings. Our center analyzes scientific and

medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

We strongly support efforts to improve antibiotic use and drug safety. It is important that any drug should clearly demonstrate efficacy and a good long-term profile before they are approved. This is especially true for cipro, which has known risks and for an indication that involves years or even decades of use.

Cipro DI had clearly not yet met that standard. There are questions about whether the primary endpoint of time to first exacerbation is clinically meaningful. Since the patient would be treated with repeated courses of this drug for years, the relevance of a one-time event is unclear. The secondary endpoints are more pertinent: frequency of exacerbations, number of severe exacerbations, and quality of life. The data provided can help generate hypotheses that the

sponsor can test in future studies, but they are not adequate as a basis of approval.

In addition to questions about the clinical relevance of the selected primary endpoint, the primary and some secondary endpoints were met in only one of the two phase 3 trials. Overall, these improvements were small, and it is not clear that they would be clinically meaningful for many patients.

The value of conducting two clinical trials is to show that the results can be replicated. While we could hope that ORBIT-3 was not successful due to random circumstances, it is also quite possible that the success of the ORBIT-4 trial was the fluke or that cipro DI is only effective for a specific subgroup of patients that hasn't yet been defined. For example, the trial differed in the number of patients from various countries, and patients differed in their baseline lung function prior to participation in the study.

This drug has serious risks, so it's crucial to identify if the drug is effective and for whom

prior to approval, and to ensure that the indication is clearly defined. These risks are inherent in the fact that the patients would be expected to take cipro DI for years or decades, and there will be subtherapeutic level of drug throughout the body during each course.

We agree with the FDA's concerns that long-term exposure would increase the risk of developing antibiotic resistant bacteria. Over time, the effectiveness of the drug may decrease while the harms to the individual patients and population could increase.

Fluoroquinolones in general, and cipro in particular, have risks for serious adverse events involving heart, brain, and tendons. It seems reasonable to assume that the risk for adverse events is lower when a drug acts locally rather than systemically, but expecting that it should be safer is not the same as proving it is. Long-term exposure may result in unexpected adverse events, which could be difficult to recognize that are due to this drug.

Clinical trials do not study enough patients or evaluate them for a long enough period of time to adequately evaluate the risk of resistance or long-term adverse events. They cannot predict the extent to which cipro DI will maintain effectiveness beyond the one-year mark. Many of these concerns are the same concerns that led members of this committee to recommend against approval of cipro DPI in November. The committee made it clear at that time that growing rates of antibiotic resistance is a matter of patient safety and public health.

Cipro DI may be a good option for some patients, but the efficacy and safety must be clearly demonstrated for the target population prior to approval. There is a need for new treatment options to reduce the number of PEs experienced by patients, however, it is necessary that these treatments have clear evidence that they will be effective and that they will not harm most patients more than they will help. Thank you for your time.

DR. BADEN: Thank you for your comments. Will speaker number 11 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. FLUME: Good afternoon. My name is Patrick Flume. I'm a professor of medicine and pediatrics at the Medical University of South Carolina. In full disclosure, my travel to attend this meeting was paid for by the sponsor, but I'm not receiving any fee to speak here, nor have I done any consulting for the sponsor.

I was a site PI for one of the studies presented today, and I have participated in several large bronchiectasis trials in the past. I am better known for my work in the world of cystic fibrosis over the last 25 years, but I have an even larger bronchiectasis program at MUSC. I have a long history of investigation of aerosolized antibiotics in the treatment of CF pulmonary exacerbations. I was the lead author of four sets of pulmonary guidelines for CF, and I was co-author

of the consensus definition for exacerbations of non-CF bronchiectasis.

The discussion here today is reminiscent of an advisory panel more than 20 years ago, when an inhaled antibiotic was being evaluated for use in cystic fibrosis patients. Concerns just like today were voiced about selection of resistant pathogens to the detriment of the patients as well as putting the general population at risk. But fortunate for our patients, that first drug, tobramycin and since then aztreonam were approved, and here we are 20 years later and inhaled antibiotics are considered the standard of care for the chronic therapy of CF patients with chronic infection of the airways.

Back then, there were great concerns that approval of inhaled tobramycin would select highly resistant strains, and we would no longer have IV tobramycin available for the treatment of our patients. But that's not how it turned out. Two-thirds of our patients have pseudomonas. Seventy percent of those patients are on inhaled

tobramycin, and when they have exacerbations, tobramycin intravenous is still a workhorse drug for us, successfully. The patients are responding, and I will add there have been known epidemic catastrophies in the general population.

So I can understand the concerns for selection of resistant bacteria, but frankly this is the expected finding when you use an antibiotic in which you will not eradicate the pathogen. It is a demonstration that the drug is actually working. And I would like to make sure everyone realizes that susceptibility to antibiotics is not the same thing as virulence in terms of predicting outcomes.

If you really want to prevent selection of resistance, well then maybe we just don't treat these patients with antibiotics, but that's not what we're going to do. We're going to continue to treat these patients. We're going to treat them because they have daily symptoms as you've been hearing and they have exacerbations and clinical worsening, in which we're going to use systemic

antibiotic therapy.

The CF guidelines recommend the use of inhaled antibiotics primarily to reduce the occurrence of pulmonary exacerbations, the same indication that was used for the non-CF bronchiectasis studies of the drug discussed today. Make no mistake, the patients who would benefit from this medication are those who have frequent exacerbations. This drug is not going to help people who are not having these events, and these events come with considerable morbidity.

This is a population with a high unmet clinical need. There are no approved products for the treatment of non-CF bronchiectasis, so everything we do is considered off label. That includes the use of inhaled hypertonic saline, chronic macrolides, and yes, inhaled antibiotics. And recently, I published our experience with inhaled antibiotics in patients with non-CF bronchiectasis in the American Journal of Respiratory and Critical Care Medicine, in which we demonstrated that patients who were benefiting as

well as a clear reduction in exacerbations.

Those patients would be devastated if I took that medicine away from them. But for them, as you've heard, we are using IV formulations, and it would be preferable to have an approved product formulated for the airways with evidence for its safety and for which there would be continued formal pharmacovigilance.

So I appeal to you to recognize the unmet clinical need for these patients. And relative to that need, recognize that the benefits of approving this product clearly outweigh the perceived risks. And I suggest that 20 years of empiric observations and experience should ease your concerns regarding these questions that you have raised today. Thank you.

DR. BADEN: Thank you for your comments. Will speaker number 12 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. WALKER: Good afternoon. My name is Kyle Walker, and I'm 29 years old, and I'm from

Toronto Ontario, Canada, living with non-cystic fibrosis bronchiectasis. I was a patient in the ORBIT-4 trial. My travel has been paid for by the sponsor, however, I am not receiving any compensation for speaking here today. I am here today to provide you background of my journey with a lung disease and insight into the daily life of a patient with bronchiectasis in hope that we can find a better treatment plan for patients like myself.

At birth, I was admitted to the neonatal intensive care unit at the Hospital for Sick Children in Toronto after immediate respiratory challenges. I would remain a patient at the Hospital for Sick Children for the next 19 years of my life. For the first 13 years, I divided my visits between two clinics: ear, nose, throat clinic for hearing loss and the respiratory clinic as a kid with chronic asthma.

It was not until the age of 13 that both of my physicians began to explore links between these issues, and after several biopsies, I was diagnosed

with primary ciliary dyskinesia, a rare disease affecting the movement of cilia. It took 13 years to diagnose me with bronchiectasis, not just a kid with asthma.

Through all of the treatments, visits, and tests, I grew up leading a relatively normal life. I played competitive minor hockey. I was class valedictorian, and in 2011 I graduated university. While I did not take my quality of life for granted, I did not appreciate how my early 20's would vary so much from my late 20's today.

I've stopped playing on my recreational company hockey team because I can't keep up. I got winded walking up a flight of stairs in our open concept office. Just this week, I couldn't complete shoveling my own driveway with several breaks, which is a challenge for somebody living in Canada. Most challenging of all, my exacerbations have become more frequent, they last longer, and they take longer to recover from.

Bronchiectasis for me has been completely unpredictable. Humid days, don't go outside long;

dusty spaces, don't go in them; smoking, being around smokers, don't do it. It doesn't matter in the short term. My exacerbations have always come out of nowhere and they aren't new to me. As a kid, I would get a chest infection, lie in bed for a day or two, convince my mom I was fine, and off I went to do something with my friends. Now they are more intense, and they keep me down longer. Most recently in October, I spent 4 days in bed and a week total at home in one of the worse chest infections I could remember. I did not fully recover for another week. I average 5 of these a year, and it's a significant obstacle for my family and my career.

My physician reached out to me about participating in the trial because, one, I have consistently shown presence of pseudomonas; and two, ciprofloxacin has been my go-to antibiotic for as long as I can remember. The reason I decided to participate is simple, because I along with many others with bronchiectasis have a desperate need for proactive treatment plans and not reactive

treatment plans.

