FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Tuesday, August 7, 2018

8:30 a.m. to 5:17 p.m.

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren D. Tesh, PharmD, BCPS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

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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: It is 8:30. We have a long day ahead of us. We should get started.

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, Teresa Eiseman. If you're present, please stand. She will be here soon.

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

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

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

Products, CDER, FDA.

DR. KIM: Good morning. Peter Kim, clinical team leader, DAIP, CDER, FDA.

DR. HIRUY: Good morning. Hiwot Hiruy, clinical safety reviewer.

DR. DIXON: Cheryl Dixon, statistics reviewer, Division of Biometrics for CDER.

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

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

DR. DASKALAKIS: Demetre Daskalakis, infectious diseases, deputy commissioner for disease control, New York City, Department of Health.

DR. HONEGGER: Jonathan Honegger, pediatric infectious diseases, Nationwide Children's Hospital, Ohio State University.

DR. TESH: Lauren Tesh, designated federal officer.

DR. BADEN: Lindsey Baden, infectious

diseases Brigham Women's Hospital, Dana Farber Cancer Institute, Harvard Medical School in Boston.

DR. WEINA: Peter Weina, infectious diseases, Walter Reed National Military Medical Center.

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

DR. GRIPSHOVER: Barbara Gripshover, adult infectious diseases, University Hospitals, Cleveland Medical Center, Case Western Reserve University, Cleveland.

DR. LO RE: Vincent Lo Re, Division of Infectious Diseases, Department of Biostatistics, epidemiology, informatics, University of Pennsylvania.

MS. ANDREWS: Ellen Andrews, consumer representative from the Connecticut Health Policy Project.

MR. HAWKINS: Charles Hawkins, a CF patient representative.

DR. EVANS: Scott Evans, pulmonary medicine, University of Texas, MD Anderson Cancer Center.

DR. MASUR: Henry Masur, Critical Care Medicine Department, Clinical Center, NIH.

DR. PROSCHAN: Michael Proschan. I'm a statistician at the NIAID here at the home of the Stanley Cup Champion, Washington Capitals.

DR. S. GREEN: Stuart Green. I'm the acting industry representative to the panel today.

DR. BADEN: 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, as a gentle reminder, individuals will be allowed to speak into the record only recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members

take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that the members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'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 USC, 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 USC, Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a 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 purposes of 18 USC, Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAS, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application 207356, amikacin liposome inhalation suspension sponsored by Insmed, Inc. for the proposed indication of treatment of nontuberculous mycobacterial lung disease caused by mycobacterium avium complex in adults as part of a combination antibacterial drug regimen.

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

connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have had concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Stuart Green is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Green's role at this meeting is to represent industry in general and not any particular company. Dr. Green is employed by Merck and 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 with the firm at issue. Thank you.

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

FDA Introductory Remarks - Sumathi Nambiar

DR. NAMBIAR: Thank you, Dr. Baden, and good morning, everybody, and welcome to today's meeting of the Antimicrobial Drugs Advisory Committee. We're here to discuss NDA 207356, amikacin liposome inhalation suspension.

The applicant is Insmed, Inc. The NDA was submitted under subpart H, otherwise known as accelerated approval. The proposed indication is treatment of nontuberculous mycobacterial lung disease caused by mycobacterium avium complex as part of a combination antibacterial drug regimen for adult patients.

Just to note that the population studied in the clinical trials only includes patients with refractory MAC, and no studies were conducted in a broader MAC population. The NDA was granted priority reviews, as the product has qualified

infectious disease product designation. The product also has breakthrough therapy and orphan product designations.

The clinical development program included a phase 3, open-label, randomized trial, study 212, where ALIS plus an optimized background regimen, or OBR, was compared to OBR alone in subjects with refractory MAC lung infection. In the applicant's presentation, OBR is referred to as MDR.

The primary endpoint in this trial was microbiologic. It was a surrogate endpoint of sputum culture conversion. Study 112 was a phase 2 placebo-controlled trial, and study 312 is an open-label, single-arm extension study 212, where all subjects received ALIS.

I'll spend a couple of minutes talking about accelerated approval. It's a reasonable approach for a drug that treats a serious condition and provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit.

It's important to note that for products approved under accelerated approval, one must still meet the statutory standards for safety and effectiveness as they are for traditional approval. Also, an application for accelerated approval should include evidence that the proposed surrogate endpoint is reasonably likely to predict the intended clinical benefit of a drug.

For drugs that are granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated clinical benefit, and these trials must be conducted promptly to facilitate the determination of whether clinical benefit has been verified. Ideally, the confirmation trials should be underway at the time the marketing application is submitted or there should be agreement on the design and conduct of such trials before approval.

In general, the confirmatory trial would evaluate a clinical endpoint that directly measures clinical benefit in the same population that was studied to support accelerated approval. However,

it is possible that this trial could be conducted in a different but related population where one can verify the predicted clinical benefit.

During the design of study 212, we were aware that there was a fair degree of uncertainty in the surrogate endpoint as sputum culture conversion. Some points that were considered during those discussions were that there is a high unmet need in patients with refractory MAC lung disease. There was an expectation that there would be some supportive efficacy demonstrated in a clinical outcome.

In the phase 2 trial that had been conducted, study 112, there was a positive trend observed in the 6-minute walk test distance. There's also an expectation that data on durability of sputum culture conversion 3 months after completing MAC therapy and clinical outcomes in those who were continuing study 212 could be reasonably assessed.

Today, we are seeking the committee's input on the uncertainty regarding the surrogate

endpoint. The results of study 212 have not demonstrated any clinical benefit of ALIS -- on clinical endpoints I should say. Patients with persistent positive cultures were discontinued from study 212 and had the option to enroll in study 312, which is a single-arm extension study to receive ALIS. Comparative assessment of later outcomes is very difficult because of the large amount of crossover. There are also limitations of the available literature, which we'll discuss further today.

As part of our review of this application, we reviewed the literature to see if there might be additional information available that can support the correlation between the surrogate endpoint and the clinical benefit. We provided this as an addendum to the briefing document for today's meeting.

Dr. Kim will go into a detailed discussion about the literature that we reviewed. In general, there are some retrospective, non-randomized studies that suggest a higher mortality rate in

patients with MAC lung infections who remain culture positive despite treatment compared to those who converted to culture negative.

Some of these studies are from single centers or have enrolled only a specific subtype of MAC lung disease. Hence, it limits the ability to generalize to the overall population. The main limitation from the literature that we reviewed is that it is possible that converters are inherently different from the non-converters in certain disease or patient characteristics; and hence, it makes it difficult to assess a sputum culture conversion as a surrogate for a clinical outcome.

I will briefly touch upon the studies that have submitted to support this application next. Study 212 is an ongoing randomized, open-label study in adults with refractory MAC lung infections. Data cutoff for the submission of this NDA was based on the date when the last subject completed this month 6 visit. The study used a 2 to 1 randomization, and the patients were stratified based on smoking status prior or prior

OBR at screening.

As I've already mentioned, the primary efficacy endpoint was culture conversion by month 6. A converter was a patient who had negative sputum cultures for MAC for 3 consecutive months at anytime within the first 6 months. A key secondary endpoint was changed from baseline to month 6 in the 6-minute walk test distance.

Just to point out, a large number of patients -- about a third of patients who receive ALIS plus OBR discontinued treatment prematurely compared to 8 percent in the OBR-alone arm. Among the reasons for treatment discontinuation, the occurrence of adverse event was the most common reason for discontinuation. In terms of the results for culture conversion, 29 percent of patients in the ALIS plus OBR achieved sputum culture conversion with their 3 consecutive negative cultures compared to 9 percent in the OBR-alone arm.

There's no difference between the two treatment arms in terms of the 6-minute walk test

distance and other clinical endpoints assessed with 2 patient reported outcomes, St. George's Respiratory Questionnaire and the EuroQol 5-dimensional questionnaire. On neither of these measures was a treatment effect demonstrated.

Study 112 was a phase 2 study. It was a randomized, controlled trial in adults with refractory NTM lung infections. It was a double-blind, placebo-controlled phase through day 84, which was followed by an open-label extension phase for an additional 84 days. The trial utilized a 1-to-1 randomization and was stratified by the presence or absence of cystic fibrosis and the predominant NTM organism at baseline MAC versus M. abscessus. All subjects received ALIS plus OBR on the extension phase.

The primary efficacy endpoint was changed from baseline on a semi-quantitative scale for microbial culture assessed at day 84. Negative mycobacterial culture at day 84 was a secondary endpoint and changed from baseline, and the 6-minute walk test distance was the tertiary

endpoint.

Similar to study 212, there are a reasonable number of patients discontinued prematurely from the study, and the main reason for treatment discontinuation was the adverse events. This is a busy table, but really to look at the change from baseline in the semi-quantitative scale, you can see that the trend was more in the ALIS arm compared to the placebo arm, but this finding was not statistically significant.

More patients in the ALIS arm achieved a negative culture at day 84 compared to placebo. And as I mentioned, this was a secondary endpoint in the trial. There was also a benefit demonstrated in the 6-minute walk test distance with a positive finding in patients who were treated with ALIS compared to those who received placebo.

Study 312 is an ongoing study. It's an open label extension of study 212. Patients were enrolled in 212 and did not achieve culture conversion or had a relapse or recurrence by

month 6. Here all subjects received ALIS plus OBR. The primary objective of this trial is to evaluate long-term safety and tolerability of ALIS treatment for up to 12 months. No comparative efficacy or safety assessment is possible from this study.

In terms of safety database, at the proposed dose, the safety database is just under 600 patients exposed to ALIS for varying durations. There was no difference in mortality between the two treatment arms with 4 percent in each arm. Serious adverse events were more common in the ALIS plus OBR arm. Adverse events and adverse events of interest and discontinuation due to adverse events were more common in ALIS plus OBR arm. Hospitalizations were more common in the ALIS plus OBR arm. Most hospitalizations were due to respiratory reasons in both study arms.

Today, we have applicant presentations and time for clarifying questions of the applicant. That will be followed by FDA presentations. Dr. Kim, who was the medical team leader for this application, will provide a

presentation regarding efficacy findings. Dr. Hiruy, who is a medical officer, will discuss the safety findings, and there will be time for clarifying questions. After lunch, we will have the open public hearing, followed by discussion and questions to the committee.

We have 3 working questions in which we seek input from the committee today. The first one is, is the surrogate endpoint, the sputum culture conversion based on 3 consecutive negative sputum cultures, is reasonably likely to predict clinical benefit?

The second question is, has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of ALIS for the treatment of mycobacterial lung disease caused by M. avium complex as part of a combination antibacterial drug regimen for adult patients?

If you voted yes, please provide any recommendations regarding labeling, and also please comment on the design of the trial that will need to be conducted to confirm clinical benefit. If

you voted no, please provide recommendations regarding additional studies or analyses that are needed.

The third question is, has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of ALIS for the treatment of nontuberculous mycobacterial lung disease caused by M. avium complex as part of a combination antibacterial drug regimen for adult patients with limited or no treatment options?

If you voted yes, please provide any recommendations regarding labeling and also comment on the design of the trial that will need to be conducted to confirm clinical benefit. If you voted no, please provide recommendations regarding additional studies or analyses that are needed.

That ends my presentation. Thank you.

DR. BADEN: Thank you, Dr. Nambiar.

We'll now move to the applicant presentations.

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 nonemployee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of the meeting.

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

We'll now proceed with the applicant's presentations.

Dr. Streck?

Applicant Presentation - Paul Streck

DR. STRECK: Good morning, Mr. Chairman, members of the advisory committee, and FDA. My name is Paul Streck, and I'm the chief medical officer at Insmed. Thank you for this opportunity to present our data supporting our NDA for accelerated approval of amikacin liposome inhalation suspension or ALIS. Our proposed indication is for the treatment of nontuberculous mycobacterial, or NTM lung disease, caused by mycobacterium avium complex known as MAC as part of a combination antibiotic regimen in adults.

This proposed label includes patients enrolled in our clinical trials who are unresponsive to treatment. Based on the beneficial effect in these patients and the high unmet need in this disease, we are also proposing including newly diagnosed MAC patients in certain circumstances. The recommended ALIS dose is 590 milligrams once daily.

The ALIS NDA was submitted under the FDA;s subpart H accelerated approval regulatory pathway.

This allows the FDA to approve drugs faster for serious diseases based on achievement of a surrogate endpoint. This pathway is well defined with specific criteria outlined in regulation and guidance documents.

To qualify the drug must treat a serious condition with high mortality or life-limiting morbidity. It must provide a meaningful advantage over available therapy, and the drug should demonstrate an effect on a surrogate that is reasonably likely to predict a clinical benefit. The ALIS NDA fulfills each of these criteria for accelerated approval.

NTM lung disease caused by MAC is a serious condition with progressive morbidity and increased mortality risk. ALIS provides a meaningful advantage over available therapy since there are no approved therapies for NTM lung disease caused by MAC. In fact, prior to ALIS clinical trials, there were no prospective randomized clinical trials evaluating novel treatment options for NTM.

Importantly, in our pivotal phase 3 study,

ALIS demonstrated a highly statistically significant ability to attain culture conversion defined as 3 consecutive monthly negative sputum samples in adult patients. As I will explain, this is a critically important endpoint, which lastly fulfills the third criterion since the achievement of culture conversion is reasonably likely to predict clinical benefit of durable culture conversion, which then allows patients to stop their NTM therapy.

As discussed with the FDA, durability of this effect will be confirmed using data from the second part of our currently ongoing clinical trial. The study is fully enrolled, and the ongoing data continue to support the benefit of ALIS.

In addition to accelerated approval, the FDA has also designated ALIS a breakthrough therapy. The breakthrough therapy designation expedites drug development and review for serious conditions were preliminary clinical data indicates substantial improvement over available therapy. ALIS was

granted this designation in 2014 for the treatment of refractory adult patients with NTM based on promising phase 2 results.

The FDA has also designated ALIS a qualified, infectious disease product. This designation is only in serious or life-threatening infections. This recognizes that NTM can pose a serious threat to public health. Finally, ALIS is also designated orphan drug. All of these designations recognize the seriousness of the disease, the high unmet medical need, and call attention to the need for new therapies.

Turning now to the active components of ALIS and its formulation, amikacin liposome inhalation is a broad spectrum aminoglycoside antibiotic that's been used for decades. Its bactericidal properties disrupt and inhibit protein synthesis and target bacteria, including NTM.

In susceptibility testing, amikacin is one of the most potent bactericidal agents against NTM. However, when delivered parenterally, it has poor lung tissue penetration, and there are known risks

of systemic toxicity.

ALIS is a novel inhaled formulation of amikacin that addresses the limitations with parenteral amikacin used for the treatment of NTM lung disease. The ALIS liposome, depicted on this slide, is composed of 2 biocompatible lipids, both of which are major components of pulmonary surfactant.

ALIS is formulated with a high drug to lipid ratio, which allows for an efficacious dose of amikacin to be delivered in a short nebulization time. ALIS liposomes are suspended in a 1.5 percent saline buffer that's slightly hypertonic with a neutral pH.

ALIS is administered by oral inhalation to focus delivery to the site of infection, and therefore minimize systemic risks. The liposomal amikacin is delivered directly to the lung via the LAMIRA eFlow nebulizer system, which utilizes a nebulizer handset and portable control unit. This device is approved and widely used in the U.S. to deliver products that treat pulmonary diseases such

as chronic obstructive pulmonary disease and cystic fibrosis. When nebulizing ALIS with this device, the aerosol droplets are relatively small, and 70 percent of the droplets are within the respirable range.

ALIS has unique biological attributes that contribute to its efficacy profile. One of the key features of the ALIS liposome is that it is phagocytized by macrophages at high levels. This is important because MAC commonly exists inside macrophages, which produce additional barriers for treatment. Drugs with poor membrane penetration such as aminoglycosides therefore have diminished ability to access intracellular bacteria. When incubated side by side with cultured macrophages, ALIS liposomes facilitate delivery of significantly more intracellular amikacin than free drug, as shown in these images.

In animal studies, inhalation of ALIS resulted in a 274-fold increase in amikacin delivered into the lung macrophages compared to amikacin administered intravenously. Additionally,

ALIS was shown to penetrate and have activity against MAC biofilms in vitro.

Altogether, ALIS is formulated to combine the proven bactericidal activity of amikacin with a novel liposome that penetrates biofilm and improves macrophage uptake. This allows for the achievement of high concentrations of amikacin at the site of infection, which is necessary for effective treatment.

With all this in mind, let's review why the goal of NTM therapy is durable conversion defined as having persistently negative sputum samples during treatment that continues after completion of treatment. This indicates that the bacteria are no longer present in the lung, and therefore further infection related lung damage and resulting morbidity is stopped.

The microbiologic goal of eliminating the infection means that patients can come off all MAC therapy. This is an important goal for patients and physicians because it eliminates treatment tolerability issues. This durable conversion goal

is the central tenet for antimicrobial therapy and the standard used for treatment-resistant diseases like tuberculosis and NTM.

We will share literature to support the attainment of culture defined as 3 consecutive months of negative sputum samples and reasonably predicts for durable culture conversion once patients have completed and stopped therapy.

Culture conversion is an important milestone because it predicts durable culture conversion with symptomatic and functional improvement. Furthermore, NTM guidelines recommend 12 months of negative sputum samples after achieving culture conversion, which is the definition of treatment success. Culture conversion is indeed a surrogate that is reasonably likely to predict a durable culture conversion. This is important because stopping therapy is clinically meaningful.

We utilize culture conversion and the durable culture conversion as the endpoint supporting accelerated and full approvals in our pivotal study. This aligns with FDA

recommendations that culture conversion by month 6 is adequate to support accelerated approval and that full approval of ALIS will be based upon demonstration of durable culture response in patients obtaining culture conversion measured after all patients are off MAC therapy for 3 months.

Our ALIS NDA submission is supported by three key clinical studies conducted in adult patients with NTM lung disease who had not responded to at least 6 months of antibiotic therapy. Throughout our presentation today and in our briefing materials, we referred to this antibiotic therapy as a multidrug regimen. You've heard that FDA is using the term "optimize background regimen," but both phrases refer to the same guideline-based antibiotic therapy.

Our initial phase 2 study compared ALIS added to a multidrug regimen versus an inhaled empty liposome placebo added to the multidrug regimen. This study demonstrated clinical benefit of ALIS and provided data to support culture

conversion as a surrogate informing the pivotal study.

The pivotal study supporting approval is study 212, a phase 3, randomized, controlled, open-label study in patients with confirmed MAC infection who had not responded to prior guideline-based therapy. Study 212 compares ALIS when added to a multidrug regimen versus the multidrug regimen alone. Efficacy and safety are also supported by study 312. This is a phase 3, open-label study, evaluating safety and the ability to attain culture conversion in patients who did not convert in study 212.

Our clinical program demonstrates that ALIS in combination with a multidrug antibiotic regimen has a superior ability to achieve culture conversion by month 6. The results are reasonably likely to predict doable culture negativity in adult patients. This is clinically meaningful because achieving 12 months of negative cultures while on therapy means that patients can then stop all NTM therapy. This allows patients to begin to

feel better.

The goal of microbiologic treatment is to eradicate the disease since stopping the persistent infection is expected to improve morbidity. Recognizing that there are no data to definitively show improved morbidity, we observed evidence from culture conversion.

Patients with negative cultures by month 6 demonstrate greater improvement in how far they can walk in 6 minutes compared to those whose culture remained positive for NTM. This supports that culture conversion predicts that stopping the infection should lead to meaningful functional improvement. From a safety point of view, the delivery of ALIS by inhalation minimizes systemic exposure and, thus, the known toxicities of IV amikacin.

Adverse events did increase when ALIS was added to the combination of antibiotic therapy. These were primarily respiratory events, and most events were mild to moderate and resolved without discontinuation.

Today, we will review the efficacy and safety data from our program and discuss the improvement in outcomes that ALIS brings to patients with NTM caused by MAC. First on the agenda is Dr. Shannon Kasperbauer. She will discuss the unmet needs of patients with this serious disease. Next, Dr. Eugene Sullivan will review the design of our clinical studies and efficacy results. Subsequently, Dr. Peter Sallstig will present the safety data from our NTM trials. And finally, Dr. David Griffith will conclude with a clinical perspective on the benefit-risk of ALIS.

We also have additional experts to help answer questions. All external experts have been compensated for their time and travel. Again, we thank you for this opportunity. Now. I will invite Dr. Kasperbauer to the lectern.

Applicant Presentation - Shannon Kasperbauer

DR. KASPERBAUER: Thank you, Dr. Streck.

Good morning. My name is Shannon Kasperbauer, and I'm an infectious disease physician at National Jewish Health with an

expertise in bronchiectasis and nontuberculous mycobacteria. We see over 1600 patients a year in our mycobacterial clinic.

To begin, nontuberculous mycobacteria, or NTM, include nearly 200 mycobacterial species. They are ubiquitous in the environment and can be found readily in the water and soil. NTM are transmitted from the environment to humans via aerosol inhalation.

Once inhaled, NTM can cause a chronic indolent respiratory infection in susceptible people and are associated with progressive lung destruction. The bacteria persist within the lung tissue as well as within pulmonary macrophages. These organisms are highly resistant to a wide range of antibiotics due to a variety of mechanisms, both innate and acquired, including the production of biofilms.

NTM lung disease has become a growing concern. Over 80,000 people have confirmed diagnoses of NTM lung infections in the United States, and the annual prevalence is increasing by

an estimated 8 percent per year. More than 80 percent of NTM lung disease is caused by MAC. This disease is serious and life threatening.

NTM is an opportunistic pathogen usually occurring in people with preexisting lung disease. The most important host susceptibility factor is underlying structural lung disease such as bronchiectasis, emphysema, or specific genetic disorders. Immunocompromised patients so also susceptible to NTM lung disease.

A number of analyses have demonstrated prognostic factors for disease progression and mortality. These include pulmonary hypertension, extensive disease radiographically, and lung cavitation. Not surprisingly, NTM disease has a tremendous impact on patients. The progressive structural damage leads to a vicious cycle that impairs patient quality of life. We see a worsening of the underlying bronchiectasis and development of cavities leading to debilitating symptoms such as weight loss, which in turn leads to an increased difficulty tolerating medications,

which then further complicates the ability to treat this infection.

The negative impact of NTM disease on quality of life is due to a range of symptoms that often worsen over time if the infection is not successfully treated. The most common symptoms are profound fatigue, loss of energy, and malaise. The majority of patients also have a chronic or recurring cough, often with sputum production. Other patients may report fever and weight loss among other symptoms.

Here's a visual example of the progressive lung damage that occurred over time in one of my patients with refractory NTM. From left to right, you can see the progressive volume loss in cavitation over time despite continuous treatment.

The goals for treatment of MAC related NTM disease are the same as those for any other serious opportunistic lung infection. We want to achieve durable culture conversion and to see radiographic and symptomatic improvement over time. The ATS/IDSA guidelines define the primary

microbiologic goal of treatment for MAC lung disease as 12 months of negative sputum cultures while on therapy.

The correlation between culture conversion and symptom improvement has been noted in the published literature. In a study of 180 patients undergoing therapy for nodular/bronchiectatic lung disease, culture conversion significantly correlated with symptom response over time, as shown here.

At the start of therapy, patients had similar key symptoms regardless of whether they ultimately went on to convert. Over time, we can see a clear benefit in symptom improvement in those who convert compared to those who don't. This is consistent with what I see in my practice. However, achieving culture conversion can be difficult. Standard of care treatment is lengthy and challenging for both patients and physicians.

Currently, there are no FDA-approved therapies for NTM lung disease. The initial regimen to treat MAC lung disease requires multiple

antibiotics over a prolonged course of therapy. It typically consists of 3 oral antibiotics with or without parenteral aminoglycosides, depending on the disease severity. This treatment should be continued until culture conversion is achieved and then sustained for 12 months. This means that even when therapy is successful, the typical course of treatment is 12 to 18 months long.

Completing this recommended treatment is often hard for patients due to side effects as well as the prolonged duration of treatment. Unfortunately, only 40 to 60 percent of MAC lung disease patients achieve culture conversion on standard-of-care therapy.

In the absence of culture conversion, patients may remain on therapy indefinitely. For patients who do not achieve culture conversion on standard-of-care therapy, additional treatment options are limited. These include modification or intensification of first-line therapy; addition of parenteral agents such as amikacin; salvage therapies; and possibly even surgical resection.

Treatment in refractory patients is often prolonged and associated with poor efficacy. Without culture conversion, patients continue to experience increased morbidity.

Data show a significant decline in lung function when patients do not achieve culture conversion with initial treatment. In a large study, NTM lung disease was associated with a decline in lung function over a 5-year period. The treatment failure group, those who did not convert, depicted in dark gray, had a greater FEV1 decline with a median decline of 52 mLs per year, which is considered a rapid decline in lung function.

Failure to achieve culture conversion with today's standard of care is also associated with higher mortality rates. MAC lung disease has been reported to carry a 5-year, all-cause mortality risk ranging from 5 to 40 percent. Deaths attributed to NTM lung disease were more frequent in those with persistently positive cultures after 12 months of therapy.

Radiographic deterioration can occur over

time in patients with NTM lung disease who do not achieve culture conversion. A retrospective chart review of 126 MAC patients demonstrated an increased risk of radiographic progression in patients with persistently positive sputum cultures. Another observational study of 40 patients with untreated MAC lung disease showed radiographic deterioration in 98 percent of patients over a mean follow-up of 6 years.

These data strongly suggests that sputum conversion decreases mortality risk and risk for radiographic progression.

To summarize my presentation, there is a clear unmet medical need for effective evidence-based therapeutic options for the treatment of NTM lung disease caused by MAC. As you will see today, ALIS in combination with current antibiotic regimens offers adult patients the chance for eradication of infection in this debilitating disease. This would mean a chance to stop combination antibiotic therapy, which could lead to improve morbidity and mortality outcomes.

Given that many patients are unresponsive to standard of care therapy, newly diagnosed patients may also benefit from early treatment success in order to prevent progressive lung damage. In order to stop disease progression, a new option is needed now.

Thank you. Dr. Sullivan will now share the efficacy results.

Applicant Presentation - Eugene Sullivan

DR. SULLIVAN: Good morning. My name is Gene Sullivan. I'm the chief product strategy officer at Insmed. I'm a pulmonologist by training, and I've worked in academic medicine and industry, and also at the FDA, where I served as the deputy director of the Division of Pulmonary Allergy Products. I will share the efficacy results from our clinical development program.

Listed here are the three clinical studies that support the benefit of ALIS added to a multidrug regimen. First, starting with our pivotal phase 3 study, study 212, study 212 was designed with input from clinical experts and was

discussed with the FDA and incorporated FDA feedback. It is a randomized, open-label, multicenter study in adult patients with MAC lung disease who are persistently culture positive for at least 6 months while on a guideline-based multidrug treatment regimen.

Patients were randomized 2 to 1 to either ALIS 590 milligrams once daily plus their multidrug regimen or to their multidrug regimen alone. The primary endpoint was culture conversion defined as the achievement of negative sputum samples for 3 consecutive months by month 6. Once the month 6 sputum culture results were available for the last patient enrolled, the database was locked, and the primary and key secondary endpoints were analyzed. This portion of study 212 is complete.

Patients in either arm who achieved the primary endpoint and remained culture negative through month 6 continued in the study to complete their course of treatment, which is 12 months following their conversion date. Patients who did not achieve culture conversion through month 6 were

enrolled in study 312, which I will present later.

Following completion of 12 months of treatment after achieving culture conversion, patients in study 212 will stop all MAC therapy. These patients will then be assessed at 3 months and through 12 months off all antibiotic therapy. As agreed with the FDA, the primary endpoint of sputum culture conversion by month 6 will serve as a surrogate endpoint under the accelerated approval pathway. The durability endpoint at 3 months off all MAC treatment will then serve as the confirmatory evidence supporting full approval.

The primary endpoint in study 212, achievement of culture conversion, represents a central goal of antimicrobial therapy. Each month, 2 to 3 sputum samples were obtained and were sent to 1 of 3 centralized labs, which were blinded to treatment assignment. In order to achieve culture conversion, all of these sputum samples had to be negative for 3 consecutive months. This rigorous definition ensures that the observed event represents a definitive and significant change in

the patient's status.

Importantly, the investigators and patients were blinded to the culture results until the month 6 results were available. The date of conversion was defined as the date of the first of the 3 consecutive monthly negative sputum cultures. This primary endpoint supports our accelerated approval application.

The primary endpoint is intended to predict future durable culture conversion. We also tested a number of secondary and exploratory endpoints to assess the clinical impact of treatment with ALIS and of culture conversion. These included the 6-minute walk test distance and the time-to-culture conversion, as well as the St. George's Respiratory Questionnaire.

The results of all of these analyses are presented in the briefing book. Today, I will present the results of the first in the hierarchy, the change in the 6-minute walk test distance. I will also present another important prespecified endpoint, which was the change from baseline at

month 6 in walk test distance comparing patients who converted to those who did not overall and by treatment arm.

As discussed with the FDA, the primary endpoint of the study, culture conversion by month 6, will be the surrogate endpoint in support of accelerated approval, and the ongoing, fully enrolled, study 212 will then confirm durable efficacy.

Patients who achieved culture conversion during the first 6 months continue in the study to complete their course of treatment, which is 12 months of therapy following their date of conversion. This is in keeping with the ATS/ISDA guidelines, which state that the primary goal of treatment is 12 months of negative cultures on therapy. At that point, all MAC therapy is stopped. Durable efficacy will be established based on the negative cultures off all MAC therapy for 3 months. This is the confirmatory endpoint for full approval.

Study 212 enrolled adult patients who had

not responded to a prior guideline-based multidrug regimen. These patients have limited or no treatment options. Patients had to have persistently positive MAC cultures while on a multidrug regimen within the 12-month period prior to screening. The multidrug regimen must have consisted of at least 2 antibiotics for at least 6 consecutive months.

Confirmation of ongoing MAC lung infection was documented by at least 2 positive sputum cultures, 1 positive culture within 6 months of screening and 1 positive culture at screening. Finally, the study only included patients with susceptible amikacin MICs less than or equal to 64 at screening.

Based on advice from clinical experts treating MAC lung disease and in consultation with the FDA, a 15 percent treatment effect in culture conversion was determined to be meaningful, particularly in this population with limited treatment options. Assuming a culture conversion rate by month 6 of no less than 20 percent in the

ALIS arm and 5 percent in a multidrug regimen alone arm, randomization of approximately 351 patients with a 2 to 1 randomization ratio was predicted to provide at least 90 percent power at a 2-sided significance level of 0.05.

Note that the expectation was that in this difficult to treat population, only 20 percent would convert, and this magnitude of effect would be considered clinically meaningful. For the primary analysis, all patients who dropped out prior to conversion were considered treatment failures.

Baseline demographics were comparable between the two treatment arms. The mean age was 65 years, and the majority of patients were female. The highest percentage of patients were enrolled from the U.S. and the majority of patients were white. These demographics are generally consistent with the epidemiology of the U.S. MAC population. Baseline characteristics were also generally comparable between the two treatment arms. The majority of patients were taking 3 or more

antibiotics as part of their multidrug regimen at screening.

I'd like to point out that the median duration of NTM lung disease in this population was quite long, 4 years in the overall population, and was somewhat longer in the ALIS plus multidrug regimen arm. So these patients were sick for a long time without successful treatment. The majority of patients in each arm had been on their multidrug regimen for more than 24 months prior to screening. Most patients had underlying bronchiectasis, were not current smokers, and most had not received prior nebulized IV amikacin.

This slide shows the patient disposition at the end of treatment as of the date of cutoff. A total of 336 patients were randomized, 224 patients in the ALIS plus multidrug regimen arm and 112 patients in the multidrug regimen alone arm. Of the 336 total patients randomized, 185 completed treatment and 67 patients had treatment ongoing beyond month 6 at the time of the data cutoff.

Seventy-five patients in the ALIS plus

multidrug regimen arm discontinued treatment with ALIS most commonly due to an adverse event or withdrawal by patient. In the multidrug regimen alone arm, there was no new investigational drug to discontinue, but 9 patients in this arm discontinued their multidrug regimen.

Turning now to the results. Study 212 met the primary endpoint with a higher proportion of patients treated with ALIS achieving culture conversion by month 6. The absolute difference between treatment groups was 20.1 percent, and this finding was highly statistically significant.

This study demonstrated that treatment with ALIS converted significantly more patients than a multidrug regimen alone within 6 months. Recall that these patients entered the study with MAC lung disease and persistently positive sputum cultures for a median time of more than 4 years.

The time course of the benefit is more clearly represented by this figure, showing a cumulative proportion of patients achieving culture conversion during the first 4 months of the study.

As I mentioned, the date of conversion was the date of the first of the 3 consecutive negative monthly cultures. Therefore, in order to achieve culture conversion by month 6, the first of the 3 negative cultures must have occurred by month 4. Following initiation of treatment, the benefit of ALIS over a multidrug regimen alone can be observed as early as 1 month.

Turning now to the functional assessment, there was no apparent effect of the treatment with ALIS on 6-minute walk test distance at month 6. It is possible that while culture conversion may be associated with a contemporaneous benefit on 6-minute walk distance, the treatment group comparison may not have been able to detect a treatment effect given the proportion of converters at month 6. Therefore, we also examined a prespecified exploratory analysis of improvement in 6-minute walk test distance comparing patients who culture converted to those who did not.

The change from baseline to month 6 in the 6-minute walk test distance was superior among

patients who converted as compared to patients who did not convert. In the overall population, the effect size was nearly 25 meters with a p-value of 0.01. As you can see, this was driven by both an improvement among converters and the decline among non converters. Thus, this change in culture status has meaningful implications from both a microbiologic and a functional standpoint.

If we look only at the patients who were treated with ALIS post-multidrug regimen, the findings were similar with an effect size of over 30 meters and a p-value of 0.005. In patients who received multidrug regimen alone, there were few converters, but the point estimate of the effect size was similar. In these difficult to treat patients who have very limited treatment options, achieving culture conversion was associated with a functional benefit after just 6 months of treatment.

There is a key distinction to note between this analysis and the one I just shared. Study 212 was open label, so the walk test results by

treatment group on the previous slide, where patients knew whether they were taking study drug, do not represent a blinded comparison. This can complicate interpretation since there is a large volitional component to the 6-minute walk test.

In contrast, because patients were blinded to their culture conversion status, this analysis does represent a blinded comparison. This increases the reliability and importance of this finding. So culture conversion is associated with functional improvement and treatment with ALIS allows patients to achieve culture conversion.

Finally, in study 212, the recovery of post baseline isolates with an MIC of greater than 64 was uncommon. An isolate with an MIC of greater than 64 was recovered at least once in 24 patients or 10 percent who were treated with ALIS. It should be noted that an isolate with an MIC of greater than 64 was recovered at least once in 4 patients, or 3 percent, in the multidrug regimen alone arm in the absence of exposure to amikacin in the trial.

As you have seen, the data from study 212 established that a higher proportion of patients treated with ALIS achieved culture conversion by month 6. While the FDA had agreed that this primary endpoint of culture conversion by month 6 was an acceptable surrogate for use in the study, particularly given the unmet need and seriousness of the disease, today the agency is asking you to consider whether culture conversion by month 6, as defined in study 212, is reasonably likely to predict for the clinical benefit of durable culture conversion.

To help address this question, we can present interim data on durability from study 212. I want to highlight that these interim data have not yet been reviewed by the FDA. As of April 2018, durability results are available for 48 of the 65 patients on ALIS who achieved culture conversion by month 6 and for 7 of the 10 patients who achieved culture conversion on multidrug regimen alone.

As you can see, 81.3 percent of patients who

achieved culture conversion on ALIS have remained culture negative throughout the course of treatment and through 3 months after having stopped all MAC treatment. In contrast, none of the patients who achieved culture conversion on their multidrug regimen alone have remained culture negative at this time point. These interim data strongly support the surrogate endpoint of sputum culture conversion by month 6 as predictive of durable efficacy.

Next, I'll present the design and results from study 312. Study 312 is an ongoing open-label extension study in patients from study 212 who did not achieve culture conversion through month 6 regardless of treatment group. All patients in study 312 received ALIS plus their multidrug regimen during the 12-month treatment period.

Although this is a single-arm study primarily intended to provide further safety information, the objective nature of the culture conversion endpoint allows this study to provide support for the culture conversion findings of

study 212, particularly among the prior multidrug regimen alone group. Therefore, we also assessed culture conversion by month 6 as a secondary endpoint.

The efficacy endpoints in study 312 were selected to align with those used in study 212. These include the proportion of patients achieving culture conversion by month 6, time to culture conversion, and mean change from baseline in 6-minute walk test distance at month 6.

Since this is an ongoing study and not all patients had completed the month 6 visit by the data cutoff, I will present only preliminary data regarding culture conversion. Overall, 59 patients from the prior study 212, ALIS plus multidrug regimen arm, and 74 patients from the prior multidrug regimen alone arm were enrolled. At the time of the data cutoff, 49 and 62 patients, respectively, had at least the first 3 monthly sputum culture results and were therefore assessable for culture conversion status.

Here we can see that continuing or

initiating ALIS results in culture conversion, providing further support for the benefit of ALIS in refractory MAC patients. In those patients with available data at the time of the data cutoff, 6 percent of the prior ALIS group achieved culture conversion with extended ALIS treatment in study 312; 27 percent of patients receiving ALIS for the first time achieved culture conversion by 6 months.

Again, we see the benefit of ALIS in these patients who have had MAC lung disease for several years and who have very limited treatment options. And this finding is very similar to and supports the 29 percent rate of culture conversion observed in the ALIS plus multidrug regimen arm in study 212.

Finally, in study 312, isolates with an MIC of greater than 64 were recovered from 8 of 133 patients. An isolate with an MIC of greater than 64 was recovered at least once in 4 of the 59 patients who were in the prior ALIS plus multidrug regimen group and in 4 of the 74 patients

who were in the prior multidrug regimen-alone group.

Finally, I'll refuse study 112, which was our phase 2 proof-of-concept study. In addition to providing early evidence of the efficacy of ALIS, study 112 also provided evidence that culture conversion following the addition of ALIS leads to durable culture conversion. Study 112 was a randomized, double-blind, placebo-controlled study of ALIS in patients with NTM lung disease who were persistently culture positive on previous treatment.

In contrast to the two studies I previously discussed, this study enrolled both patients with MAC and patients with mycobacterium abscessus. Another significant difference is that this study enrolled patients with and without underlying cystic fibrosis.

The overall objective was to evaluate the safety, efficacy, and tolerability of ALIS versus placebo added to a background multidrug regimen. Randomized double-blind treatment was administered

for 84 days. After the double-blind phase, patients entered into an open-label phase where they received ALIS plus their multidrug background regimen for another 84 days and were then followed for an additional 12 months off ALIS.

The selection of the primary endpoint for this phase 2 study was influenced by the relatively short duration of the randomized double-blind period. The intention was to select a primary endpoint that was thought to be attainable within 84 days of treatment. Therefore, study 112 utilized a novel primary endpoint not previously applied in clinical studies for NTM, mycobacterial density as assessed by a semi-quantitative scale, or SQS, which is a means of quantifying mycobacterial growth.

The primary endpoint was the change from baseline to day 84 in the SQS. The proportion of patients with a negative sputum culture was also evaluated at day 84. Although true culture conversion was not prespecified, a post hoc analysis provided early evidence that culture

conversion leads to durable conversion.

The primary efficacy endpoint in study 112 showed a trend in favor of the ALIS plus multidrug regimen group versus placebo. However, this difference did not reach statistical significance. The key secondary endpoint, the proportion of patients with a negative sputum culture at the end of the double-blind phase, demonstrated a substantial treatment difference of 25 percent in favor of ALIS with a nominal p-value of 0.003.

We also conducted a post hoc analysis of true culture conversion. This provided early evidence that culture conversion did predict for durable culture conversion. By the end of the open-label phase, day 168, 20 of the 89 patients, or 22.5 percent, had achieved culture conversion defined as 3 consecutive monthly negative sputum cultures. Three additional patients subsequently met the definition of culture conversion during the 28-day off-treatment period.

Of the 23 total converters, 17 completed the 12-month follow-up. 14 of the 17 patients, or

82.4 percent, had sustained negative cultures 12 months after stopping ALIS. These data provided early evidence that sputum culture conversion is an appropriate surrogate since it predicts for durable culture conversion.

We also reviewed culture conversion and mortality in the three studies in our NTM program. This evaluation suggested that culture conversion may be associated with a decreased mortality. Specifically, the mortality rate in non-converters was 8.2 percent, nearly 5 times higher than that in converters, 1.75 percent. This further emphasizes the importance of effective treatments to improve the rate of culture conversion.

In conclusion, results from our three studies demonstrate a consistent benefit of ALIS in combination with a multidrug regimen in the treatment of patients with NTM infections caused by MAC. The pivotal study, study 212, clearly demonstrated that a significantly greater proportion of ALIS patients achieved culture conversion by month 6 compared to patients

receiving multidrug regimen alone.

This finding is supported by the interim results of study 312, which showed that refractory patients who received a multidrug regimen alone in study 212 could achieve culture conversion when ALIS was added, and the negative sputum culture and culture conversion data from study 112 further support the results from study 212.

In addition, data from study 112, along with the interim durability data from study 212, support the use of culture conversion by month 6 as a surrogate for the ultimate clinical benefit of durable culture conversion. Durable culture conversion is clinically meaningful as it allows patients to come off all MAC therapies and is expected to result in symptomatic and functional benefit.

These data definitively establish that the addition of ALIS to a multidrug regimen is effective in achieving culture conversion. This rigorously defined culture conversion endpoint is likely to predict ultimate microbiologic cure

following a complete course of therapy, and thus represents a meaningful advantage over available therapy.

Thank you. I'd now like to invite Dr. Sallstig to the lectern to present the safety data.

Applicant Presentation - Peter Sallstig

DR. SALLSTIG: Good morning. I'm Peter Sallstig, vice president of clinical development at Insmed. I will now share the safety results from our clinical development program for ALIS.

Overall, we concluded that the data supports that ALIS oral inhalation therapy has an acceptable safety profile. The adverse event incidence rate is higher with ALIS plus multidrug regimen than for multidrug regimen alone. The most common adverse events for this inhaled therapy or respiratory events. Most of these were mild to moderate, and the majority result without discontinuation. Furthermore, the rate of serious adverse events and adverse events leading to death were similar between the treatment arms.

Our primary safety population comes from our pivotal randomized controlled study 212, which included 223 patients treated with ALIS added to the multidrug regimen compared to 112 patients treated with a multidrug regimen alone. This randomized control population best reflects the adverse event profile when ALIS is added to multidrug regimen in patients with NTM lung disease caused by MAC. Please keep in mind that study 212 was open label, which might have influenced adverse event reporting.

Later, when I review adverse events of special interest, I will expand the safety population to include all 388 unique patients with NTM who were treated with ALIS and a multidrug regimen. This cohort of patients from studies 212, 312, and 112 will be called the NTM pooled group.

The mean duration exposure to ALIS from study 212 was 214 days representing 105 total patient-years of experience. In our NTM pooled population, mean exposure to ALIS is 199 days with 164 total patient-year of exposure.

Before I share an overview of adverse events, let me review the definitions we use for treatment-emergent adverse events compared to FDA. These definitions did result in small numerical differences. However, we believe it does not alter the overall safety conclusion.

For the ALIS plus multidrug regimen arm, adverse events that occurred on or after study day 1 and within 28 days after last study drug dose were considered treatment-emergent adverse events. Adverse events that occurred on or after study day 1 and within 28 days after the end of treatment visit were considered treatment-emergent adverse events for the multidrug regimen arm. This was prespecified in the statistical analysis plan for 212.

AEs were collected until the patient completed all follow-up and exited the study, which might have been up to 12 months after last dose. This was done for both treatment arms. Lastly, Insmed's data database of reported adverse events includes all events up until data cutoff in July

2017.

A greater proportion of ALIS plus multidrug regimen treated patients experienced an adverse event in study 212. This increase could be the result of adding another antibiotic on top of background multidrug regimen. Also, please bear in mind that all patients who entered this study had been on the multidrug regimen for at least 6 months and may have been conditioned to tolerate the multidrug treatment regimen in this open-label study.

Seventy-nine percent of adverse events were mild to moderate, or grade 1 or 2, in ALIS plus multidrug regimen treated patients compared to 86 percent with multidrug regimen alone. Serious adverse events and adverse events leading to death were similar between the treatment arms. Adverse events leading to discontinuation of ALIS were reported in 18 percent of patients.

Allow me to review in more detail. Here you see the most common adverse events in study 212. Respiratory adverse events were the most commonly

reported and included dysphonia, cough, dyspnea, hemoptysis, and oropharyngeal pain. These were more frequently reported in ALIS plus multidrug regimen treated patients compared to the multidrug regimen alone.

The majority of the common respect or adverse events were mild to moderate. While adverse events at times led to treatment interruptions, the majority resolved following interruption. Less frequently, these adverse events led to discontinuation of ALIS plus multidrug regimen. Most events resolved following discontinuation.

Adverse events of grade 3 or higher were reported in 21 percent of patients receiving ALIS added to a multidrug regimen compared to 13 percent of multidrug regimen alone. The most common grade 3 or higher adverse events with ALIS plus multidrug regimen were respiratory in nature.

Adverse events did at times lead to treatment interruption in patients with an adverse event of grade 3 or higher. The majority resolved

following interruption. Less frequently, these adverse events led to discontinuation of ALIS. Most events resolved following discontinuation. Looking specifically at adverse events leading to discontinuation of ALIS, these were predominantly related to the respiratory system. Most were non-serious and 70 percent had resolved once treatment was discontinued.

Moving to serious adverse events, serious adverse events were reported in a similar proportion of patients in each treatment arm of study 212. The most commonly reported events were respiratory in nature. Pneumonia and exacerbation of COPD were the most common and reported in a higher proportion of patients in the ALIS plus multidrug regimen arm than the multidrug alone arm.

While serious adverse events led to ALIS interruption in some patients, the majority resolved following interruption. Less frequently, these serious adverse events led to discontinuation of ALIS plus multidrug regimen. Most events resolved following discontinuation.

Next, allow me to review adverse events leading to hospitalization. We included this information both in our submitted NDA as well as in our briefing book as part of the overall SAE data set. For this analysis, we included all adverse events leading to hospitalization and excluded planned hospitalizations.

The rate of hospitalization was higher in the ALIS plus multidrug regimen arm versus multidrug regimen alone arm. While keeping in mind the 2 to 1 randomization, there was also a higher number of hospitalizations with ALIS plus multidrug regimen versus multidrug regimen alone, 79 events versus 25 events, respectively. We also observed that the number of events may have been impacted by an outlier. This component of the FDA's review is ongoing as mentioned in the briefing book.

When looking at the adverse events leading to more than 2 hospitalizations, the imbalance was driven mainly by exacerbations of COPD and pneumonia. When we look at fatal adverse events in study 212, we see that a similar proportion of the

11 deaths were reported in both arms with 3 percent of patients receiving ALIS plus multidrug regimen and 4 percent of patients receiving multidrug therapy alone. The majority were due to respiratory adverse events in both arms. Looking at our NTM pooled population, 3 additional fatal adverse events were observed. These were also respiratory related.

Next, I'd like to review two adverse events areas of special interest. The first includes respiratory adverse events. The four categories of respiratory adverse events of special interest depicted here were analyzed to further characterize potential risks. Overall rates for these events in study 212 for bronchospasm, hemoptysis, COPD exacerbation, and allergic alveolitis were higher in the ALIS plus multidrug regimen treated patients and were consistent across the NTM pooled population. Allow me to walk you through these adverse events of special interest in some greater depth.

To investigate the relationship between ALIS

plus multidrug regimen and reported pulmonary events, we looked at a number of preferred terms listed under each main category as seen on this slide. Although 29 percent of patients receiving ALIS were considered to have bronchospasm, this was driven mainly by dyspnea, which was reported in 22 percent of patients receiving ALIS plus multidrug regimen in study 212.

When looking specifically at the preferred terms in study 212 for patients on ALIS, bronchospasm and bronchial hyperactivity were reported in 3 percent and less than 1 one percent, respectively. Please note that these events were mild or moderate and none were serious.

Turning to COPD, in the ALIS plus multidrug regimen arm, there was a higher rate of COPD exacerbation with 8 percent versus 4 percent in the multidrug alone arm. For two-thirds of the ALIS patients, these adverse events were mild to moderate and all but one resolved.

Moving onto allergic alveolitis, we considered these potential events to include

pneumonitis, allergic alveolitis, interstitial lung disease, and respiratory disorders. Three percent in the ALIS plus multidrug regimen arm versus 1 percent in the multidrug regimen arm experienced an adverse events of special interest of allergic alveolitis in study 212. Six out of the 7 events in the ALIS arm resolved.

Moving now to serious respiratory adverse events of special interest, few of these were reported as SAEs. As you can see, the percentage of patients experiencing a serious respiratory adverse event of special interest was low and similar between the groups. For each of these respiratory categories, SAEs were reported in 3 percent or less of the patients in the ALIS arm.

Next, looking at systemic amikacin related adverse events, adverse events related to the well-known systemic toxicity of aminoglycosides such as nephrotoxicity and neuromuscular adverse events were balanced between the treatment groups and were infrequent. We think this is an important observation because these two types of adverse

events are why physicians avoid the use of IV amikacin.

These results support our expectations for fewer systemic risks when directly administering ALIS to the lung. There was, however, an imbalance in ototoxicity between the arms. That imbalance was driven by more reports of tinnitus and dizziness in patients treated with ALIS plus multidrug regimen. Tinnitus was the most frequent reported by 8 percent of ALIS plus multidrug regimen patients. The majority of these events, 85 percent, were mild and the rest moderate.

There were no serious adverse events in the ototoxicity category for either arm. Audiology results showed no trend in the change from baseline in the mean decibels over time between the two treatment arms when tested in months 3 and 6. Of the 17 ALIS patients who reported tinnitus, 59 percent had prior hearing related history and 41 percent had previously received aminoglycosides.

All reports of tinnitus were mild to moderate, and none lead to ALIS discontinuation.

Six patients did interrupt study drug. Of those, 4 had their tinnitus resolved within 30 days. Overall, roughly half of all tinnitus events resolved, and those that didn't, the majority, 88 percent, had prior hearing related history and 63 percent had a history of prior aminoglycoside use.

To summarize this safety presentation, while adding ALIS to a multidrug regimen did increase the incidence of adverse events, the reported serious adverse events and adverse events leading to death were similar between the treatment arms. Respiratory adverse events were most commonly reported on the inhaled treatment arm.

The majority of all adverse events were mild to moderate and most resolved without discontinuation. Because ALIS is not systemically delivered, there was also a low risk for amikacin related adverse events. Lastly, there was no differences between ALIS and the comparator arm in any laboratory shifts from baseline.

Thank you. I will now Dr. David Griffith to

provide concluding remarks.

Applicant Presentation - David Griffith

DR. GRIFFITH: Thank you, Dr. Sallstig.

My name is David Griffith. I'm one of the co-principal investigators for ALIS. I am also the lead author of the 2007 ATS/IDSA guidelines for the diagnosis and treatment of NTM disease. I'm a pulmonary physician with approximately 30 years of experience treating patients with this progressive disease.

NTM lung disease is a chronic, debilitating, and potentially life- threatening condition with variable rates of progression. I want to emphasize there is no approved therapy. As you've heard, the goal of available treatment is the durable eradication of the underlying infection as evidenced microbiologically by sputum culture negativity.

Eradication of the infection will halt further disease progression and predict for improvements in morbidity. However, treatment success with the currently recommended

macrolide-based regimen is not adequate, ranging from 40 to 60 percent. Clearly, current MAC therapy fails many patients. For instance, it is significantly harder to treat these patients' NTM lung disease than patients with multidrug resistant tuberculosis.

Let me show you a radiograph of one of my patients who had a poor microbiologic and clinical response to current MAC therapy. This patient has severe MAC lung disease. The radiograph on the left is from 2005. She was originally macrolide susceptible but developed macrolide resistance. The radiograph on the right is after 15 years on therapy with multiple medication combinations, with clear radiographic progression and sputum that is persistently culture positive for MAC. Unfortunately, she currently has chronic hypoxic respiratory insufficiency and is being evaluated for lung transplantation.

If there is one consistent theme of the presentations this morning and that I know to be true from my clinical experience with patients like

the one shown on the previous slide, it is that patients with MAC lung disease urgently need better, more effective treatment options. Simply stated, current antibiotics are not sufficient. The available companion agents to the macrolide, ethambutol, rifamycin, fluoroquinolones, and clofazimine, have limited potency. It is the macrolide that is the basis of the, albeit limited, treatment successes for MAC lung disease therapy currently.

ALIS in combination with a multidrug antibiotic regimen will change the current MAC paradigm. It is the first treatment advance for patients in more than 20 years. ALIS demonstrated superior ability to achieve culture conversion compared to guidelines-based therapy alone. More patients converted when ALIS was added to their guideline-based treatment than those who did not receive ALIS.

It is important to remember that these were difficult to treat patients, patients who had not achieved culture conversion during prior prolonged

therapy, and that the definition of culture conversion was extremely rigorous. ALIS is not without risks, but they are manageable. MAC infection as well as MAC therapy are already hard on patients. It should surprise no one that adding another drug, ALIS, to this challenging multidrug regimen does increase the incidence of adverse events. However, it does not appear to add a significant burden to patients since reported serious adverse events were similar to guideline-based therapy.

Respiratory adverse events were the most commonly reported with the inhaled route of administration. Dose interruptions often prove sufficient to manage these adverse events. I found that I could keep patients on therapy through diligent management of events when they occurred, interrupting treatment when needed, but primarily by educating patients and setting proper expectations on the potential side effects of therapy.

What could ALIS therapy mean to specific

patients? It could mean culture conversion and associated clinical benefit even for those with extensive disease.

Here you see two radiographs of one of my patients taken 10 years apart. As you see, this patient has extensive lung damage. On the left, you see primarily right-sided bronchiectasis in the mid and lower lung field. On the right, we see the progression of the lung damage with vial [ph] loss, consolidation, and retraction of the lung tissue.

She started MAC therapy more than 10 years ago. She developed macrolide resistance. She has been through more than 10 antimycobacterial medications, yet she remained persistently and strongly AFB culture positive, and then she was recruited into study 112.

Following the addition of ALIS to a multidrug regimen, she had her first negative culture in more than 10 years. She subsequently has met disease success criteria with 12 months negative sputum cultures while on MAC therapy and has been off all medications for more than

6 months. She also has improved symptomatically with improvement in cough, sputum production, exercise tolerance, and overall sense of well-being. And not insignificantly, she has also improved appetite with weight gain. This is the outcome I want for all patients.

Culture conversion matters because it is the necessary first step in helping patients meet treatment success criteria of durable conversion and discontinuation of all MAC therapy. Published studies support that culture conversion is sustained throughout the course of MAC therapy.

Here are four studies which show that 84 to 98 percent of patients who achieved culture conversion maintain culture negativity throughout the course of MAC therapy. These data provide strong support that culture conversion is a surrogate, which is reasonably likely to predict durable culture conversion. Durable conversion allows patients to stop MAC therapy, which is inevitably associated with improved symptomatology.

Eradication of the organism and

microbiologic cure are clearly beneficial. Published data summarized in today's presentations are consistent with what I see in my practice. Patients experience improvements in their symptoms, function, and mortality once MAC has been eradicated.

ALIS is the most significant and important advance in the treatment of MAC lung disease since the introduction of macrolides more than 20 years ago. MAC lung disease is a debilitating, potentially life-threatening condition. ALIS fills and unmet need because it has demonstrated superior benefit over today's standard of care in patients who had been refractory to treatment.

ALIS in combination with a multidrug regimen increases attainment of sputum culture conversion by month 6. That is the antimicrobial goal of treating physicians since sustained culture conversion is the basis of successful therapy. Further, it has low systemic exposure and minimal risks for ototoxicity and renal toxicity and an overall acceptable safety profile.

These studies have clearly shown that the benefits of ALIS outweigh the potential risks in patients with limited treatment options. Additionally, these clinically important ALIS results hold promise for other MAC patients. The ALIS mechanism of action is the same for newly diagnosed and treatment refractory patients, so it is reasonable to extrapolate the demonstrated safety and efficacy to all patients with MAC lung disease who also urgently need better treatment options.

Further, using ALIS in first-line treatment would mean that patients would get the two best drugs with significant activity against MAC lung disease, a macrolide and amikacin sooner. Concomitant use of these two MAC medications in initial treatment would be expected to decrease the chance a patient will develop acquired mutational resistance to either of these drugs.

This is exactly what we have learned from our extensive experience with the treatment of tuberculosis. In that situation, we use isoniazid

and rifampin since they have the best in vitro and in vivo activity against mycobacterium tuberculosis and are potent enough to protect each other against the emergence of acquired mutational resistance. This relationship is all the more important for macrolides and amikacin as they are the only two agents with demonstrated correlation between in vitro susceptibility and treatment outcome for MAC lung disease.

Given the inexorably progressive and life-limiting morbidity, we should use our experience to give patients with MAC the best chance for early intervention and a cure. Based on my experience, the benefits of ALIS outweigh the potential risks for patients all along the continuum of MAC lung disease.

I now invite Dr. Sullivan to the sponsor's responder microphone to answer your questions.

Clarifying Questions

DR. BADEN: I would like to thank the applicant for putting in such effort over the years and conducting such complicated studies and for

presenting such a wealth of complex data so succinctly. I am sure there are many questions from the committee.

Before we start the questions, I just would like to remind the committee that we will systematically go through the questions. Let Lauren or I know if you have a question. If in a given line of questioning, you have a follow-on, please get my attention so that we can develop themes as much as possible. Time is limited, so both questioning and answering should be as succinct as possible.

I will start with the first question, which you presented a tremendous amount of data, but there are data that are not present that I think are important. Did you collect -- how did you handle the diversity of MAI at baseline and through the course of the study? How do we know it's a persistent organism versus continual new acquisition? What efforts did you do to understand the organism over time in a given patient?

DR. SULLIVAN: You're asking --

DR. BADEN: We need to turn on the microphone. Perhaps you can come to the lectern until that is solved.

DR. SULLIVAN: So are you asking about the specific subgroup of MAC or are you asking about genotyping?

DR. BADEN: No. In a given individual, are they colonized -- or colonization versus infection, but at baseline do have a single strain of MAC, and that's the only one through time, or do they biodiversity, and they may have persistence of the organism or they may be continually reinfected?

What evidence do you have about the organism through time in the individuals treated?

DR. SULLIVAN: I see. So the first part, these are patients who are not simply colonized. This is clearly infection given the decision by the physicians to treat and often treat for as long as 4 years or more. I have some data on the specific subsets. We have not yet performed genotyping of all of the data, of all of the samples to identify any diversity issues.

DR. BADEN: So you don't know if through time, it's the same organism or different organisms in a given patient?

DR. SULLIVAN: Not at the moment. That would require more extensive genotyping testing, which have not been conducted yet.

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

DR. MASUR: I think it's on the same thing. But in terms of characterizing the organisms, do you have data on their resistance pre-therapy and post-therapy? In other words, was there a correlation with either the macrolide or amikacin in terms of response other than greater than 64 with amikacin? And did resistance develop during or after therapy?

DR. SULLIVAN: So there are a lot of elements to that. The most important, clinically important, MIC testing that's done clinically is to the macrolide. That's the only one that's ever been shown to correlate with clinical outcomes. We do have information on the outcomes in patients who

are macrolide resistant at baseline, and I can show you that.

What we saw was we still had an effect. ALIS still had a superior ability to achieve culture conversion, but overall in both the MDR and the ALIS group, the incidence of conversion was lower. So on the left-hand column is those who are clarithromycin susceptible. You can see in the ALIS group, there was 33.7 percent conversion verses 10 in the MDR. When they were resistant and the threshold is typically 32, the percent of conversion with ALIS was 13.7 and 4.5 in the MDR group. We excluded patients who had amikacin resistance at screening.

DR. MASUR: Then post-therapy, though -- so it makes sense that clarithromycin susceptibility and amikacin susceptibility at baseline were predictive. Did resistance develop in those who failed to convert or converted late?

DR. SULLIVAN: We saw amikacin, and the way we looked at it was any specimen with an MIC of greater than 64. Generally 64 is considered the

threshold that represents mutational resistance, so that's the clinically relevant mechanism. And there were patients, as I presented, who developed an isolate, at least one isolate, of an MIC greater than 64. But I hadn't shown you what you're asking, which is the outcomes of those patients.

Culture conversion was uncommon in patients who developed an isolate of greater than 64. Only 1 of the 24 in the MDR group, or 4.2 percent, achieved the culture conversion and none in the MDR alone.

DR. BADEN: But you do not know if those are the same strains present at baseline?

DR. SULLIVAN: No. We have not done the genotyping that's required for that.

DR. BADEN: Dr. Green?

DR. M. GREEN: This is just a quick follow-on question. Do you have any data on the timing of emergence of resistance? I know you're getting specimens at set time points, and presumably you're doing susceptibility of each of those. And you've just told us there's emergence

of resistance. So when does it occur, and is it going to be after months of therapy, one month of therapy? Is there any predictive value to that or any knowledge of the timing?

DR. SULLIVAN: So the time course among those 24 patients, one actually was at baseline, meaning prior to any administration of drug, and the 23 were after baseline. And there was no particular pattern. Some occurred at month 1, 2, 3. It didn't appear to be coming late.

DR. M. GREEN: And just quickly, in your study, so if they were resistant at baseline, they weren't eligible for study. If they became resistant on therapy, they stayed in the study?

DR. SULLIVAN: Yes. And just one minor clarification. The entry criteria was based on the screening value because, as you know, it takes many weeks for that to come back. So we ended up with that one patient I referred to who, at the baseline, although having been amikacin sensitive before, was resistant at baseline.

But once they achieved -- or once an isolate

was demonstrated to be an MIC greater than 64, they stayed in the study. In fact, 20 percent or so of patients subsequently had an isolate that was less than 64, reverted back to a sensitive. So we're not sure the significance of that.

DR. BADEN: Thank you. Dr. Brittain?

DR. BRITTAIN: I have two quick questions. The first one relates to slide CO-62. That was fast. This was interesting. I just wanted to get a little bit more information because I understand that this phase 2 trial, it's not the same population. It's a broader population than the current -- than your indication.

I know the numbers are really small, but can you give us any information about the subset that's like the population of interest?

DR. SULLIVAN: And do you mean in regard to the overall outcomes, or do you mean in regard to this specific issue?

DR. BRITTAIN: I'm particularly interested in this, the durable cultural conversion.

DR. SULLIVAN: Let me see if we have that

broken down by CF. I think you're referring to the abscessus or the CF, and I do have that to show you.

Here are the numbers, the 20 over 89 achieving culture conversion by day 168. So remember that some group of patients got drug during the 84 days and some got placebo, and then the other half added ALIS during the next 84 days. So this is by day 168, 22.5 percent, and 3 additional met the definition, meaning they had their third of 3 at the 28 day. This is the data on the converter, so 19 of those were the non-CF MAC.

It really was that observation -- now, this was a small study, a short duration of treatment, but the signal we saw the strongest was in non-CF MAC, and that's why we carried forward that population.

DR. BRITTAIN: I see. And my other question relates to the study design, which is on CO-34. I wasn't sure I fully understood the rationale for taking the non-converters off at month 6 because

that doesn't give a chance to get a long-term randomized comparison of both clinical and culture. So I was wondering why you made that choice and if that choice was agreed to by FDA.

A related question to that is, when will you get the results from the ongoing study on the long-term endpoints?

DR. SULLIVAN: Sure. Yes. The decision was made in discussion with the experts who were advising us. Because of the long duration of treatment, it was deemed difficult to enroll patients into a study that could last 24 months and require multiple visits and multiple samples, and not give them the chance to try ALIS throughout the course of that.

Given that our surrogate endpoint was at month 6, which actually requires randomized treatment to go to a month 8, because we couldn't find out the results in month 6 to month 8, it was determined that because the primary endpoint, even the ultimate primary endpoint, is looking at the number of patients as randomized who achieved

culture conversion by month 6, maintain it through treatment, and maintain it 3 months off treatment, that those patients, once they've already not achieved that first element, they were no longer willing to contribute. They were already nonresponders. So it was a balance of those factors.

You asked about the FDA's input, and they did point out what they've mentioned today, which is that makes it difficult for the other endpoints, not the primary endpoint. And we recognize that, but it was felt that there would be a lot of missing data anyway for things like 6-minute walk test and stuff after 2 years, even if we allowed them in.

So we felt that there had to be this sort of rescue ability to receive the drug, and we had specified the 6-month period for the surrogate endpoints. That was the rationale.

I think the second part of your question was about timelines for the remainder of the data, and I'd like to bring Dr. Streck to the podium to kind

of walk through that.

DR. STRECK: Thank you. Paul Streck. The trial will continue when patients receive their full course of treatment, and subsequently will be followed 12 months off therapy. The entire trial will finish at the end of 2019 with subsequent analysis, and then if appropriate, sharing results with the agency.

DR. BADEN: A follow-on to this question, slide 50. I just want to make sure I understand. Aren't these data the 18 -- I think you said 48 of 65 have made it to the final endpoint or am I misinterpreting these data?

DR. SULLIVAN: That's right. And this was particularly presented today to address this issue of this culture conversion at month 6 predictive of durable. So what we said is we have this ongoing data. Forty eight patients have reached the three months off, which is the primary endpoint, and of those 48, 81 percent achieved it.

DR. BADEN: But these are the ones reaching -- in the previous slide, they're reaching

the secondary primary endpoint. I'm using the wrong term.

DR. SULLIVAN: That's right, the latter analysis.

DR. BADEN: The latter. So these are the latter analysis not vetted by the agency, but data available as of April of this year.

DR. SULLIVAN: Exactly.

DR. BADEN: Suggesting 80 percent have persistent culture negativity a year after completing therapy.

DR. SULLIVAN: And 3 months after stopping.

DR. BADEN: And 3 months, 3 months post completion.

DR. SULLIVAN: Exactly.

DR. BADEN: Okay.

DR. EVANS: Can you explain that slide specifically? The 80 percent, you said it was 48 or 65, or something like that. But then you had zero percent, and that said 7 of 10, and I don't understand those numbers.

DR. SULLIVAN: Yes. If we could maybe bring

that back up. So we're presenting it by treatment group. At month 6, 65 in the ALIS group and 10 in the multidrug regimen had achieved culture conversion at month 6. We now have data at 3 months off of all therapy for 48 of the 65 and 7 of the 10.

So that says that if you achieved culture conversion -- and they're very small numbers of 7. But if you achieve cultural conversion with MDR --

DR. EVANS: So that's zero percent of 7.

DR. SULLIVAN: That's right.

DR. EVANS: Okay.

DR. SULLIVAN: Yes.

DR. BADEN: Follow-on? Dr. Proschan?

DR. PROSCHAN: Yes. Just related to that, -- can you keep that slide up for a second, that same slide? Related to this, you'd like to see the same relationship between early conversion and durable conversion in both arms to believe that the difference between arms in the early conversion predicts the difference between arms in durable conversion.

So it's a kind of interesting that zero of seven, obviously a small sample size, it seems to be predicting the durable conversion in the ALIS group but not in the other arm. Of course, if it has to be different in the two arms, this is a better thing. If it were the other way around, it would be quite disturbing.

DR. SULLIVAN: Yes. I take your point exactly. I'm looking at the N of 7. Could I have the slide of the four studies showing from the literature?

This is a little bit of external information that may give you some comfort. These are several studies which looked at culture conversion by month 6, and then these are the percentage of patients who maintained that throughout. So these obviously are studies that did not include ALIS. They're various regimens. So what we are seeing so far in this to 212 study seems to be consistent with what's been reported in the literature.

DR. BADEN: We have several follow-ons. But getting back to your CO-50, how do we know that's

durable conversion versus prevention of reacquisition, given that they're on additional agent for that period of time or at least 12 of the 15 months?

DR. SULLIVAN: I think that's somewhat definitional. The bug has been eliminated, and consistent with the guidelines, the drugs are continued and there's no further growth. The period off of all MAC treatment is now 3 months. So there's nothing there preventing reinfection, at least for those 3 months.

I don't know the extent that the current guidelines consider that in addition to treating the disease, you're also preventing during it. But my understanding is that the intention is that the duration of treatment is primarily to eradicate the organism. This is something that maybe Dr. Griffith could add some more color to.

DR. GRIFFITH: Yes. Thank you. Dave Griffith. This is a little bit semantic. I actually prefer the term "microbiologic recurrence" since the word "relapse" has specific prognostic

significance, and we do believe that patients do re-acquire organisms from the environment in some circumstances. But in terms of treatment success, some definitions have recently been published and elimination, durable elimination, of the original infecting organism is still I think the consensus definition of treatment success.

I do agree with you the genotyping information, when it becomes available, is going to be very interesting. But also keep in mind that 99.9 percent of clinicians in the United States who take care of this disease do not have access to genotyping.

DR. BADEN: Thank you.

Dr. Lo Re, a follow-on?

DR. LO RE: Vincent Lo Re. From that slide 101 that was shown up, just because there's been so many different definitions of culture conversion, durable versus 3 negative cultures within 6 months, could you just go through, what were the definitions of culture conversion on this slide for each of these studies? Were these durable culture

conversions or the definition for the surrogate endpoints that were used in study 212?

DR. SULLIVAN: I'll bring up Dr. Griffith because one of those papers is from his group, generally, even the other papers used. I just want to clarify what this represents is people who initially achieved culture conversion, and by month 6 is typical. And Dr. Griffith will talk to that.

So this is the percentage of people who initially achieved culture conversion, which is sort of comparable to our surrogate endpoint, and how many of those maintain negative cultures throughout the course of treatment. But let me let Dr. Griffith, since the Wallace paper is from his group.

DR. GRIFFITH: Thank you. Dave Griffith. In these studies, treatment success was defined by the American Thoracic Society guidelines definition of treatment success. You can see that one study was prior to the 2007 guidelines, but the other three utilized 3 consecutive negative sputum

cultures with at least a month apart between the cultures as defined by ATS/IDSA guidelines.

I would like to take this opportunity, if possible, to reemphasize how rigorous the definition of sputum culture negativity was in 212. It required 2 to 3 sputum specimens a month apart on three occasions. For some patients, it required 9 separate negative specimens to meet the criterion for sputum culture negativity.

DR. BADEN: Dr. Lo Re?