My experience in the trial was positive. I will concede that day-to-day life managing a treatment plan that involves refrigerated medicine and a nebulizer, it's challenging. However, these challenges don't come close to trumping the positives. My day-to-day cardiovascular strength felt the best it had been in years.

Months into the study, I felt 23 instead of 28, which as mentioned has been a significant difference in day-to-day life for me. The inhalation through a nebulizer came with a surprising benefit. It immediately loosened my chest upon dosing, and I could bring up a large amount of phlegm. It acted like my PEP mask, which I use for daily physiotherapy.

As someone who was an early user of the TOBI podhaler in Canada, I immediately knew this was a better treatment for me. The podhaler, which was an inhaled powder, was an irritant to both my lungs and my throat, and it had made things worse. Most importantly to me, my exacerbations while I was on

the trial were reduced. They were shorter when they did occur, and they were much easier to recover from. Just one less exacerbation a year for me can make a mass of difference to my family life and my career. This is a critical goal for me.

I know cipro works, and I believe that you know that cipro works. For me, it's the only drug that has ever worked. I'm not naive enough to think there will be concerns with the application, especially around the topic of resistance. It's one of the first questions I had when asked to participate. However, as mentioned, I average about 5 exacerbations a year. My treatment plan has never changed: 10 days, 500-milligram tablets twice a day. That's 50,000 milligrams of cipro in a year. My understanding at this study and this treatment plan is that it yields an annual intake of approximately 17,000 milligrams of cipro in a year. That's 65 percent less cipro than I average today, and as noted, my exacerbations were less.

I flew to Washington to share all of this

with you because I'm tired of waiting for a treatment. I'm tired that the core of my treatment plan is for once I get sick and do not prevent me from getting sick. My ask of this committee is very simple. I, along with others with bronchiectasis, desperately need proactive treatment plans that reduce frequency of exacerbations.

I turn 30 in 35 days from today, and I want my 30's to be about building a family, furthering my career, and traveling, and this application is the most optimistic I've ever been about the prognosis of those with bronchiectasis. Simply put, those of us with bronchiectasis have been waiting for this, and we need this. We can't keep waiting. Thank you.

DR. BADEN: Thank you for your comments.

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. I have been instructed that we have a break at 2:30, so we will take a short 10-minute break, and right at the end of the break, we will resume with further clarifications to the applicant. We will make this 10 minutes start at 2:40 exactly.

(Whereupon, at 2:31, a recess was taken.)

Clarifying Questions (continued)

DR. BADEN: We shall resume. Thank you all. And we will resume with the clarifying questions for the applicant. And where we left off, Dr. Schaenman, you were next on the list. And I guess, to the applicant, if there are issues to clarify from the discussion with the FDA, with the agency, maybe we'll start with if there are things that you wanted to clarify from that discussion, and then we'll resume with our list because there were many issues raised.

DR. GONDA: Thank you very much. So I would just like to say that we have been very focused on the most severe spectrum of bronchiectasis and very selective on patients with Pseudomonas aeruginosa

for all the reasons that you have heard. So as others previously mentioned, we really are looking at the segment, approximately a set of the patients with the most severe form of the disease. And resistance has always been on our minds. We are dealing with inhaled antibiotics, so you always spread a lot of [indiscernible] to each development program as well as in the phase 3 studies.

I'd like to invite first Dr. VanDevanter to speak about his analysis of the resistance.

DR. VanDEVANTER: Thank you. As was mentioned by the public comment and also by Dr. Gonda, when you treat chronic infection with antibiotics and you don't sterilize the lung, then of course activity is defined by selection for less susceptible isolates. You've seen the box and whisker plots that we have provided before, but if I could have the slide up.

I want to talk from the standpoint not of the change from baseline but from the change after the first treatment cycle to after the 6th treatment cycle. I think this is the most

reasonable way to try and predict what might happen at the 7th treatment cycle, or the 9th treatment cycle, or the 13th cycle.

Here I've highlighted at visit 3, the end of the first on cycle, visit 4, the end of the off cycle, and again 13 and 14. And what I'd like to show you is histograms that overlay the susceptibilities of those plots. If I could have slide up, please?

On the left-hand side, you see the ends of the 1st and 6th cycles. The 1st cycles are solid lines. The dashed lines are for the last cycle. And you can see there's a clear separation between the blue lines and the gray lines. There's movement there, and I think we've all acknowledged that, that when there's an end of an on cycle, there's a distinction between the placebo group and the treatment group.

If we go to the right-hand side and look at the end of a year of treatment and look at the distributions of those curves, it's really clear that, yes, there's a change in susceptibility from

baseline, but the lion share of that change occurred over the 1st cycle, and it's really very modest differences. Admittedly, there are differences, but very modest differences between the 1st cycle and the 6th cycle.

So I just want to say that, as was mentioned in the public comment, this is really quite similar to data that came before this committee more than 20 years ago, the distinctions being that that was 6th month data on two-thirds the number of patients, but the question was the same: Are we taken a cornerstone therapy and furthering it away by preventing exacerbations if it's a rescue therapy that's required? And it was said -- I don't need to repeat -- that tobramycin continues to be a standard of care for treatment of pulmonary exacerbations in two-thirds of the patients inhaling.

So this gives me some level of confidence. Admittedly, there's reason for concern. But this may be a phenomena related to how we use these very high concentrations in the lung, that we get this

culling of the pseudomonas herd and then regrowth. And what we don't see in this study is a continual incremental step; at every visit we see a change. But that change is not as dramatic as we would predict if significant changes incrementally occurred at each cycle.

DR. BADEN: Please keep the slide up because of follow-on questions. And to the panel, let us know if you have follow-on questions so we can build on a theme. I have a follow-on question.

The issue of the end of 1st and 6th cycle off cycle and how the curves come together, might that be a reflection of differential fitness associated with detectability and not loss of resistant clones, but really an artifact of what you're able to detect given your detection methods?

DR. VanDEVANTER: I hope I didn't give the impression that I think that the resistant clones are lost. What I believe is that they've been overgrown by healthier organisms. So the 2-log changes that we see in that population is just a reflection that the clones with less susceptibility

don't compete very well in the lung in the absence of pressure.

So the clones have not gone away, but given our sampling system, we're much more likely to detect a clone with higher susceptibility.

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

DR. GRIPSHOVER: Yes, it's a little bit related to that. Talking about them overgrowing back, when you look at the slide that shows how the colony kind of goes down and then it goes back up --

DR. VanDEVANTER: Yes?

DR. GRIPSHOVER: -- it almost looks like the active arm is a little bit higher than placebo, when it grows back. And I noticed when -- somebody had the CF total tobr [ph] curve, it doesn't do that. In the CF patients, the tobr did not -- it kept it suppressed. On the time that you were off cycle, it didn't grow back up to the same. And I don't know if that's the difference of the drug, if it's the difference of the disease because we keep

trying to extrapolate CF and non-CF. But I had noticed that it grows back up.

DR. VanDEVANTER: Slide up, please. I'm trying to understand -- I don't see that the end of off treatments are higher than baseline. They certainly are about around baseline. And to your point, there was a little bit of a difference observed in the tobramycin studies. But I think, again, what's important is the tobramycin studies were only 3 cycles; this is 6 cycles. And actually the effect of the antibiotics at the end of the 3rd cycles on CFU was moderate.

I remember a discussion about whether if only we'd run that study for 4 or 5 cycles, we might see that inhaled tobramycin didn't work at all. In this context, really, we see essentially the same sort of CFU drop a year later that we saw at the beginning, perhaps attenuated somewhat. And we have to accept that there are going to be environmental changes to what's a very complex infection with continued treatment and relapse. But I don't have any indication from this that the

effect is going away, and it certainly doesn't look like there are any means that are greater than the beginning at baseline.

DR. GONDA: Dr. Sethi, please come to the microphone.

DR. SETHI: I wanted to address the question regarding CF. The sampling in that was not regular sampling as we did, as was done by Aradigm on a monthly basis. So the shape of the curve is that a lot of the sampling was done after a cycle.

Next slide. If you can see on that, it's not always -- for example, 16 and 24, both are at the beginning of the on cycle. We don't have the regular. So you get the impression, but it's more related to the timing of the sampling. Otherwise, they seem to have the same cyclical patter that when they go on cycle, they have a bigger drop; when they go off cycle, it comes back up.

DR. GONDA: Thank you. I'd like to invite Dr. Froehlich to the podium. There are a couple of questions. One of them was concomitant medication in the two trials, and the other one was the

history of discussions with FDA about the endpoints. Thank you.

DR. FROEHLICH: Slide up, please. Just to remind you, this is the slide I presented this morning in my safety presentation where you see the reduction in concomitant and antibacterial drugs. And I believe the question was whether we have it separated by ORBIT-3 and ORBIT-4.