DR. LO RE: Just to follow on, just two questions. Could you just elaborate how the definition of surrogate endpoint for the 3 consecutive negative cultures on each month, why was it 3 versus 2 versus 4? How was that formulated? And then just to clarify again, this was not durable in that this was on treatment and this was not 3 months off treatment for these studies here.

DR. GRIFFITHS: No. This was just defined as at the end of treatment for each of the studies, and there were variable definitions for that.

DR. SULLIVAN: And that's typically what's reported. Because the 3 months off wasn't reported in this, we would have provided that. You asked about how we selected, and it was in consultation with the experts that we wanted to be rigorous. We wanted to make sure that when we called a culture conversion, it was something significant.

Some of these patients can have a negative culture here and there, so in consultation with the experts, the 3 consecutive -- and then, as Dr. Griffith mentioned, at each time collecting 2 or 3, we said 2 or 3 samples, each of which had to be negative.

DR. LO RE: And just to further clarify, in these studies, you had said there was 1 negative culture separated by a month, then another negative culture. So why the difference that was chosen here versus these studies? I'm just trying to get a sense.

DR. SULLIVAN: I think that these studies reflected the clinical practice at the institutions. Again, we wanted to have a very

rigorous definition. So that people would believe that when we say people culture converted by month 6, it was a significant event.

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

DR. GRIPSOVER: Back on the other side, I just wondered if we knew the time course of the ones who failed in the long-term follow-up. Was it after they stopped treatment or while they were still on treatment?

DR. BADEN: And that's CO-50 slide?

DR. GRIPSOVER: Yes, Co-50 slide; that one.

DR. SULLIVAN: You know, I don't have that information. I want to emphasize, we just took this one snapshot to address this particular issue, is how likely is culture conversion at month 6 to carry forward all the way through. We haven't done the extensive look at the data past 6 months, which will be in the subsequent filing for full approval. So that will be looked at, at a later point.

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

DR. M. GREEN: I think it's been answered.

Well, actually, I do have one quick question. And this is to the slide that we saw with the four different studies but actually also to this study.

We talk about, whether you use the FDA term or your term, but the background treatment they're on when they enter study, but we don't define what that is. So how much diversity is there in that treatment? Everybody's getting a macrolide, I'm sure. What else are they getting? How many of them are getting IV amikacin in those studies that we at least saw from the literature on the slide comparing outcomes? We're not given that information at all, so it's really a variability amongst patients in all these studies, I think.

DR. SULLIVAN: Sure. And I don't have slides on the details of those studies. I can show you within our study. It is complicated because there are guidelines about the initial treatment, and they tend to be 3 drugs. Once patients have been on for 3 and 4 years, there are no guidelines to tell doctors what to do, so multiple regimens are tried. Some are dropped depending on

tolerability and so forth.

So you're absolutely right, you end up with patients who are just on a number of different types of regimens, so we tried to summarize it here, and looking at ALIS and multidrug show there's a balance between it. You can see that the majority were on the EMR, which is ethambutol, a macrolide, and the R is a rifamycin of some sort. You can see that some are on 4, some are on 3 with another drug thrown in. So there was a wide variety. This reflects the challenges in treating these patients. After several years, you are altering drugs based on tolerability and so forth.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: I have some questions that get to the 212 study and the lack of the improvement in the function at 6 months for the people who had ALIS. I see that ALIS is associated with culture conversion, and culture conversion was associated with an improvement in 6-minute walk. But ALIS is not associated with the improved 6-minute walk.

I could think of several reasons this might happen. One is the drug will not work and will not improve function. But then three other reasons that came to mind was that the adverse effects of the drug hide the clinical benefit while they're on the drug; or it's too soon to see the clinical benefit. One of your natural history slides suggested it takes some time to see the clinical benefit. And three, it's possible that despite randomization, the patients who are in the ALIS arm are more predisposed to have worse function.

So those are my thoughts, and I have two questions then. As far as looking at this too soon, was there any assessment at 8 months, before they were taken off, to look at function or symptom measures at that time?

DR. SULLIVAN: We haven't assessed anything beyond the 6 months. The cutoff for efficacy was at 6 months. We, I think, share one of those opinions that it's probably too soon. We don't think it's the drug because we do see the separation among those who convert, but as you

alluded to, we saw the general improvement in symptoms take some time. These patients have been sick for a long time and only have just started to culture convert. Again, to culture convert by month 6, it may have been month 4, 5, and 6. So it is very early in the context of the patient's illness.

DR. HONEGGER: Okay. Then the second question related to that is have you done any more analysis of the baseline factors of the patients in the two arms in 212? For instance, cavitary disease I read sometimes is associated with -- or just more advanced disease, one, they may be less likely to convert and maybe also won't improve.

I noticed that at the 6-minute walk time, in both arms, the people who converted -- of the people who improved had higher baseline 6-minute walk times. So is it possible that once you get to a certain degree of illness, you're not going to see functional improvement and maybe have more sick people in the ALIS arm.

DR. SULLIVAN: First of all, in the regard

to the 6-minute walk, baseline was a covariate in the model. We looked at a logistic regression to look for baseline characteristics that impacted the likelihood of achieving culture conversion. Looking at a whole host of factors, only two that came out. The first was the treatment with ALIS, and the other was the SGRQ. Those patients who had the higher or the worst scores at baseline of SGRQ were less likely to achieve culture conversion than those with lower, but that was the only baseline factor that seemed to interact.

DR. HONEGGER: So that's with conversion, but what about then with functional improvement in the 6-minute walk time? Did you find any other factors that could account for the lack of improvement with the drug?

DR. SULLIVAN: Right. I'm trying to think of -- the statistical analysis included important baseline factors to control for those, so I don't have any other information as to that.

DR. HONEGGER: Do you have information on -- in some of the papers, they classify the lung

disease as cavitary or fiber nodular. Do you have any baseline characterization of the populations in that regard?

DR. SULLIVAN: Well, that was very challenging because in order to accurately do that, you'd have to have CAT scans for everyone. It's difficult to discern that on a chest x-ray. And even with CAT scans, there can be arguments about what's a cavity and what's a dilated bronchus, and so forth. So we didn't do CAT scans on everyone, so we don't have a careful phenotype that you're describing for baseline cavitary disease.

DR. HONEGGER: Thank you.

DR. BADEN: Just following Dr. Honegger's comment, the ALIS-treated converters better 6-minute walk, other fact FEV1, other things that you measured, does anything else correlate with clinical benefit in that selected subgroup?

DR. SULLIVAN: With culture conversion? Spirometry was performed as a safety measure, and we don't have that.

DR. BADEN: I see.

DR. SULLIVAN: We looked at SGRQ to see whether that correlated, and it went in the same direction but was not statistically significant.

DR. BADEN: Dr. Daskalakis, follow-on?

DR. DASKALAKIS: That was actually my question, the spirometry, so I withdraw.

DR. BADEN: Dr. Proschan, a follow-on?

DR. PROSCHAN: Yes. I think the most likely explanation for why you're not seeing a difference in 6-minute walk test is that most people didn't convert in both arms. I mean, 70 percent even in the ALIS arm didn't convert. So that's I think the most likely explanation.

DR. BADEN: It is now 10:40. We will take our break. We have many more questions. And as I discussed with the applicant, after the break, we'll proceed with the agency's presentation, clarification's with the agency, and then we'll come back to the applicant for further clarification questions to better understand these data. There are many more questions; trust me.

So well now take a 10-minute break. Panel

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

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

DR. BADEN: It is now 10:50 or 10:51. We shall resume and will now proceed with the FDA presentations.

Dr. Kim, please present the clinical efficacy data.

FDA Presentation - Peter Kim

DR. KIM: Good morning. My name is Peter Kim, and I'll be giving FDA's presentation of clinical efficacy for amikacin liposome inhalation suspension or ALIS. This morning, we'll discuss the microbiologic surrogate endpoint as well as efficacy data for ALIS.

Regarding the microbiologic surrogate endpoint, we reviewed the literature to assess whether there is information to support a relationship between sputum culture conversion and

clinical outcomes in patients with mycobacterium avium complex or MAC lung disease. We focused on studies that included patients with infections due to MAC only or those that included MAC along with other NTM species.

We found that limited data are available based mainly on retrospective, non-randomized studies or exploratory analyses from non-randomized subgroups that evaluated the relationship of sputum culture conversion and clinical outcomes. The main limitation of these studies is the difficulty in assessing if there are differences in patient characteristics between converters and non-converters that might have an impact on clinical outcomes.

We will highlight the findings reported in 6 publications. During our assessment, we'll evaluate the study design, primary objectives, and analyses performed, findings, and if available, information on sputum culture conversion and study limitations.

The first study that we'd like to highlight

was by Griffith, et al. published in 2006. This was a retrospective chart review of 51 patients at a single medical center over a 15-year period identified as having clarithromycin resistant MAC lung disease. The primary objective was the assessment of risk factors for macrolide resistance. The authors noted in the paper that 1-year mortality in patients who remained sputum-culture positive was 34 percent versus zero percent for patients who became culture negative.

We noted the following limitations. Patients had to be fit enough to undergo surgical resection and compliant enough to tolerate greater than or equal to 6 months of injectable aminoglycoside therapy. Such patients may be more likely to convert their sputum cultures to negative versus non-surgical candidates or those unable to comply or tolerate with greater than equal to 6 months of IV aminoglycosides. The inability to convert to a negative sputum culture might reflect more severe disease or be a marker for a worse outcome due to other patient characteristics.

The next study that will highlight was by Moon, et al. published in 2016. This was a retrospective chart review of 34 patients with macrolide resistant MAC lung disease from a single center. The primary objective was assessment of clinical characteristics, treatment outcomes, and resistance mutations.

The authors noted that all-cause mortality was 50 percent. Mortality attributed to MAC lung disease was 26 percent. Mortality was more frequent in patients with fibrocavitary disease at 68 percent than in those with nodular bronchiectatic disease at 27 percent. Patients with unfavorable outcomes, that is sputum non-conversion or death, were more likely to be acid fast bacilli smear positive at the time of detection of macrolide resistance.

We noted the following limitations. Determining attributable mortality with any degree of certainty in this population can be difficult. While those with unfavorable outcomes were more likely to be AFB smear positive at the time of

detection of macrolide resistance, no evidence provided that achieving culture conversion translates to clinical benefit or reduction in mortality. The presence of AFB smear positivity might reflect more severe disease or be a marker for a poorer outcome.

The next paper that will highlight was by Jenkins, et al. published in 2008. This was a randomized, open-label prospective, multicenter trial that enrolled 371 patients. The primary objective was assessment of mortality due to NTM lung disease, which could have been due to MAC or two other mycobacterial species; failure of treatment and relapsed comparing the addition of clarithromycin or ciprofloxacin as third drugs to a backbone regimen of rifampicin and ethambutol for two years.

The authors noted a mortality analysis in those with sputum culture conversion versus those who did not convert based on a post-randomization event, that is needing a fourth drug because the patient was culture positive at 12 months. Of 32

patients requiring a fourth drug at the end of their first year because they did not convert to sputum culture negative, 13 percent died from mycobacterial disease compared to 1 percent who did not require a fourth drug.

We noted the following limitations. Determining attributable mortality with any degree of certainty in this patient population can be difficult. No difference was reported in all-cause mortality between patients who remained culture positive and those who became culture negative. The mortality analysis was based on the post-randomization event of sputum culture remaining positive at 12 months and not by the randomized group.

The inability to convert to a negative sputum culture might reflect more severe disease or be a marker of a worse outcome. The assessment of mortality due to mycobacterial disease, based on the requirement of a fourth drug at the end of the first year, did not take into account 120 of the 371 patients enrolled in the study.

The next paper that we will highlight was by Ito, et al. published in 2012. This was a retrospective study of 164 patients with MAC lung disease at a single center. The primary objective was assessment of predictors of 5-year mortality. The analysis was non-randomized and univariate.

Based on our review of information provided in the article, among the 117 patients with microbiologic outcomes, mortality rates for those who remained sputum culture positive versus those who are sputum culture negative were 30.6 percent and 17.6 percent, respectively. Five-year mortality was lower in treated MAC patients who achieved sputum culture conversion versus those who did not convert, however, the result was not statistically significant.

Regarding limitations of the study, some patients were left untreated due to lack of symptoms, patient refusal, or severe disease, raising concerns that these patients were inherently different from those that were treated. If all 117 patients with microbiologic and survival

outcome data were included in the analysis, the mortality rates were similar between the treated and the untreated groups. The inability to convert to a negative sputum culture might reflect more severe disease or be a marker for a worse outcome.

The next paper that we'd like to highlight was by Griffith et al., published in 2015. This was a retrospective study of 180 patients with nodular bronchiectatic MAC lung disease at a single center treated according to ATS/IDSA guidelines with standard macrolide-based treatment and at least 12 months of follow-up. The primary objective was to determine whether a semi-quantitative culture scale correlated with clinical disease status and if it was predictive of long-term culture conversion to negative.

After 12 months of treatment, 82 percent of the patients had sputum culture conversion to negative. An early change in semi-quantitative sputum culture scale correlated with subsequent long-term sputum culture conversion, improvement in cough, and early radiologic improvement.

We noted the following limitations as were noted by the authors. There was a question of whether this study could be generalizable to other centers given that the study data were obtained from a single center with more than 20 years of experience with performing semi-quantitative sputum AFB cultures. Additionally, the patient population was limited to those with nodular bronchiectatic MAC lung disease and did not include patients with fibrocavitary MAC lung disease. It has also been noted that treatment outcomes, relapse, and reinfection may differ based on clinical phenotype of MAC lung disease and host factors.

The final study that we will highlight was by Koh, et al., published in 2017. This was a retrospective study using registry data from a single center of 481 treatment-naive patients with MAC lung disease who underwent anti-mycobacterial treatment for greater than or equal to 12 months. The primary objective was to assess the effect of clinical phenotype of MAC lung disease on treatment outcomes and redevelopment of NTM lung disease

after treatment completion.

This was a non-randomized analysis. Out of 481 MAC patients, 58 percent had non-cavitary, nodular bronchiectatic disease, 17 percent had cavitary nodular bronchiectatic disease, and 25 percent had fibrocavitary disease. Favorable outcomes were more frequent in those with non cavitary disease than those with any form of cavitary disease. Cavitary disease was independently associated with an unfavorable outcome.

Out of 402 patients with favorable outcomes, 29 percent experienced redevelopment of MAC lung disease during a median follow-up of 13.6 months. Relapse occurred more frequently in those with fibrocavitary disease within a median of 6 months. Reinfection occurred more commonly in those with nodular bronchiectatic disease within a median of 13 months.

The nodular bronchiectatic form was an independent risk factor for redevelopment of MAC lung disease. Mortality among patients with sputum

culture conversion to negative was not provided to compare with those who remained culture positive.

Our conclusions from the review of the literature -- and we reviewed other articles as well, but these were the ones that we highlighted for this presentation -- limited data are available based mainly on retrospective non-randomized studies or exploratory analyses from non-randomized subgroups that evaluated the relationship of sputum culture conversion and clinical outcomes.

The main limitation of these studies is the difficulty in assessing if there are differences in patient characteristics between converters and non-converters that might have an impact on clinical outcomes. So we had to ask the question, are patients who convert to sputum culture negative inherently different from those that remain culture positive? Do they have less severe disease?

We look forward to receiving your input on the uncertainty regarding the microbiologic surrogate endpoint.

Now, to circle back to the phase 3 study 212

surrogate endpoint, during discussions related to the protocol, there was an expectation of supportive efficacy in a clinical outcome, namely the 6-minute walk test given the positive trend observed in the phase 2 study.

We note the data on the durability of sputum culture conversion 3 months after completion of MAC therapy and clinical outcomes are being collected in patients who continue in study 212. However, patients with persistent positive cultures discontinued study 212 with the option to enroll in study 312 to receive ALIS. Therefore, a comparative assessment of later clinical outcomes will be limited.

Now, for the discussion of efficacy data for ALIS. The clinical development program for ALIS, study 212 is the phase 3, open-label, randomized trial comparing ALIS plus an optimized background regimen, or OBR, versus OBR alone in patients with refractory MAC lung disease. FDA is using the term OBR, whereas the applicant's using the term MDR, but they mean the same thing, the background

regimen.

The primary endpoint was a surrogate endpoint of sputum culture conversion. Study 312 is an open-label, single-arm extension of study 212, where all subjects received ALIS plus OBR. It includes subjects who did not achieve culture conversion by month 6 or had a relapse or recurrence by month 6, and study 312 may provide supportive safety data. Study 112 was the phase 2, placebo-controlled trial and provides supportive safety and efficacy data.

Phase 3 study 212, this is the ongoing randomized, open-label study in adult subjects with refractory MAC lung disease. The data cutoff for this NDA submission was based on the date when the last subject completed their month 6 visit. The study includes 2 to 1 randomization to ALIS plus OBR versus OBR alone stratified on smoking status and also prior optimized background regimen screening whether they were on treatment or off treatment for at least 3 months.

This is a schematic of study 212. At

baseline, subjects were randomized in a 2 to 1 ratio to ALIS plus OBR or OBR alone. Subjects continued on therapy until month 8 when the culture results through month 6 were made available. If subjects experienced culture conversion, that is they had 3 consecutive negative sputum cultures by month 6, then they continued on study therapy for 12 months from the first negative sputum culture.

Durability of culture negativity is then assessed 3 months after the completion of the 12 months of study therapy. All non-converters or subjects that experienced a relapse or recurrence discontinued treatment in study 212 at month 8 and were given the option to enroll in the single-arm extension study 312.

Study 212 endpoints, as we've mentioned, the primary efficacy endpoint was culture conversion by month 6. A converter was defined as a subject who had negative sputum cultures for MAC for 3 consecutive months at any time within the first 6 months. The key secondary endpoint was changed from baseline at month 6 in the 6-minute walk test

distance.

This table displays subject disposition for study 212. A total of 336 subjects were randomized to treatment and comprised the intent-to-treat population. The safety consists of all but one subject randomized to the ALIS plus OBR arm who did not receive ALIS treatment. At the time of the initial analysis supporting the NDA, subjects could have completed treatment as defined in the protocol, discontinued treatment prematurely, or were still on treatment.

A subject was considered as having completed treatment as defined in the protocol if they, one, were a converter who successfully completed 12 months of their study treatment regimen from the first of 3 negative cultures used to define conversion; or two, were a non-converter who successfully completed all dosing and protocol requirements up to and including the month 6 study visit.

Approximately 20 percent of subjects were still on treatment at the time of data cutoff. Of

note, 4 times as many subjects randomized to ALIS plus OBR as compared with OBR alone discontinued treatment prematurely. The most common reason for discontinuing treatment prematurely in the ALIS plus OBR arm were adverse events and withdrawal by subject. In the OBR alone arm, the most common reason for discontinuing treatment was withdrawal by subject.

This table displays the demographic and baseline characteristics for study 212. As you can see, the mean age of subjects in both treatment arms was around 65. The majority of the subjects were female with a slightly higher proportion of females in the ALIS plus OBR arm. The majority of subjects were of white race, and approximately 60 percent of subjects were from outside the U.S. and 40 percent were from inside the US.

The majority, or actually 90 percent of subjects, in both arms were on an optimized background regimen at the time of screening, and approximately 90 percent of the subjects were not current smokers at the time of screening.

The results of the primary endpoint, culture conversion by month 6, are reported in this slide. Significantly more subjects achieved culture conversion by month 6 in the ALIS plus OBR arm, that is 29 percent, compared to the OBR alone arm at roughly 9 percent.

As a reminder, culture converters had 3 consecutive negative sputum cultures at any point during the first 6 months of the study. However, it was possible that after meeting this definition, a subject could have relapse or recurrence of MAC by month 6. Relapse or recurrence was defined as having at least one positive culture on solid media or greater than 2 consecutive monthly positive cultures on liquid media. Therefore, we performed a sensitivity analysis considering a subject who achieved culture conversion but then met the protocol definition of relapse or recurrence by month 6 as a failure.

Three subjects in each arm met the protocol definition of relapse or recurrence by month 6. Based on the sensitivity analysis, 27.7 percent of

subjects in the ALIS plus OBR arm compared to 6.3 percent of subjects in the OBR alone arm achieved culture conversion, and this result was also statistically significant.

This figure summarizes the cumulative proportion of subjects achieving culture conversion by month of first of 3 consecutive negative cultures that was needed to define culture conversion. Data are shown through month 4 since the first negative culture had to occur by month 4 for the subject to be considered as having achieved culture conversion by month 6. Note that approximately 5 percent of subjects in both arms had their first negative culture at the baseline visit.

The results of the 6-minute walk test distance are presented in this slide. The treatment difference in meters in the change from baseline to month 6 was assessed using an analysis of covariance model, or missing data for month 6 were imputed using a last post-baseline observation.

While this analysis differs from that presented by the applicant, the overall interpretation of the results are the same. No statistically significant difference was found between groups in the change from baseline to month 6. For both treatment groups, there was a decrease in distance walked from baseline to month 6, and the decrease in distance walked in the ALIS post-OBR group was numerically worse than that observed for the OBR alone group.

The applicant has presented the results for change from baseline to month 6 the 6-minute walk test distance based on converter status. This was prespecified in the protocol as an exploratory analysis. However, the division has concerns with this analysis since converter status is opposed to treatment classification. Our assessment is that the 6-minute walk test analyses, based on converter status, are not a direct comparison of the effect of treatment. We are interested in whether treatment with ALIS has an effect on 6-minute walk test distance.

This slide is a descriptive presentation of the mean change from baseline to month 6 by converter status for each treatment arm. Only subjects who had both baseline and month 6 6-minute walk test results are included in this analysis. As noted by the applicant, the mean change in 6-minute walk test distance is greater for subjects who converted compared with those who did not convert for each treatment group. And there was a mean increase in the distance walked for converters compared to a mean decrease or little change for non-converters.

As previously mentioned, we are interested in whether treatment with ALIS has an effect on 6-minute walk test distance, and that was not shown in the trial. Analysis by converter status cannot be fully understood since both converter status and 6-minute walk test distance our outcome variables. Though this analysis does look like converters have improved 6-minute walk test distance, ALIS was not able to show this benefit in the overall population despite having an increased proportion of

converters.

Now for the phase 2 study 112. Phase 2 study 112 was a randomized-controlled study in adult subjects with refractory NTM lung infections. It included a double-blind, placebo-controlled phase through day 84 followed by open-label extension phase for an additional 84 days. It included 1 to 2 randomization to ALIS plus OBR versus placebo that consisted of dilute liposomes plus OBR stratified by the presence or absence of cystic fibrosis and by the predominant NTM organism at baseline, which could have been MAC or M. abscessus. All subjects received ALIS plus OBR in the extension phase.

The primary efficacy endpoint for study 112 was changed from baseline on the semi-quantitative scale for mycobacterial culture at day 84, the secondary endpoint was negative culture at day 84, and the tertiary endpoint was changed from baseline in 6-minute walk test distance at day 84.

This slide displays subject disposition in the double-blind phase of study 112. A total of

90 subjects were randomized into the double-blind portion of the study. The modified intent to treat and safety population consisted of all but one subject randomized to the placebo arm who did not receive treatment.

Nine subjects, all in the ALIS plus OBR group discontinued treatment prematurely during the double-blind phase. Most discontinued treatment prematurely due to an adverse event.

Four subjects, all in the ALIS plus OBR group did not complete the double-blind phase. The reasons for discontinuing the study early included death, adverse event, withdrawal of consent, and lost to follow-up, one subject each. Of the 80 subjects who completed treatment, 78 went on to enroll in the open-label extension phase of the study, where approximately 24 percent of subjects did not complete treatment primarily because of adverse events.

This table displays the demographic and baseline characteristics of patients in study 112, which were generally similar across treatment arms.

The mean age of subjects was 58.5 years. Approximately 88 percent of subjects were female. The majority of the subjects were white. Approximately 19 percent of subjects had CF and two-thirds had predominantly MAC lung infection, though some could have been co-infected with other NTM.

Regarding the primary endpoint result for study 112, the change from baseline at day 84 on a semi-quantitative scale was not statistically significant between ALIS plus OBR versus OBR and placebo.

At day 84, a greater proportion of subjects in the ALIS plus OBR group, that is 31.8 percent, achieved a negative culture as compared with subjects in the placebo OBR group, which was about 8.9 percent. It should be noted that these results are slightly different than those presented by the applicant. In the applicant's presentation, 3 subjects in the ALIS arm with missing data at day 84 were excluded from the analysis.

In the analysis presented here, subjects

with missing data are treated as not having a negative culture. The results are also presented by strata. The results for the strata of subjects with MAC and absence of CF are generally similar to the results in the phase 3 study.

Six-minute walk test results for study 112 are summarized in this slide. Overall, subjects in the ALIS plus OBR group had a mean increase from baseline of 21 meters compared to a mean decrease of 25 meters in the placebo plus OBR group. This difference was statistically significant.

When looking at the strata of MAC and non-CF subjects, the population studied in phase 3 study 212, subjects in the ALIS plus OBR group had a mean increase from baseline of 16.3 meters compared to a mean decrease of 13.1 meters in the placebo plus OBR group.

These results led to the use of the 6-minute walk test as the clinical endpoint to be assessed in the phase 3 study 212. However, as previously discussed, similar results were not observed in phase 3 study 212.

Study 312, this is the ongoing, open-label extension of study 212,. The cutoff date for study 312 data in the current NDQA submission was the same as used for study 212. Subjects from study 212 who did not achieve culture conversion or experienced a relapse by month 6 had the option to enroll. All subjects received ALIS plus OBR.

The primary objective of study 312 was to evaluate the long-term safety of ALIS treatment up to 12 months. Secondary efficacy assessments were to include culture conversion and change in 6-minute walk test distance by 6 and 12 months. From the agency's perspective, study 312 provides limited safety and no comparative efficacy data.

Additionally, since this study is currently ongoing, and now all subjects have completed the month 6 visit by the time of data cutoff for the report, interpretation of the efficacy data is further limited and will not be presented at this time.

This slide provides the subject disposition for study 312. At the time of data cutoff, 15 to

20 percent of subjects had completed the study. Another 20 to 22 percent discontinued treatment prematurely, and approximately 60 percent were still on therapy. Of note, approximately 15 percent of subjects newly started on ALIS plus OBR in study 312, as those subjects previously on OBR alone in study 212, discontinued due to an adverse event.

Efficacy conclusions. In phase 3 study 212, significantly more subjects in the ALIS plus OBR arm achieved culture conversion by month 6 compared to the OBR alone arm in study 212. However, there was no difference in 6-minute walk test distance results at month 6.

Regarding the phase 2 study 112, it provides limited supportive efficacy information as a greater proportion of subjects in the ALIS plus OBR group achieved a negative culture at day 84 than subjects in the placebo plus OBR group. There was a trend in favor of the ALIS plus OBR group observed for 6-minute walk test distance at day 84. Thank you for your attention.

FDA Presentation - Hiwot Hiruy

DR. HIRUY: Good morning. My name is Hiwot Hiruy. I'll start the safety presentation with the overall exposure to ALIS, discuss the safety analysis methodology and go over the key safety results, including death; premature discontinuation; serious adverse events, which I refer to as SAEs during the presentation; treatment-emergent adverse events, TEAEs; and adverse events of interest, which will be referred to as AEIs, for the pivotal phase 3 study 212 and the phase 2, study 112. An abbreviated safety presentation of study 312, the single-arm extension study of -- extension of study 212 will also follow the presentation of study 212.

Additionally, analysis of hospitalization for study 212 will also be presented. I will conclude the safety presentation with salient summaries from the safety presentation.

Looking at the overall exposure to ALIS, there were 820 individuals exposed to ALIS. Eight hundred and two of these were exposed to multiple

doses of ALIS. 388 of the multidose exposures, so about 48 percent, occurred in patients with refractory nontuberculous mycobacteria NTM infection. The remaining 414 patients were patients with pulmonary pseudomonas infection. Most of them were CF patients.

Looking specifically at the refractory NTM population, the vast majority, about 91 percent, were non-CF patients with refractory mycobacterium avium complex, MAC disease. And the remaining 9 percent were comprised of non-CF patients predominantly infected with mycobacterium abscessus and patients with underlying CF.

There was heterogeneity in the doses, dosing regimen, and duration of exposure among the multidose exposures. ALIS dosing in studies of patients with pulmonary pseudomonas infection were cyclic, 28 days on and 28 days off, while all patients in the refractory NTM studies were dosed daily. Also, earlier studies in CF patients used dosing that ranged from 70 milligrams to 560 milligrams, while the latter studies, including

all three NTM studies, were conducted at the proposed dose of 590 milligrams.

All patients in the refractory NTM population were exposed to ALIS at the proposed dose of 590 milligrams and the proposed daily dosing regimen. However, the duration of exposure, even in the NTM population, varied from 3 months to 20 months.

For the safety analysis of ALIS, the refractory NTM population was considered the primary safety population. As previously mentioned, 91 percent of NTM population was comprised of non-CF refractory MAC infection.

Of note, there was significant difference in the design of the pivotal phase 3 study from the phase 2 study. Study 212 only included non-CF patients with refractory MAC infection, while study 112 had heterogeneous study population, which included CF patients and patients with refractory M. abscessus infection.

Study 212 also had an open-label, randomized design for the first 8 months that compared ALIS

added on to the optimized background regimen, OBR, and compared it to OBR-only arm. On the other hand, study 112 had an initial double-blind, placebo-controlled portion for the first 3 months that compared ALIS added on to OBR to OBR plus inhaled diluted empty liposomes as placebo.

Due to these differences in the patient population comparator arm and duration of treatment, safety data for the two studies will be presented separately. The safety result of study 312, the single-arm extension of study 212, will be briefly presented separately as well.

It should be noted that though the primary safety population was the refractory NTM population, safety data from patients who are exposed to multiple doses of ALIS, including patients with CF and non-CF bronchiectasis were reviewed as an integrated safety data set to look for low-frequency adverse events. The findings from the integrated safety data set showed similar adverse event profile as to what was seen in the refractory NTM population and will not be covered

in the presentation.

Adverse events of interest were identified based on adverse effects of aminoglycosides class of drugs that the active ingredient of ALIS amikacin belongs to, and based on the inhalation and route of administration, potential for ensuing local irritation and inflammation.

The AEIs, based on class effect, included pooled terms looking for clinical and laboratory indications of nephrotoxicity, clinical signs and symptoms of neuromuscular disorders, and clinical signs and symptoms of ototoxicity, both auditory and vestibular. Although the likelihood of these AEIs were deemed low given the local administration of amikacin, the safety data set was reviewed for these AEIs.

AEIs based on route of administration included allergic alveolitis, bronchospasm, cough, dysphonia, exacerbation of underlying lung disease, hemoptysis, pneumothorax, and upper airway irritation. Terms with asterisks are AEIs identified both by the applicant and the agency.

The agency has also added additional AEIs based on potential adverse effects of inhaled products.

Looking at mortality during development of ALIS, there were 32 deaths reported. All except one occurred in the three NTM studies. Since the design of study 112 and 212 offered ALIS treatment at the end of the randomized portion of the studies, mortality comparison between ALIS-treated versus comparator arm is limited to the randomized portion of study 112 and study 212.

There were 15 deaths during the randomized portion of these two studies, and looking at the ALIS-treated versus the comparator arm, there was no significant imbalance in mortality. About 13 deaths occurred in the single arm extension phases of the two studies and subsequent long-term follow-up period. Additional detail regarding the death during the randomized portion of study 212 and 112 will be discussed in the safety presentation of the respective studies.

We will now focus on the safety findings of the pivotal study 212, I know you've seen this

picture before, but I'm going to briefly review the design of the study 212 as it relates to the safety analysis. As mentioned in the previous presentation, study 212 patients were randomized to either ALIS plus OBR versus OBR-only arm and continued on their respective treatment until month 8.

Although the study design was to compare 6 months of treatment, since the results of month 6 sputum culture were only available at month 8 visit, patients in the study were continued on their respective treatment until month 8. After month 8, per the study protocol, non-converters and patients with relapse discontinued the study. Some were enrolled in the single arm, study 312.

In further communication with the applicant during the review process, the agency has learned that some safety data was collected in patients who discontinued, however the optimal comparative safety data from study 212 comes from the first 8 months of the study.

Looking at the baseline characteristics of

the safety population in study 212, overall, the two study arms were well matched for age, race, ethnicity, and region of enrollment. However, there were some imbalance with predominance of females in the ALIS plus OBR arm with 74 percent of participants being female in that arm compared to 61 percent in the OBR-only arm.

To gain further understanding of the study population, the agency reviewed the medical history of the participants reported at baseline. Approximately 90 percent in each study arm were on OBR treatment at time of enrollment. Close to 75 percent of patients in each study arm had a history of bronchiectasis.

Some differences were noted. There were more patients with a history of pulmonary resection in the ALIS arm, about 11 percent versus 5 percent in the OBR-only arm. There was also a slightly higher percentage of current smokers in the ALIS arm compared to the OBR arm.

Comorbidities reported at significantly higher percentage in the OBR arm included COPD;

33 percent in the OBR arm compared to 22 percent in the ALIS arm; pulmonary cavitation, 17 percent into OBR arm versus 12 percent in the ALIS arm; deafness, 30 percent in the OBR arm versus 21 percent in the ALIS arm; and dyspnea, 13 percent in the OBR-only arm versus 8 percent in the ALIS plus OBR arm.

The agency's definition of treatment-emergent adverse events differed from the applicant. The applicant defined TEAEs differently for the two study arms. For patients in the ALIS plus OBR arm, TEAEs were defined as adverse events that occurred between day 1 up to 28 days post the last dose of ALIS, while for the OBR-only arm, TEAEs were defined as all AEs that occurred between day 1 and end of treatment, which may be up to month 16. There was concern that this definition may potentially result in differential follow-up time for the two study arms.

In addition, there was also concern that the effect of ALIS may extend beyond 28 days post the last dose. Since the optimal comparative safety

data comes from the first 8 months, the agency defined treatment-emergent adverse events as AEs that occurred between day 1 and day 247, which is the month 8 visit.

Overall, there was no imbalance in mortality. Of the 17 deaths in study 212, 3 occurred prior to randomization and 14 occurred after first dose of the study drug. Looking at the death after study drug administration, 9 of the 14 deaths occurred in the ALIS-treated arm for 4 percent mortality in that arm compared to 5 deaths in the OBR-only arm for 4.5 percent mortality in the OBR-only arm. Of note, the sponsor classified three of the deaths in the ALIS plus OBR arm as non-TEAE based on their previously mentioned definition.

The table summarizes the demographics, timing, and cause of death for the 14 patients. Pulmonary events, respiratory failure, COPD, exacerbation, and pneumonia accounted for the majority of deaths in both arms. Note that 5 patients in the ALIS arm discontinued study drug

due to worsening clinical condition prior to their death. Patients in both arms have underlying comorbidities that may have contributed to their death. However, for patients that received ALIS, the contribution of ALIS to their death cannot be ruled out.

Looking at premature discontinuation, significantly more patients, about a third of the ALIS-treated patients, discontinued study treatment prematurely compared to 8 percent in the OBR-only arm that discontinued their OBR regimen. The main reason for discontinuation in the ALIS-treated patients were discontinuations due to adverse events, which accounted for 17.4 percent of patient discontinuation.

Looking further into the 39 discontinuations due to adverse events, 31 of the 39 discontinuations were due to AEs classified as adverse events of interest. Withdrawal by subject also occurred at higher frequency in the ALIS-treated arm compared to the OBR-only arm.

The graph on the slide illustrates timing of

adverse events occurrence in the study. Note that the red plots represent ALIS plus OBR arm, and the blue represents the OBR-only arm. The top graph shows the cumulative probability to the first treatment-emergent adverse event in the Y-axis and study day start of adverse events in the X-axis. The Y-axis at the bottom plot shows the number of patients at risk, which is defined as patients that have not had their first adverse event and have not discontinued from the study.

As you can see, the number at risk for day 1 starts with the total population for each arm, 223 in the ALIS-plus OBR arm and 112 in the OBR-only arm. The number at risk decreases as more patients experience their first TEAEs. Overall, the graphs show that there was a higher incidence of initial treatment-emergent adverse events reported in the ALIS plus OBR arm in the first few weeks after initiation of treatment. About 80 percent of the ALIS-treated patients experienced their first TEAEs within the first month while TEAEs accrued slowly for the OBR-only arm.

This table shows the serious adverse events experienced by more than one patient in the study. Overall, there was a slightly higher incidence of SAEs, and the ALIS plus OBR arm was 20 percent experiencing SAEs as compared to 16 percent of patients in the OBR-only arm. Most of the SAEs in both arms were related to respiratory system.

Serious adverse events of pneumonia, COPD exacerbation, allergic alveolitis, pneumothorax, respiratory failure, dyspnea, and anxiety occurred more frequently in the ALIS-treated arm as compared to the OBR-only arm. Hemoptysis, acute myocardial infarction, pulmonary cavitation, and MAC infection were reported at a higher rate in the OBR-only arm.

Looking at hospitalizations, which are a subset of serious adverse events, excluding unrelated and planned surgical admissions, there were 82 hospitalizations in 41 patients compared to 23 hospitalization in 15 patients. Of note, in both study arms, respiratory events were the main cause of hospitalization. About 60 percent of patients in each study arm experienced one

hospitalization, and the remaining 40 percent had multiple admissions with one extreme of 10 hospitalizations in the ALIS-treated arm.

Examples of respiratory admissions are presented in this table and include exacerbation of underlying pulmonary disease, lower respiratory tract infections, hemoptysis, respiratory failure, dyspnea, pneumothorax, and a couple of cases of Arikayce-induced pneumonitis in the ALIS-treated arm.

The next two slides summarize TEAEs that were experienced by more than 10 study participants. Overall, TEAEs were 4 times as frequent in ALIS-treated arm as compared to the OBR-only arm. Even after accounting for the 2 to 1 randomization, there was significantly higher frequency of TEAEs in the ALIS-treated arm.

Looking at the number of subjects that experienced at least 1 TEAE, it was comparable between the two arms. However, ALIS-treated patients tended to have more than one event compared to OBR-only arm. With the exception of

upper respiratory infection, infective exacerbation of bronchiectasis, and decreased appetite, all other TEAEs occurred more frequently in the ALIS-treated arm compared to OBR-only arm.

These TEAEs are presented in bold on the slide. The red box indicates TEAEs that were significantly higher in the ALIS-treated patients and include dysphonia, cough, dyspnea, and upper airway irritation. Tinnitus and wheezing also occurred at a higher frequency in the ALIS-treated patients compared to OBR-only arm.

The incidence of AEIs in the two study arms are summarized on this slide. With the exception of nephrotoxicity, there was higher incidence of all other AEIs in the ALIS-treated arm compared to OBR-only arm. There was considerably higher incidence of dysphonia, cough, bronchospasm, hemoptysis, ototoxicity, upper airway irritation and exacerbation of underlying lung disease.

Of note, the incidence of ototoxicity was driven mostly by the vestibular component with a higher incidence tinnitus in the ALIS-treated arm

compared to OBR-only arm. Most of the reports of AEIs were not classified as serious. However, there were more pneumonias, allergic alveolitis, and pneumothoraces that were classified as serious in the ALIS-treated arm.

Next, I will briefly present the safety findings in study 312. As mentioned in an earlier presentation, study 312 is the single-arm extension study 212. Participants were comprised of patients from either arm of study 212 that did not achieve culture conversion or had a relapse after 6 months of treatment.

These patients were offered 12 months of ALIS along with their OBR, and the study is ongoing since all participants in study 312 are receiving ALIS and the safety comparison is mainly looking at TEAEs occurring early in ALIS treatment versus longer use of ALIS.

There were 3 deaths in study 312, and all 3 deaths occurred in patients treated for longer than 7 months with ALIS in study 212 and were continuing on ALIS 312, as they did not culture

convert. All three had underlying comorbidities that may have contributed to their deaths. Two of the three had diagnosis of fungal infection, 1 scedosporium, and 1 pulmonary aspergillosis. Given the complexity of their medical condition, teasing out any contribution of ALIS is difficult.

There were similar rates of premature discontinuation with 20 percent of patients starting on ALIS discontinuing prematurely compared to 22 percent of those that were continued on ALIS. However, reason for premature discontinuation differed between the two groups. In patients that were initiated on ALIS, discontinuation due to adverse events accounted for the 11 of 15 discontinuations, while discontinuation due to withdrawal by subject and discontinuation due to lack of efficacy were the main reasons for discontinuation for patients that were continued on ALIS.

Both groups had approximately a 20 percent rate of SAEs reported. Respiratory SAEs were the most common in both arms. There was a

significantly higher proportion of TEAEs in those that were started on ALIS, about 93 percent experiencing TEAEs as compared to those continued on ALIS. Similar to the observation in study 212, the respiratory and infection system organ class accounted for the majority of the TEAEs.

The next two slides summarize the AEIs noted in study 312. Compared to patients continued on ALIS, patients getting initiated on ALIS therapy experienced significantly higher events of dysphonia, cough, bronchospasm, exacerbation of underlying disease, hemoptysis, upper airway irritation, and ototoxicity. This difference in AEIs may be reflecting that most patients that had AEIs in the main study, study 212, as a result of ALIS therapy may not have elected to continue on ALIS. And those that continued on ALIS were the ones that were able to better tolerate ALIS therapy.

Study 112 is the final NTM study to be discussed. Briefly, study 112 was the randomized, placebo-controlled, phase 2 study comparing ALIS

plus OBR to OBR plus placebo, which was inhaled diluted empty liposomes for the first 3 months of the study, followed by an additional 3 months of open-label treatment with ALIS for patients from either arm of the randomized study that elected to participate. There were also 28 days and 12 months off-treatment safety follow-up for a subset of the participants.

The safety presentation for the study would mainly focus on the first randomized 3 months, as that portion of the study had a comparative arm. Overall, there were 9 deaths during the study. Two additional deaths occurred off study. Of the 9 deaths, there was only one death in the ALIS plus OBR arm in the double-blind phase, and none in the OBR plus placebo arm.

The death in the ALIS arm was of a 64-year-old female with a history of bronchiectasis, with pulmonary exacerbation that progressively worsened. That patient died on day 91 of the study, about 13 days post the last dose of ALIS. There were 8 additional deaths

during the open label and 12-month follow-up phase. Due to the design of the study, all 8 patients that died had exposure to ALIS either in the double-blind phase or in the open-label phase.

Looking at premature discontinuation in the double-blind phase of study 112, about 9 patients, which is about 20 percent of patients in the ALIS arm, discontinued treatment prematurely. Seven of the 9 discontinuations were due to adverse events, and the infective exacerbation and dyspnea accounted for most of the discontinuations due to AE. All 4 patients that prematurely discontinued from the study were also in the ALIS-treated arm. Death, adverse events, and withdrawal by subject and loss to follow-up accounted for one discontinuation each.

Looking at SAEs in the double-blind phase of study 112, a significantly higher number of patients, about 18 percent in the ALIS-treated arm experienced SAEs as compared to 9 percent in the OBR plus placebo arm. Most of these SAEs were infection and infestation and respiratory in

nature.

The next two slides present TEAEs observed in study 112. Most study participants in both arms, 93 percent in ALIS-treated arm and 88 percent in the placebo arm, experienced at least one TEAE. Events in the red box highlight AEs that were significantly higher in the ALIS-treated arm. For example, 50 percent of ALIS-treated patients experienced exacerbation of underlying lung disease compared to 22 percent in the OBR plus placebo arm. The majority of these were infective exacerbations of bronchiectasis.

Similar to the previous observations in study 212, dysphonia, cough, upper airway irritation, wheezing, and dyspnea, occurred at a higher rate in ALIS-treated patients compared to the OBR plus placebo arm.

Looking at adverse events of interest, dysphonia, exacerbation of underlying lung disease, cough, upper airway irritation, bronchospasm, and ototoxicity had a higher incidence in the ALIS plus OBR arm compared to OBR plus placebo arm.

In conclusion, the safety analysis from the pivotal phase 3 study 212 showed that there was no imbalance in death between the ALIS-treated arm versus OBR-only arm. Frequency of SAEs was slightly higher in the ALIS plus OBR arm, about 20 percent compared to the OBR-only arm.

More ALIS plus OBR-treated patients discontinued treatment prematurely. More ALIS plus OBR-treated subjects discontinued treatment due to adverse event. With the exception of upper respiratory infection, infective, exacerbation of bronchiectasis, and decreased appetite, there was a higher incidence of all AEs reported by more than 10 patients in the study in the ALIS plus OBR arm. A significantly higher proportion of ALIS plus OBR arm experienced AEs, including dysphonia, cough, dyspnea, upper airway irritation, hemoptysis, and tinnitus.

Most AEIs were also more common in the ALIS plus OBR arm compared to the OBR-only arm. More ALIS-treated patients were hospitalized compared to those receiving OBR alone. And looking at the

safety summary from study 112 and 312, similar to the findings in study 212, safety data suggests that AEs related to respiratory tract and AEIs were more common in patients initiated on ALIS treatment. Even in study 112 where inhaled placebo, which was diluted and empty liposomes were employed, adverse events were more common in patients who received ALIS compared to inhaled placebo.

All three studies show that the highest at-risk time for TEAEs were the first 4 to 6 weeks after initiation of ALIS treatment. This concludes the safety presentation.

Clarifying Questions

DR. BADEN: Thank you very much, Dr. Hiruy.

We will now move to clarifying questions for the agency. Are there any clarifying questions? Please remember to state your name for the record before you speak. If you can please direct the questions to the specific presenter. Let myself and Dr. Tesh know. If you have a question, we'll try to build on themes where possible.

Dr. Green, you have the first question.

DR. M. GREEN: It's a two-part question. The first is very simple. In the placebo arm for 112 where they got the empty liposome, was that delivered with hypertonic saline or not?

DR. HIRUY: I believe it's normal saline, but the applicant may correct me.

DR. SULLIVAN: The placebo would have been delivered with the same diluent as ALIS.

DR. M. GREEN: So with hypertonic saline.

DR. SULLIVAN: With the same 1.5, not what's typically used hypertonic.

DR. M. GREEN: Okay, but you characterize that. I think it's just important because hypertonic saline has side effects. And in the 212 study, there's no placebo. So some of the side effects that we're seeing could be from the delivery route, the delivery of the saline as opposed to the drug itself. So just confirming that is very helpful and understanding what's drug associated versus what's the vehicle around the drug. Thanks.

DR. BADEN: Dr. Evans?

DR. EVANS: I just wanted to comment -- just to clarify, in addition to causing side effects, it actually may have antimicrobial effects, too, hypertonic saline, in terms of a big ciliary clearance and function of antimicrobial peptides and whatnot. So it may go both ways.

DR. BADEN: Dr. Proschan?

DR. PROSCHAN: Yes. This concerns the definition of a successful surrogate or whatever. I'm assuming that that wording comes from some regulatory, reasonably likely to predict clinical -- is that right?

DR. NAMBIAR: Yes, you're correct. This is Sumathi Nambiar. Yes, you're correct. That's how it's written in the regulation.

DR. PROSCHAN: I would argue that that's not what should you should be looking at. You should be looking at whether the change in the surrogate, the difference between the two arms in the surrogate predicts the difference between the two arms in, this case, the longer conversion -- it

really shouldn't be whether it predicts because you could have it predicts in both arms, but the relationship between the surrogate and the outcome you're really interested in might be different in the two arms.

Then you could have a situation where even though it's in the surrogate outcome and there's a benefit. There could be harm in the long-term outcome. So I would argue that that's not the right definition. That should not be the definition.

DR. BADEN: So you're getting at should the surrogate predict a salutary outcome.

DR. PROSCHAN: Yes. So what I'm saying is the criteria should be does the difference in arms between the surrogate predict the difference in arms of the outcome you're really --

DR. BADEN: Of some clinical benefit --

DR. PROSCHAN: Right.

DR. BADEN: -- meaningful benefit.

DR. PROSCHAN: Right, and that might not happen even though it predicts within each arm.

But there might be a different relationship between the two arms. There's a cancer paper. I think it's by Korn and Freedland, where they talk about that.

The other issue I guess -- well, it's not a clarifying question, so I'll stop there.

DR. BADEN: I don't know if the agency wants to comment. If not -- okay. Dr. Brittain?

DR. BRITTAIN: I'm trying to reconcile slide 30 that the FDA presented just now on the efficacy slides and CO-47 that we saw before from the sponsor. They give a very different impression. I can see there are some differences. The sponsor's looks like it's covariate adjusted. This looks like it's straight means.

One of the big differences is that there's 104 people in this one for the non-converter and the drug arm versus 159 on the sponsor's analogous slide. But the impression is so different. Here you see -- again, I want to first say I definitely agree that it's hard to interpret these sorts of data because it's classified by a post-baseline

stratum.

So that makes the interpretation challenging anyway. But on this slide, the non-converters in the drug arm seem to be quite different than the ones in the control arm, whereas you didn't get that impression at all in the corresponding sponsor's slide. So again, there's been a lot of differences, but I wanted to get your comment on that.

DR. BADEN: So we'll have the agency comment now, and the applicant can put this on the list of clarifications for the Q and A, subsequently.

DR. DIXON: Hi. This is Cheryl Dixon. I'm the statistical reviewer. The differences between these two slides, as our analysis is presented and the sponsor's, yes, as you know, ours is just based on a raw assessment of the means. And this was done primarily because, as we said, we didn't quite agree with the subgrouping based on an outcome measure. So I just wanted to give a descriptive presentation straightforward.

The analysis that was presented by the

sponsor is based on an analysis of covariance that did adjust for the baseline value as well as the randomized stratification factors.

One other point to note, in both analyses, including the one presented by the sponsor, it's just based on observed values. So their Ns are the actual Ns of who should have been converted and non-converted, but the numbers used in the analysis are the same numbers as our reporting in our slide.

DR. BRITTAIN: So I'm not sure I understood -- again, one of the very big differences in terms of sample size is the 104 here versus the 159 in the sponsor's. Do you understand why those are so different?

DR. DIXON: Right. Their analysis -- the 159 that you're reporting is the number of non-converters that were on the ALIS plus OBR arm alone. However, in the analysis that's presented by the sponsor, that negative 10.5 meters corresponds to only 98 subjects. And then there is a slight difference between ours and theirs in that we used -- the analysis used all available month-6

values regardless of whether the subjects were still on treatment.

DR. BRITTAIN: So it sounds like the primary difference is adjusted versus not.

DR. DIXON: Yes.

DR. BRITTAIN: Okay.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: I had a question for the FDA regarding the terminology of optimized background regimen. I had assumed that that wording had come from the sponsor, but it sounds like it's from FDA because the sponsor is using the term "multidrug regimen."

I just want to question the appropriateness of that labeling. In response to Dr. Green's question, it really looks like there is a great diversity of regimens across the patients in both arms. And it's not really clear to me if they were all under the care of an ID specialist or a pulmonologist with expertise and mycobacterial infections. And in addition, there was almost 20 percent of patients who were only on two drugs,

which is counter to the ATS/IDSA guidelines.

So I guess I'm just questioning the use of that word "optimize" and wondering how the terminology can help us interpret the difference between the two arms of the studies.

DR. HIRUY: So the reason we did not choose to use multidrug regimen was because we thought that it might be confused with multidrug resistance. So we wanted to use another terminology. As ID physicians, we just wanted to make sure that we're talking -- in terms of the choice of optimized, it's just that patients that were enrolled should have been following the guidelines, so must have at least two regimens and must be in compliance with what the ATS/IDSA guideline considers as treatment regimen.

DR. SCHAENMAN: Right. I guess this would be a question for the sponsor, then. I'm just not quite sure if that was true or not.

DR. KIM: This is Peter Kim. We also borrowed the phrase "optimized background regimen" from the TB literature as well, where it's used

just as the background regimen. I guess we could have called it background regimen. We're just trying to differentiate from MDR given MDR often means multidrug resistant.

DR. SCHAENMAN: I can appreciate that [inaudible - off mic].

DR. KIM: Thank you.

DR. BADEN: Dr. Weina, a follow-on?

DR. WEINA: Well, I was actually struck by that difference in terminology as well, and it caused me to kind of think a little bit about how individuals were randomized or brought into the study. The fact that this was refractory disease, were they just continued on the same failing regiment, and all we did was add another drug to a failing regiment? And then as a comparator, they were continued on a already failing regimen or was there an optimized background regimen that was added to this to try and improve their outcome?

So that becomes really critical here when we're talking about whether they just continued with their failing or not.

DR. KIM: This is Peter Kim again. Once again, I apologize for the phraseology and the connotation. We probably have to ask the sponsor for an additional explanation. But it did appear to us that subjects were continued on whatever regimen they had been on; that there is no change to what we call OBR or BR. Maybe we'll call it just BR for now, for background regimen. So they were on whatever they had been on.

DR. BADEN: So it is what's in the name. But the issue of at time zero when they're randomized to ALIS versus continued, as best as you can tell, very little was changed in the background regimen at time zero.

DR. KIM: This is Peter Kim. That's our understanding.

DR. BADEN: And we'll ask the applicant to clarify, subsequently.

Dr. Daskalakis?

DR. DASKALAKIS: A question that may have a follow-up question for the FDA. I thought it was really interesting in your review of the

literature, the distinction between a converter and a non-converter and how there may be some baseline differences in those converters.

Just thinking about this, the studies that include folks who are refractory, by including only refractory individuals, have you not already supplemented the study with people who are already in that non-converter framework?

DR. KIM: This is Peter Kim. That's a good question, although it looks like based on the baseline characteristics, it looks like about, if I recall correctly, about 10 percent of subjects, at least in the OBR arm, had cavitary disease. Additional people may comment, but it seems like -- once again, this comes down to the clinical phenotype.

So it appeared to us, based on the literature, that cavitary disease tended to be more difficult to treat and people tended to have a relapse of the infection, whereas those with nodular bronchiectatic disease, perhaps subjects characterized as those with what's been called the

Lady Windermere syndrome tended to kind of brew along and perhaps didn't necessarily need treatment right away. But then even when they were treated, there was a decent percentage, somewhere between 30 to 50 percent, which tended to get reinfected. That was our understanding based on literature.

DR. DASKALAKIS: My follow-up on that is -- and I think it's probably for both -- then wouldn't it be important to then -- I know it's small numbers, but try to stratify the analyses based on manifestation of mycobacterial disease as well as severity. And I ask that because doesn't that potentially also impact clearance versus non clearance and potentially adverse side effect versus no adverse side effect?

So if your baseline is bad, will you more likely have a bad respiratory outcome?

DR. KIM: Oh, go ahead.

DR. HIRUY: So as the applicant mentioned, not everybody had a CT scan at day 1. However, when we looked at the medical history, there were actually more patients with a history of cavitation

in the OBR-only arm compared to the ALIS arm. But I do agree that would have been helpful to distinguish the two and their different presentations.

DR. KIM: This is Peter Kim. May I add on to that?

DR. BADEN: Please.

DR.KIM: So I think you're getting at the heart of our question as well. Are there patients that are just inherently going to clear their sputum -- or more likely to clear their sputum than others? And whatever factors there might be that lead them to clearance, are they in some way -- do they in some way have less severe disease?

I don't know the answer to that, and we've been trying to figure that out, and it's a good question.

DR. BADEN: So there are at least three or four more follow-ons here. Dr. Proschan?

DR. PROSCHAN: I actually see this as a non-issue because you're asking whether it predicts longer term conversion. It's irrelevant whether it

predicts it by noting that people who convert early are different in other respects. The fact is it still predicts. So if you're really interested in just saying whether it predicts, then it really doesn't matter whether it's causing or not causing. As long as it predicts, that's what your criteria are.

So I would argue that it doesn't matter whether there are differences between converters and non-converters that could explain the differences. Conversion is still predicting whether you're going to have a durable conversion.

DR. BADEN: Dr. Kim has a response, and then Dr. Brittain.

DR. KIM: This is Peter Kim. I guess our question is what does that mean when they microbiologically convert? Does that mean an improvement in symptoms in patients? Does that mean an improvement in radiology?

Based on our read of the ATS/IDSA guidelines from 2007, it appears that you cannot necessarily rely on improvement in symptoms or improvement in

radiology, which then, once again, leads us to a microbiologic endpoint.

So I guess that's what we're trying to wrestle with, does a microbiologic surrogate endpoint result in improvement in how the patient feels, functions, or survives. That's what we want to know. And I don't know that we know the answer, and that's why we tried searching the literature.

When we first got this project, we were like, all right, this is going to be great because there's a clear difference. Right? And then we started looking at the guidelines, both the ATS/IDSA guidelines and the British Thoracic Society guidelines, and then references listed in those guidelines. And we started to realize that this advice might not necessarily be based on an improvement on how the patient feels, functions, or survives.

Perhaps the experts on the applicant side can clarify because a number of them are involved with the guidelines writing. But it really seems to us we're still wrestling with a final

confirmatory endpoint that shows that the patients are somehow improving in how they feel, they function, or survive. And maybe at the end of the day when that final analysis occurs 12 months off therapy in study 212, maybe we'll see something. But we are concerned that at that time point, we're going to have very few patients on randomized groups.

DR. BADEN: Dr. Cox, do you have a comment?

DR. COX: Yes, just to add to what Dr. Kim is saying. This is a very important point. What we're trying to understand is the relationship between sputum culture conversion and clinical benefit. So are the patients better off, which is getting to the feels, functions, or survives.

One of the reasons that we think this is a key issue is if we look at the trial results, we look at the sputum culture conversion rates, and then we also look at some of the other endpoints, the St. George's Respiratory Questionnaire, the quality of life assessment, the 6-minute walk test, ideally maybe we haven't looked long enough out;

there are some other questions. But the real question is are the patients better off? Are they clinically benefiting from this? And how do you get at that? How do you understand that from the available information?

Does that help, Mike? Which is a little bit different than I think --

DR. PROSCHAN: No, it actually doesn't because --

DR. COX: -- which is different than early and late.

DR. PROSCHAN: Okay. So I agree that that's a different question and my point doesn't address that. My point is simply that the fact that there might be differences between converters and non-converters is irrelevant. If conversion is predicting what you're really after -- and you're saying maybe it doesn't because maybe you're not interested in 3 months after finishing treatment; you're interested in something else.

But all I'm saying is if conversion predicts the outcome that you're really interested in, then

it doesn't matter whether there are differences between converters and non-converters. It doesn't matter whether that's why it's predicting it or whether there's some other reason that it's predicting it. It's still predicting it.

So I take your point that maybe you're not interested in conversion following 3 months after discontinuation of treatment, but I don't think that affects my point that it doesn't really matter whether converters are different from non-converters and whether that explains why it's predictive.

DR. BADEN: I think it sounds like you're starting on the foundation that conversion is predicting clinical benefit already.

DR. PROSCHAN: No. I --

DR. BADEN: I think, if I hear you correctly, is that conversion, if you use that as the endpoint, then that allows randomization to be applied. If you're then subsequently stratifying conversion, you have now mitigated the randomization element, and that then impacts other

conclusions drawn, based upon a post-randomization event.

DR. PROSCHAN: Of course. This is all based on post-randomization because you're looking at converters and non-converters.

DR. BADEN: So your point is that randomization to conversion is a solid observation because it's based on randomization.

DR. PROSCHAN: No, no, no. What I'm saying is it does not matter. If you're interested in whether this short-term outcome, 6-month outcome, predicts the outcome of real interest, it doesn't matter why it predicts it. It doesn't matter that there are differences between converters and non-converters. The fact is if this predicting what you're interested in long term, then that's what you care about. And it doesn't matter whether that's because converters are older or whatever, it's still predicting the long-term outcome if it is indeed predicting it. You could argue about whether it is.

DR. BADEN: Of conversion, but not

necessarily the functional outcome predicated on conversion.

DR. PROSCHAN: No. I'm saying if it predicts the outcome that's of real interest, whatever that is, whether it's after 3 months discontinuing or whatever, whatever the real outcome is, I'm just saying it doesn't matter why it predicts it. If it does predict it, then it doesn't matter that there are differences between converters and non-converters.

DR. BADEN: Dr. Cox?

DR. COX: So what we're trying to predict here is clinical benefit, which is generally looked at as the patient feels better, functions better, or survives longer. So when we talk about predicting clinical benefit, that's what we're trying to get at, and that's what we're asking for the committee. It's in essence one of our questions. So we're asking folks to think about that and weigh in on it.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: I don't know if I have

anything to add now. I do think, again, it seems like the question of whether the initial culture conversion is going to predict the subsequent one is pretty straightforward. I think we already have the answer, actually.

Really, the heart of the question appears to be what is the clinical outcome at the long term, and we don't have a randomized comparison for that. And that's the essence of the problem I see.

DR. PROSCHAN: That is a great point; not saying the other points weren't great, too.

(Laughter.)

DR. PROSCHAN: But by definition, the way they collected the data, they are definitely going to see a relationship between the short-term and the long-term outcome because they said in order to have this long-term thing, you have to first get the short-term benefit. So by definition, you're going to induce a correlation between those two.

I think your point is excellent that if they had -- I think that was a big mistake on their part. I think they should have looked at that post

3-month outcome in everyone, not just the people who had the short-term benefit.

DR. BADEN: We have several more follow-ons on this theme. Dr. Green?

DR. M. GREEN: I just wanted to clarify that while there appears to be a mathematical difference between the number of patients with cavitation between the two groups, it's important to note that the variable right before that is resection, and it bounced in the opposite direction. And probably why they got resected is because they had cavitation.

So to my eye, it looks like those two are pretty similar, about 22 percent in the ALIS plus OBR to 25 percent in the other group, and the numbers are smaller. So when you start thinking that maybe the populations are different because one has a greater risk of cavitation than the other, it's balanced, I think, by the fact that they needed resection and understanding what drives resection, typically, I think in this population. Although I'm a pediatrician, so maybe I shouldn't

comment on that.

DR. BADEN: Dr. Kim?

DR. KIM: This is Peter Kim. I guess the other question, then, if you bring up the issue of cavitation, then the other issue is why weren't necessarily the people on the background regimen resected as well? I don't know the answer to that.

DR. M. GREEN: I think those are treatment decisions by practicing physicians prior to entry in the study of how they were managed. If it's not an exclusion, if they don't say if you've had a resection, you can't be in study, that's probably why they took comers who were eligible, and they documented the data.

DR. BADEN: Mr. Hawkins, still staying on this theme.

MR. HAWKINS: I just was curious with respect to whether the NTM should be treated at all with background regimen or is it worth treating the recalcitrant patients with this new drug? You're not sure if it's worth treating MAC at all or only are you not sure if it's worth treating MAC in

these patients who have already failed for a year of treatment?

DR. KIM: This is Peter Kim. Just to clarify, you're asking specifically about the use of ALIS in a broad population of NTM or MAC patients versus treatment in a limited population of those with refractory MAC? Is that what you're asking?

MR. HAWKINS: No, more -- you're not sure whether sputum conversion is worthwhile. But isn't that the goal of the whole year that they were on the OBR achievement in general? And ALIS is being used in these recalcitrant patients now. So are you speculating whether it's worth converting anyone to no NTM or are you speculating whether it's worth trying to get this recalcitrant group to go to zero?

DR. COX: So let me just try and reframe the question a little bit. I think what we're asking is what's the information that tells us about sputum culture conversion, and then what subsequently happens to the patient. Does the

patient do better? Does the patient not do better? Does the patient do worse?

So we're looking at what's available to us from -- and that's why Dr. Kim reviewed the literature. What can we learn from literature? What do the trials tell us? And you can look at -- and that's why I mentioned some of the clinical outcomes that are measured in the trial versus the sputum culture conversion endpoint, because, really, I think what everybody wants here is to be able to find and identify a treatment that will provide benefits to patients. The patients will feel better, they'll function better, and they'll survive longer.

So the question is, really, what's the relationship of what we've observed as far as the treatment effect in this study compared to what it is that we want to do here? Which is to benefit patients. So it's not really speculating. It's more just trying to figure out what we can tell and what we can learn from the available information.

Does that help some with your question?

MR. HAWKINS: I think so. So there's the assumption that NTMs cause adverse effects in patients, and the desire is to get rid of it. But with this small group of patients that fail treatment, can we do better. Is that --

DR. COX: Right. And is the treatment effect having an effect, and what is that effect? We see the effect on sputum culture conversion. Does that translate into clinical benefit for patients, based on some other information that we have? And if so, what is that information and what's the expectation, et cetera?

DR. BADEN: Along those lines, and one of the arguments put forward by the applicant, is by causing culture conversion with treatment, you actually can stop treatment. So there is less NTM treatment, subsequently, because you have converted the culture to negative.

I'm interested in your thoughts as to the value of that because I'm not sure it's feels, functions, or survives, but there is a change in the sociologic practice in how we treat these

patients that was put forward.

DR. COX: Is that a question for me?

DR. BADEN: No, it's a question just to the agency in general; not to you, Dr. Cox. But that's put forward as a benefit. A benefit is culture turns negative; these patients get less treatment.

DR. COX: Right. I think maybe at the heart of this is really, what is the benefit of treatment? And I think once you can figure out what you're going to establish the benefit of treatment is, I think you're in a much better position to be able to answer these questions. Because if therapy is highly beneficial, then it would offset the adverse effects of the treatment, et cetera. But if the value of the treatment is unknown, then simply stopping the value of an unknown treatment is a less beneficial situation.

So that's why I think you really do need the information to understand what the benefit of the treatment is in order to be able to understand how you're weighing things here.

DR. BADEN: Agreed.

There are still at least three more follow-ons from Dr. Honegger, Daskalakis, and Weina. Dr. Honegger?

Dr. Honegger, a follow-on?

DR. HONEGGER: I was just getting to the point of the question of is it necessary to look for these covariates that predict culture conversion. And I think the value is that we don't have efficacy data to support it, and we're just trying to understand that. I realize if we had clean functional efficacy data, then of course it's not necessary to understand all the covariates. But when you don't have that, it's nice to have some explanation. So looking at covariates might be reassuring.

DR. BADEN: Dr. Lo Re?

DR. LO RE: Just to go on with Dr. Honegger, the other issue is that if these variables that you're talking about are effect modifiers, and that the effect of the drug is different in different groups, and the magnitude of the effect is different, knowing what those variables are such

cavitation that was mentioned before, Lady Windermere versus not, would be very valuable at the outset.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: Just a conceptual question. So I know that we're looking at this drug potentially for accelerated approval, but it seems as if knowing what the long-term follow-up of 212 would be is important. So is there a reason why we're having the conversation before we have that long-term follow-up?

DR. BADEN: Dr. Nambiar?

DR. NAMBIAR: Let me try. The purpose of this application was really for a subpart H approval because there is an unmet need that's addressing a serious disease, based on the surrogate endpoint if adequate evidence had been provided.

Now, the design of the study is such that this particular study in its long term will not address the question of does the surrogate endpoint really translate into the clinical benefit. So

both for questions 2 and 3, we are seeking the committee's input on what might the design of the long-term study look like, which can confirm the clinical benefit should one make -- I mean, with the underlying assumption that the surrogate endpoint is reasonably likely to predict clinical benefit.

DR. BADEN: Dr. Weina?

DR. WEINA: I'm just maybe trying to understand the question and frame it a little different, and see if I'm kind of on track or not. This would be really easy if we had 90 percent of people who were converters, and then in the other arm it was 10 percent. But basically we have 70 percent of people that are failing. They're just not converting.

MALE VOICE: It's better than 90 [off mic].

DR. WEINA: So if 70 percent -- yes, and it is better than 90, marginally, but it's better.

So the question then becomes what we're really looking at by looking at converters is, quote/unquote, "eradicating the organism and having

a micro biologic cure." But if we have eradication of the organism and microbiologic cure, we would expect the symptom benefit, the functional benefit, the decreased mortality and everything else.

Since we're not seeing the functional benefit, is it therefore reasonable to assume that the spirometry, the 6-minute walk test, symptoms not improving, all of that means that we haven't actually eradicated the organism or truly gotten microbiologic cure. We're just sampling it wrong? We're just not picking up destruction that is still continuing to take place.

DR. NAMBIAR: I suppose those are all the uncertainties and making the link between microbiologic eradication or sputum culture conversion and a final clinical outcome. By eradicating the organism or not having it in three consecutive cultures, does that necessarily affect the disease process? Does the disease process, which is underlying in a lot of patients who have NTM, does that continue on its course, or does one actually have an effect on the progression of the

disease?

As we had mentioned, in study 112, there was a trend towards a clinical benefit, which went along with this benefit in a microbiologic endpoint.

DR. WEINA: In a very small group of individuals.

DR. NAMBIAR: In study 112, if you look at it, it was at an earlier time point. It was at day 84. So our hope was the second study, which was done, which went longer because the assessment was really at 6 months, that the effect seen on the microbiologic endpoint, there would be some correlation.

We agreed it was not powered for a finding on the 6-minute walk test, and that wasn't the expectation. But a trend in the right direction, some benefit on patient-reported outcomes, that then I think would in some way balance some of the uncertainties that one has with the surrogate endpoint really reasonably likely to predict clinical benefit, and that's why we are here

seeking your input.

DR. BADEN: So if I hear you correctly, it's not that the NTM is driving the bronchiectasis, but perhaps the bronchiectasis is facilitating the NTM. And they're having a negative co-interaction, but the NTM may not be the primary driver.

DR. NAMBIAR: I wouldn't claim to be an NTM expert, but my reading of the literature is I think it's very hard to really separate out the two that distinctly. I think it certainly seems like there might be a patient population that has structural disease and are inherently more susceptible to developing NTM disease. But I think it's hard to say that there's no evidence to support that NTM can make the underlying condition worse.

So I think it's a bit of both, but you have the NTM experts in the room, and maybe they can help answer that question.

DR. BADEN: The hour is late. Lunch is upon us. It is 12:37. We'll now break for lunch. There are many more questions both for the agency and the applicant, which we will continue after

lunch, after the open public hearing session.

We'll reconvene in this room at 1:30. Please take any personal belongings that you may want. Committee members, please remember there should be no discussion of the meeting during lunch amongst yourself, the press, or any other member of the audience. Thank you. See you at 1:30.

(Whereupon, at 12:38 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

Open Public Hearing

DR. BADEN: It is 1:30, and we have a full agenda still to work our way through. We'll now resume with the open public hearing element of the presentations.

Both the FDA and the public believe in transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes 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, the 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 this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their considerations of the issues before them.

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

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and

any organization you're representing for the record.

MS. LEITMAN: Good afternoon, and thank you for the opportunity to address the committee. I'm Amy Leitman, the director of policy and advocacy for NTM Info and Research, a nonprofit patient advocacy organization for those with pulmonary nontuberculous mycobacterial disease. Our constituency includes patients, their caregivers and families, and the physicians and researchers who work tirelessly to help them.

Insmed has supported our organization financially, but I have no financial interest in the company, nor have I received any compensation for my appearance today.