Slide up, please. Here you see it's separated, and when you look at the data -- ORBIT-3 is on the left, ORBIT-4 is on the right -- there's some numerical differences, but in principle it's the same pattern in both studies.

DR. BADEN: Can you leave that slide up for a second? Some of the panel members were studying it.

DR. ALLENDE: I have a question. Fluoroquinolones, do you mean all fluoroquinolones or do you mean ciprofloxacin only?

DR. FROEHLICH: All fluoroquinolones. Most of it was levo, levofloxacin and ciprofloxacin.

DR. ALLENDE: Thank you.

DR. BADEN: Dr. Green, do you have questions on this?

DR. M. GREEN: No.

DR. FROEHLICH: Please allow me a quick comment on the history of our interactions. There were comments made about the timing of our statistical analysis plan and how this relates to discussion with the FDA.

By way of history, in 2011, we received orphan drug designation. We had many discussions with the agency, and we started our clinical trials in April and June of 2014. In May of 2014, we received qualified infectious disease product designation, recognition of the pseudomonas targeted; we have our patient population. And in July of 2015, we had a meeting with the FDA in which we proposed, to a certain degree, in the light of qualified infectious disease product, that we could do additional or whether we could change analysis.

We discussed, amongst others, the importance of the frequency analysis. We proposed whether we

would be able to pool those studies. And unfortunately, we left the meeting without any changes to the study design of our two individual studies. And the SAP that was finally reviewed by the FDA and approved in 2016 was finally a result of this meeting in 2015.

DR. BADEN: And that was prior to unblinding the SAP finalization?

DR. FROEHLICH: Yes.

DR. GONDA: Yes. It was quite a while before we finished the studies, yes; long time before we finished the studies.

So that brings me to the question of what was prespecified and what wasn't. FDA, as we mentioned, prespecified a time to first of all exacerbations and severe exacerbations. EMEA asked us very early on that we should look at the moderate and severe exacerbations. So they were prespecified, and they were analyzed according to the prespecified plan before we unblinded. So therefore, it's no other post hoc decision. This was prespecified by EMEA.

Can we have the slide up, please? Interestingly, before I speak, the evolution of the definition of pulmonary exacerbations has also changed. They're not only in bronchiectasis but also in cystic fibrosis and COPD. Generally, it is not believed that an exacerbation is only an exacerbation when it requires and intervention. In our case of course, the intervention is the use of antibiotics. So moderate and severe exacerbations, in our case, are those that require the use of antibiotics.

As you can see, if you look at that endpoint, you clearly see that we've got a modest impact of inhaler versus placebo when you take what I would say is the more modern definition of an exacerbation, one that requires intervention with antibiotics, and it was prespecified.

I'd now like to also look at the impact that this has -- slide up, please -- on our perception or on our belief of what is really important for the patients. If you look at the result for the moderate and severe exacerbations using the

counting process and adjustment for stratification of macrolides, we are now beginning to see clearly a much greater concordance between ORBIT-3 and ORBIT-4. And as I said, certainly, the nature of [indiscernible] were prespecified before it.

Just to make another note about the importance of frequency, which is the focus on the first exacerbation, one of the analyses that we have done, which is really interesting, is to look at -- slide up, please -- the serial Kaplan-Meier. This is looking at the time to first exacerbation, looking at the time to second set, and fourth. And this is retaining all the patients in the analysis. So we are looking at all exacerbations.

What we see in ORBIT-4, is that Linhaliq begins to act very early on, and it has an impact on the first, second, third, and fourth exacerbation. Slide up, please.

With ORBIT-3, we don't see an effect on the first exacerbation, and we begin to see an effect on the second exacerbation, and the third exacerbation, and the fourth exacerbation, and so

on and so forth. So the primary reason we believe, for reasons that we don't fully understand, it just took Linhaliq a little longer to show the effect in the ORBIT-3 study. As I said, we don't fully understand that.

One of the issues that we have noticed, and somebody mentioned the per protocol analysis -- slide up, please -- is that when you look at the per protocol analysis -- and we were actually quite surprised when we did the sensitivity analysis, which was prespecified comparing the FE [ph] analysis with the PP analysis -- is that when you remove the subjects who had major deviations from the protocol, it's got a particularly large impact on the frequency of exacerbations in the ORBIT-3 study.

When you look at what we would call the correct frequency analysis, you adjust it for the baseline macrolides, and you take the deviators from the protocol -- again, the studies are now beginning to look much more similar. Thank you.

DR. BADEN: Dr. Follmann, you had a

follow-on question?

DR. FOLLMANN: Yes. It just had to do with the multiple event analysis. The Kaplan-Meier curves where you look at the difference in time to first event is defined randomized comparison. When you start looking at time to second event, it's no longer a randomized comparison. You're looking at the subset of people who actually had an event. You don't know if they're balanced by the groups or anything. I view it as equivalent to an observational study in terms of quality of evidence.

DR. GONDA: I would like to invite Dr. Janet Wittes to -- sorry. Excuse me.

CDR TRACY: May I just add to that last point. Could we see the slide?

DR. GONDA: Serial Kaplan-Meier.

CDR TRACY: In ORBIT-3.

DR. GONDA: Yes. Slide up, please.

CDR TRACY: This isn't the one that I was thinking of. Was there one more shown after this?

DR. GONDA: There was one before -- ORBIT-4

and ORBIT-3.

CDR TRACY: It was the table that showed full adherence and per protocol sampling groups.

DR. GONDA: Sorry. Thank you. Slide up, please.

CDR TRACY: Yes. It looks like the stratified analysis is a subset analysis within the per protocol population. Am I reading that correctly?

DR. GONDA: No, sorry. I did not explain it. If you look at the frames, it is using the counting process, the per protocol patient population, and then stratified for macrolides at baseline.

CDR TRACY: Yes. So the per protocol -- just to support what my colleague just said, the per protocol, also there was about 80 percent -- that is about 80 percent of the full analysis --

DR. GONDA: Correct.

CDR TRACY: -- sample. You're further carving out subsets of the individuals, so I can't

feel that this is an unbiased analysis.

DR. GONDA: No, no. I just wanted to explain that one of the things that affected the results of ORBIT-3 and made very little difference to ORBIT-4 was that there were a lot of protocol deviations. And the most common protocol deviation, major protocol deviations, was the use of antipseudomonal antibodies for reasons other than pulmonary exacerbations. And this is why we did the analysis, which looks at the respiratory events that are treated in antibodies, so that kind of takes the problem away.

As I showed in the slide in core, in the core analysis, when we look at any event, therefore, it's a respiratory symptom event and it was treated with antibiotics, we see in fact an even stronger efficacy. Slide up, please.

This is another way of removing the reduction of the population because now we're allocating all the patients and we're allocating all respiratory events that require interventions and antibodies. And as you can see, we have a

positive impact only compared to placebo in both studies.

CDR TRACY: May I ask a question about this analysis. Is this the use of antimicrobials during treatment that in your model you're adjusting for that, or is this where you're counting the use of an antibiotic before PE as an event?

DR. GONDA: This is the frequency analysis using the counting process, and it's counting all the events that have respiratory symptoms that were treated with antibiotics, which is an endpoint used in other clinical trials.

CDR TRACY: Does that also include the PEs in this analysis?

DR. GONDA: Yes, it's both PEs and any other events that are respiratory that require treatment with antibodies.

DR. HILTON: And is this in the per protocol subset?

DR. GONDA: No, no, no. This is all patients. This is everybody.

I think there was another question about the

serial Kaplan-Meier, and I'd like to invite Dr. Janet Wittes to answer that question, about a population used in the serial Kaplan-Meier analysis.

DR. WITTES: This is Janet Wittes. The serial Kaplan-Meier, the population used -- slide up -- was the initial population. However, you're right, that as time goes on, there are exclusions based on what happened. So it's an analysis, I would say a highly suggestive analysis, but there are some issues related to the kinds of problems that you're describing.

DR. GONDA: Thank you.

DR. BADEN: Other clarifications or that was what you had?

DR. GONDA: Sorry. The other question was about the significance of the effect, and I'd like to invite Dr. Chalmers to speak to that.

DR. CHALMERS: Thank you very much. I think this is a very important question to address, is whether the reductions in the frequency of exacerbations that we've seen in these trials are

clinically meaningful. I think we heard from the FDA briefing document and during some of the discussion earlier, a discussion of one event every 2 years, that's essentially a number needed to treat, which a lot of us clinicians are very used to using for clinical decision-making.

To orient you to the kind of numbers needed to treat we look for in research, a good analogy is COPD where we prescribe inhaled corticosteroids or bronchodilators, and their numbers needed to treat are between 3 and 5.

So if you look at the results of the ORBIT studies, the number needed to treat we heard for ORBIT-4 for prevention of PEs was 2. The number needed to treat for ORBIT-3 would be 4.5, obviously not statistically significant.

In the pool data, the number needed to treat would be 3, so well within that range that we recommend therapies and other conditions. Then the number needed to treat in ORBIT-4 to prevent a hospital admission is 6, which is really exceptional for an event as serious as a hospital

admission.

So my view of this data from a clinical point of view is that it's better than anything we've seen previously in bronchiectasis and comparable to effects that we look for in other conditions. And I think you heard very clearly during the public meeting from the clinical community, there's agreement that this is a highly significant clinical effect, and that we would want to prescribe this therapy if made available.

To support that, I'd just like to ask Dr. Tino to also give his opinion as a prescribing physician in the U.S.

DR. TINO: Thanks, Dr. Chalmers, and I can appreciate the ability and the opportunity to give you my perspective. As an academic faculty member at the University of Pennsylvania and as an experienced clinical researcher, I don't think there's any escaping the fact that ORBIT-3, for example, did not show a statistically significant impact on the primary endpoint. But I think what you've heard from all of us, and I get the feeling

in the room that there's a movement towards understanding that the frequency of exacerbations is really the clinical meaningful endpoint, and the time to exacerbation, again, is a surrogate for that more clinically significant endpoint.

As a clinician, what I see and what I look at is the totality of the data. And the totality of the data in that, what I see is a reduction in moderate to severe exacerbations of 30 percent and more; a reduction of severe exacerbations of 40 percent, and I'm looking at that pooled data; a decrease in hospitalization; and a decrease in total antibiotic use.

So I look at that, and I compare that to what we have available now with its clearcut concerns about safety and clearcut concern about poor tolerability. So with a patient in front of me looking at this data compared to what we have and compared to the absence of other options, I don't see this benefit as being marginal. I actually see this benefit in the appropriate subset of patients, those with chronic pseudomonas

infection with frequent exacerbations, I see the impact that we've discussed here as clinically meaningful. Thank you.

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

DR. HILTON: Yes, I do. I just wanted to remind you that I also asked for the phase 2 outcome of colony forming units mean levels by group over time and also the time to serious PE incidence.

DR. GONDA: In the ORBIT-2 study?

DR. HILTON: In both, please.

DR. GONDA: So in ORBIT-2 as well as in the --

DR. HILTON: Oh, no. I'm interested in ORBIT-3 and ORBIT-4.

DR. GONDA: Thank you. This is Kaplan-Meier for moderate and severe exacerbations. Slide up, please. This is the ORBIT-4 results for the time to first moderate or severe exacerbations. Slide up, please. This is the ORBIT-3 results for time to first moderate or severe exacerbations.

If you allow me one more slide which relates

to the pooled analysis. We did conduct the pooled analysis in the same way as the meta-analysis is being done. We stratified by study. And as we mentioned, these studies were identically designed and run concurrently in very similar genometrics [ph]. So we did the pooled analysis and stratified by study.

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

DR. CLARK: I had two questions for Dr. Tino. The first was, is the natural history of non-CF bronchiectasis really predictable from one year to a second year? And it could be significantly affected by the etiology of the bronchiectasis, which wasn't captured in these studies?

DR. TINO: Thank you. That's a very appropriate question. We talked about the etiology of bronchiectasis, and certainly it is a heterogeneous disease. And there are circumstances where, for example, the natural history, it could potentially be impacted by specific therapy. But when we approach these patients clinically, I think

there is a movement, both at the bedside and I think in the research community, to get away from the idea of approaching it simply specifically from an etiology standpoint and look at a group of what we're now clinical phenotypes.

Among those clinical phenotypes that have been identified, both in Europe and the United States, it is the chronic pseudomonas group that are targeted in studies such as this. And in that population of patients, regardless of etiology, I think we've got a reasonably good idea of what the natural history in that subgroup.

In terms of predicting natural history from one year to the other, I think it's very difficult to do that. What I can say is that the previous history can oftentimes predict the future, so people who are frequent exacerbators typically, even when treated with other things like airway clearance, typically tend to behave similarly, at least over a period of several years. But we don't have a lot of great data to specifically predict that in an individual patient. I hope that answers

your question.

DR. BADEN: Dr. Carvalho, you had a follow-on question to this line?

DR. CARVALHO: I do. Thank you. This has come up before, and this is one of the things that has bothered me with these types of studies. As Dr. Tino appropriately pointed out, there are a lot of phenotypic variations in some of these obstructed lung diseases that are now being looked at very individually because every patient is so heterogeneous in this entire situation.

Therefore, I would ask has anybody looked at -- again, asking if anybody's ever looked at the data using the patients that are on control, looking at the 2 years let's say prior to treatment, and then looking at the year of treatment, and then seeing other patients, too?

DR. GONDA: Dr. Chalmers has done a very nice study, investigation of the different phenotypes, which I think addresses this. Dr. Chalmers, will you please come to the podium?

DR. CHALMERS: I don't think anyone's done

analysis of this data or any of the other bronchiectasis trials specifically using patients as their own control as you've described, but there is one analysis that's been done that does address this phenotype question.

Could I have slide up, please? This is using registry data to look at one of the most well described phenotypes, which is the frequent exacerbator phenotype. Forgive me, but the text is a little small, but I'll point out the colors. These are looking at patients and their prior exacerbation history, and the first graph on the left is the first year of the study; the second is the second year; and the third is the third year of the study.

The patients in red are patients that have 3 or more exacerbations per year. And if you look at their behavior in the following year, the vast majority of those patients continue to have either 2 or 3 exacerbations per year. So they're a very consistent phenotype to the question that was asked earlier.

If you look at the patients that have two or more events who would also have been included in this trial, you can see that there are much less consistent phenotype. Many of those patients do continue to have frequent exacerbations, but about half of the patients have zero or 1 exacerbation in the subsequent year.

If we could have the subgroup analysis? We're able to look at the consistency of prior exacerbations versus future exacerbations in the trial. And you've seen this data already during the core presentation, that the consistency between the two trials, ORBIT-4 and ORBIT-3, was much more consistent in those patients that are in the red bars there, the patients that have more events, and are therefore more likely to respond to a treatment that reduces exacerbations because they're at much higher risk.

Slide up, please. This is the data that I'm referring to, where it's much more difficult to show a benefit of a drug in a population that's not going to have as many events, and that's why we

would tend to, in clinical practice, target these drugs of the patients who have a long history of very frequent exacerbations. And that's represented here by the patients that had more than 3 exacerbations in the prior year.

Does that answer your question?

DR. CLARK: Yes, thank you.

DR. BADEN: Dr. Tracy?

CDR TRACY: Just along those lines, because we anticipated that question again, that was the purpose of my sensitivity analysis, where I fit the data using prior number of exacerbations as a continuous variable, or really I guess as an ordinal one rather than this categorical variable, that any time we cut data like that, we lose information, as is in the case with the 2 to 3 and more 4, 4 more.

So I did do that analysis where I treat prior number of exacerbations as a continuous variable. And as I showed in my slide 20, overall results do not change to that from when you include prior number of exacerbations as that two-level

categorical factor.

DR. BADEN: I will ask that everyone try to shorten and target their questions and responses, as we have many more questions and little time. Dr. Hilton?

DR. HILTON: I think I just haven't been clear yet. I'd like to see the phase 2 outcome used in the ORBIT-3 and the ORBIT-4 data, if you have that. We're asked to comment on possible outcome variables, and I know that you have that data, so I'd love to those slides.

DR. GONDA: Sure. Slide up, please. The primary endpoint in ORBIT-2 was the change in the colony forming units for Pseudomonas aeruginosa at 28 days. There were two reasons why we selected it. One of them was that we really didn't know how else to measure the efficacy of the drug. This was our first trial with these drugs, so microbiology was a good endpoint for this.

Then we did the exploratory endpoint, which was time to first exacerbation. This study, the patient could not continue with the study drug

treatment after their pulmonary exacerbation, so we couldn't look at the frequency. So the only thing that we could look at was the time to first exacerbation. And also looking at the microbiology beyond the 28 days again would have been confounded by the fact that these patients took the study drug treatment. So the only really valid data is the 28-day microbiology pause to time to first exacerbation.

DR. HILTON: Did you analyze ORBIT-3 and ORBIT-4 using that endpoint?

DR. GONDA: Yes, we did.

DR. HILTON: Could we see that?

DR. GONDA: C-5, slide up, please. If you look at the same endpoint, the 28-day reduction, and with the Pseudomonas aeruginosa, again we see highly statistically significant results. In fact, all of our microbiology results consistently throughout all of the preclinical and clinical development showed very high statistically significant and clinically meaningful reductions in pseudomonas. Thank you.

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

DR. SCHAENMAN: Yes. I'd like to ask a follow-on question along the topic of resistance and CFUs. I'd like to take a look together at the table 26 in the document that you all provided. I don't think it's been shown in slide form here.

DR. GONDA: Would you please rephrase? Sorry.

DR. SCHAENMAN: So it's been asserted several times by the sponsor that the increase in MIC does not impact patient response. Dr. Sethi asserted that because patients are being treated at the same rates with fluoroquinolones in the placebo and the inhaled cipro arm, that there's no decrement. However, we don't really have any data regarding how they responded to that therapy.