In October 2015, the FDA convened a patient-focused drug development meeting on pulmonary NTM disease, which more than 100 people attended in person and online. Before, during, and after the meeting, we gathered comments from patients about their experiences with burden of illness and what they would like to see in the

development of treatments for their disease.

These comments reflected a deep desire for treatments that focus on treating the infection where it is and which are not as toxic to the rest of the body. These comments also correspond with patient feedback as defined by the FDA in its recent draft guidance as patient-experienced data and patient-focused drug development.

It's important to understand the toll this disease takes on patients and their loved ones. Patients miss out on the occasions and the lives of the people they care about most, not just the milestones, but the little moments in life they cannot participate in because their illness and their treatments make them feel so bad. The costs is too high to count.

Amikacin does treat NTM effectively. The bigger problem for patients has been tolerability, with side effects ranging from tinnitus, to vision and hearing loss, to loss of kidney and liver function. Patients must weigh the desire to survive their illness against the burden of

suffering permanent harms of treatment, and no patient should have to make that choice.

It is one, however, that my step-mom Fern faced. After 18 years of treatment for NTM, which included tens of thousands of doses of IV medication, some of it amikacin, her kidneys failed. Faced with the significant loss of her quality of life, she could not continue. She passed away in October 2014, one year and 2 days before the very meeting that would definitively bring our patients' collective voices to the foreground of the fight against this disease.

It is a choice faced by one of the patients who spoke at that meeting. Mary called us earlier this year to let us know that her treatments were no longer working and there were no other treatment options for her to try. So she had decided not to continue. Mary was a remarkable woman. We were blessed to know her and spend time with her. Last month, we were notified of her passing.

It is a decision that Bill could not face. Bill was one of our support group leaders, and last

year in despair over his illness and the side effects of his treatment, he took his own life.

These three people we have loved and lost are just the tip of the iceberg. There are so many others. The cost is too high to count. Every time this disease takes a patient, it feels like a personal loss. Each one is like losing a battle in an ongoing war, and finally having an approved treatment for NTM lung disease would be a win that can turn the tide, ushering in hope, and sparking more interest in developing better treatments for these patients whose needs are so great and whose options remain so limited and so challenging.

Right now, there are tens of thousands of people with NTM lung disease, and they have been waiting on the edge of hope for years. Inhaled liposomal amikacin is not the answer to every pulmonary NTM infection; we understand this. But this disease requires multiple drugs to treat it, and until now, none of them had undergone clinical trials. That has finally changed, and that can change everything.

Liposomal medication takes advantage of a technology that has been around for decades, and Insmed has harnessed it to create a safer, more effective version of a previous off-label treatment that has been used for decades to treat NTM lung infections. In doing so, they have also accomplished something that we have long wished for, rigorous testing in a clinical trial to demonstrate that which has been understood for so long by clinicians. Amikacin does treat NTM effectively.

As we've heard today, inhaled liposomal amikacin has demonstrated safety and efficacy in treating MAC lung infections, and patients should be given the opportunity to use it. It is the first step forward in what will surely be a long march to developing more effective treatments for NTM lung disease, but that first step must be taken if we're ever going to make progress. We must start making that progress right now, or we will continue to suffer so many more losses, and so many more people will continue to suffer.

On behalf of Fern and Mary and Bill, on behalf of all the patients, their families and friends, on behalf of the dedicated providers and researchers trying to help them, I urge you to approve this drug. Without it, the cost will be too high to count. Thank you.

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.

DR. RUOSS: Hi there. My name is Stephen Ross, and I am a pulmonologist and a faculty member at Stanford University in the school of medicine. Thanks for the opportunity to talk. For disclosure, my travel is supported here today, but I'm not compensated for my time at this meeting.

A brief outline on a patient. I recently had a call from a patient who I've cared for, for many years, for his mycobacterial infection and with bronchiectasis and cavitary disease. And the conversation wasn't abstract; the conversation was about his medical problems. As he's a physician

now retired due to his pulmonary diseases, he was of course very familiar with the limits of therapies and the risks that a life might be cut short by progressive disease.

We talked on about his worsening status with his unrelenting infection despite many therapies, his progression of symptoms due to his bronchiectasis and cavitary disease. And it was his hope that there might be a future state where better therapies would be available and used. And this marks one week from his death due to his unrelenting infection and his unrelenting disease.

So this isn't a rare circumstance. As we've heard, infections can be persistent. They can be lethal. The prevalence, as we've heard even today, is of course increasing for these mycobacterial diseases. We certainly need better antibiotics.

As director of our large and, unfortunately, growing and flourishing NTM and bronchiectasis program at Stanford, I've gained an increasing appreciation for the complexities present in these diseases. And with this perspective, I'd like to

share some important points that may not be fully appreciated by those who are actually not caring for these patients.

First, it wasn't random sequence that I described our program as being for bronchiectasis and NTM infections. While the question today before the panel is a question specifically on a drug for NTM infection, it's critically important that we all appreciate that these patients are typically grappling with two distinct diseases. They have their underlying bronchiectasis and they have an NTM infection. Please recall that these are two diseases. They don't overlap perfectly.

There are some important clinical circumstances that are associated with that. Bronchiectasis is an almost universal companion disease in patients with NTM infection. Bronchiectasis involves chronic, progressive, and non-reversible airways injury. The central features of bronchiectasis include cough, sputum production, symptomatic airflow obstruction, and the notable risk for infections not necessarily

limited to NTM. The symptoms of bronchiectasis are typically the most common and limiting circumstances for these patients.

Repeated infections, very importantly, including NTM, drive progressive injury of airways disease and result in worsening pulmonary function and symptoms. So controlling infections is a key feature in management of these patients. There's a big and huge catch here, which is that eradication of active infection with NTM does not often or always markedly alter patients symptoms circumstance.

Successful antibiotic treatment can improve some things for patients. Cough can be reduced, sputum production can be less, fatigue and weight loss can improve, activity levels can improve, pulmonary function can improve but not always and not for a consistent set of these clinical features. Thus, clinical features common to bronchiectasis are a rather unreliable marker of antibiotic therapy success in pulmonary NTM infection.

We do, however, have a good test. It is serial cultures. That can measure success of an antibiotic treatment regimen. Cultures remain our best clinical test. To rely on clinical parameters that assess symptomatic bronchiectasis will not be a valid guide to best measure of NTM therapy success.

As I commonly say to patients, as we discuss their possible antibiotic treatment, I hope I can clear your infection so you won't have worsening pulmonary symptoms, but you shouldn't think that you're clearing of infection will make your bronchiectasis symptoms go away completely. I want to clear the infection because I want to stop progression.

In conclusion, as a program director committed to this field and as a site investigator in the Insmed ALIS trials, it's my strong recommendation that you view culture data as the primary and most reliable measure of treatment success of ALIS for NTM infection, using bronchiectasis clinical monitoring as a primary

measure of antibiotic effect or risk creating unnecessary uncertainty. Thanks.

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. PHILLEY: My name is Julie Philly. I'm a pulmonologist and critical care physician at the University of Texas Health Science Center at Tyler and a specialist in nontuberculous mycobacterial lung disease. I want to thank each of you for the opportunity to be here today to witness this process and to read a concise statement of my personal thoughts about this drug and about the sponsor.

I want you to know that I requested to attend this meeting, and it's important that I convey the following message for myself, my colleagues, and the patients that I treat, and that I accept no compensation for my time to do such.

Choosing to become a specialist in NTM lung disease was not a lifelong calling or a dream I had

that has become the greatest focus of my efforts and career. It is the definition of a chronic disease state with the need for multiple antibiotics fraught with multiple side effects.

As you've seen today, the majority of available evidence has been from retrospective data based on small trials, from small regions of the country, published by small groups of physicians that have been advocating for multicenter, randomized-controlled trials for many years.

The trial design discussed today was the product of multiple collaborative efforts, specifically guidance from the FDA and from thought leaders from North America and from around the world. I want to say that I was actually shocked the sponsor chose adding this drug to refractory patients, and from what was mentioned today, to a failing regimen was chosen. But I was more shocked that 30 percent of patients, nearly 30 percent of patients converted their sputum.

If you are a specialist in this disease field, your response is, Hallelujah! This is

great! Thank goodness! I also wanted to point out that the dysphonia, and the cough, and the bronchospasm do not compare to renal failure, or blindness, or many of the other diseases and side effects that we see with the other drugs that we use to treat.

While there are no easy answers to study this drug, sputum conversion within 6 months in refractory patients is not an easy goal to achieve. While the debate continues about endpoints, I do want to point out that sputum conversion is the endpoint in the ATS guidelines that we currently follow in this country.

I have used this drug in this steady compassionately for the sickest of the sick and have had treatment success defined not only by sputum conversion, walk test, and other objective measures, but importantly through the eyes of the patient experience, which I recognize and treat every day. And when I place patients on 3 to 5 drugs, the first question they do ask me is when can come off? Sputum conversion does matter

emotionally, spiritually, socially; emotionally and financially, which are things that will always be difficult to measure, and yet this is the practice in the art of medicine.

While I don't have the words to adequately convey my message today, and I know that, I hope that you will not deny the honesty or the sincerity of my intention. This drug has a place for our patients, and this trial represents a pivotal step for the study of nontuberculous mycobacterial lung infection, and I'm grateful for your time and attention.

DR. BADEN: Thank you. 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.

MR. LEITMAN: Good afternoon. My name is Philip Leitman, and I am the co-founder and president of NTM Info and Research. You heard from my daughter a few moments ago. We're a patient advocacy group for those who suffer with NTM lung disease. I am a volunteer. I receive no personal

benefit for my appearance here today. Thank you for the opportunity to speak to you.

Today, August 7, 2018, is one of the most important days in history of NTM lung disease. I'm here today to speak for my wife, Fern, who started a movement with NTM Info and Research and who cannot speak because she has passed away. During the course of Fern's 18-year battle, at various times she used the majority of drugs that the doctors here have used on patients or to help patients with refractory NTM.

In 18 years of treatment, she never had a culture conversion, but she did live for 18 years. She saw her children graduate college and our grandchildren born. But she didn't have a negative culture. She had a positive life. She had more than -- ad this is correct -- more than 26,000 doses of intravenous medication, and that kept her alive. In the end, Fern died from kidney failure because she didn't have the options that we're hoping will be available after today and in the future.

Many years ago, prior to Insmed's work, Fern and I heard about liposomal formulations and the possibilities with amikacin. It was before Insmed existed. It was before anybody was working with it. It made sense to us. It was exciting to us. The one benefit that stands out with inhaled medication is that it does less systemic damage, and it works.

While I know this committee is to look at specific results from the trial, I share with you my personal family experience, knowing that no treatment has benign and not treating when treatment is needed is worse. Over the course of that 18 years, we knew a number of patients who said I don't want to tolerate any side effects. It was probably a dozen people that we knew personally. Each of them died.

It is my belief, based on our direct experience with various treatments and what we have heard today from clinicians, researchers, and through information that we have gathered by attending meetings, that if inhaled liposomal

amikacin had been available 20 years ago, my wife Fern would be alive today.

There are patients in this room and there are others who are listening and watching who deserve a chance to improve their lives, to live, and to have a treatment that I believe is less toxic and will work for them in ways that no other treatment can at this time. Treating an NTM lung infection is a marathon. It's not a sprint. We know that. Treatments are long and arduous. Bronchiectasis plays a role as does airway clearance. So patients suffer from the symptoms of illness and also some side effects from the treatment.

What's in front of you is a potential treatment with fewer side effects and a major benefit, better treatment, fewer side effects, and hope. If we can do one thing to make the course of treatment for these patients better, it is approving this drug, and I urge you to do so. Today is about our responsibility as family members, patients, professionals, to speak up, to

urge you to make this treatment available because it has the potential to extend, improve, and change lives in a way that has not been available before.

When I look back, I do not have regrets because of who I was married to, but if we succeed today, we will ensure that others have the help that Fern and I so long wanted for her and for everyone else. Thank you.

DR. BADEN: Thank you. 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.

DR. KARDACHI: Hello. My name is Julie Kardachi. I'm 59 years old, and I live in New York City. I'm a doctor of occupational therapy and an associate professor of occupational therapy at Touro College, School of Health Science. Insmed supported my travel here today, but I'm not being compensated for my time.

I was diagnosed with MAC in April 2010 after a routine medical for a volunteer position at Mount Sinai Hospital, where I was planning to teach a

fall prevention and strengthening program for community-dwelling older adults, a program I co-developed. At that time, my colleague and I already taught the program in several sites in New York City, and I was also teaching occupational therapy full time and working one day a week in the rehab department at the NYU Langone and Rusk Rehabilitation Center.

Part of the medical screening process for the Mount Sinai volunteer position was a chest x-ray after a positive tuberculous skin test result due to my having been vaccinated for TB during my childhood in Australia. The chest x-ray revealed bronchiectasis. Subsequent bronchoscopy testing to find out why the chest x-ray showed bronchiectasis revealed MAC. Unlike many others with this disease, I had no symptoms, was not sick, and it did not take several years to find out what the problem was.

I started on a MAC all-antibiotic cocktail of rifampin, ethambutol, clarithromycin, and then azithromycin in June 2010. Taking that all

cocktail, while necessary and possibly life-saving, was expensive and very challenging to my body. Those heavy antibiotics have serious side effects, including hearing and vision damage, which required further specialist referrals, visits, and testing to monitor any changes to my vision and hearing. Those additional doctor visits took a toll on both my energy levels and my finances.

In addition, those drugs had less long term but equally difficult side effects for me: bowel urgency and frequency; nausea; yeast infections; and made me feel generally unwell and fatigued most of the time. I did what I could to maintain my health during those 4 years with vitamins and probiotics and other measures to support my system, and that was also very costly.

I took these drugs daily for 4 years with no change in my positive cultures until I participated in the Arikace trial. I continued working full time as a college professor while on the antibiotic regimen and am fortunate to work in a department that gave me additional support, especially for

very active classes that I could not manage on my own.

For example, teaching students how to lift and move patients is very hard to do with reduced energy and shortness of breath. But I did give up my clinical position at the rehabilitation department and greatly reduced my involvement with the fall prevention program due to my lower energy levels and multiple doctor appointments. So there was an impact on my income through giving up my clinical job and on my community involvement and service.

I'm very fortunate to have an extremely supportive husband and understanding friends and colleagues who accepted my need to sometimes cancel or cut short engagements due to feeling unwell or lacking energy. I ran out of gas very suddenly in those days and often had to take extra time resting at home while on vacation and traveling. I joined the Arikace study in 2012 and received my first negative culture as a result at the end of the trial, the first since my diagnosis.

So what does it mean to me to have a negative culture conversion? For the first time since my diagnosis, I was given the chance to improve my health, especially after I stopped all those medications. In the years since, I've built up an exercise regimen, and now I consistently work out, which has greatly improved my strength and endurance. Whereas previously I had to stop and rest frequently during walks and other activities, I can now do that without stopping. On even the steamiest New York City days, I can manage subway steps without being short of breath.

I am teaching full time and teach very active classes. I resumed my clinical work in 2013 after my health improved and continued that for two years until my doctoral studies took precedence, and I got my doctorate in 2016. I resumed my community involvement, and just knowing that this drug might be available to me should my disease progress and that I have a chance of receiving effective treatment helps me remain hopeful and positive about my own future. As someone who did

not have a culture conversion on the oral cocktail alone, I now have hope. Thank you for hearing my testimony.

DR. BADEN: Thank you. 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.

MS. HAYS: Hello. My name is Melissa Hays. I am 50 years old, and I'm a wife and a mother of two. My son is a sophomore in high school, and my daughter recently graduated from Texas A&M University. I'm a stay-at-home mom, but stay active in volunteering in my community. Insmed supported my travel here today, but I'm not being compensated for my time.

As you can tell, this is not easy for me, but this is how passionate I am for you to see a face of this horrible disease. I was diagnosed with pulmonary MAC in 2014. My journey with this lung disease has been a long and honestly quite painful one. I was misdiagnosed for years, leaving me with more questions than answers, and I was

undergoing numerous scans, subjecting myself to large amounts of radiation, trying numerous drugs that were giving me no relief at all.

I decided to get a second opinion and was given a bronchoscopy to confirm the suspicion of pulmonary MAC. We began a tough course of antibiotics taken early. I took azithromycin, ethambutol, and rifampin, but to no avail. Having dealt with the harsh side effects of these medications for several years, I was ready to try anything considering nothing else was working for me. I was at an all-time low in my life with this disease. The mental, physical, and emotional, even spiritual toll was beginning to take over the clarity of my life.

Pulmonary MAC robs you of the ability to perform everyday tasks that we often take for granted. I felt the embarrassment of not being able to hold conversations, to have to constantly clear my throat or coughing nonstop. I can no longer enjoy a quiet dinner at a nice restaurant, or even go to the movies, or even sit through a

quiet church service for the fear of having a coughing fit, followed by the stares of people thinking that you're infectious. I can no longer make it through a cycling class or exercise much at all due to being very fatigued easily, not able to catch your breath. I cannot even get quality rest at night either because of the coughing or the pain of the bronchiectasis.

Now, this disease was filtering into my daily life with my family and friends because I would avoid a lot of the things that I really enjoyed doing, and I began to isolate myself. Here I was from the outside looking in, a very young, healthy woman, but in all honesty, I was trapped by this disease.

I was referred to an infectious disease doctor who thought I would be a good candidate for the ALIS and happily began the treatment of the inhaled version of amikacin, and it wasn't perfect at the start. I had to tweak the doses due to the side effects, primarily loss of voice, which my husband and kids loved, and the nausea.

I scaled back to 3 times per week to tolerate the drug, but for the first time in many years, I began to feel relief. My coughing started to subside, my sputum production was up, and during the first month of treatment, I actually tested negative; negative, which is a word I haven't heard in a very long time.

This medicine worked quickly, and I have continued to stay negative during the course of treatment. I was able to return to my cycle classes, my energy level was higher, and I can enjoy those quiet places I actually once feared. It made an impact on my recovery from this debilitating lung disease, and I would love to see this drug available for everyone to have the same opportunity.

My story is one of hope. Hope and faith are such huge components of pressing on to find a cure, and I want to continue to improve my health and live a healthy and vibrant life. And honestly, after hearing all the discussions this morning, I'm even more passionate for you to see a face, to be

able to hear our stories, and I thank you for your opportunity to let me share my story.

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.

MS. MALANGA: My name is Elisha Malanga, and I'm speaking on behalf of the COPD Foundation, a nonprofit organization with the mission to prevent and cure COPD. We also provide research, education, and support for NTM and bronchiectasis, including the United States Bronchiectasis and NTM Research Registry, a consolidated database of NTM and noncystic fibrosis bronchiectasis patients involving 15 academic medical centers nationwide.

Insmed is a COPD Foundation corporate partner, but was not involved in the preparation of the statement, nor did I receive any financial support for my participation today.

My purpose today is to describe the large unmet need, priorities, and preferences of those with NTM pulmonary disease often made more complex

given the presence of preexisting lung conditions. Once diagnosed with NTM infection, patients face an uncertain future of progressive lung damage and burdensome treatment side effects.

There is no one typical patient with NTM lung disease, and the current treatment options vary widely based on extent of infection, underlying medical conditions, and risk-benefit assessment of the treatment proposed. Most NTM patients must add multiple NTM medications to an already extensive routine of treatments intended to stabilize lung function.

Current NTM guideline-based treatment regimens of oral and IV antibiotics, and in some cases off-label inhaled antibiotics, cause severe side effects that can further disrupt patients' lives and create additional health issues such as hearing loss and kidney damage. Despite prolonged use of multiple medications, many NTM patients do not achieve the desired outcome of sputum culture conversion.

Along with our patients at NTMIR, we

conducted a patient survey in January 2018. Of the 314 respondents, 204 had NTM. Twenty percent of those with NTM used inhaled antibiotics. The type, dose, and duration of inhaled antibiotic use varied for nearly every patient.

Patients reported between 1 and 10 exacerbations annually, defined by an episode that required treatment by a healthcare provider and/or that required the start of a course of antibiotics. Survey respondents wanted additional options that get away from systemic antibiotics, yet deliver more targeted benefits, including sputum culture conversion. They understood that there is a risk of developing resistance to any antimicrobial treatment, but they acknowledged the urgency and importance of reducing infection.

We understand that the long-term safety profile is always an important consideration. However, the serious unmet need in this population and the patient's existing use of systemic antibiotics should also be considered. There are no perfect data that adequately captures when

someone with NTM will have a bad breathing day, when they will walk a mile, or when they were hardly make it to their mailbox, or when they will stop responding to their treatment regimen.

This is life for these patients, a life of daily uncertainty and limitations. Therapeutic options that can further improve NTM disease burden represented by a culture conversion are a clinically meaningful step forward for patients.

Before I conclude, I want to read just a few statements from the NTM patient-focused drug development held in 2015. A patient described her day-to-day life with the following.

"Some days I can walk forever and some days I can't walk a block." She noted it could be something as simple as the rain that could throw off her stamina. Another said that people tell her she is better than her numbers, referring to how sometimes she feels better and can do more than the measures say she should.

Lastly, another described their unmet need by saying, "We need to have treatments that will be

less toxic and more effective." She went on to note that she had hope because of the PFDD meeting and the fact that people were listening to patients.

I urge you to consider the large unmet need in this complex, difficult-to-treat patient population as you consider the data before you today. Too few patients with NTM lung disease have a realistic chance of improvement in disease burden. It is time to give another effective option to this patient community for improved treatment success and lower overall burden of treatment. Thank you for accepting these comments today.

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.

DR. O'DONNELL: Good afternoon. I'm Ann O'Donnell. I'm the division chief of pulmonary critical care and sleep medicine at Georgetown University here in DC, and I am a PI on multiple

bronchiectasis and NTM studies, including the studies cited in this committee. But I have no financial interest, and I haven't received any compensation for being here today.

I have a couple of points to make. One, I would like to speak briefly to the endpoint issue that's been discussed at length today. And I applaud the FDA for convening an endpoint meeting in June regarding bronchiectasis. We didn't cover NTM there, but it is a very complex issue, and I think we all understand how difficult it is to find the right endpoint when we're trying to assess these clinical trials.

But I would just reiterate what Dr. Philley said, that the endpoint that we use in practice in order to decide the duration of therapy is sputum conversion, and the ATS/IDSA guidelines do recommend 12 months of therapy post sputum conversion. So I hope that that at this point would be an acceptable endpoint for this trial, as we don't have a composite endpoint that we can really look at that fully addresses all the

questions that were raised today.

I also want to address the issue of salvage therapy in this disease. I have to say, many of you know that I really am a bronchiectasis person, and I've been involved in a lot of pseudomonas trials. But currently in my practice, I probably see 5 to 6 new NTM patients every week and about 20 to 25 follow-up patients. And most of those patients here in DC are referred to me because they're failing their therapy or they're not tolerating their therapy, so there's a huge problem with doing regular therapy for NTM infections.

What salvage therapies do we have right now? We're talking about things like IV amikacin with the side effects we've already talked about. We're talking about using clofazimine. And my infectious disease colleagues on the panel probably know how difficult it is to actually obtain clofazimine for our patients. It's a very complicated IRB/IND type process that most physicians in the community are just not going to attempt. So clofazimine as a salvage therapy is difficult for us.

We have drugs like linezolid, tedizolid, that are difficult for patients to tolerate. So the issue of salvage therapy is very, very challenging for our patients and for us physicians in the trenches to try to figure out.

I would just conclude by saying that there's been a lot of clinical trials in bronchiectasis and now in NTM using inhaled antibiotic therapy. Clearly, we have not reached the perfect endpoint or the perfect decision-making, but we're in such a difficult position with these patients, with this growing patient population that's primarily older women who are being forced to resort to these therapies that are either not approved or have to be compounded, or we have to really work hard to get for these patients.

I realize that the drug we're talking about today is far from perfect, but the side effects profile that we've heard, though challenging, is certainly less than some of the other quote/unquote "salvage therapies" we have. This really is a lifelong disease for these patients. I can't

emphasize that enough, like you've heard already that we have to take care of these patients, really, for as long as they keep coming back to us because this is not a disease that we can cure at this point.

So any additional thing in our armamentarium that the patient can actually access is going to be a great help to this patient population and to our infectious disease and pulmonary colleagues around the world. So thank you very much.

DR. BADEN: Thank you. Will speaker number 9 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. MIGLICCO: Hi. My name is Linda Miglicco, and I'm from the Dallas area. Although my travel has been supported by Insmed, I'm not being compensated for my time or opinion. I traveled to DC in hopes to help provide a voice to NTM. Besides the obvious inconveniences any illness inflicts upon it sufferers, there are numerous aggravations that a person with

mycobacteria must endure.

The major one, in my opinion, is the sheer lack of knowledge in this disease. No one knows exactly how each sufferer got this disease, so you constantly are questioning am I ever going to be able to take a shower or garden without the worry if I'm going to re-contract it again.

My story begins with me being diagnosed with rheumatoid arthritis in February 2013. Around the same time, an unrelated abdominal CT picked up some areas of concern in my left lung. My pulmonologist ordered scans and tests, however, it was becoming apparent that my health was declining. And as such, I was sent from my first bronchoscope in August 2013.

September 13, 2013, it was confirmed these areas were both those of RA nodules as well as MAC. I then started my treatment regimen of clarithromycin, ethambutol and clarithromycin. The follow-up bronchoscope completed in May 2015 confirmed I now had an aspergillus fungus in my lungs. I was given an additional prescription to

my regimen for approximately 6 weeks.

I completed the therapy for the MAC infection in October of 2015, 25 months after beginning it. Living with this disease definitely has its ups and downs. I know I'm a fortunate one. I've had conversations with people who are on continual oxygen or have even had lung removal, so I realize how fortunate I am at this point. However, I also know that with this mysterious disease, my fortune can run out at any time.

Besides living with the knowledge that I can take a turn for the worse, I spend my time worrying about things other people barely even think about. I spent January through the end of March completely housebound. This year's flu epidemic was a frustration for most, but for me, it had the potential to be life or death. I must stay mindful of what might be an uncomfortable week of bed rest and fluids for most can be a hospital stay at best and a very real possibility of death for me.

The biggest impact NTM coupled with RA has had on my day-to-day life is accepting that I must

be flexible because my health can change at any time. The other big impact with this disease is expecting the need to educate almost everyone about it, including many medical professionals.

Just to give you an example, I had a surgery scheduled, which coincidentally was during the same time as the Ebola outbreak and ironically in a hospital very near where the primary patient had been treated.

My NTM prompted concerns in the pre-op conversation. The nurse reviewing my medical conditions became alarmed upon hearing the word "tuberculosis." I explained the condition to the nurse but was unsuccessful at calming her nerves. I was then told I would actually have to go through special screening, be in isolation if the surgery wouldn't be canceled altogether.

In conclusion, what compelled me to come talk to you was a simple commercial. This commercial shared some exciting news about a new drug that helped at-risk individuals from contracting HIV. I was frustrated because we know

what causes HIV, and we know if you take precautions, your chances of contracting it are near zero.

We don't know what causes NTM. We cannot tell someone we love not to do X and they're assured not to get this disease. Treatment options are critical and of most importance, but we need additional research in the disease itself. We must gain further knowledge into the root cause. I'm compelled to prevent anybody else from following this path. Thank you.

DR. BADEN: Thank you. 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. O'BRYAN: Hi. I'm loud, aren't I? I'm Marcia O'Bryan, and I'd like to say that Insmed was kind enough to pay my travel expenses, but I'm telling my story for free, and this is my story.

I just flew over 2200 miles from Palm Springs to come here today to talk to you for 5 minutes, and that's a pretty long time to fly for

a 5-minute little talk, but I think it's that important. I think it's worth the trip. I hope it's worth the trip, if you catch my drift.

This meeting is about hope for all of us who have MAC. And you keep hearing the word "hope" over and over again. And since I was diagnosed with MAC over 13 years ago, after a misdiagnosis of asthma, I've been on amikacin, azithromycin, ethambutol, rifampin, clofazimine, Levaquin, and I don't know how many other kind of drugs. But not one of these drugs was developed for MAC. There is no drug that has been developed for MAC until now. At least we're hoping, if you catch my drift.

Well, like so many other people with MAC, I've been on treatments for months and months at a time, multiple drug cocktails orally, the IV antibiotics, and all that kind of stuff. We get a little bit better. We go on a drug holiday. We get a little bit worse, and we go back on the drugs. And we do it again and again, and we do it for years.

Like many others also, I had surgery. I had

my right middle lobe removed, and I have another one waiting in the wings to be removed. That's not fun. This bug just doesn't seem to go away. It's lurking, deep in my lungs right now, and it's trying to destroy them, and it's doing a pretty good job.

This new drug therapy that we're here for today, ALIS, it's like -- I know this is going to sound corny. It's like having inhaled hope. I say ALIS is another name for inhaled hope. When you have very few options on drugs because you've been taking so many other drugs, that's what this new drug therapy is. It's inhaled hope.

I've made a lot of friends in California and across the country who have MAC, and I'm sure that they would shout for joy if this drug were to be approved. That's if they could shout. I'm sure they would jump for joy to if they could jump. You see, when you have this lung disease, it limits some of your living.

Yesterday on the plane coming here, I had to be on oxygen. A simple thing like getting on a

plane, it is just not simple anymore. And when I go to sleep or even think that I might fall asleep -- and by the way, thank you for not being too boring because I might have fallen asleep, and then I would have had to put my oxygen on and didn't want to have to do that. But that's what I have to do.

When I go to sleep, I have to put my oxygen on, and you have no idea how it affects you doing something that you do every day because you don't dare not do it, because you can't go to sleep without your oxygen on. I know it sounds kind of like a silly little thing, but it gnaws at you after years and years of doing something that you used to take for granted, breathing.

Well, I'm about to run out of time, but I want to tell you that our spirits are lifted by the thought of having ALIS. Even if there's no guarantee of a cure, we're deeply moved by the thought that we will have the opportunity to try something that is expressly intended to benefit those of us who have MAC. We need more awareness

of the disease, better trained physicians regarding this disease, and new drug therapies.

But wait! We have a new drug therapy, don't we? We hope it's approved. Now the ball's in your park, and we're hoping. Please make it happen. And thank you for letting me share. Thank you from the bottom of my lungs. And a special shout out to Insmed. Putting it mildly, you are our heroes.

DR. BADEN: Thank you. Will speaker number 11 step up to the podium and introduce yourself? Please state your name and the organization you're representing for the record.

MS. SPERRY: Hi. My name is Tracy Sperry. I'm the chief development officer for NTM Info and Research, and I'm not being compensated for my time today. I'm actually here to read a statement from a patient who could not be with us today at the last minute.

"My name is Laura Kelly. I'm 59 years old, and I live in Atlanta, Georgia. And I'm also the NTM support group leader in Georgia. I'm so sorry I wasn't able to come in person to tell you my

story.

"In 2015, I did participate in the FDA NTM patient meeting and was able to share my experiences with NTM up to that point. In 2006, at the age of 46, through a random chest x-ray, nodules were discovered on my lungs. I was asymptomatic. After several CAT scans and then finally a bronchoscopy, I was diagnosed with NTM. I thought to myself, 'Thank God it wasn't cancer.'

"Thanks to a veteran NTM patient from Boston, who unfortunately is no longer with us, I was advised to apply to the amazing NIH for their study on NTM. I was accepted. During my first visit in June of 2007, it was discovered that I have alpha 1 antitrypsin deficiency. I am ZZ homozygote. I was immediately started on 3 antibiotics.

"After a few months, it appeared the drugs were positively impacting the bacteria. However, shortly thereafter, I started experiencing peripheral neuropathy in my feet, which has never resolved. I also have significant ringing in my

ears and hearing loss.

"I was then put on my moxifloxacin, rifampin, and azithromycin. I stayed on these from 2008 to 2012. I continued to culture monitor it to heavy growth despite four years on these drugs with some progression on my CT scans. Clofazimine was added. I had a great tan, but continued to culture heavy.

"Life with this disease is frightening as we learn more and more about it. We educate ourselves through the Internet, support groups, our doctors. NTM is everywhere. It's in our tap water, showers, soil, dust, lakes. It's impossible to escape.

"A sample of what we go through, when walking in our neighborhoods and we hear the sound of a blower, we run in the other direction. When in the produce section of our grocery store and we heard the sound of thunder, we rush in the other direction. Many of us give up our beloved showers for tedious baths. Many of us, due to are loud and constant coughing or extreme fatigue stop going out in public or spending time with our friends.

"Our days begin and end with pulmonary clearance. This entails not only performing but carefully cleaning and sterilizing equipment, so we are not reinfecting ourselves. It's incredibly frustrating. The saddest part is that there are no approved therapies. We are constantly seeking and hoping for something new, for threads of hope.

"If we are lucky that the current antibiotics clear up our bacteria like me, we reinfect. What is the long-term use of these oral antibiotics doing to my body, my future health? I feel very much like I have that cancer diagnosis with a slow death sentence unless someone develops a therapy that soon becomes approved and will destroy this bacteria without killing me.

"In 2013, I applied to participate in the Insmed clinical trial for ALIS and started the trial in May. I apparently received the drug for the first 90 days and then continued for another 90. Prior to the trial, I had decided to go to National Jewish for a consult in August. I sent them a sputum in June, and having been on ALIS for

a month, it was negative, my first negative in years. I sent at least two more to National Jewish over the next few months. They were negative as well.

"In November of 2014, I had a bronchoscopy at the NIH to make sure I was negative. The washings [ph] cultured negative and my CT scans significantly improved. Finally, in January of 2015, I stopped all antibiotics after 8 years.

"I have since been cultured with mycobacterium avium complex, a new bacteria as I had only cultured intracellularly in the past. Fortunately, there are finally some promising therapies being developed. The problem for me and many like me is it's taking too long for them to be improved.

"I know that your priority is to make sure that approved drugs are safe, however, I can assure you that having this disease is not safe. It affects us mentally, emotionally, and physically. It can completely consume your life and your thoughts. Thank you for listening."

DR. BADEN: Thank you. 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.

DR. SRINIVESAN: Good afternoon. Thank you for the opportunity to speak today. My name is Dr. Varuna Srinivesan. I'm a physician with a masters in public health from Johns Hopkins University. I'm a senior fellow at the National Center for Health Research, which analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

As a physician, I care for my patient's well-being, and that is why I feel it is important to advocate for the approval of new drugs only if they are proven safe and only if this information is backed up by scientific data. For this reason, I have strong concerns about the safety and efficacy of the drug in question today, ALIS. I

will briefly describe these concerns.

Number one, there are several problems with the clinical trials and the sponsor's emphasis on cultural conversion. In study 212, patients are excluded from the study after 6 months if they do not convert to a negative culture relapse. They are then given the option to reenroll into a secondary study. The drug takes quite a while to be effective, and 6 months is too short to accurately test the relapse and recurrence rate of MAC in these patients. Both relapse and recurrence are more likely to occur after 6 months than within 6 months.

According to the American Journal of Respiratory and Critical Care, despite long-term negative sputum cultures on anti-mycobacterial therapy, sustained mycobacterial eradication may not be possible in a substantial number of patients, especially those with nodular bronchiectatic MAC pulmonary disease once treatment is discontinued.

Numerous studies report and overall relapse

rate of 25 to 48 percent in patients with MAC pulmonary disease. These occurred in a medium time of 6 months after the completion of therapy with an interquartile range of 6 to 30 months. More so, patients with nodular bronchiectatic disease manifestations have a higher risk for relapse than those with other disease manifestations.