The central hypothesis behind use of inhaled antibiotics is to break that vicious cycle that you introduced early, and that's really dependent on the decline in CFU. I was just concerned when I saw that table 26, which looks at CFU decline

stratified on MIC.

Although, again, it has been stated, based on the clinical endpoints, that the resistance that's engendered by the on again/off again use of inhaled cipro is not detrimental, I think that this data that you shared with us electronically concerns me. What this suggests is that the robust decrease in CFU is really observed in those patients that have sensitive strains in that first column. Well, if you look at the last two columns where people have MICs over 4, now that decrease is negative 0.5, and you can see from the confidence intervals that it's no longer statistically significant.

So my concern, and would like some reassurance on this, is that with long-term use, as has been stated, this is a product that would be used for years, predictably. My concern is that you would see ongoing creep and lack of efficacy, inability to reliably decrease CFU and see effect.

The last issue I wanted to mention is that once you get an MIC above 4, now an oral

fluoroquinolone is no longer on the table. So we very much appreciate the comments from patients and patient advocates, but I think our worry from a infectious disease perspective is that if a go-to oral antibiotic is no longer effective, maybe we're not doing patients a service.

DR. GONDA: Thank you very much. Dr. VanDevanter will come to the podium to answer your concerns about resistance.

DR. VanDEVANTER: Thank you. First, I want to point out that 20 percent of the patients entering the study already had an MIC of 4 or greater, and I'll leave it to my clinical colleagues to decide whether they thought that oral quinolones were off the table. I'll tell you, in CF, that's not the case, that susceptibilities are not generally used to guide treatment for exacerbations.

To your point about this slide, it's a great point, that the organisms with higher MICs -- and the statistical test is that the proportion of patients that had at least a half-log or a 1-log

reduction. I want to point out, though, that there is a little bit of confounding here because patients that have lower CFUs to begin with tend to have higher MICs during the study because we've culled out the susceptible organisms.

If I could have this slide up, please? In the microsummary, we did a logistic regression where we looked at the effect both of the ciprofloxacin MIC -- so here we have a comparison of less than 4 micrograms per mL to greater than 8, so that's very resistant; then if there's such a thing as mildly resistant, 4 to 8 to greater than 8 -- and then also included the starting sputum density.

It turns out that patients who have a very low sputum density of course have a basement effect. There's very little opportunity to lose CFUs if you're already at a very low level. So I agree with you that patients that had higher MICs, if you look at a univariate analysis, definitely didn't have as robust a CFU change, but there is clearly a relationship, and the magnitude of these

relationships is really informed by the starting density that we're talking about.

DR. BADEN: Along the assessment of resistance, any assessment of resistance outside of pseudomonas and outside of the lung, such as the GI tract.

DR. GONDA: Thank you very much. Again, Dr. VanDevanter, could you please come to the podium? He's our microbiologist. Thank you.

DR. VanDEVANTER: As was mentioned by Dr. Allende, we didn't sample any organisms outside the lung, and although we didn't look at susceptibilities for any other organisms -- pardon me. Slide up, please. I want to point out that this was predominantly a pseudomonas infected population. These are 5 organisms that were identified for not only culture but also to look at changes in densities during this study. So pseudomonas obviously the primary pathogen, and then also E. coli; coliform; H. flu; Staph aureus, and Strep pneumo.

This just shows you the number of times per

visit that an individual organism was identified, and just to point out that the lion share of the isolates were pseudomonas. About 20 to 25 percent of the patients had Staphylococcus aureus. And these other organisms are really very minor players.

I show you this first so that I can show you the next slide -- slide up, please -- to show you that although we saw this very nice cyclic change in pseudomonal densities, two things. First of all, it wasn't really an obvious pattern of changes in the other organisms that would suggest there's a continuous ongoing selection in the population, although there may have been. And also, we're really talking about organisms that are multiple orders of magnitude less in density in the subset of patients that have those organisms. There's really no evidence that we can see that there are organisms that are benefiting from the continuous treatment. So although we don't have susceptibility tests, there's no indication of an overgrowth of one of these other organisms.

DR. BADEN: So no susceptibility for those four other organisms.

DR. VanDEVANTER: Correct.

DR. BADEN: And as we heard in the open public session, the issue of NTMs is a significant one. Any assessment of NTM, was it detected, and was there any resistance detected in that setting?

DR. VanDEVANTER: I'll turn this over to Dr. Gonda.

DR. GONDA: Thank you very much. We excluded patients who are on active treatment for non-TB mycobacteria. And if there'd be any [indiscernible], that would be a very, very small number of people who might have been carriers of NTM but they did not have the NTM disease.

DR. BADEN: But did you monitor any evolution of the NTM in those who were carriers?

DR. GONDA: We didn't monitor the evolution of the NTM, but there were no reports of these patients having developed the NTM disease. I also want to mention we do have our second NIH grant to look at the effect of Linhaliq in Mycobacterium

avium and Mycobacterium abscessus. We have done preclinical work in the biofilm model of NTM of Mycobacterium abscessus and avium, also in the microphage model and in a rodent model. And what we see in contrast to ciprofloxacin, Linhaliq is very effective in both of these species. In the rodent model, we see efficacy of Linhaliq against both types of microbacteria, and there is no emergence of resistance in the rodent model.

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

DR. GRIPSHOVER: What about --

DR. BADEN: And I do encourage everyone on point because we have limited time.

DR. GRIPSHOVER: It's a quick thing. Did you only look for those five bacteria? What about stenotrophomonas, aspergillus? Did you look for other pathogens as well, or were you only looking for those pathogens?

DR. GONDA: Thank you. Those that we have seen were those that were prespecified by FDA, but we looked at others. And Dr. VanDevanter, again,

will show you the other bacteria.

DR. VanDEVANTER: Slide up, please. During the course of this study, there were 50 species in general that were isolated among about 6700 respiratory specimens. So I showed you five on that original slide. There was actually a sixth that was included in the density measurements, and that was Moraxella catarrhalis.

Importantly, the lion share of these were only sporadically isolated. If I could have the next slide. This is a listing of those organisms that were identified at greater than a half a percent during the studies. The species in blue are the species that had a greater numerical prevalence in Linhaliq patients. All the others had a greater presence in the placebo patients.

You can see from the confidence intervals that there's really nothing dramatic going on. There may be a little bit more isolation of haemophilus and klebsiella, a couple klebsiellas and a serratia in the placebo patients, but overall, we didn't see anything that would suggest

that there was a treatment related increase in prevalence.

DR. BADEN: Thank you. Dr. Honegger?

DR. HONEGGER: Most of my questions have been answered already. I did have one follow-on. I know you addressed that you do not -- you have the seasonality as an explanation for the discordance between ORBIT-3 and ORBIT-4; although I just wanted to ask if you have any data you could show on, for instance -- because I know they were in both north and south hemispheres and you enrolled throughout the year I believe.

Do you have data on, for instance, the proportion of patients who are enrolled during respiratory season or winter season for the particular geography and their outcomes?

DR. GONDA: Well, we had the enrollment almost concurrently in both trials, and almost all the geographies were identical. So they were predominantly U.S., Western Europe, and Australia. Unfortunately, I don't see that the seasonality would explain the difference. Thank you.

DR. HONEGGER: And my second question is referring to the idea of an inhaled antibiotic and the possibility then of subsequent treatment with ciprofloxacin, for example, for a systemic infection. This may have something to do -- I guess there's precedent for using this with tobramycin, but since this is a new use of ciprofloxacin by this route, pathophysiologically, do you know your agent's penetration into the bronchial wall, for instance, or the interstitium?

I know that there's not a lot in the plasma, but what about the other areas that would be relevant for an actual infection?

DR. GONDA: Thank you. We were obviously concerned that there might be something happening, so I'd like to invite our chief medical officer to speak about the investigations on infections at other sites.

DR. FROEHLICH: Slide up, please. This slide shows you the incidence of systemic infection observed in both studies. Urinary tract infections were the only category of systemic infections that

were slightly high in Linhaliq than in placebo, but we did not see any change in the course in treatment of UTIs. They're both very similar and the duration of treatment was very similar. We looked at any differences in sinusitis, upper respiratory tract infections, and they're listed on this slide, lower respiratory tract infections, and we didn't see any differences. We did not see any difficult to treat infections.

DR. HONEGGER: Did you have organisms in these infections? And if so, was quinolone resistance assessed?

DR. FROEHLICH: We did not have for these individual infections individual organisms.

I would like to ask Dr. Sethi to speak about the use of antibiotic courses during the study.

DR. SETHI: I just want to add on to what was just said. There were no organisms, either at the investigative level or at the DSMB level. There were no reports of serious infections related to resistant organisms in the course of the study.

I just want to go back to your question

about why does the systemic antibiotic work when the inhaled antibiotic has resulted in a higher MIC? This is somewhat speculative, but there are two possibilities, and some of this is based on the work that I've done in the context of COPD. One is that the inhaled antibiotic doesn't get in everywhere, in these lungs. So when you give something systemically, it may get into areas of the lung where the inhaled -- not an issue of the bronchial wall but just an issues of ventilation imbalance and ventilation mismatching throughout the lung. That's one explanation.

The other possible explanation is that -- and this may apply also to CF and COPD. When we suppress the colonizing pathogen, we're reducing inflammation. And what's actually driving the exacerbations is other organisms coming in, some new strains that we have shown in COPD or viruses even. And if you have a less inflamed airway, it's less hospitable to these other pathogens that come in. And that's why systemically when an antibiotic is given, it still

works. Again, as I said, these are hypotheses and need more work, but they could be potential explanations for that.

DR. BADEN: Thank you. Dr. Weina?

DR. WEINA: I'm trying to understand in light of the question that we've been asked -- the question is actually is there safety and efficacy in the delay of time to first exacerbation? And then of course, there was the discussion of Dr. Chalmers, which he said that reducing the frequency is the key objective and time to first exacerbation is not used. And then Dr. Wittes got up there and said, well, yes, but the assumption's underlying the analysis of frequency. Pulmonary exacerbations are not valid, so we're doing the counting.

What endpoint should be using? With hindsight being 20/20 and looking at the studies you have done, what endpoint should we be using? I mean, obviously, something's changed from 18 months ago, or more than 18 months ago -- when the study was designed. But what endpoint should we be using

now?

DR. GONDA: The study was designed about eight years ago. It was quite a while ago. I think we always believed -- and I think our discussions with patients and the key opinion leaders was the reduction of the frequency of exacerbations, and particularly those that require interventions with antibiotics, including IV antibiotics, that they really were the most important results for the patient. And I think that we heard it during the open public hearing. I think from our perspective, that is the endpoint that we should be looking at.

DR. WEINA: But frequency itself or some other surrogate marker of frequency, or some other way of looking at frequency?

DR. GONDA: I think that looking at the frequency -- we obviously think that the counting process is a better method because of this interdependence between pulmonary exacerbations. But I just want to emphasize that the analysis using the negative binomial and using the counting

process with these analyses were very similar. The difference was in the confidence intervals rather than the estimates of the effect.

Let me just go to -- brings me to the question about the pooled analysis. I started talking about it. We did the pooled analysis according to the rules or meta-analysis. Slide up, please. In other words, when we pooled the results, we pooled it by study. So these are the results, the way that one would be using them in meta-analysis, of the different clinical trials.

So we think that the best estimate of the efficacy is from the pooled analysis, and you can see the point estimates, they're all favorable of Linhaliq over placebo. I also think that the p-values, these are nominal p-values. This was not prespecified analysis; we started reaching primary endpoint in both studies. But nevertheless, these p-values are quite impressive.

DR. BADEN: Thank you. Dr. Hawkins? No? Dr. Ofotokun?

DR. OFOTOKUN: I'm just trying to wrap my

mind around the -- maybe as I'm shown that this is effective or will be effective -- the target population again. So about 32 percent of people with non-cystic fibrosis bronchiectasis, 30 to 40 percent will have pseudomonas. And in the data that you showed us, about 20 percent of those with pseudomonas had resistant pseudomonas at baseline. How effective was this agent in those with resistant pseudomonas at baseline?

DR. GONDA: Thank you. They obviously was a concern for us. We took a brave step by including patients who did have resistant pseudomonas. There are more than 4 micrograms per milliliter of MICs, so we looked at that. Slide up, please.

This was a very important investigation for us because we really wanted to know whether this would impact the efficacy and also what would happen if the bacteria developed, MICs, higher than 4 micrograms per milliliter during the study. And as I mentioned, I'm pleased to say that we do see efficacy even in patients who got -- we see a suggestion of efficacy, and we wanted to take these

results with the caveat that we now have much smaller groups of patients, so we've got confidence intervals that we didn't see loss of efficacy in the patients.

If you slice and dice it -- slide up, please -- even in more narrow strata, then you can again see that patients who got MICs less than 2 micrograms, patients who are within MICs between 2 to 8 and greater, that we are seeing efficacy. And the same is true when we look at the MICs that emerged during the clinical trial. And I think that that can be readily explained by the very high concentrations of ciprofloxacin in the sputum watched throughout the 28 days of very on-treatment cycle.

DR. BADEN: Dr. Follmann, do you have a quick follow-on?

DR. FOLLMANN: Just a comment that I made earlier today, which is that I think this is not the best analysis that could be done. You're looking at MIC in December to predict what happened the previous May. You should do a different

analysis that uses May to predict June.

DR. BADEN: There are two remaining questioners, Dr. Gripshover and Dr. Carvalho. Can we ask your questions succinctly so we can get to the actual task at hand?

DR. GRIPSHOVER: Yes. It's a very quick question, and I don't even know if you'll have the data. But I noticed that in both trial, we know there were about 20 percent that ended up dropping out, some for adverse effect, but about 10 percent were withdrawal by subject.

Do you know why? Did you collect any data on why they were dropping out? Is it hard to do this thing 20 minutes a day, every day? We heard someone talk about carrying their things around. It seems to me that was a large amount that dropped out, and I don't know if you know why people chose to withdraw, if you collected the data or not.

DR. GONDA: I'd like to ask our chief medical officer to speak to that.

DR. FROEHLICH: Slide up, please. This shows you the reason for dropout. There are a

variety of reasons. I assume that you asked specifically of the withdrawal by subject. Yes. We do not have any detailed data on this topic.

DR. BADEN: Dr. Carvalho?

DR. CARVALHO: My question has already been answered. Thank you.

Questions to the Committee and Discussion

DR. BADEN: Thank you. I think this concludes the committee's deliberations and clarifications from the applicant. I'd like to thank the applicant for providing a tremendous amount of data and explanation as well as the agency in your presentations and response to the questions.

We will now proceed with the questions to the committee and panel discussions, which we have conducted. I would like to remind public observers 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've entered your vote. Please press the button firmly that corresponds to your vote. If you're 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, and the DFO will read the vote from the screen into the record. Next, we'll go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We'll continue in this same manner until all questions have been answered or discussed.

May we present the question?

DR. NAMBIAR: Thank you, Dr. Baden. Just a couple of points. Today's meeting, we've heard discussions about the benefits and risks of ciprofloxacin dispersion for inhalation for the proposed indication for the treatment of non-cystic

fibrosis bronchiectasis patients with chronic lung infections with Pseudomonas aeruginosa.

You've heard about the efficacy and safety findings from each of the two phase 3 trials, ORBIT-3 and ORBIT-4. Some key discussion points we've heard relate to the differences in the efficacy outcomes between the two trials with regard to time to first exacerbation and frequency of exacerbations likely due to treatment effect demonstrated.

You've heard presentations from the FDA and the applicant and comments from the 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 one voting question. 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 one voting question we have for you is, has the applicant provided substantial evidence of

the safety and efficacy of ciprofloxacin dispersion for inhalation in delaying the time to first exacerbation after starting treatment in non-cystic fibrosis bronchiectasis patients with chronic lung infections with Pseudomonas aeruginosa? 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 duration. Thank you.

DR. BADEN: Are there questions about the wording of the question? Dr. Green?

DR. M. GREEN: Yes. I would just like to get clarification on whether it would be appropriate as a committee member to answer this question both trying to address time to first exacerbation but also total number of exacerbations since that's been such a subject for conversation during the day's progress.

DR. NAMBIAR: I think we would suggest you can vote on the question as it asks, but certainly any comments you have or additional feedback you

have can be brought up as part of the discussion.

DR. BADEN: Thank you for that clarification. Any further discussion on the question?

(No response.)

DR. BADEN: If there is no further discussion on the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may 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. So voting is now open.

(Voting.)

DR. BADEN: Everyone has voted. The voting is now complete.

DR. TESH: For the record, the voting results is yes, 3; no, 12; abstention, 1; non-voting, zero.

DR. BADEN: Now that the vote is complete,

we will go around the table and everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. I think there are two or three members who have to leave particularly expeditiously. So we'll start with Joanna.

DR. SCHAENMAN: Joanna Schaenman from UCLA. With some misgivings, I voted no. I think that inhalational antibiotics, especially once-daily liposomal formulations, are an excellent strategy, however, I didn't feel that we sufficiently met the burden for safety and efficacy. I think focusing on a primary endpoint of frequency and acquiring more granular data regarding reasons for exacerbations and clinical response to fluoroquinolones, which could be performed perhaps as a follow-up of previous study patients, would help us get to the level of evidence needed for us to feel more favorably about this type of medication.

DR. BADEN: Is there another member who has to leave quickly? Dr. Hilton?