In addition, the pivotal trial is an open-label study without a placebo control. Even the primary endpoint would be affected by the knowledge that one is taking a new drug. The secondary endpoint, the 6-minute walk test, can be dramatically affected by motivation in an open-label trial. If a patient knows they are taking a new drug, they may be motivated to see how well it is working and thus not give up as easily. This knowledge and the act of taking the drug or the placebo could affect adverse events reporting.

The patient's characteristics differ between the ALIS and the control arms of the pivotal study. For example, in one group, more patients that were male, more had COPD, more had cystic fibrosis, and

more had a past history of smoking.

My second concern is none of the endpoints provide useful information about how the drugs affect patients' lives. An MAC infection causes severe respiratory problems, but the endpoints do not measure clinical symptoms, and they should. My third point is that the studies lack diversity. Almost all patients are white, very few or black, Asian or Hispanic, and very few were over the age of 65.

A study published in the American Journal of Respiratory Care and Clinical Medicine helped shed some light on the prevalence of NTM. Although a majority of patients in this study were white, it shows that Asians and Pacific Islanders in general have shown to have significantly greater risk for disease with a prevalence twofold that of whites.

Additionally, whereas white women have a 50 percent higher prevalence than white men, among Asians and Pacific Islanders, men were more affected than women. In fact, Asian Pacific Islanders, men were twice as likely as white men do

have the NTM. In other words, many of the patients who would be interested in treatment for MAC would have no information about safety or effectiveness of ALIS for patients like themselves.

In addition to demographic differences, the safety and efficacy of ALIS may be affected by the patient's underlying conditions. ALIS may interact with other drugs that the patient in these studies might be taking. Unfortunately, the sponsor did not report whether the patients would be taking other drugs.

As the FDA mentioned in their presentations, ALIS also has several systemic side effects as nausea and diarrhea. Tinnitus and vomiting were present even though patients were taking an inhaled form of amikacin. This makes us very concerned about the safety of ALIS and the long-term side effects. No information is provided about drug interactions for these patient, and there is a worrisome lack of information about the patient profiles and individual diseases that we suffer from.

In all these studies, patients have respiratory symptoms that in some cases seem to be getting worse than better with ALIS. The bottom line, patients need treatments that are safe and effective. ALIS may be safe and effective for the specific patient population, but the sponsor has yet to identify that population. If there is a specific population for whom the benefits of ALIS outweigh the risks, the population needs to be part of the indication before the FDA should approve this drug. Thank you.

DR. BADEN: Thank you. Will speaker number 13, our final speaker, step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. FATIBENE: My name is Michelle Fatibene, and I've only had this trip paid for. I've been dealing with NTM for 7 years. My NTM comes with a bonus, hemoptysis episodes, which have progressed from teaspoons two fractions of a cup. It's terrifying because I never know when the bleeding will start or stop, and I can't just put pressure

or do much else to help stop it.

How has NTM impacted my life? My world has shrunk, slowly at first, but then faster, as the different cocktails of meds so far have not worked, and my lungs keep getting worse and worse.

NTM has impacted me both professionally and personally. Professionally, my career has taken a big toll. My work requires regular client meetings, but what if I wake up feeling totally fatigued, and I have to cancel the meeting, potentially multiple times? And what if I'm at a workplace and I have a coughing fit and has hemoptysis? I would freak out everyone around me, and I'd feel so embarrassed. I'm anxious right now, because it could happen now, so I do limited work from home only with people who know me well and understand my situation.

On the personal front, NTM has impacted me in countless ways. Let me give you some examples. Family dynamics have changed. I rely so much more on my husband to take care of things that I used to take care of because now I'm just too tired. I

used to be very active, both socially and physically. Now I hesitate to make plans because I have to cancel them frequently. I can feel good one day, totally out of energy the next, or good in the morning and bad in the afternoon. It's unpredictable and very frustrating.

In the winter. I avoid going anywhere with many people in a closed space as someone else just said. If I'm in a group and someone coughs, my stress level spikes because catching bronchitis or the flu for me has complications.

Vacations are much more limited because I avoid flying since I tend to get sick after a flight. I drove to this meeting. If this meeting had required flying, I would not have come. I used to enjoy walking or hiking. Exercise is what everyone recommends, but I cannot do anything that makes my heart rate increase too much, whatever that may be on that particular day, otherwise I start coughing and bleeding. I can only do short walks on a flat surface.

Each day starts and ends with NTM concerns.

A shower has to be very short because it releases NTM in the air. I look up the weather mostly with fear. If it's very cold or humid, it means I need to stay indoors. My appetite is not strong. During my last IV treatment, I lost 10 pounds, which I didn't need to lose, and I haven't been able to gain it all back after a whole year. Sleep is very challenging because it gets interrupted by coughing.

All these changes have resulted in a lot of isolation for someone who was always on the go. Now I spend a lot of time by myself resting. Thank God for the internet, but I miss so much interacting with people all day. But perhaps the most insidious impact of NTM is loss of hope, and I think that's a recurring theme among the speakers.

When I was first diagnosed, friends and some doctors said, "Don't worry. There are new medications coming out all the time." Not for NTM. I think I have the best care. I've taken a dozen or so different meds, some really tough IV regimens, and my results come in time after time

showing no conversion to negative.

It's really difficult to keep feeling optimistic, but ALIS has given me hope because for the first time I'll be able to take a medication specifically developed for NTM. I've listened to the adverse effects, but I want to have a shot at conversion. When my colonies are 100. I feel sick. When my colonies are 10, I feel much better. And I have to believe that if my colonies are zero, I'll feel much better.

Please, on behalf of myself and other patients in my situation, please make ALIS available and keep us hoping. Thank you very much.

DR. BADEN: Thank you. On behalf of the committee, I'd like to thank all of the speakers for taking your time to come here and share your stories, both your humor and the seriousness of this matter. We take all of your comments quite seriously, so thank you all for making the time and the travel to share your thoughts.

The open public hearing portion of this meeting has now concluded, and we'll no longer take

comments from the audience. The committee will now turn its attention to the task at hand, the careful consideration of the data and the public comments.

The challenge that we have time wise is that I think we have dozens of questions from the committee members and significant comments from the applicant as well. The program suggests that we take about a 5- or 10-minute break, which we'll do, and then we'll come back and resume the questions and clarifications to the applicant and the agency before we proceed to the voting process.

So we'll have a 5- to 10-minute break. Please move quickly.

(Whereupon, at 2:37 p.m., a recess was taken.)

Clarifying Questions (continued)

DR. BADEN: We shall resume. The agenda has us adjourning at 4:00 p.m. I think that is highly unlikely given the amount of questions that I'm aware of that the committee has. So I will do my best to keep our discussion over the next hour to hour and a half as focused as possible, and then

we'll proceed with the voting. I suspect we may go closer to 5:00 p.m., just for those to adjust their travel accordingly, given the significant issues that I think need to be aired so a proper and informed discussion can occur.

So at this point, we have completed the open public session. We still have many questions, both for the agency and the applicant. What we'll start with is the applicant with Dr. Sullivan, who has some responses or some follow-ons from the earlier discussion, probably leading with the elephant in the room, as I was informed, which is, what does culture conversion mean and why do we care?

DR. SULLIVAN: Thank you, Mr. Chairman. Yes, we heard three sort of lines of inquiry and some requests to hear from the experts that we have with us on three separate topics. The first topic I think is that issue of can we consider the achievement of microbiological cure to be itself a clinically meaningful benefit?

As you know, the study 212 confirmatory endpoint on the specific recommendation of the

agency, the confirmatory endpoint was durable culture conversion. Now you're asked to consider whether that can be itself clinically meaningful. Dr. Kasperbauer will come up and give her perspective on that.

There was another line of questioning that had to do with the application of the guidelines, particularly in the refractory patients, and people entering the trial, should they have stayed on their background regimen and so forth. We have Dr. Griffith with us, who is the author of those guidelines, and he'll comment on that.

Finally, there was a conversation about the expectation for when you might see a functional benefit following treatment, either following initial culture conversion or eventual durable culture conversion, and Dr. Flume has some comments about that. So we'll begin with Dr. Kasperbauer.

DR. BADEN: With each presentation, may we have then a discussion with the presenter if the committee has clarifying questions?

DR. SULLIVAN: Absolutely.

DR. KASPERBAUER: Thank you. Shannon Kasperbauer. I think it's imperative that I first just comment on the emphasis of the urgency of this need. This morning, I presented data at an increase in 8 percent per year in prevalence, and that's been reflected in multiple different studies, in multiple different countries.

We've heard from our colleagues and our patients today the importance of culture conversion, i.e., cure, whether or not that has physical, financial, spiritual, or emotional benefits. But simply stated, in our field of infectious disease, eradicating the pathogen means cure. The goals and mantra of our treatment our culture conversion, sustaining that for 12 months, and getting people off therapy, which of course limits their toxicity, has importance for stewardship, et cetera. But most importantly, patients feel better when they have effective therapy.

So as I would like to just review this slide again, there was a significant difference in those

patients that had culture conversion versus those who did not that was seen later in their course of treatment.

Now, I'll emphasize that the mean time to culture conversion in this study from Griffith's group was 110 days, so we appreciate the fact that clinical symptoms can lag behind the time of when we see culture conversion in our practice. And as you've heard, several studies, albeit with their limitations, have shown a decrease in mortality in those patients that see culture conversion.

Finally, I'll quickly comment on the question that came up with the rigor of the sputum interrogation in these patients. This study had the most rigorous rules for sputum investigation that I'm aware of in the published literature, looking at 3 serial days each month of sputum investigation. And if a patient was not able to expectorate, they were brought in for sputum induction.

So I think these are valid and reliable results. Thank you.

DR. BADEN: I will ask the committee if you have follow-on questions because this is such an important point. In study 212, what evidence of -- because we're struggling with the issue of the surrogate endpoint of culture negativity with clinical benefit. So in prospectively collected data, the evidence for clinical benefit is what?

DR. SULLIVAN: The whole premise of this application was subpart H, in which the initial approval is based on a surrogate endpoint, which itself isn't clinically meaningful, with the idea that the benefit on the surrogate can be reasonably likely to predict something meaningful.

I think that's the second issue, and we've showed some data on that. And there's been some discussion as to whether we can conclude that in fact culture conversion at month 6 can be reasonably likely to predict durable conversion.

It's whether durable conversion itself can be considered to be the confirmatory evidence of clinical benefit. And again, this was the chosen and agreed upon suggested by the agency because

it's difficult to do this.

We've had the experts come and say it is meaningful. This is why we treat. There was some question as to whether we should even treat, I suppose, because what's the good of conversion? But this is the goal of therapy it. The immediate benefit is patients come off their other meds, which is very important to them.

Then you've seen the association with mortality with symptoms, x-rays, and so forth. And I understand the criticism of those, that those are all post-randomization comparisons. However, if the question is, is it better to convert, to have microbiologic cure than to not have microbiologic cure? The only way to scientifically would be to randomize patients to microbiologic cure versus not microbiologic cure, and that's of course impossible.

So we're left with these observations that show up again and again in the literature that, in fact, when you achieve culture conversion, you see the benefits, and our clinical experts say that is

their experience as well.

DR. BADEN: Dr. Green?

DR. M. GREEN: This is just a quick question, and this is relevant to what we're talking about. We've been shown the data for the 6-minute walk test at the 6-month time point. We haven't been shown data for 9 months for those that continue on.

Are these patients undergoing sequential testing with the walk test and with the survey, and are those part of the follow-on study whose results are not available yet because the study is ongoing? Because I think that would be clinically useful, and it would be important to us to know whether or not those data are being collected.

DR. SULLIVAN: Yes. The initial application is based on data up to 6 months; 6-minute walk distance and SGRQ are being collected and will be collected at the end of treatment, and we'll see that. That sort of merges into the question about when might we expect clinical benefit.

DR. M. GREEN: But just at the end of the

treatment, which is the 12 plus 3 or are you getting it sequentially over time?

DR. SULLIVAN: There will be another at I believe it's 8 months.

DR. BADEN: Dr. Weina?

DR. WEINA: In reference to clinical endpoints, are you following and going to collect data and report data on other clinical endpoints like body weight, inflammatory markers like ESR and CRP, spirometry, things like that as well?

DR. SULLIVAN: The other clinical markers that are being collected will be the SGRQ. There are some inflammatory markers, IL-6, CRP, and the 6-minute walk distance, and BMI is also being collected.

DR. BADEN: Dr. Brittain on this theme?

DR. BRITTAIN: I'm trying to understand, now that I'm hearing that you will have some clinical endpoints in the long term, on the long-term patients, how you will interpret and analyze them since you don't have the randomized comparison.

DR. SULLIVAN: Well, that's been a

limitation that's been pointed out by the agency, and we recognize because of the design of the study that we'll be able to characterize the patients -- from pre-treatment to end of treatment, we'll be able to characterize what happened to those, but it's difficult.

I think even if the study, if we had everyone stay in, there would be a lot of missing data. And this is what it sort of went into. When you have a treatment duration that takes so long, a study that takes 2 years for patients to accomplish, this was part of what went into the selection of, well, if we can go with durable culture conversion and microbiologic cure as the clinical benefit, then that's a little harder -- I mean a harder endpoint. It's more easily demonstrated, as we plan to do.

DR. BADEN: Thank you. With NTM's big brother, TB, early culture conversion was deemed an important parameter, yet subsequent studies have not borne that out as clinically important. How do we interpret those data across the mycobacterial

spectrum, or is it just two different problems?

DR. SULLIVAN: I think Dr. Griffith is probably the expert to talk to about that. I would like to bring him to the podium.

DR. GRIFFITH: Thank you. Dave Griffith. There is quite a difference of course in testing antibiotics for tuberculosis than for nontuberculous mycobacteria, the most important one being we do not have potent antibiotics, or as potent antibiotics as are available for tuberculosis. For instance, there is no early bactericidal activity that can be measured in the evaluation of NTM drugs.

Having said that, this study design is actually fairly similar to recent study designs in a somewhat analogous situation, which is patients who have multidrug resistant and extensively drug resistant tuberculosis, where drugs like bedaqualine, linezolid, delamanid are added as, if you will, single agents to add-on therapy to patients who are on multiple medications.

I will certainly confess, the ideal way to

test antibiotics for nontuberculous mycobacterial diseases, there is still not consensus on that. But this study design I think is a reasonable one. And as I say, I think it does have a correlate in the TB world.

DR. BADEN: But in the MDR/XDR arena, as opposed to just early culture conversion for the treatment of TB, which hasn't borne out?

DR. GRIFFITH: Well, actually it was sputum culture conversion to negative, which was the primary endpoint, particularly for the bedaqualine study.

DR. BADEN: But for the fluoroquinolones, it didn't lead to better cures.

DR. GRIFFITH: That's correct, and there are a lot of things, of course, that go into that. I will say also that the idea of adding a single drug to a failing regimen doesn't translate exactly from TB to nontuberculous mycobacteria. That's a process with many layers, and I know we don't have time to go into that. But certainly that part of it is not analogous.

DR. BADEN: Thank you.

If not, then your second consideration?

DR. SULLIVAN: Thank you, and that's Dr. Griffith to talk about how the guidelines apply in these refractory patients. There was a question about the patients who enter the trial maintaining on their background regimen. They have been on it for a number of years and presumably have cycled through a number of different regimens. So there was a question about that.

DR. GRIFFITH: Dave Griffith. I think we partially covered that talking about the treatment design for drug-resistant tuberculosis. The guidelines are squishy about what to do with patients who fail standard therapy. There's reasonably good data that first-line therapy with macrolide rifamycin and ethambutol, plus or minus an aminoglycoside, is pretty good therapy. But after that, all bets are off.

The bottom line is there is essentially no proven effective salvage therapy. You've heard some of the alternatives from some of our speakers,

like clofazimine for instance, or inhaled generic amikacin, or fluoroquinolones. There just is no information about that.

I would like -- no one stepped up to do prospective trials back in the 1990s to look at the efficacy of macrolides, but there is quite a strong body of evidence from observational studies that they are in fact effective. But for these other agents, there's nothing.

As you have heard, this represents the first prospective randomized trial of a drug specifically for MAC. This has not been done before. No one else has stepped up to do this kind of study. There's just not much money from anybody. As a matter of fact, the National Institutes of Health only within the last year funded their first clinical trial for MAC lung disease.

So I would only emphasize the unique nature of this trial, and I would hope that at least we could laude the sponsor for taking on this task, which no one else has done.

DR. BADEN: Several follow-on questions.

Dr. Schaenman?

DR. SCHAENMAN: Thank you for that clarification. That's very helpful. I was just thinking that in our prior discussion of the background therapy, there wasn't any comment provided as to whether this was all daily versus intermittent therapy. And in addition, I was just wondering if there was any review by the sponsor in terms of were these regimens picked in a good fashion based on previous failures or based on any available culture results.

DR. GRIFFITH: Well, I can only speak to the, -- as you saw, most of these patients had been on medicine for years and had been on multiple different regimens. And it was the choice of the referring physician what regimen they received. So I can tell you that if I were reviewing all of those regimens, I would not call them optimal, but they were what patients had been on and were tolerating. So there really was the addition of a single agent to that regimen.

DR. SCHAENMAN: So they could have been

intermittent or daily. It was just whatever the recommended --

DR. GRIFFITH: Correct.

DR. SULLIVAN: For the most part, these patients because they're refractory, as you I think are referring to, the guidelines call for initial therapy in some cases 3 times weekly. But in these refractory patients, these are patients who have moved to daily therapy.

Sometimes in the case where there are two drugs, that doesn't on its face seem optimized, but it may reflect the tolerability of the patient. So if they had an optic neuritis, they came off ethambutol, so they end up on two. And at this time, 4 or 5 years later, it doesn't reflect what you might consider optimal initial therapy.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. Just while we're talking about the salvage patient and failing therapy, I was curious, is there data about a clinical response to leaving people on these failing antibiotics for years? Why did they stay

on therapy for 2 years? Do we know there's a clinical response?

DR. GRIFFITH: I think it's more a negative response being off medication. I think physicians keep patients on medicine with the hope that they can perhaps suppress symptoms, not so much that they're going to result in sputum conversion and improvement.

DR. GRIPSHOVER: So there isn't data that anyone's looked, like you take them off and people get worse?

DR. GRIFFITH: No, not that I'm aware of. I will tell you also that a patient of mine who has been on therapy the longest has been on therapy for 20 years, off and on, and has converted her sputum to negative with ALIS.

DR. BADEN: Dr. Weina?

DR. WEINA: So I just want to be really clear on what I was trying to point out when I brought up the idea of adding a drug to a failing therapy. And the issue is this. If you already know that the person has been refractory so that

they're not going to convert, and you keep them on the same drug and use that as a comparator for a trial in which you've added another drug, you already stacked the deck so that -- I mean basically, it's like placebo, right?

DR. BADEN: Or you're saying functional monotherapy.

DR. WEINA: Right. Functional, you're doing --

DR. GRIFFITH: But that's what I mean. I'm not saying there's an exact equivalence to TB or to HIV as far as the failing drugs because there may be some hidden resistance or anything. But what I'm saying is that you stack the deck because if you already know that they've gone 6 months, or 8 months, or 10 months, or a year without converting and you keep them on that same drug, they're not going to convert over the next 6 months.

DR. WEINA: Well actually, 10 percent did.

DR. GRIFFITH: Okay, so 10 percent compared to the 30 percent. But I mean we were talking

about the fact that, wow, that 30 percent is better than the 10 percent that was. But okay, again, you're not really -- it's not a fair comparison it seems like.

DR. WEINA: I'll step right from the microbiologic aspect to it. But this is what patients would otherwise maintain.

DR. GRIFFITH: Sure.

DR. WEINA: So in the odds of ALIS, they would have proceeded to --

(Crosstalk.)

DR. GRIFFITH: I'm just trying to be clear on what I meant by adding to the failing therapy --

DR. WEINA: I see.

DR. GRIFFITH: -- that it may not be statistically a fair comparison. I'll turn to our statisticians on that.

DR. WEINA: And the question is, with the medicines at hand, this is the way they would have gone on. If we had ALIS, what does that do to it? So I think it's exactly the comparison that we need

to decide whether there's a benefit of ALIS. ALIS achieves culture conversion, where continuation of what's available does not.

DR. BADEN: Dr. Green?

DR. M. GREEN: This is to Dr. Griffith, and I think it's pertinent particularly to question 2 that we're going to be addressing.

Can you tell us what the rate of culture conversion is in the de novo treatment naive patient?

DR. GRIFFITH: All over the map. I can tell you ours and I can tell you what meta-analyses showed. The 40 to 60 percent is a figure that is fairly consistent among a number of meta-analyses looking at MAC lung disease. We have a success rate of 83, 84 percent. Our colleagues in South Korea, Dr. Koh's group, have similar success rates. But I can tell you, across the board in North America, in Asia, and Europe, that is not the case.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: This is just a follow-up actually to the first two points you have that have

been addresssed this afternoon, as far as the effect of treatment. And I apologize because I know that it probably seems ridiculous to ask, is there a benefit of treatment? What we were shown, though, is that if cultures clear, then there are better outcomes for the patients.

But to address the FDA's point, are there certain patients who are more likely to clear, and therefore they do better because they have some favorable characteristics beforehand, just to address that question? Can you address that maybe with historical data, before we had macrolides or something like that, to show that, fundamentally, treatment and clearance themselves lead to better outcomes?

DR. SULLIVAN: I see. I'll start, and then since you're referring to the previous literature, I'll go back to Dr. Griffith. The data from the trial we analyzed to look at baseline characteristics that could predict. And the one that I mentioned that shook out from this logistic regression was the SGRQ score. That's a

non-validated instrument in this disease, but it somehow shook out that the more impacted on SGRQ, the lower likelihood of achieving conversion. But in terms of the historical literature, maybe I better ask Dr. Griffith.

DR. GRIFFITH: Thank you. I'm actually one of the few people whose career has spanned the pre-macrolide, macrolide, and now I hope ALIS era of treatment. There is precious little data from the pre-macrolide era looking at treatment response in MAC. That's all I can tell you. Some of it comes from our place. And treatment responses were reasonable, but there were so many caveats in patient selection and exclusion of patients. We have tried to do it to make some comparison, but it's almost impossible,

DR. BADEN: But I guess along those lines in study 212, for those who have converted and stayed durably culture negative, don't you know how much treatment has been averted versus those who say culture positive, how much treatment has been continued? Shouldn't that be knowable that perhaps

there is a treatment differential within the data that haven't been looked at that way?

DR. GRIFFITH: I can only tell you this, that when I was looking to help design study 112, I was asked what did I predict would be the rate of sputum conversion for patients who received a single inhaled antibiotic in addition to their treatment? And my advice was zero percent. So that would be my comparison. In fact, it turned out to be 10 percent, so I guess you're saving that differential between the 10 percent who converted and in the 30 percent who did.

Which by the way, if I might add -- I'm sorry,

DR. BADEN: No. I'm just saying that those are actual data that you have in your data set --

DR. GRIFFITH: Right.

DR. BADEN: -- that could be shared, that impacts clinical practice in terms of speaking to a potential clinical benefit.

DR. GRIFFITH: There is no other similar data. I don't know what to what to say. It's a

unique study.

I'm sorry. I forgot what I was going to say.

DR. SULLIVAN: There had been the third element if --

DR. BADEN: Please.

DR. SULLIVAN: So the question was about the expectation and why maybe we didn't see a clinical effect on 6-minute walk so early. I do want to clarify that the surrogate endpoint is not intended to represent eradication of the organism because that's achieved, and then patients are treated for another year because the assumption is you haven't eradicated. After 12 months, maintaining negative, that's what represents true eradication.

I'd like to bring Dr. Flume to the podium to talk about that sort of expectation of when you might see clinical benefit.

DR. FLUME: Thank you. I'm Patrick Flume. I'm a pulmonary physician at the Medical University of South Carolina in Charleston, where I'm the director of our cystic fibrosis center, but I also

lead large programs in bronchiectasis and nontuberculous mycobacteria.

I'd like to just offer some insights into the 6-minute walk data and how I perceive them. As one of the committee members astutely noted, should we even expect an antibiotic to have an impact on the 6-minute walk? And the answer to that is no because the antibiotic doesn't have any effect on the cardiopulmonary or the muscular systems. Its intent is to treat the infection.

As you've heard here today, NTM is a systemic infection. These patients have symptoms of fatigue and they lose weight. Their appetite is poor. It's not just respiratory symptoms. So when we think about how best to analyze the 6-minute walk data, this actually is the preferred way to sort of think about it. If I have that effective antibiotic result, in this case culture conversion, now I can compare to see if I have a difference in those.

So when you look at the overall study patients or even separate those on ALIS or those on

multidrug regimen, the first thing that is appreciated is the consistency of those data. And I'd like to put just a little bit of context to the 6-minute walk data.

The 6-minute walk has been a test that's been used in clinical trials for a number of years. People have focused on, well, how much matters? What's the minimal clinically important difference? And recent studies in the COPD literature have demonstrated repeatedly that that number is 25 to 35 meters.

Now, those studies have now been expanded to include other patients, including heart failure patients, patients with interstitial lung disease, and even patients without cardiopulmonary disease. And a systematic review that was recently published gave that number at 30 meters.

Then just recently in the Blue Journal, there was an interesting publication. Normally when we look at 6-minute walk data, we did an intervention that should improve like with cardiopulmonary rehab. But it can go the other

direction, and what's the minimal important difference in terms of a bad outcome with exacerbations or death? And that number turned out to be 30 meters. And in an accompanying editorial on that issue, the Blue Journal said I think we have our number, and that number's 30 meters.

So when I look at these numbers and I'm seeing mean differences of 31 and 25 meters, those are consistent with what we see as the minimal important difference. And that's after only 6 months of therapy. So I would actually argue that those are actually compelling data to demonstrate a functional improvement.

DR. BADEN: In these data, what struck me for the converters, the 20.7 meters converters, N equals 65. Eleven of those 65 converted with the threat of ALIS, not actually receiving ALIS. So how do we think about the data on those who converted prior to receiving the first dose, which was 17 percent of the 65? How do we think about those data on this analysis?

DR. FLUME: I still would include them in

the converters, and what I'm looking at is the surrogate there is the culture conversion relates to this improvement in functional status, and then you take a look at the 30 percent rate of conversion compared to a 10 percent rate. That to me is a compelling connection.

DR. BADEN: Dr. Andrews?

MS. ANDREWS: Oh, it's gone.

DR. BADEN: Please keep that slide up.

MS. ANDREWS: The slide with the -- yes. Thank you. This is on people at the end of 6 months who are left in treatment. This includes the 1 out of 4, 1 out of 3 that left often because of adverse events. Right? Disproportionately.

DR. SULLIVAN: This is the change from baseline to month 6, yes.

MS. ANDREWS: Right. And it's on people who stayed in the -- who didn't leave the study --

DR. SULLIVAN: Yes.

MS. ANDREWS: -- because of adverse events.

DR. SULLIVAN: Yes.

MS. ANDREWS: And you don't know a whole lot

about why -- I mean, you know what their adverse events were, but you don't know their health. And people disproportionately left that arm much more than they did the regular background treatment.

Am I right?

DR. SULLIVAN: Yes. The numbers that you've seen so far are folks who discontinued treatment due to adverse events. There are two ways -- now that we run trials and we try to keep patients in, if you want to stop treatment, please stay in the trial, and we did that. So the numbers that you saw that were projected where end of treatment, so those are people who discontinued treatment, not necessarily who discontinued the study. That's a separate --

MS. ANDREWS: They're down by like a hundred and something from what you started with, the total end here.

DR. SULLIVAN: So there are some, but I'm just clarifying that --

MS. ANDREWS: Well, 100 out of 300.

DR. SULLIVAN: Well, 75 out of 261, that's

300.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: On this same slide, a couple of questions. First of all, I guess I'm having trouble understanding -- there's no question that there's an advantage on conversion at this month. And I'm going to maybe talk about in a moment there's no question there's an advantage at the end, we already know.

But given there's an advantage of the people who convert, the greater proportion convert on drug -- that's clear -- this is indicating that the people who convert walk longer. Why is it that the overall randomized analysis, the difference is going in the wrong direction? I would have expected maybe it wouldn't be significant, but I'm surprised it's going in the wrong direction; not by a lot, but it is going in the wrong direction. It just seems hard for me to put all those things together. It just seems sort of inconsistent.

DR. SULLIVAN: Yes. And there are these almost identical sort of flat -- I think a comment

earlier --

DR. BRITTAIN: Yes. It just strikes me as odd. And maybe that relates to my next question, which is back on the previous slide, which is that -- and I think this is the point that others maybe have made, is that we don't if that higher value, that 21 meters is relative to the minus 10, we don't know if that's happening because they have converted or because something about --

The converters are sort of revealing a certain category of patients, and I don't know what it is. That's why I go back to the randomized comparison, I'm not seeing any difference. And it's hard for me to put all that together and understand it.

DR. SULLIVAN: That's entirely fair, and I think it's exactly the comment that the agency has made, that when you do these studies -- and it's done a lot in the literature, where you compare outcomes of converters versus non-converters, that's not a random assignment. But the problem is that you could never do that experiment. You

couldn't take two people and say I'm going to magically randomize you to conversion and you not. And that's the only way to show what you might want to see.

So what we're left with are these observations that are repeated throughout the literature. Here we've shown it at 6 months. The literature referenced that we look at lung function differences, radiographic differences, mortality differences, but they all have that basic intrinsic difficulty, which is these are not random groups.

DR. BRITTAIN: Right. But the randomized comparison --

DR. SULLIVAN: Yes, and we did not see that at 6 months.

(Crosstalk.)

DR. BRITTAIN: -- answers [indiscernible] the direct question.

DR. SULLIVAN: Right. And absolutely, it was not seen at 6 months. It's possible. And to the point Dr. Flume made, the idea is that you're not going to see it until you achieve your

microbiological, and then you will start to see some clinical benefits either at 6 months or later. So your point is well taken and the data are what they are.

DR. BADEN: Dr. Proschan?

DR. PROSCHAN: Yes. Just in response to that, you do see, numerically anyway, the non-converters on ALIS are doing worse than the non-converters on the multidrug regimen. And of course there are many more non-converters than converters. So you put those together, and it's reasonable that it would go the wrong way.

DR. BRITTAIN: In fact, in the unadjusted presentation that the FDA did, there was a very big difference -- I mean, not a big difference, but I think it was 13 versus zero among the non-converters.

DR. BADEN: So are you suggesting --

DR. BRITTAIN: The adjustment that was done here, was that prespecified? I know it was exploratory but prespecified. Was the adjustment prespecified? And is it the same adjustment

for all the comparisons? I'm just kind of curious how that worked.

DR. SULLIVAN: This was a prespecified analysis, and I think the agency has expressed their concerns about the whole nature of converters and non-converters, so as was suggested, did just a descriptive look. But because we had seen this in the 112 study, we said let's look at it again. And we prespecified it as exploratory because it is an unorthodox thing

DR. BRITTAIN: The covariates were, the particular covariates in the analysis.

DR. SULLIVAN: Yes.

DR. BADEN: Just building on Dr. Proschan's comment to make sure I understand it -- and please comment as well -- if in the ALIS multidrug regimen, there's a null effect on the walk test, 6-minute walk; yet in a subgroup of converters, there is a significant benefit, then the implication is there's an equal amount of harm in the non-converters.

Is that one way of interpreting these data

or do we get benefit in the subgroup but no harm even though there's a null effect? Help me understand how to interpret these data.

DR. SULLIVAN: That's an interesting way to look at it. So you're saying because the subset of converters, the 65, we saw that increase -- I mean, we see what happens in the non-converters with ALIS, at least a change from baseline, and we see a 10-meter change from baseline mean, ALIS mean.

DR. BADEN: On the next slide, you show that it flatlines, so we'll accept that it's flatline and no different in the overall group. Yet in a subgroup, there's a benefit. Therefore, there must be a reciprocal decrement.

DR. SULLIVAN: And the reciprocal decrement I think is shown on the slide.

DR. BADEN: No, no, correct. And therefore, as we think about these data, as we think about risk-benefit, perhaps there's a subgroup of benefit, but there may be a subgroup of non-benefit or harm in just thinking about the potential implications of these data.

DR. SULLIVAN: Well, I wonder if that just is not harm of the drug but a change from baseline in patients who have not achieved any benefit, so a decline in their capacity. I think that might be equally valid.

DR. BADEN: Thank you.

DR. PROSCHAN: We haven't seen any p-values for the comparison, for example, of non-converters in the two arms, so this could easily be just the play of chance that happened to be non-converters did a little worse in the ALIS arm than in the other arm. That's not necessarily a statistically significant difference.

DR. BADEN: Sure, although they do give an ESP [ph] value above the 2 blues and the 2 pinks.

DR. PROSCHAN: But that --

DR. BADEN: I know. No, your point's well taken. The data are complex.

Dr. Daskalakis?

DR. DASKALAKIS: It's Demetre Daskalakis. I know that we haven't seen any of the data on the St. George's Questionnaire. Can you share what you

do have?

DR. SULLIVAN: Yes, absolutely. I'll bring Dr. Streck to the podium to talk about the St. George's.

DR. STRECK: So again, the SGRQ, as you're aware, is a patient-reported outcome that looks at three specific domains: symptom, activity, and impact. It's approximately 50 questions where patients are asked to answer true/false questions, as well as a scale of overall how they're feeling.

Certainly, at month 6, we saw a slight worsening in both groups. The scale runs, just for everybody's review, from zero to a 100; 100 is the worst, zero is the best. So we saw an approximate 4-point change in the ALIS plus multidrug versus 0.38 in the multidrug alone. Again, being on active therapy at 6 months, not a surprising outcome.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: For those of us who aren't familiar with the scoring, how much worse is that?

DR. BADEN: What's clinically significant?

DR. DASKALAKIS: What's clinically significant.

DR. BADEN: Four.

DR. DASKALAKIS: Got it.

DR. BADEN: If during any of this discussion, the agency has comments, please get my attention. We want all input.

Dr. Green?

DR. M. GREEN: And just to clarify, I think you said this earlier, this endpoint is also being applied sequentially, so I think at 8 months and certainly the 3-month off, because perhaps this could have detriment because it's clear that there's treatment-associated side effects, but those results in eradication, the long-term benefits could come with the knowledge that you're living through treatment-associated side effects.

So just to confirm, you're doing these sequentially?

DR. SULLIVAN: Yes.

DR. BADEN: Dr. Sullivan, other follow-ons from earlier? We have at least a dozen comments

from panel members from earlier, and we'll get to those if you still have the comments, but we'll first turn over to Dr. Kim.

DR. KIM: Hi. This is Peter Kim. We actually have a clinical outcomes assessment expert as well who would be interested in commenting on the SGRQ results.

DR. BADEN: Thank you. Please state your name, and thank you for sharing your thoughts.

DR. CAMPBELL: Good afternoon. My name is Michelle Campbell, and I'm part of the clinical outcome assessment staff in CDER. A couple of things to remember about the SGRQ, its original development was for asthma and COPD. It is, as was mentioned, on a zero to 100 scale, where 100 is worst health status. But it's important to remember that there are 3 domains in the instrument that combines a form of total weighted score. So you may be seeing things are being weighted in a direction not in the symptoms, but maybe their overall quality of life is overtaking some of the score.

Additionally, the 4-point change has been listed as a minimal clinically important difference where we at the agency are looking at within meaningful patient change is 4, which was established in the COPD population but has not been established in this patient population. So it's unclear if we're actually measuring the correct things for this patient population and do we know what is correct for meaningful change.

So we would encourage additional work in this area to make sure that we are truly capturing what's important to these patients and that we have an interpretable score that we know what's going on in the direction.

DR. BADEN: Thank you.

If no other follow-on questions there, I'll ask to clerical questions while members of the committee get back into the earlier mind-set.

Any blood levels, any done during the study? And number two is compliance. Do you have any measures of how often did patients actually use this daily or do you have any measures of those two

parameters?

DR. SULLIVAN: Yes, and I'll answer them in reverse order. For the pharmacokinetics, I'll ask Dr. Rubino to come to the podium.

The way we measured compliance in this was based upon returned vials. It's important to note that that could recommend a noncompliance. But also if there were any interruptions around an adverse event, that would be captured in the numbers that I'll show. We defined these 3 buckets, and you can see the majority of patients were in the central bucket, 80 to 120 percent compliant, but some were in the 32 points.

DR. BADEN: 120 percent compliant.

DR. SULLIVAN: Yes.

DR. BADEN: Good. We strive for that.

DR. SULLIVAN: In terms of the pharmacokinetics, I'm going to bring Dr. Rubino who's our pharmacokinetics expert.

DR. RUBINO: Thank you. Chris Rubino from ICPD. We provided clinical pharmacology consulting throughout the ALIS program, both in the CF and in

the NTM.

There were subsets in both studies, 112 and 212, where they collected pharmacokinetics. Did you have specific questions around the blood levels?

DR. BADEN: Were they done and what did they show, particularly more than a single dose? And people on chronic therapy, do we have some sense of what the systemic exposure is?

DR. RUBINO: Certainly, yes. They were collected throughout. They were sparse sampling. These were phase 3 clinical trials. It's an inhaled drug. And actually, if I could have the one with the urine first, please. It would be the next one, PK-9.

So it's important to realize that this is essentially a topical administration, so we're getting very little bioavailability, and because the amikacin is completely eliminated via the urine, we can look at urine excretion over time. And these numbers are relatively small, but they're also consistent with what we saw in the CF program

with larger numbers. And about 7 percent of the administered dose is coming out in the urine. So the overall exposure is very low, but we were able to quantify it in plasma.

In terms of -- can we go back to the next one -- when you compare exposure overall between these NTM patients and patients receiving systemic therapy, we get much lower exposures, much lower AUCs and Cmaxes in the systemic circulation compared to systemic administration. So you're looking at AUCs in the 20 range versus over 100 AUCs, 500 NTB patients, 235 in CF and slightly lower in healthy volunteers.

DR. BADEN: But you're seeing systemic exposure.

DR. RUBINO: Yes.

DR. BADEN: Dr. Green?

DR. M. GREEN: Just to explore this further, did you see any differences in these levels by any patient clinical profiles; so those that at least have been noted to have cavitary disease versus not anything, that might identify patients who are at

greater risk for systemic absorption from those who are at lower risk for systemic absorption?

DR. RUBINO: We did not. As mentioned was mentioned, we didn't note cavitary disease in every patient, so we weren't able to look at that. But we looked at age, creatinine clearance, body size, race, FEV1, baseline FEV1. In none of those -- body size was slightly predictive of the amount that came out in the urine when you looked across all patients, but nothing else was suggestive.

DR. M. GREEN: I might recommend that you knew the information on some as having cavitary disease and you knew the information on some having surgical resection. And it might be worthwhile, since you know it in those, to at least look at it because it could give -- they may not be large enough to confirm the association with that clinical description, but it might identify something that might suggest to the physician putting the patients on, that this patient deserves to have a level here or there versus others who may

not.

DR. BADEN: Dr. Masur?

DR. MASUR: I wasn't clear from what you were saying about drug exposure in terms of whether there's any correlation with response because one could presume at least that some patients get a larger dose because of their inhalation and their lung architecture than others. But did you look to see whether the nonresponders had a dramatically lower a urine concentration than the responders?

DR. RUBINO: We did not, mainly because of the small numbers. We had approximately 40 patients with blood levels in the 212 study, so the numbers were just too small to tease that out. There is quite a bit of variability. It's inhaled administration. So as opposed to IV administration where we're very sure of those exposures, there is a lot of variability. It's all low, but it's variable.

We did look in CF at FEV1 outcomes, and in those studies, they were getting three different doses. And you couldn't differentiate between dose

or AUDC. AUC did not provide anything better than dose did for correlations with FEV1.

DR. BADEN: Dr. Weina?

DR. WEINA: A follow-on to that. Was there a difference in the pharmacology of healthy individuals versus individuals that had disease, first of all?

DR. RUBINO: There were no healthy volunteer studies with ALIS. They were not conducted. There was a slight difference between CF and NTM patients. They're much older in the NTM population.

DR. WEINA: And did you do any studies, radiolabeled studies, imaging studies of the distribution of the drug when it was inhaled?

DR. RUBINO: Not in humans. I believe there were animal studies.

DR. WEINA: So you don't know -- the speculation could be that it's just going to be going to the well ventilated areas -- potentially to the well ventilated areas of the lung and not necessarily to the areas in which there's mucus

plugging or where the bug may be hiding as well.

DR. RUBINO: Right. And just a correction, we didn't do them as part of the pharmacokinetic program, but there were very early studies in the development program looking at just a few healthy volunteers in a few patients, but there's not much data from that.

DR. BADEN: If no more follow-on questions, we'll go back to the list. And our committee members may or may not recall --

(Laughter.)

DR. BADEN: -- their thoughts from a millennium ago.

Dr. Andrews?

MS. ANDREWS: It's about whether there were any clinical questions.

DR. BADEN: Okay. I'm not going to force questions. I just want to make sure all questions that are not yet answered have a chance to be aired.

Dr. Lo Re?

DR. LO RE: This is for the sponsor. So

outside of the data in patients with refractory NTM, do we have data on efficacy and safety in other patients who are just perhaps initially starting treatment?

DR. SULLIVAN: So not in NTM. All the NTM work is essentially refractory NTM. The drug was initially being developed for a different indication, pseudomonas in CF patients. So it was administered in a different way. It was administered -- I think it was alluded to by the FDA. So the early development program looked at suppression of pseudomonas in CF patients akin to what -- there are a few approved drugs in that arena.

DR. BADEN: So I have a follow-on, which is another data set that I've not heard discussed yet. What are the implications to other flora, thinking about potential harms? Inhaling an aminoglycoside, one may think that the flora may become resistant. Systemic exposure, the GI flora may become resistant.

What data do you have on the selection and

amplification of antimicrobial resistance in non-mycobacteria in these patients?

DR. SULLIVAN: In the clinical trials, we did not collect data on other flora within the sputum.

Dr. Griffith, you have anything to add to that?

DR. GRIFFITH: No.

DR. BADEN: Okay. So we don't --

DR. SULLIVAN: We didn't collect and analyze any other --

DR. BADEN: Okay. So there are no data on the impact on the colonizing flora of these patients.

DR. SULLIVAN: That's fair to say. We have it from the CF program, but not in the NTM.

DR. BADEN: Dr. Green from earlier?

DR. M. GREEN: Yes. I just have to find this on my notes. Could you clarify interrupted versus discontinuation, which was noted in there. And for those individuals who interrupted therapy because of a side effect, when they went back on to

therapy because it was interrupted, did the side effect recur?

DR. SULLIVAN: The protocol allowed for temporary brief interruptions to manage adverse events -- typically, that might be something like dysphonia -- until the events subsided.

Why don't I bring up Dr. Flume to talk about how these interruptions were enacted and so forth and the effect on the --

DR. FLUME: Patrick Flume. I can tell you how I do it in clinical practice and what we did in the clinical trial. Some of the adverse events that you saw listed on there are pretty typical of aerosol therapies.

We use a lot of aerosol antibiotics, dornase, hypertonic saline in our patients, so we educate our patients about what they might expect such as cough, dysphonia, maybe in the sense of chest tightness or breathlessness. Most of those when they have them are really just tolerance issues. They're transient and they're mild. But when they are felt to be problematic for the

patients, we'll stop the therapy until the symptoms resolve.

An example of this comes from our guidelines about dealing with complications in CF with hemoptysis being one of them. So we don't think of these drugs like hypertonic saline and dornase as causing hemoptysis, but the fear is that if they are coughing of blood, it's going to create problems with the healing process. So we'll stop drug, stop aerosol therapy. Once it resolves, say 2 or 3 days later, we'll reinstitute the therapy. That was our practice with these patients in my clinical experience as well.

DR. BADEN: Dr. Proschan?

DR. PROSCHAN: I don't remember what I was going to say before, but --

(Laughter.)

DR. BADEN: No. If you have questions, we want to air all considerations.

DR. PROSCHAN: Okay. Thanks. I was just wondering whether -- this is to the FDA -- before the trial started, you accepted the endpoint or at

least thought it was somewhat reasonable.

Has there been any data that's come about in other places? I know you presented some data from other studies. None of that really said -- it sort of was consistent with conversion, which is good. So has there been any data that's made you doubt what you thought was okay at the beginning?

DR. NAMBIAR: It's not that there's any particular new data. I think, as was mentioned during earlier discussions, when we had discussions with the applicant about the design of the study, I think there was an acknowledgement that the available information is not perfect, that this is not the best surrogate endpoint. However we did recognize that there was an unmet need and the patients needed options.

We were certainly encouraged by the findings in study 112. I know there has been discussion around is 6 months good enough to detect any kind of benefit on clinical endpoints. What we had at hand were the results of the phase 2 trial, where in fact, there seemed to be some benefit on a

clinical endpoint.

So at that point, taking into consideration the unmet need, the fact that we saw some clinical benefit and we hoped that that would be reproduced in study 212, we were willing to accept the uncertainties. And then when we got the results of study 212, we see a benefit on the microbiologic endpoint. However, we are not able to see any trend. Again, we're not looking for a statistical finding on the clinical endpoints, but we are not seeing the trend we were hoping to see or what we saw in study 112.

So we went back to take a look at the literature and see are there any new studies, is there any other new information that would help us make the link between the surrogate endpoint and a clinical benefit. And as you've seen, the data are what they are. They are generally from retrospective studies or observational studies, and it's very hard to conclude.

Is there a suggestion that people who can work do better? Yes, there is, but you heard the

limitations of the study. So that's where we are.

DR. BADEN: Thank you. Dr. Evans?

DR. EVANS: I actually have two questions. One relates back to some of what's already been discussed. This is for the sponsor.

It was mentioned in the applicant's presentation earlier that one element might be difficult to understand about the 6-minute walk study is that as there was no inhaled placebo control, there might be volitional issues. And we have actually brought up a couple of other issues so far today about whether there might've been side effects of just the vehicle if you had included a placebo control.

As someone who uses a lot of hypertonic saline in my patients, I might even argue that we might see a difference in things like the compliance rate, the delta between the two groups for compliance, and even perhaps the microbiology might have been different had we included the hypertonic saline and perhaps the empty vehicle liposomes.

I know you spent months laying out this trial, so what I'm asking you now is what is the rationale for not including a blinded placebo group, an inhalational placebo group?

So that's question number one, if you will. Well, go ahead if you'd like to respond to that.

DR. SULLIVAN: In the phase 2, we used an empty liposome --

DR. EVANS: Indeed.

DR. SULLIVAN: -- to create a visual a comparator. When we started talking with the agency about design of phase 3, they raised a concern that if we used empty liposomes as the comparator, there might be some difficulty in ascertaining safety issues related to the liposomes themselves. So if there were some harm from the liposome, you wouldn't catch it if you did an ALIS versus empty liposome.

So that was really -- and then because the primary and confirmatory endpoint were the subjective en point, we felt that that was the best option so that we'd maintain the ability to really

see what's drug related as compared to an empty liposome, which might have its own theoretically adverse. So it was really a safety comparison that drove that, keeping in mind that the efficacy endpoint was objective, so it would be less subjective volition.

We always knew that the 6-minute walk test, at least by treatment group, would have that overhang. I did point out that the comparison, limited as it is between converters and non-converters, in fact, patients didn't know at that time whether they had converted, so there was an element of blinding there.

DR. EVANS: Right. And I agree, actually. As I think about the IDEAL trial, ideal probably would have been only hypertonic saline, hypertonic saline plus vehicle. I know that's more groups than I'm sure you wanted to deal with, but --

DR. SULLIVAN: In very rare disease, it's very difficult to have multiple treatment arms.

DR. EVANS: Okay. The other question I wanted to ask about was regarding lung disease. I

think there were reported 7 instances of something that was variously categorized as allergic alveolitis, ILB, hypersensitivity, and pneumonitis -- I think were the designations.

Question one of that is how were those diagnosed? And then it sounded like, based on the presentation, 6 of them got better. What happened to the 7th?

DR. SULLIVAN: You're right. It's very difficult to diagnose allergic alveolitis in this population that has these fleeting infiltrates and so forth. So I'd like to bring up Dr. Donohue, who was chair of the DMC and saw these cases coming in. He also has quite a lot of experience treating these patients, and I think he has a perspective on this issue of allergic alveolitis.

DR. DONOHUE: Thank you for the question. I'm Dr. Jim Donohue, former chief of pulmonary, Chapel Hill, where we have a lot of mycobacteria. I was chairman of the DMC, and I've been treating at Davits [ph] for 42 years, started in 1976. So I was with the original streptomycin guys.

But anyway, the study was really interesting. As you know, behind your question is allergic alveolitis can be due to just the MAC itself. Cecile Rose at National Jewish described this as hot-tub alveolitis, and it's MAC, which just causes diffuse alveolar damage in an alveolar. So we have that in the background.

Now, we were very interested on the safety committee whether or not an inhaled antibiotic would cause any harm other than just the effect, the mechanical effect. And I've done hundreds of these studies where you give a drug, an inhaled drug, to a sick patient with an irritable airway. You're going to get the side effects here.

So the problem was that, as you know, in pulmonary, every time there's a little gray on an x-ray, it's called ground glass. And treating doctors call that alveolitis sometimes, or maybe it meets small airways disease, or something else. And I thought most of the time, looking at these cases with an infectious disease expert and a statistician, that it was more reflective of the

MAC. It was just alveolar edema. We didn't see much of anything else.

Now, what really made us not harp on it was that it resolved. And even a couple of cases with the interruptions that we've heard about it, again it resolved. So it really didn't meet the standards that you and I are used to in pulmonary medicine when you really do have an allergic pneumonitis where it would be persistent with a more clinical deterioration. These were self-limited.

Again, it's hard to tell. When trying to be very careful with this, there was so much bronchospasm going around from just the mechanical process of inhaling an antibiotic. So we thought most of them, and the committee -- we mentioned them. We wrote back to the company. There was an imbalance, but they were all resolved. And we had the benefit of that resolution by the time we adjudicated it.

DR. EVANS: In that seventh case, it sounds as if we have a pulmonary progressive case.

DR. SULLIVAN: Let me bring up Dr. Sallstig. I think we have similar experiences. It may have been a patient who had underlying interstitial disease.

DR. SALLSTIG: Thank you. Peter Sallstig. If I understood correctly, your question was with regards to that one single patient who, unfortunately, did not resolve. So this patient was an 80-yea- old male who had a worsening of their interstitial lung disease. This patient had also underlying scleroderma. So scleroderma was his predominant disease, and the interstitial lung disease was considered secondary to that lung disease. The patient was in the trial, discontinued on day 220, and approximately 300 days after having stopped ALIS, the patient passed away due to interstitial lung disease.

DR. BADEN: Dr. Masur, questions from earlier?

DR. MASUR: It was resolved [off mic].

DR. BADEN: Thank you. Dr. Schaenman, questions from earlier?

DR. SCHAENMAN: I have a question for the sponsor regarding the drug formulation. We're already using inhaled amikacin, admittedly off label for treating of NTM. I didn't really get a good sense from the initial presentation as to why a liposomal is so much presumably preferable to the naked amikacin that is currently used.

I also wanted to know if the liposomal formulation that you developed was truly novel or if there might be analogous liposomal inhalation drugs that are already in use that would give us a benchmark. For instance, does this differ significantly from inhaled AmBisome or is it similar?

Finally, I was curious about the dosage determination as that wasn't mentioned, and that spirometry was used as a safety measure, but we haven't really seen that data. And a related question is why was spirometry not used for a clinical endpoint?

DR. SULLIVAN: Okay. A lot in there.

DR. SCHAENMAN: I know, a lot, sorry.

DR. SULLIVAN: I'm going to try to him them sequentially, and please let me know if I haven't hit it. In regards to the formulation and the liposome and the potential beneficial effects of the liposome, I could bring up Dr. Sasha Rose to give some information about what that adds.

Dr. Griffith has done a review of the literature of what's available for inhaled amikacin. I might bring him to talk about what's known about inhaled straight amikacin, but Dr. Rose can address the nature of the formulation.

DR. ROSE: Hi. my name is Sasha rose. I'm a microbiologist and senior scientist at Insmed. I've been working with NTM and researching them for over 10 years, and I've done a fair amount of the ALIS preclinical efficacy work.

Can we pull up CO-10? What we saw in the earlier presentation was a visual representation of fluorescently labeled amikacin either within ALIS or free drug. And this was put upon cultured macrophages for a 24-hour period. And as you can see, there's a lot more fluorescence inside of the

macrophages, meaning amikacin got delivered at much higher levels when encapsulated versus free drug. Now again, this is a visual representation.

Can you please pull up slide BI-3? So we quantitatively did this same experiment via flow cytometry. And as you can see here in a dose-dependent fashion, when ALIS is incubated with the cells over the same 24-hour window, we see significantly more amikacin internalized inside of the cells. Now why this is important is because these bacteria are primarily residing within macrophages. The more amikacin we can deliver to the site of infection intracellularly, the better efficacy we will see.

DR. SULLIVAN: So that's formulation. I'm not sure whether you'd like to hear -- because there is very limited information about the actual safety and efficacy of off-label use of injectable amikacin. If you'd like to hear more about that, I can bring up Dr. Griffith.

Is that -- nodding yes.

DR. GRIFFITH: Thank you. Inhalation of

generic amikacin is exactly what's been wrong with NTM lung disease therapy for the last 20 years. It's been around -- I think the first publication was some time in the mid-2000s. Actually, Dr. Ruhas [ph] who spoke earlier was an author on that paper. I did look at the World's Literature on that. People want to use that. They want to use it instead of parenteral amikacin. It's widely used. But I can tell you they're probably not more than 120 or 130 patients reported using that for MAC, and the results are all over the map.

Just to sum it up, that's apples and kumquats. This is a prospective randomized trial, and there is nothing but anecdote about -- I guess last as an editorial statement, if there was some major signal there over the last 10 years, we should have seen it, but it's not there.

DR. BADEN: And if I understand theoretically, the size of the liposome should disperse more evenly, and the lipid carrier should be internalized by the macrophages. So theoretically there's an advantage, although it's

not been looked at compared to free amikacin in vivo, if I'm understanding the data correctly.

Is that correct?

DR. SULLIVAN: I'm not sure I follow exactly that --

DR. BADEN: No. I was re-stating what I think I have heard, is that given the 4 to 6 microns, the liposomal format should disperse better in the lung parenchyma than free amikacin or not?

DR. SULLIVAN: Well, the dispersion of the distribution to the lunch is more a matter of the admitted characteristics out of the nebulizer, so the droplet size. So there are two important measurements. One is the droplet size that comes out of the nebulizer, and that's what determines where it goes in the lung. And that was optimized, but the intention was to select an optimal MMAD aerodynamic diameter to get the drug to the lung. The size of the liposome is optimized for a phagocytosis by the macrophage, and they're an order of a magnitude different.

Then I think your maybe last question, if I got them all, had to do with FEV1 and why that wasn't a --

DR. SCHAENMAN: Right. But also, are these liposomes like any other liposomes that we might have experience with?

DR. SULLIVAN: I don't have a comparison of particularly the lipid content and so forth. I know that these are novel, and I can't actually speak to the difference between the amphotericin liposome.

The last one was I think the FEV1 and why that wasn't an efficacy endpoint. We took a lot of this from this bronchiectasis experience, that that was felt to be a very insensitive measure because these patients have a lot of underlying structural fixed bronchiectasis and then also a lot of mucus and so forth. So there would be a high degree of variability and also a limitation on what you could do to improve that. So that was not felt to be an optimal efficacy endpoint.

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

DR. WEINA: Just a follow-on on the liposomes and the macrophages. And liposomes are great because they're picked up by the macrophages and they're gobbled up by them, so it helps to concentrate the amikacin there. But the issue is that we know that mycobacterium will actually modify the functionality and the ability of macrophages to phagocytose.

So the data that were shown of the increased uptake by amikacin was that in just uninfected macrophages or did you also try that in infected macrophages?

DR. SULLIVAN: Let me bring Dr. Rose.

DR. ROSE: Sasha Rose. Could you please pull up slide CE-4? So we didn't directly look at uptake of liposome and infected macrophages of NTM, but we did look at intracellular efficacy of a dose-ranging ALIS against three different strains of MAC. And as you can see here, as the dose increases, the killing increases of this intracellular population. So vertically, we are seeing still intracellular accumulation in a dose-

dependent manner.

DR. SULLIVAN: I think there's also another element to this, is that during the nebulization, a certain portion of the liposomes liberate a certain degree of amikacin. So what actually is delivered to the body is a combination of a little bit of free amikacin and the liposome encapsulated. So there's some amikacin for the non-macrophage organisms.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: And why 590?

DR. SULLIVAN: So the dose was selected on the basis of a number of factors. As you well know, it is difficult to do extensive dose ranging in a rare disease. The way we came at this dose was, first of all, considering PK considerations, we knew that this dose achieved sputum concentrations that were in excess of the MICs for most MAC isolates. And it did so well limiting systemic exposure, so we kind of achieved that at PK goal.

We also had the safety and tolerability

experience from -- I mentioned earlier that it was initially developed in cystic fibrosis, and there was also some studies in non-CF bronchiectasis where there had been dose ranging done. So given the limitations of the different populations, CF patients, and a different cycling of drugs, given all that, we had identified a dose of 590 that was well tolerated in the CF population. We felt that was reasonable to take forward in phase 2, and then we saw in phase 2 what promising results.

DR. BADEN: Thank you. Dr. Daskalakis? Dr. Honegger?

DR. HONEGGER: My question is for the FDA, but it might be the sponsor, too. As far as the safety of the drug, I realize a lot of the effects might be just reversible effects associated with inhalation. But hospitalizations caught my eye, and I'm trying to decide how significant that is.

I was trying to think what more data you could give me. Do you have a time course like you did for the treatment-emergent adverse effects? When did these hospitalizations occur? Was it just

at the beginning?

I'm trying to figure out are these just patients who have COPD or bronchiectasis and they're coughing more from their drugs as expected, and they just get diagnosed with an exacerbation and get hospitalized or are they really sick? Maybe the timing would be helpful.

DR. HIRUY: I do not have a plot as the other one, but they were all over. They were not like at the beginning.

DR. HONEGGER: Okay.

DR. HIRUY: The problem is we had some limitation in the data to look at how long the hospitalizations were because it was limited data that we got. My understanding, the way I interpreted it was similar to yours, that these were patients that were inhaling something and then having exacerbations. If you look at it, they kind of mirrored the SAEs, so the percentage difference in the SAEs were very similar to the percentage difference in hospitalizations because they were a subset of the SAEs.

DR. BADEN: I had the same question, but for the applicant, because I think it was a 50 percent increase in hospitalizations or about a 5-6 percent absolute increase during the treatment period. And I'm curious as to your thoughts as to why there was such an increase in hospitalizations during treatment.

DR. SULLIVAN: Sure. I'll bring up Dr. Sallstig to the lectern to go through that analysis of hospitalizations.

DR. SALLSTIG: Thank you. Peter Sallstig. With regards to why there was a higher proportion, what we know for a fact is that there was a higher proportion of respiratory events that actually led to hospitalization. We also know that if we're looking at the events per se, at the number of hospitalization events, there were also outliers. There was, for instance, a patient there who had already had 3 hospitalizations even prior to being randomized.

I would like to share this patient profile with you because I think this is actually very

important, just to give a bit of an understanding. This is a 76-year-old current smoker, 50 pack-year smoking history, so medical history of COPD, bronchiectasis, hearing loss, hypothyroidism, so a very sick patient.

The important fact here is that this patient, already even before coming and being randomized, during the screening period had, as you can see, exacerbation of bronchiectasis, lower respiratory tract infection, and infective exacerbation. And this happened within a 1-month period before the patient actually was randomized. Then we can see that this patient had an additional 10 hospitalizations throughout the trial. Very important here is that this patient actually remained on ALIS without no interruption.

DR. BADEN: If you can pull up slide CO-78, because there are a number of hospitalizations and there are a number of patients hospitalized.

Am I reading this correctly? There is 19 percent versus 13 percent, so 6 percent more patients hospitalized. Correct?

DR. SALLSTIG: That is correct.

DR. BADEN: So it's not just that one patient was hospitalized 10 times. So I'm trying to understand, as Dr. Honegger raised, so more patients are being hospitalized on this therapy, can we understand that they have sensitive airways and this is causing airway reactivity leading to hospitalization or what's going on there?

DR. SALLSTIG: Well, we have done a deep analysis, so we've really looked into each patient that has had a hospitalization, and quite frankly we have not been able to decipher any specific underlying mechanism why these patients might be more prone. What we do know, as has already been mentioned before, is that these patients have severe underlying disease. So they have their COPD. They have the NTM disease.

So they have been carrying the NTM disease for quite a long period of time, but we have not been able to really specifically outline what it is that has contributed to them becoming hospitalized.

Perhaps I can ask Dr. Patrick Flume also to

give his perspective on hospitalizations.

DR. FLUME: Thank you. Patrick Flume. So we've learned a great deal in our investigations of studies, patients with bronchiectasis and cystic fibrosis, and as we pay attention to hospitalization to see is the drug doing anything there.

One of the first lessons is that for some of these conditions, and especially COPD and bronchiectasis, the history of events is highly predictive of future events. So one of the things we don't know -- I've not seen it -- is how much we about their history of events except for that one patient. And we could all ask why that patient was actually enrolled in the study.

So that's certainly one possibility. And the other one is exactly what you alluded to, that when you have a drug which causes AEs like cough or a sense of dyspnea, does the patient or the clinician perceive that as an exacerbation of their disease warranting a hospitalization? Sometimes it might be just part of the AE profile, and that's

it, and they could have walked through it another way, but they decided to go to admission to the hospital.

You're not going to be able to tease that out, but they clearly knew they were on it. But what I found most remarkable is how many of those patients remained on drug, so at least those doctors and those patients concurred that it wasn't the drug; they were willing to stay on it.

DR. BADEN: It gets to Dr. Evans' point about open label versus double blind, but that ship has sailed.

Dr. Masur, a follow-on?

DR. MASUR: Do you have a sense as to what the distribution of durations of hospitalizations were? In other words, were these mostly short durations or prolonged durations?

DR. SULLIVAN: Unfortunately, the data, the way it's collected is the adverse event is associated with the hospitalization, and then the data is the duration of the adverse event itself. So the patients are obviously not hospitalized for

the whole duration of the adverse event. So I don't have that information. The duration of the adverse event really isn't telling.

DR. BADEN: Thank you. A follow-on, Dr. Honegger?

DR. HONEGGER: Just real briefly, just to get at more of a qualitative appreciation of the side effects like the cough, do people who take this, who 45 percent have cough, is it just for an hour or so after or a few minutes afterwards for most of the patients, or are they coughing all day long more so than the patients who did not get the drug?

DR. SULLIVAN: The majority of patients, it's typically either during the administration or immediately after and lasts a minute to 10 minutes for the majority.

DR. BADEN: Thank you. Dr. Weina?

DR. WEINA: I have a real quick question for the agency, and that is one of the things that we were talking about, was the issue of accelerated approval versus full approval. So accelerated

approval, based upon the negative sputum and the surrogate endpoint, and then full approval would be later on, I assume, after the trial with durable culture conversion and more evidence, and what happens if that fails?

DR. COX? So accelerated approval -- and Dr. Nambiar went through in some of your slides serious disease and provides meaningful benefit beyond existing therapies. It's based on the surrogate endpoint. And the surrogate endpoint is one that's reasonably likely to predict clinical benefit.

Following an approval based upon a surrogate endpoint, prior to approval, we agree upon a study to be done that will provide the evidence to essentially demonstrate the clinical benefit. So that would typically be, if the surrogate happens at an earlier point in time and the clinical change takes more time to occur, then you would do a study that would look to be able to demonstrate that clinical benefit.

Now, what actually the design of that study

will be and where that information will come from I think is something that we're asking your advice on. And you've heard some discussion about 212, and 312, and how patients are changing there. So I think that's something worth talking about a little further, too.

DR. HONEGGER: Okay. Then just to be clear, their slide CO-12 showed that, basically, 312, if you will, or the ongoing work with 212 is not the agreed-upon endpoint for full approval at this point. It's still up in the air.

DR. COX: So I guess maybe the way I would think about it is will that study give you the type of data that will help you to understand the clinical benefit?

DR. BADEN: So can we suggest new study?

DR. COX: That is certainly within your purview to do so.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: I do have a follow-up on that, back to slide CO-50 that we've seen many times. If the worst case scenario -- I see it says

data has not yet been reviewed by FDA. But aside from that, if I'm understanding it correctly -- and I'd like you folks to let me know if I'm interpreting it correctly -- that the durable culture conversion endpoint -- not clinical, it doesn't have anything to do with clinical, but durable culture conversion endpoint is such that of the 212 people randomized to the drug arm, at least 48 will be successful, because we already have 48, and of the 112 randomized to the other arm, at most 3 will be successful.

Am I correct about that? I haven't done a test, but I would think that would be highly significant.

DR. SULLIVAN: At the time the trial was designed, it was discussed at length, and the plan at that time was that this trial would be the confirmatory trial. The agency suggested to us, recommended to us, that the confirmation of clinical benefit, the confirmatory endpoint was what we put on that slide.

Now I think there's some discussion about

whether that was wise or whether you all agreed with that. That's why it was on the slide, that that's the way the study was -- [audio gap] -- in discussion. So we agreed upon the surrogate, given the seriousness of the disease, and we agreed upon the confirmatory endpoint.

There was this expectation, based on 112, that we thought we might see a clinical benefit, but that was a secondary endpoint. But the endpoint, the confirmatory endpoint, was recommended to us to be this. There was not a recommendation for an additional later clinical endpoint. And your interpretation of this result is correct. This is an interim look at what we will see at the end, so worst case is how you described it.

DR. BRITTAIN: What I'm saying -- I just want to get confirmed that I understand it correctly -- is these data already demonstrate the difference on the durable conversion endpoint. The worst-case scenario is you have at least 48 successes in one arm and you have fewer than 3 in

the other, and it's a 2 to 1 allocation.

DR. SULLIVAN: Right. And you pointed out, and I want to acknowledge the agency has not seen this data. This was primarily to address that first part of the surrogacy question; is it reasonably likely to predict something? And we're seeing consistent with the literature that in fact, if you achieve it, 81 percent of them maintain it.

You're looking at it in the light of the confirmatory endpoint, and that's actually correct. But we haven't done the statistics on it as we would when the study is complete. But you're right that the worst case would be that 48 remain and 3 more of the others, and that will be the comparison at the end.

DR. BADEN: Okay. And I think Dr. Gripshover from earlier today.

DR. GRIPSHOVER: Yes. One got answered and I have one left. It's just a quick question. I was trying to think of other clinical things that we might be able to measure. Did you look at weight gain at all? We hear that -- as an

objective; weight as an objective marker of response?

DR. SULLIVAN: We did look at BMI, and we'll continue to do so. But we didn't see, at this point, any treatment related impact on BMI.

DR. BADEN: So I think that has gone down the list. Any other questions from committee members? Dr. Honegger?

DR. HONEGGER: I have questions about the questions.

DR. BADEN: Okay. We'll get to that once we're done. Any other questions for the applicant or the agency about the content?

(No response.)

DR. BADEN: If not, then we will conclude the clarification session, and we'll stay in session until the rain stops.

(Laughter.)

Questions to the Committee and Discussion

DR. BADEN: Any discussion among the committee about what we've heard this morning? I think we've had plenty of discussion already about

the controversial and complex issues. If not, then we shall go to the questions. I have procedural matters.

We'll now proceed with the questions to the committee and panel discussions. I'd like to remind public absorbers that while this meeting is open for public observation, public attendees may not participate except at the request of the panel.

We will be using electronic voting system for this meeting. Once we begin a 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 vote will be locked. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will 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 the same manner until all three questions have been answered.

So we will then see the first question, and we'll see if there are questions about the question. Is the surrogate endpoint of sputum culture conversion, based on 3 consecutive negative sputum cultures, reasonably likely to predict clinical benefit?

Are there questions about the question? Dr. Honegger?

DR. HONEGGER: I have a question about question 2. Sorry.

DR. BADEN: So if no questions about the question, then we can go to the question. Shall we start the voting process?

(Voting.)

DR. TESH: The vote for the record is 8 yes; 6 no, zero abstentions, and zero no voting.

DR. BADEN: So we will go around and starting on the right with Dr. Proschan to confirm

your vote and state any key aspects of the vote. Remember, the agency values our rationale as much as our actual vote, so please share the key elements, as they will be recorded.

DR. PROSCHAN: Yes. I voted yes. I think I've already said what guided my thinking is that, first of all, I don't think that it's -- as I said, it's not a problem that converters are different from non-converters if its conversion still predicts what you think is the most important thing, which some people think is conversion after discontinuing treatment for 3 months.

I do have the problem, again, that what I think is the most important question is does the difference between arms in conversion predict the difference between arms in, say, long-term conversion? But I'm convinced because I think the relationship between -- I think converters did even better when you look at on the ALIS arm.

If it were going the other way around where conversion -- like we saw on that slide where there was zero percent prediction of long-term conversion

in the control group, if we had seen it the other way around, I'd be bothered. But given that we saw it in the right direction, I'm pretty convinced.

I haven't seen data that makes me feel really uncomfortable about that outcome. Regarding this business of whether it correlates with 6-minute walk results, I did a quick calculation, and I said suppose if you didn't convert, it would have no effect on your outcome on 6-minute walk. And if you did convert, then it would improve it by 30 meters, say.

When I did that, I calculated that the expected difference between arms is 6 meters. So I would expect a 6-meter benefit, and I went the other way around, a few meters declined. But I don't think those results are inconsistent with what I would expect, so I really saw nothing that made me think that it wasn't a reasonable outcome.

DR. BADEN: Thank you. Dr. Masur?

DR. MASUR: I voted yes. And I think we've discussed many of the issues, but certainly the prior study by Griffith I think was at least

convincing. The 6-minute walk, there are so many different ways that one could interpret it. There are different ways to look at what difference is biologically important. But that at least gave me some confidence that the endpoint we're looking at is likely to have a clinical benefit, although it would certainly be nice to have longer-term follow-up and more granularity on that.

DR. BADEN: Dr. Evans?

DR. EVANS: I think I would fall almost exactly in line with that, which is I don't think there's any doubt in my mind that patients who achieve microbiologic clearance will ultimately do better. Now. I don't know that we really understand all the mechanisms underlying that and how much of that's drug driven. But regardless, I would rather my patients not have culturable AFB in their sputum, and consequently that's where we're going.

DR. BADEN: Dr. Hawkins?