DR. HILTON: I also am on the fence. I want it to work. I want to vote positively to support the patients, but I'm really concerned about the absence of a clearcut explanation for why ORBIT-3 and ORBIT-4 findings are so different. I wonder if enhanced measures of adherence during a future trial might be helpful. It's just very hard to figure out. Thank you.

DR. BADEN: Thank you. We'll now resume on this side with Dr. Harkins.

DR. HARKINS: Michelle Harkins. I voted yes. This is a difficult patient population that is very heterogeneous, and we don't have therapies for them. It would be nice if the trials were not discordant in the results. I think people might feel better. But as a pulmonary provider, I want to be able to offer something to these patients that would be covered by their insurance. I've used TOBI for a number of years in the CF population and haven't run into significant issues. And I suspect this will be similar, but again, that's just a guess.

I think looking at frequency of exacerbations is really key. And if there were some way potentially to -- I know you mentioned biomarkers and other things at the end of your handout, but some way to figure out which patient population is really going to benefit from this drug would be helpful.

DR. BADEN: Thank you. Dr. Daskalakis?

DR. DASKALAKIS: I voted no or actually answered no to the question in terms of the substantial evidence for the efficacy of ciprofloxacin dispersion for inhalation in delaying first exacerbation. I think that was a very specific question that we were asked. I think that the data are a lot more convincing for preventing recurrence, especially in specific populations in the absence of a biomarker, which we heard about, at least folks who have more severe illness as defined by more frequency baseline exacerbations.

I think, though, it would be good to figure out a way to create a study where you focus on those higher risk populations. Another question

maybe for the FDA, to really have us think about considering this other endpoint as a significant one. I think if this question were framed differently and we were looking at that endpoint, my vote would be different.

So I think that perhaps rather than creating a new study, a hard to recruit population, that there may be a role of really saying can we look back at these retrospectively and say can we decide a population of folks where we could label this drug correctly to make sure that we target the people who will really get benefit and have lower risk.

So I voted no and really wish I could vote yes because I think that having another tool in the toolkit to address this population that really needs to improve their quality of life I think is really significant. But as it stands now with the question asked, I think I responded the way the data shows, which is we don't have enough evidence that this prevents a first exacerbation.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: I voted yes in spite of the fact that ORBIT-3 did not meet the primary endpoint. The reasons I voted yes were there was a positive trend in the patients who had the most severe disease. There was a positive trend in more clinically relevant secondary endpoints, and ORBIT-4 met the primary and secondary endpoint.

It does appear to be safe overall in a very sick population. My answer was influenced by the compelling unmet need and also by the choices I had for A and B in the question. If I answered yes, I could provide recommendations for labeling. If I answered no, then I have to talk about additional studies. I don't feel that additional studies are necessary. I feel that the labeling, though, should not state that this is indicated to prevent first infection. It should be the labeling would address the endpoint of frequency of exacerbations.

As far as additional studies, I do feel -- not for approval, but additional studies in children, PK studies and safety trials particularly in children will be important. It will be

important to do monitoring for the long-term effects on antimicrobial resistance both in the lung and then outside of the lung. And I do think it might be important to look at -- despite the fact that there was no apparent seasonality effect, I think it would be interesting to have studies that incorporate respiratory viral testing in terms of the ability of this drug to prevent pulmonary exacerbations.

DR. BADEN: Thank you. Dr. Ofotokun.

DR. OFOTOKUN: I voted no, and it was a very difficult choice for me because I realize that this is an area where we need intervention. This is a disease that we really, really need an intervention in this disease.

What informed my no decision, vote, was the discordance of the ORBIT-3 and ORBIT-4 study. I just couldn't find a rational explanation for why those two studies were different. ORBIT-3 could have been a chance, and ORBIT-4 could have been a chance. So it really was difficult for me to weigh those two obviously different studies.

Also the benefit in ORBIT-3, in my interpretation, was for the most part marginal, and most of the benefits were in subjects, participants, who had severe disease, and they were very few in the study. So what was driving the difference was in those who had 4 or more exacerbations, and there were extremely very few in the study. So it was difficult to actually weigh the significance of very few people driving the outcome that we were looking at.

Then of course, a lack of differences in the quality of life, ORBIT-3 and ORBIT-4. Like I said, an overwhelming majority of participants in the study were people with mild disease, and I think this may have driven some of the marginality of the outcome that we saw.

I think going forward I agree with everybody. I think, to me, the frequency of events is probably more important than the time to event, and I think that should definitely be considered in a subsequent design. And I think an objective measure of adherence, even though the sponsor

indicated that over 90 percent of the population or 80 percent of the population had more than 90 percent of adherence, it would be good to have an objective measure of adherence in the study.

Then a number of other secondary endpoints that would have been very important were not really analyzed clearly like antibiotic sparing. Some data were presented to that effect. Sparing of other types of secondary treatment of this condition like steroids, using, would have been an endpoint that I would have loved to see in a subsequent study going forward.

The issue of efficacy was so difficult to assess, especially efficacy related to inhalation product, so cough, bronchospasm, and hemoptysis. We don't know if it was due to the inhalation itself or if it was due to the disease process. And there's a way to incorporate this into subsequent study design. It would be very helpful in trying to evaluate the significance of this type of side effects.

DR. BADEN: Thank you. Dr. Baden. I voted

no. The question is delaying time to first exacerbation. The data were unconvincing on that point. I think the totality of the evidence, particularly looking at the frequency of exacerbation are more convincing, although still require I think some more data to support that key finding.

So I think the inconsistency between the two studies, the nature of the endpoint being imprecise and needing a better endpoint. I think we all agree on the logical candidate. I remain concerned about the resistance beyond pseudomonas in the GI tract with other organisms in the respiratory tract, with NTMs because one can rob Peter to pay Paul, and the burden is to ensure that we minimize that concern for those patients.

I think, as mentioned before, how do I identify those patients at highest risk? It was alluded to by a number of exacerbations one can sort out which population will have enough event rate to make it easier to study. And as mentioned, the overall use of antibiotics, the duration of

hospitalization, there were some data alluded to, but I think better quantification of the antibiotic used to prevent versus the antibiotics used to treat.

In the open public session, the last speaker commented on that, and I thought that would be an interesting way to try and weigh the overall antibiotic use, which I think would be influential.

DR. WEINA: Peter Weina. I voted no. The issue before me was a couple of things. One of them had to do with, of course, the fact that they have two trials that have two very different outcomes, and no matter how we tried to explain what the difference was, there was nothing that was really convincing there.

I think part of our job is weighing the patient in front of us versus good antibiotics stewardship. The issue of resistance really concerns me. Very low plasma concentrations encourage resistance. As a matter of fact, that's how we induce resistance in groups that we want to study drug resistance in. So we actually develop

it. Very high local concentrations can overcome that increased MIC for a short period of time, but may not do us a favor in the long run.

That kind of leads us to the issue of understanding our responsibility for managing the expectations, who may actually end up on the treatment, and are we doing people a favor by providing a drug that's going to have short-term gains, but in the long run is actually going to potentially destroy other options that we have.

So some of my concerns have to do with a better endpoint or at least before opening up the database, maybe reassessing the statistical analysis plan and finding really good endpoints. But it's also the issue that this drug is unlike potentially what we may have in CF, is that this really is going to be a long-term use of unknown duration with unknown problems that come down. And longer trials are probably not the answer because we have the issue of efficacy, which you see in clinical trials versus effectiveness, what people actually do in the real world and in real life. So

maybe this is a phase 4 recommendation in the long run when this does become available.

DR. BADEN: Thank you. Dr. Green?

DR. M. GREEN: Michael Green. I voted no but I wanted to vote yes. I have real concerns with the primary endpoint choice for this study and recognize the impact that guidance from the FDA had on these decisions, but I also recognize that this is not the agency's fault and reflects the thinking at the time of design of this study. It seems quite clear that the issues relating to the impact of potential treatment on the total number of recurrences and the impact of these recurrences and their severity seem more critical as each episode can lead to ongoing progressive lung disease and destruction.

We have seen data presented on the number of occurrences but not truly the impact of these episodes. Having said that, the data on recurrences, including the impact on patients with moderate to severe events and in those patient with a history of more frequent recurrences prior to

enrollment in both trials, and the totality of endpoints in both trials is very difficult for me to discount.

The safety profiles are not generally impactful on my thinking and I believe the issues of resistance have actually been assessed and reasonably addressed. As I said, I wanted to vote in support of approval, but I recognize that this vote would not strictly be in response to the FDA's specific question on the evidence of impacting time to event.

If this drug were to be approved, despite our vote, it would make sense to label the product for those with moderate to severe disease, that is those that have at least 4 episodes in a year, as this endpoint seemed to be met, at least to my standard, in both studies.

DR. GRIPSHOVER: Barb Gripshover. I voted no for most of the reasons that everyone has already said. I think that the specific question, for that endpoint, I think clearly the trials don't match up, and I think that that -- so I can't say

that it definitely showed efficacy and safety to preventing the first one. I hear and understand the huge need from patients, and it does look like the drug might have good effectiveness in the right population, which to me doesn't seem to be people who had more frequent exacerbations for sure.

So I think maybe looking at that specific group in particular and looking at hospitalizations and antibiotic use, and also quality of life -- it was interesting the study didn't show a benefit, but we heard stories of amazing changes. So it's hard to imagine that if decreasing frequencies, we wouldn't be able to somehow impact the quality of life as well. Then still also, I'm concerned about resistance, and I think we definitely need to follow that long term.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Dean Follmann. I voted no. As had been mentioned by a few people, I thought the studies were inconsistent not just on the time to first event endpoint, but on the frequency endpoint as well. If we were voting on frequency

endpoint, I'd probably vote no also.

This heterogeneity basically was known going in, and we read the FDA materials. They mentioned how it was felt to be important to do two independent studies partly because of the mixed results in this disease with other drugs. I thought too it was important to see consistency, which we didn't see and which didn't seem to be explained. So that's the reason for my no vote, and I would have voted no on either endpoint.

Some additional comments, I prefer the frequency endpoint using, as Dr. Wittes did, the Andersen-Gill counting method for analysis. This is a more elegant way to deal with the data. I think it also better gets at the course of the disease instead of just looking at time to first that's reflective of what happens over the course of a year. We see in the data also it's a more sensitive measure to have smaller p-values than we had for time to first event, so that's another reason.

Sort of a technical thing, I was thinking

about this during the course. Really when we do time to event, we're asking the question does the time to first event differ between the two groups, or the null hypothesis I should say, is the time to the first event the same, and is the censoring distribution the same. So technically, that's what we're testing with the time to first event. And I think with the Andersen-Gill, we're also testing an additional null assumption that the blackout periods are the same.

I think that's basically an ok thing to do, just to understand that this is a somewhat more complicated model. It's a somewhat more nuanced null hypothesis that we're testing, but to me it seems to be the right one. So maybe that's a little inside baseball, but I'm comfortable with that analysis and that endpoint.

Just a couple of other comments. It seems from this study, from the FDA's experience and so on, that heterogeneity is a concern, so going forward we might want to overpower this study, maybe have something bigger than 90 percent power

to try and remedy this heterogeneity concern.

It's been mentioned by a few other people we see more of an effect in people who've had 4 or more exacerbations in the prior year, so there's different ways we could try and do that. One would be to enrich a study so we have more of those patients, or maybe prespecify a subgroup of people who had 4-plus pulmonary exacerbations in the prior year.

Another thing that could be done, we talked about how these studies are going to be relatively short compared to how they would be used, so we might want to look at the treatment effect over the course of the study. I don't think that was done here, but a simple thing to do would be to look at the treatment effect over the first 6 months and then compare it over the next 6 months, see if it's consistent or if it tends to wane.

Then finally, I don't know if this is possible. We talked a lot about the heterogeneity. One design that's possible would be to do a crossover study where you would study people

cycling on drug for say 9 months followed by a washout, and then they cycle on placebo for 9 months. This can be a more efficient kind of design. It might help identify subgroups of patients for who the treatment is really beneficial.

With ORBIT-3 and ORBIT-4, you've had an open label period at the end of the study, so you have a mini crossover trial there, I think, for the people who were on placebo, and then they got open label drug. So you might be able to work with that data to do some simple power calculations to see if -- like a crossover trial would have legs to do. So that's my comment.

DR. BADEN: Thank you. Dr. Clark?

DR. CLARK: Yes, I also voted no, again, due to the discordance of the studies without a clear explanation, the modest benefit and ORBIT-4 and concerns about the validity of some of the additional non-prespecified analyses. I'm also concerned, like others, about the durability of any beneficial effects.

As far as future things to focus on, I agree a number of pulmonary exacerbations, the duration of exacerbations, use of antibiotics, hospitalizations, and healthcare utilization costs seem more meaningful than time to first exacerbation. I also think it might be important to record the etiology of the bronchiectasis to assess for heterogeneity to standardize adjunctive therapies, including airway clearance. I also like the idea of a crossover with patients acting as their own controls.

DR. HAWKINS: Yes. I abstained. If I strictly answered the question, my vote would be no. I like others felt that the frequency of pulmonary exacerbations was a more important endpoint, and I believe that was met. The FDA's guidance didn't allow us to answer that question because we should answer the primary endpoint as the question was posed.

I'm a little bit concerned, though. We have these studies that take a long time to develop and we have concerns about resistance and other things.

I think at some point we have to take a leap of faith and allow the study. If in fact the only question was resistance, perhaps some of these studies should be approved because it takes so much time to actually complete some of these studies. If there's strong evidence of things like resistance that we can't know until the future, then perhaps we should allow studies to go forward.

DR. BADEN: Mr. Zimmerman?

MR. ZIMMERMAN: First of all, I want to thank the committee and the applicant for having me, and bigger thanks to the community for speaking up today. I think it's really important to keep sharing your stories, so thank you all.

I voted no. I also really wanted to say yes, but no to the question as it was posed. If the question were frequency of pulmonary exacerbations, I would have been closer to yes. I think that's really important, kind of like what Dr. Clark said. The frequency of pulmonary exacerbations, duration, antibiotic use, hospitalization, those are much more important than

time to first exacerbation.

I was also concerned about the variability between the two studies and the resistance, I think, especially for the gentleman who spoke up earlier who's 29. If this were approved today and he was on it, he could potentially be on the drug for 50 years. What would happen then? And I know, like Dr. Weina alluded to, we can't do a 50-year study, but maybe we do a 10-year study, or maybe the answer is approve it and follow these patients for 10 or 20 or more years. Thank you.

DR. BADEN: Dr. Carvalho?

DR. CARVALHO: Thank you. I voted yes. I had difficulty with the way the question was posed because I had difficulty with the word "substantial" and I had difficulty with the primary endpoint. Nevertheless, I think that this would be worth a shot to go forward. It's a heterogeneous disease as I think just about every member has mentioned. ORBIT-3 was a little bit demographically different than ORBIT-4, and the pooled data actually went in the right direction.

Having said all this, I do have some caveats. I think the concept of nontuberculous mycobacteria really should be also addressed. The testing as completeness for microbiology assessment should be done. Also, I do agree that this should be headed towards moderate to severe disease where that might be where the data is strongest.

DR. J. GREEN: Jonathan Green, and I voted no. Again, I think many of the reasons have already been stated, so I won't repeat them, but the question that was asked was quite specific, and I did not feel that that was met.

That being said, does that mean I don't want this drug to be available? No. I would like my colleagues who treat these patients in the outpatient setting to be able to have a drug such as this available for judicious use for the right subset of patients, which are most likely -- again, the more severely affected, but however, that was not the question that was posed.

I think that there is a role for this. I would like the patients to have it available on

label so it can get paid for, and I think that there is a group that it would be very useful for. But this specific question that was asked, did they present substantial evidence for time to delay and time to first exacerbation, I did not think that was met.

DR. BADEN: Thank you. So the vote is 12, 3, and 1. The summary comments, for those who voted to approve, we need to offer something to our patients who have this unmet need. By approving it, insurance will cover it and allow better access. The totality of the data with the frequency of exacerbation provided evidence of efficacy. The safety, no concerns on safety, however, there needs to be studies in children. It is a heterogeneous disease. The NTMs need to be assessed and the issue of targeting the moderate to severe, those with moderate to severe disease.

The no's, the themes that emerged, there were several. One of the largest was the inconsistency between the two studies without a clear explanation; then there were substantial

design concerns and suggestions for future: what is the primary endpoint be it the frequency of PE or duration; hospitalization; one can orchestrate a better primary endpoint; the enrichment for those at higher risk, therefore with more events. One could think of crossover designs. One could think of different periods of study, the first 6 months, the second 6 months. And as noted, the counting method may be a better way to actually evaluate the robustness of the findings.

Other concerns included understanding the reasons for the exacerbations; understanding the measures of adherence; ways to assess sparing of other medications; better assessment of resistance; the nature of the modest benefit; the durability of the benefit; might the etiology of the bronchiectasis matter; all issues that complicate the ability to interpret, some of which can be dealt with in the design.

I would like to thank the members for a wonderful discussion over the last eight hours, I guess, and to the presenters from the agency and

from the applicant for providing so much data for us to discuss.

Before we adjourn, are there any last comments from the FDA?

DR. NAMBIAR: Thank you, Dr. Baden. I'd just like to thank the committee for the very useful feedback and thoughtful discussions. Thanks to the applicant for all their work on this NDA and their presentations today. I'd also like to extend our sincere thanks to the presenters at the open public hearing and to the patients for presenting their experiences. Thank you. Safe travels.

Adjournment

DR. BADEN: Thank you. Panel members, please take all your personal belongings, and this meeting is now adjourned.

(Whereupon, at 4:14 p.m., the meeting was adjourned.)