MR. HAWKINS: I voted yes. As a patient, when I was first cultured with MAC, I was a CF

patient, so I was not showing symptoms of NTM disease per se, but I was told that we were going to treat it to avoid future complications and future damage. And as we heard from the doctors and physicians and scientists who spoke in the audience, that's the standard level of care that they're going for.

So these are the scientists that work in this field for their whole careers, and their goal is for eradication of sputum cultures. So I think we need to look at what these scientists are attempting to do as valid when we make our determination up here. Thank you.

DR. BADEN: Thank you. Dr. Andrews?

MS. ANDREWS: I wish you had a maybe button. I voted no because I just don't know. And I didn't see anything that made -- we need more tools in the toolbox, absolutely, and this does seem safer, and so I'm not worried about it the way I am about other things.

But in terms of saying that this is related to clinical outcomes, a 6-minute walk test that is

missing a whole ton of people from the beginning who left because of adverse events, which may fall more heavily on people who aren't well and can't walk as well, I don't know what to make of those, that test.

It concerns me that this wasn't a blinded study and that everybody knew who was in which piece; that worries me. So I think I would like a lot more outcomes, patient-reported outcomes especially, and I would like to know a lot more about people who left and why they discontinued treatment.

DR. BADEN: Dr. Lo Re?

DR. LO RE: I voted no. I could not make a determination of the likelihood of clinical benefit from the data that were presented to us. The six studies that the agency had presented evaluating the outcomes of sputum culture to me were not sufficient to confirm the impact of culture conversion on improvement in either symptoms, functional benefit, or mortality.

As we heard, these studies were limited by

small sample sizes, the lack of adjustment for important potential confounding variables. Particularly, the severity of non-tubercular mycobacterial disease were generally from single centers or were retrospective. In addition, study 212 that we saw showed no difference in the 6-minute walk test between ALIS and the optimum background regimen groups.

That being said, as the clinicians in this field have noted, the sputum culture conversion is the main outcome of treatment in clinical practice, and it does lead to discontinuation of NTM treatment if durable. It is possible that sputum conversion from study 212 might predict future clinical benefit, but current data from well-designed prospective studies right now are not available, and I guess we'll have to wait for the longer clinical outcomes from 212.

My read on this is I think that this field needs well designed studies to examine the outcomes of sputum culture conversion, and I think it would be certainly prudent to conduct this in

postmarketing analyses if ALIS receives accelerated approval.

I also think that analyses to better understand the factors that are independently associated with sputum conversion are needed. And potentially, there should be consideration to perform population representative studies using data from electronic health records, perhaps clinical integrated systems like Kaiser Permanente or Veterans Health Administration, where microbiological data, outcomes data, are available and might facilitate this.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. I voted no also, although I would have liked to have a maybe as well.

DR. BADEN: Closer to the mic, please.

DR. GRIPSHOVER: Sorry. I don't think that we have clear evidence that sputum conversion leads to clinical benefit defined as feels better, and more functional, and live longer. It does seem to predict continued sputum conversion.

Some evidence suggests that it could in fact have clinical benefit: the improved 6-minute walk test, the converters, and some of the retrospective data from Griffith and Jenkins showing lower mortality in sputum converters. And I think the Griffith 2015 study of the 180 patients referenced by the sponsor does seems to be the first that did show a decrease in cough, particularly in sputum, with culture conversion. And if that's confirmed in other studies, I think that maybe this will turn out to be a good surrogate.

The patients who shared their stories today did report an actually dramatic clinical response, but they reported less cough, better energy, less dyspnea, and weight gain. I think that we should be able to find a way to measure that response, too, and really know that there's -- to be able to show there's a clinical benefit.

Maybe if sputum conversion is correlated with functional studies such as the 6-minute walk, weight gain, patient symptoms that begin at better reporting, and hospitalizations, which I found

disconcerting here, then in the future, it could be accepted as a surrogate. But I recognize that those studies have been hard to measure in the past because we've seen a few other inhaled antibiotics have trouble showing that as well.

Possibly if we study earlier in the disease process, we might be able to more readily discern a response to the antimicrobials themselves before there's been extensive lung disease that makes those changes harder to detect. And as sputum clearance correlates with clinical response there, then maybe we could validate it as an endpoint for more refractory disease.

DR. BADEN: Dr. Green?

DR. M. GREEN: Michael Green. I voted yes, and I apologize for my lack of brevity in advance. The primary question that the FDA is asking us today is whether or not achieving microbiological cure for patients with NTM infection in the setting of underlying lung disease likely results in a clinically meaningful improvement in patients.

This question is asked in the context of

existing evidence-based guidelines, which have for more than a decade recommended treatment with a goal of eradication of NTM in patients with bronchiectasis.

The guidelines of course are meant to be evidence based, but it has been made clear today, the evidence to confirm that treatment of NTM results in a meaningful improvement are not definitive, and yet, patients with bronchiectasis and NTM are treated aggressively with multiple medications for very long courses of therapy with 3 or 4 different medications, many of which have their own associated side effect. This is done by clinicians with direct exposures to these patients and who are considered experts by their peers, and these recommendations are clearly widely implemented.

At a minimum, clearance of sputum does lead to the stopping of what might be years of otherwise ineffective therapy, and we have seen suggestive clinical findings; at a maximum, perhaps evidence of conversion being associated with improvement in

6-minute walk time but not paired to their treatment assignment.

I can only presume that with enough follow-up of a full constellation of clinically meaningful endpoints, that sputum culture conversion will predict some manner of clinical benefit if only coming off of all the other treatment agents. Given the explanation of the rules associated with accelerated approval, it is my belief that the agency and the sponsor can generate the appropriate confirmatory trials to confirm and describe these anticipated clinical benefits.

DR. BADEN: Dr. Weina?

DR. WEINA: Pete Weina. I voted no. I think despite our reliance on clinical practice guidelines that would indicate that 3 consecutive negative sputum cultures are the standard by which we guide our clinical practice, the issue is that these guidelines are written for individuals, not for populations. Most of our evidence for the nontuberculous mycobacteria clinical guidelines are

grade 3 at best or rather just slightly better than expert opinion. And the recommendations themselves are grade D, the lowest of the strengths.

In judging the utility of this endpoint for the approval of a drug, we're looking at a population rather than an individual effect. Notwithstanding the sneak look that we had in the ongoing 212 data, which didn't show outcomes, just showed microbiological outcome, the evidence is actually lacking to support the fact that 3 consecutive negative sputum cultures will reasonably predict clinical benefit.

I don't think we've shown that people will do better microbiologically, and even clinically, based upon maybe they just have better underlying protoplasm. Maybe they have less pulmonary damage when they've started, and maybe that's why they respond better to the drugs. Clinical assessment is lacking in the population rather than individuals to inform us, and good information on BMI< spirometry, and inflammatory markers are needed for this population rather than just

individuals and anecdotal data.

DR. BADEN: Thank you. Dr. Baden. I voted no. I interpreted the question as written, likely to predict clinical benefit. Data on clinical benefit were not provided. The historical data suffer from the issues of historical data, the lack of clinical benefit being demonstrated. There is the fundamental chicken or egg problem of the underlying disease with what the NTM is synergizing with.

I think as has been mentioned, the stories from the open public session are very compelling, and there may well be some patients who benefit as seen in some of the data. But the unevenness of the data presented with the missing data and the dropouts, and the other findings raise concerns that there may be some patients who have a negative benefit and some where benefit, and that has not been properly clarified.

I think the intrinsic good of a negative culture is important, but the ability to predict a clinical benefit was not shown.

Dr. Honegger?

DR. HONEGGER: Jonathan Honegger. I voted yes. It appears that the 3 negative cultures do predict durable conversion, and it just seems extremely rational to expect that that will have some symptomatic benefit in addition to the benefit of less burden of having to take other antibiotics. There are the observational data that support it, and study 112 seemed to show that culture conversion and symptomatic benefit went hand in hand.

Notwithstanding, I recognize the limitations, and I imagine there are certain people that are just more prone to clear and have better outcomes. So the drug effect may not be as strong as it would suggest with the higher 3-month negative cultures.

DR. BADEN: Thank you. Dr. Daskalakis?

DR. DASKALAKIS: This is Demetre Daskalakis, and I also voted yes, that the surrogate endpoint of sputum culture conversion, based on 3 consecutive negative sputum cultures, are

reasonably likely to predict clinical benefit, primarily based on the fact that this is the core tenet of how one generally treats pulmonary MAC, the idea that clearing cultures is a critical piece of what we do and that it is actually for me and important clinical indicator of success as evidenced by the guidelines.

Another important point for me is that there has been a lot of conversation about the difference between a clearer and a person who's a non-clearer. And just remember the fact that 212, that the study actually recruits folks who already not cleared. So drugs have already failed them. And the fact that there is a signal that there is improvement in clearance, the way that that interacts with our assumptions about MAC, at least the ones that we have today and other nontuberculous mycobacteria, seems reasonable therefore to assume, though there is an assumption, that there is likely a clinical benefit attached to microbiologic clearance.

I also do appreciate comments by previous committee members that clearance is ultimately

clearance no matter who the patient is. And the demonstration that there is improvement on some parameters, the walk test, et cetera, with this clearance I think is significant. That's my justification. Thank you.

DR. BADEN: Thank you. Dr. Schaenman?

DR. SCHAENMAN: Joanna Schaenman. I also voted yes. I agree that negative sputum culture is reasonably likely to predict clinical benefit, and I appreciated that the adverb reasonably Was in that sentence. That is a standard goal of clinical treatment.

Surrogate endpoints are not ideal in clinical trials, but I think they are appropriate to utilize in the accelerated approval framework when we're facing an unmet need for a serious disease. I think that the surrogate endpoint is supported by guidelines, as limited as they may be, by the literature review that shows association with negative culture status and improve long-term outcomes. And the use of this endpoint is standard clinical practice by experts in NTM treatment and

is in accordance with my personal experience in treating these patients.

I hearken back to what somebody said along the way in this day that treatment of this disease is a marathon and not a sprint. That really rung true to me. This is occurring in patients who have background pulmonary disease. So I think that demonstration of clinical benefit with addition of the single agent in a multidrug treatment regimen is always going to be very challenging, even if that single agent provides significant microbiologic impact.

So therefore, objective clinical benefit is always going to be difficult to capture and would be expected to take longer than 6 to 12 months to be manifested.

DR. BADEN: Thank you. Dr. Brittain?

DR. BRITTAIN: Erica Brittain. I voted no. It was a hard question to answer. I feel the culture results, short term and durable, are very strong, but I took a fairly strict perspective to the question, even though there was the reasonably

likely terminology, that I wanted to see real evidence in the trial, randomized evidence of clinical benefit. And it just wasn't there on the randomized group comparison. In fact, it tended to be going in the wrong direction on most everything that was related to clinical evidence.

So anyway, I took a strict perspective on wanting to see evidence from the clinical trial. I do think it is really unfortunate that this trial was designed in such a way that we will not see the long-term clinical benefit. That would be the answer to the question. If you saw a clinical benefit long term, there would be just no question, and now there's going to be question.

DR. BADEN: Thank you. So 8 to 6 yes, it is reasonably likely to predict clinical benefit. The yay votes largely had the themes of these are the guidelines, this is how we practice, therefore, it's an intrinsic good to turn the culture negative. However, much data are missing in terms of longer-term follow up, and it is rational that this will have a clinical benefit, though that was

not clearly shown although there was evidence for it.

The no themes had to do with there aren't clinical outcomes. There's too much missing data. There is something different perhaps about the patients intrinsically versus the NTM being the differentiating factor or the treatment for the NTM. I think those were the primary themes.

We now have question 2. Don't worry, the fun is still coming.

Sorry. Dr. Green?

DR. M. GREEN: I wonder if the agency can clarify what the word "effectiveness" means in this, and it will be the same for number 3.

DR. BADEN: Let's read question 2, and then the agency can clarify.

DR. M. GREEN: Thank you.

DR. BADEN: Question 2 is, has the applicant provided substantial evidence of effectiveness and sufficient evidence of safety of amikacin liposomal inhalation solution, ALIS, for the treatment of nontuberculous mycobacterial lung disease caused by

mycobacterium avium complex as part of a combination antibacterial drug regimen for adult patients?

If yes, provide recommendations regarding labeling. Please comment on the design of the trial that will need to be conducted to confirm benefit. If no, please provide recommendations regarding additional studies, analyses that are needed.

Let's now ask questions about the question.

DR. M. GREEN: Thank you. I apologize for being too anxious. Can you clarify what the word "effectiveness" means in this sentence for this question?

DR. COX: It might be helpful, too, for you to clarify your question a little bit more just to make sure. I can guess what you're asking.

DR. M. GREEN: Is effectiveness the primary endpoint as stated in the study, which is microbiologic, or is effectiveness clinical endpoints, which is a secondary endpoint in this study?

DR. COX: Right? Yes. So for this study, the question is related to the surrogate endpoint. The first question was about the surrogate predicting clinical benefit. The second question I think is based on the study result for the surrogate endpoint.

DR. BADEN: And we can look at this in light of question number 3, which has a slant to the issue of effectiveness, because question 3 is limited or no treatment options.

Dr. Lo Re?

DR. LO RE: In follow-up to that, given that all of the data are in patients with refractory nontuberculous mycobacteria, it's not clear to me how question 2 versus 3 are different or what the interpretations should be. Because in question 2, it's focusing on adult patients. In question 3, it's focusing on adult patients with limited or no treatment options who at least I interpreted that's exactly the data we were shown, i.e., individuals who had refractory nontuberculous mycobacterial disease

DR. COX: Right. That and one other piece of information -- the applicant was asking for an indication for the broader population. So if you look back at their indication, it was the broader population, which is why we're asking the first question And then you're bringing up the point of what the trial population was, which is why we're asking the third question, if you will.

So that's why we asked question 2 and why we're asking question 3. You'll notice that the questions are very similar with the exception of how the populations are defined.

DR. LO RE: I guess I would just find it hard to be able to interpret question 2 in the absence of any data in the broader population.

DR. BADEN: But I guess question 2, the applicant has asked for this indication, so we're voting on this indication based on the data presented. And based on the data presented, we can evaluate both question 2 and question 3 in light of the data before us.

Is that correct?

DR. COX: That is correct.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: I'm sorry. I'm now completely lost. What is the difference in the population? Can you clarify the difference in the population between the two versus the study?

DR. COX: Sure, yes. It may be helpful to actually look at both question 2 and question 3. So let's just go through the question just so we get clarity on this.

For 2, has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of amikacin liposomal inhalation solution for the treatment of nontuberculous mycobacterial lung disease caused by mycobacterium avium complex as part of a combination antibacterial drug regimen for adult patients?

So for adult patients, remember that from question 2. I won't read A and B, which I think are identical.

Now let's go to 3. Has the applicant

provided substantial evidence of the effectiveness and sufficient evidence of the safety of ALIS for the treatment of nontuberculous mycobacterial lung disease caused by mycobacterium avium complex as part of a combination antibacterial drug regimen. And then here's where it changes for adult patients with limited or no treatment options.

So the questions are essentially identical with the difference being the patient population we're asking about.

DR. BRITTAIN: What I don't understand is how this relates back to the patients in this study, which match.

DR. BADEN: I guess the question is, for those of us who care for these patients, I think that when we take care of these patients, they get heavily treated. And heavily treated failing, we add this versus we consider this as part of the front door for initial treatment. That's how I'm interpreting this.

This data presented had our MDR, OBR, whatever acronym we want, and that was part of how

they got into the study. But my read of the question is this is saying as just part of MAC treatment in general, and question 3 is part of MAC treatment in those who have failed standard therapy. The data that we saw has OBR or MDR as part of our heavy discussion.

Am I interpreting things correctly?

DR. COX: That's correct.

DR. BADEN: So if there are no further questions on the question, or the two questions -- and I cheated. I have both questions in front of me because I got to study the nuance. So for question 2, let's now proceed to vote given the framing of them.

(Voting)

DR. TESH: For the record, the vote is 3 yes, 11 no, zero abstention, zero no voting.

DR. BADEN: This time we will start from the left. Dr. Brittain, your vote and any comments.

DR. BRITTAIN: This one I think was easy in just that it wasn't -- if I now understand correctly, this was referring to a much broader

population than what was studied.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: Joanna Schaenman. I also voted no. As was stated, the data that we are provided with was for refractory MAC and not primary treatment. A standard first line treatment regimen for macrolide sensitive patients may well be better tolerated than inhaled amikacin given the large number of patients that withdrew from the trial due to emergent AEs.

If, of course, clinical benefit could be shown in patients using the ALIS therapy for first-line treatment regimen, that would be very different, especially if that could be shown to be superior over a truly optimal 3-drug regimen. In addition, there seemed to be a small signal for amikacin resistance evolving in patients who are exposed to the ALIS drug, which would suggest to me that this treatment should really be reserved for more challenging cases.

The sponsor suggested that early treatment may prevent progressive lung disease, and I think

that's a very attractive idea. But because there's no data to support that at this point in time, I think we really need to test that assertion. So future studies should include primary treatment of otherwise uncomplicated patients, should be stratified by clinical characteristics, including symptoms and radiographic assessment.

As mentioned, it would be helpful to know what clinical characteristics predict response to therapy. This would assist with future labeling, so that we could best select patients that would be most likely to benefit from this therapy.

DR. BADEN: Thank you. Dr. Daskalakis?

DR. DASKALAKIS: This is Demetre Daskalakis. I actually have a technical issue. I think that I got closed out before I was able to press no. I changed my vote, actually. I didn't do it -- I think it moved before. So not sure if it's possible, but if it's not, then I can move to abstain. It depends on What's allowed.

DR. BADEN: Your intent was not to vote yes --

DR. DASKALAKIS: My intent was to vote no.

DR. BADEN: -- your intent was to vote no.

DR. DASKALAKIS: Correct. Continue with that? So my vote was no.

DR. BADEN: You should follow your intended vote.

DR. DASKALAKIS: Great. So for very similar reasons, given the lack of primary data on individuals using this as a first-line therapy and the potential for adverse events and toxicity, I don't think that we've demonstrated that this has a definitive role in individuals initiating therapy for nontuberculous mycobacteria. I think that the study that would need to be done is one that really does focus on individuals starting this as a first-line therapy.

I do recall a precedent, something that happened when we were discussing hepatitis c approval for another drug, where there was a model offered for interferon failures despite the fact that the drug had never been studied in interferon failures. So I think that that would also be an

interesting perspective from the agency to see if there's a modeling answer to take a look at what the expected result would be for individuals who would potentially be folks who are naive and potentially would benefit from this drug.

So all in all, I think that a study focusing on naives or modeling studies that would demonstrate what the role of this drug is in naive patients, in treatment-naive patients, would be interesting. But without that, it's hard to say that we have any evidence that it's an appropriate agent.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: Jonathan Honegger. I voted no for the same reasons that have been mentioned already.

DR. BADEN: Dr. Andrews had to go catch a flight. If she calls in, I will have her give her comments the moment she calls in.

Dr. Baden. I voted no. All data were presented in heavily pretreated, so I don't see any data on earlier treatment. It's logical to think

that it will have value in early treatment, but that needs to be studied, and that should be part of future work. And the corollary to that is there were significant data of adverse events. So there are serious risks with this compound, and that has to be weighed with evidence of benefit, which have not been shown for primary treatment.

Dr. Weina?

DR. WEINA: Pete Weina. I voted no. Besides the obvious issues here, that is the evidence that we were given in the clinical trial from refractory patients in a very limited data set that stayed on the same drugs that they were on before. So you could almost predict that they were not going to convert.

I also worry about the issue of efficacy versus effectiveness. With a greater than 30 percent dropout rate in a controlled clinical trial due to AEs, I wonder how much the dropout rate would be in the real world without the rigors of a clinical trial to support the individuals staying on the drug.

It's all about risk versus benefit. While I appreciate for the individual, it's either zero or 100 percent, it works or it doesn't work, you have to look at the clinical trial data rather than the anecdotal data.

Despite the statistically significant efficacy improvement in phase 3, I'm still bothered by the fact that when you add an additional drug to an already failing treatment, however you define failing, you still have 70 percent of the people who will never convert. Keeping in mind the clinical data rather than the anecdotal data, this is statistically significant improvement without a practical improvement.

DR. BADEN: Dr. Green?

DR. M. GREEN: Michael Green. I voted no. The data as presented were limited to refractory MTB infection into the setting of bronchiectasis in the adult patients. We'd been told that 40 to 60 percent of patients will clear with presumably first-line therapy.

Accordingly I'm left to think that given the

treatment-associated side effects, treatment should not be given as front-line therapy without additional data, but that it would be reasonable to define treatment refractory as a failure to respond to an initial course of 6 months. And in that setting, it would be reasonable to potentially move to ALIS.

At the same time, I would think it would be rational to propose a study, and also ethical, in treatment-naive subjects to receive treatment versus placebo with either hypertonic saline with or without liposome and using similar microbiologic and clinical endpoints as described. I'd encourage follow-up off treatment, presumably post-12 months if clear, and to include a composite endpoint looking at the side effects of the additional treatment regimen that are required, and coming off of these if you get to culture conversion.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. Barb Gripshover. I also voted no because, first of all, these studies done were only in refractory disease, so we don't

have any data on earlier use. I do think that looking at TB as a model, that maybe looking at it in initial treatment might be a study to go forward. If we want to treat when there's a higher burden and try to prevent the emergence of macrolide resistance, there may be a role for earlier. But clearly, I think it needs to be done in a randomized control trial.

DR. BADEN: Dr. Lo Re?

DR. LO RE: I voted no. All of the data were in patients with refractory nontuberculous mycobacteria. There was no data on the safety and efficacy of ALIS in treatment naive. I think clinical trials are needed in patients who are treatment naive, and long-term outcome should be evaluated as endpoints.

DR. BADEN: Mr. Hawkins?

MR. HAWKINS: I voted yes. As someone that's going through two courses of the triple combination therapy and had to deal with the kidney tests, and the eye tests, and ear tests, because of those significant adverse effects that are known to

occur, I considered the adverse effects found in this study to be insignificant and in line with the effects that people with CF experience when they start taking the inhaled products that we use in that disease.

I feel that if it works in the worst cases, then the likelihood that it's going to improve conditions in the best cases and a decrease in the amount of time that the healthier people have to be on these bad drugs, we should be working in that direction.

DR. BADEN: Thank you. Dr. Evans?

DR. EVANS: Scott Evans. I voted no because the patient population for which the data were derived were non-overlapping for the patients described in the question.

DR. BADEN: Dr. Masur?

DR. MASUR: Henry Masur. I voted no for the reasons that have been stated a number of times.

DR. BADEN: Dr. Proschan?

DR. PROSCHAN: Michael Proschan, and I voted no. I don't see how no data could possibly provide

substantial evidence.

DR. BADEN: The vote is 12 -- has Dr. Andrews called in or not?

MS. ANDREWS: Can you hear me?

DR. BADEN: Dr. Andrews, you voted yes. Can you please share your comments?

MS. ANDREWS: Yes. I understand that there wasn't any direct evidence on this question, but it just seems reasonable to me that if it works for people that other medications haven't worked for, harder cases, that it would work for at an earlier stage for people as well.

DR. BADEN: Thank you. So 12 noes, 2 yeses. The yeses are it's reasonable to infer that this should work given the mechanism that is understood. The complexities of a standard treatment for MAC are quite burdensome, and alternatives are desperately needed.

The noes largely were there are no data, so data need to be generated to make that assessment of benefit in this setting, though it's logical there still are no data.

So let's go to question 3.

Dr. Andrews, my understanding is you can vote. So we should put it to voting and orchestrate Dr. Andrews' vote since she's more complicated. And the rest of us, please vote as we --

MS. ANDREWS: I will have to request.

DR. BADEN: We should vote as we standardly do. So this is substantial efficacy in the setting of adult patients with limited or no treatment options.

(Voting.)

DR. BADEN: Thank you. We can trust that's her vote.

DR. TESH: Yes.

(Laughter.)

DR. TESH: For the record, the vote is 12, yes; 2 noes, zero abstention; zero nonvoting.

DR. BADEN: Interesting questions that you posed to us, as you can see by the voting pattern. We'll start with Dr. Proschan.

DR. PROSCHAN: I voted yes. I think there's

overwhelming evidence on the surrogate outcome. I don't think there's any question there is a provided benefit on the surrogate, and that's how I interpreted this question to be.

Now, with regard to safety, the only issue -- there are some safety issues, but I think both sides actually presented data that are little bit misleading because, for example, for the safety, the FDA, one of the things that they presented were events that happened in at least 10 patients. That's a problem if you have a 2 to 1 randomization. It's more likely to be at least 10 patients if you have twice as many patients in the arm. So I think that part was a little overstated, the safety concerns.

But overall, I felt like there was sufficient safety and overwhelming benefit on the surrogate.

DR. BADEN: Dr. Masur?

DR. MASUR: Henry Masur. I voted yes. I think what we've heard today is this is a tremendously complex disease to study with so many

comorbidities and confounding factors. I think what Joanna said I think rings true for those of us who don't do that much treatment of it. It really is a marathon, and how you can use a short intervention to change the overall course of the disease I think is also complex and requires a much longer study than what's here.

I think, to me, we have to start somewhere, and there's enough of a signal here for efficacy and enough of a signal that there is no major safety issue. I was comfortable moving forward because, again, this is a field that desperately needs some kind of standard against which further studies are going to be compared, so I voted yes.

DR. BADEN: Dr. Evans?

DR. EVANS: Scott Evans. I think in terms of meeting the effectiveness threshold, prespecified was 15 percent delta, and they got about 20 percent delta. So I think that was clearly met in terms of the safety profile.

The data have issues. We've discussed the need for placebo longer-term follow-up. So a lot

of issues there, but I still think the safety profile that we can infer from the available data is that the potential side effects are more acceptable than uncontrolled disease.

This is a devastating disease. I had a patient last week go on hospice for MAC lung disease after surviving to become disease free from three other cancers. I mean, it's a brutal process, and these are tolerable side effects for the most part. So I'm hoping we can get cleaner data as we go forward.

DR. BADEN: Mr. Hawkins?

MR. HAWKINS: I voted yes for the same reasons I said before the last question.

DR. BADEN: Thank you. Dr. Andrews?

MS. ANDREWS: [Inaudible - audio gap] -- I guess getting to -- it's more effective than the background treatment, so yes on effectiveness. Safety, I am worried about the adverse events, and they were serious enough for people to discontinue treatment. But they came early and people could can stop taking the medication if it's too much for

them.

So because of all of that, I think that on math, I voted yes. But, again, I wish I had a maybe.

DR. BADEN: Dr. Lo Re?

DR. LO RE: I voted yes. I thought the data from study 112 provided supportive, albeit limited, efficacy information given that a greater proportion of the refractory and NTM patients in the ALIS group achieved a negative sputum culture at day 84. I also felt that the data from pivotal study 212 demonstrated that significantly more patients with the refractory NTM who received ALIS achieved culture conversion, which is the main outcome in clinical practice, compared to the optimal background regimen, providing further supportive efficacy information.

The interim data provided by the sponsor on durable culture conversion, which leads to withdrawal of antimicrobial treatment, lends further support to this drug's efficacy. And I would applaud the sponsor for conducting such a

study among patients with a great unmet need.

I think if the accelerated approval is granted, labeling should note the limited data on long-term clinical outcomes associated with sputum conversion. I'm still concerned about the lack of difference in clinical outcomes, in particularly the 6-minute walk results, which might portend the lack of clinical benefit with sputum conversion.

However, I think given the enormous need for new therapies in these patients, the limited treatment options for refractory NTM patients and the fact that sputum conversion is the main endpoint in clinical practice, perhaps an additional appropriately designed prospective cohort study should be mandated postmarketing to better understand the longer-term impact of sputum culture conversion on clinical symptoms, functional outcomes, and mortality.

I also think additional analyses to examine if certain phenotypes of NTM and certain racial ethnic backgrounds achieve sputum conversion differently. And finally, I think we need some

data on the development of NTM resistance with ALIS.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. Barb Gripshover. I voted no. While the sputum conversion rates are very encouraging, I thought the lack of response in the 6-minute walk test was worrisome, as well as the patient-reported outcomes didn't show improvement and in fact trended to worse.

For such a strong treatment effect on culture conversion and culture conversion correlating better with the 6-minute walk test, I would have thought it would have reflected as well in the treatment group. So I'm not sure if all the adverse events of the drugs negated the effect of sputum conversion or if there were differences in the disease of people who convert.

I also find it concerning that there was a high rate of respiratory complications and hospitalizations in the treated arm. And given that there's a small number of people left in the full 12-months post-conversion treatment group

without a comparator group, I think it's going to be hard to show, from that study at least, that there is clinical benefit from this drug.

DR. BADEN: Dr. Green?

DR. M. GREEN: Michael Green. I voted yes. I've already expressed my uncertainty regarding the clear evidence that culture conversion will lead to definite improvements in respiratory status or the natural history of chronic lung disease in these patients. However, we were instructed that efficacy was based on the surrogate endpoint.

It's clear to me that ALIS does lead to an enhanced likelihood of culture conversion if only in 30 percent of patients compared to 10 percent for those who continue on their chronic NTM regimens. At a minimum, those patients experiencing culture conversion will be spared ongoing exposure to the multiple and potentially toxic regimens that have not otherwise been successful.

The safety issues are notable but generally locally manifest in the lung of which the worst are

seen in NTM bronchiectatic patient not on this therapy. I wish I was smart enough to know the best studies necessary to mandate to confirm clinically meaningful endpoint, but I would suggest using a composite endpoint that assesses the elimination of toxicity of other NTMs be included along with the other ideas that may come forward.

If approved for this indication, the label might identify that treatment-associated side effects are noted and share those, and emphasize that ongoing monitoring for recurrence and relapse of infection should be done, and also to emphasize that culture conversion will not, by in of itself, necessarily declare improvements in respiratory status.

DR. BADEN: Dr. Weina?

DR. WEINA: Peter Weina. I voted no. I wanted to vote yes. I really liked the idea of bringing more tools to bear against the onslaught of diseases that we face as clinicians and for patients. And while I applaud the sponsor for bringing this forward, I'm basically a cynic at

heart. This isn't a new product. This is just repackaging of an old troublesome drug that is currently being used anyway.

So I voted no for the same reasons as I stated earlier, principally the efficacy versus the effectiveness question, but also the fact that we've got a statistical benefit here that really isn't a practical benefit.

Finally, I always worry about the issue of off-label use, not just in the larger NTM population in which we know it's going to get used because there are no other, quote, "approved drugs" for this population, and therefore a perfect argument to use it for every single NTM patient, but also in CF and pseudomonas.

DR. BADEN: Thank you. Dr. Baden. I voted yes. As I noted previously, I'm unhappy with the surrogate because it's unclear to me what the surrogate means from a clinical benefit, but as an infectious disease provider, as a physician who cares for patients with NTM, the end, given the community standard, turning patients to culture

negative is the community standard. And these data demonstrated a benefit in these refractory patients in turning their cultures negative.

However, the side effects are not trivial. The increase in hospitalizations I think is real, however, and the many other side effects observed. However, patients are active participants in their care, so they can be part of the decision-making in managing the side effects that can be managed in part by withholding therapy or stopping therapy.

I think there are many unknowns that the company can address now without perspective data collection, which includes understanding the MAI genetics relapse versus reinfection; defining the clinical phenotypes better; they don't have the data, but I think in future studies, they need to do prospective study to define clinical outcomes that are meaningful. And in that, they need to look at what occurs with the bacterial flora because I am worried about resistance beyond the NTM that can affect these patients and their friends who they come into contact with, who may

also be susceptible.

Overall, I think the benefit in this hard-to-treat population outweighed the risk, as stated.

Dr. Honegger?

DR. HONEGGER: Jonathan Honegger. I voted yes. Coming here today actually was intending to vote no because I have concerns about the safety data, but wanted to be persuaded one way or the other. And I felt with the additional commentary about the nature of the adverse effects, I thought it was worth it in this patient population that don't have other options.

I felt good about the surrogate endpoint as far as effectiveness. I think in labeling, obviously there needs to be important mention about the adverse effects and possibly including the increased risk of hospitalization. As far as future studies, I feel like the ongoing 212 study and 312, I do think it would be helpful to have more granular detail about the hospitalizations, their nature, their duration, and to understand

that with the existing trial. But I'm afraid I also think that a new trial is needed to follow up with both clinical outcomes and safety.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: I'm Demetre Daskalakis, and I also voted yes. I think that as a salvage drug in the context refractory mycobacterium avium complex treatment, there is a clear role for this agent. I think from the perspective of labeling, it is reasonable I think to include a clear statement that we have good evidence at this point of microbiologic clearance, but not necessarily other clinical endpoints. I think that also then sparks commentary on what future studies are ongoing and studies should focus on, which is really the safety signal, as well as demonstrating either better surrogates, alternative surrogates, or other endpoints that focus on clinical function.

So it could be that taking a look at other biomarkers may be worthwhile if they're stored specimens, thinking of other things that we can look at beyond just culture to see if we can get

other surrogates that may be better than culture given the fact that this disease is so complex. Thank you.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: Joanna Schaenman. I voted yes for question 3. I think the sponsor did demonstrate a statistically significant increase in attaining culture negativity in the patients who received the study drug. This suggests to me that the AEs described associated with the liposomal inhaled product would be worthwhile for patients who have limited options.

This would specifically include older patients, many of whom have multiple comorbidities, including chronic kidney disease that would not be able to tolerate IV amikacin or some of the second- or even third-line therapies that were mentioned, as well as lung transplant recipients who also have multiple comorbidities and are at high risk for drug-drug interactions. So that's why I voted yes.

I think in terms of labeling, I just wanted to echo a lot of the things that were already said

by my colleagues. The accelerated approval process should be referenced and the fact that there are limitations, considering the fact that a surrogate endpoint was used and that clear clinical impact was not demonstrated at 6 months; that it should be indicated only for patients refractory to conventional treatment regimens; and that it's very difficult to evaluate the long-term impact of treatment with the data presented at this point in time because patients were not followed for that long and also because, as was mentioned by several of the statisticians, that the patients who did not convert were removed from the trial.

In terms of future studies, it really seems that the long-term follow-up proposed is going to be very important to see how durable cultural negativity is. I think it will be very interesting to see for the resistant or relapsed patients, weather resistance to amikacin is a predictor of that microbiological relapse, and if there are other clinical indicators of either a response or lack of response.

In addition, in looking at the St. George's Questionnaire, it occurs to me that it really seems very focused on asthma and that a more bronchiectasis specific quality-of-life questionnaire might be another missing piece for the field and something that perhaps could be developed, and could be used as a clinical assessment for this and for future studies.

DR. BADEN: Dr. Brittain?

DR. BRITTAIN: I voted yes. There was clearly a strong benefit on the surrogate endpoint, which is what we were told to vote on. So that part was straightforward. As far as in part A, we're supposed to give recommendations for a design of a study um, to evaluate clinical benefit, I would love to see the same study they did but followed everybody again -- I mean, following everybody to the end.

I don't know whether it's possible to randomize at this point, so that would be the question. Maybe they could use a larger patient population. Maybe that would make it ethical, a

patient population that isn't refractory. And maybe it could be designed in such a way that you're constantly testing people over time, so that once clinical benefit is shown -- and maybe this time it would be shown earlier -- that that would be it.

Another possibility might be to look at the data when this extension study is completed, if the results of the people on the drug arm, the 64 or whoever that are left, if it's so clear-cut that their results clinically are better than what anyone could ever hope to see in this population -- I'm sort of dubious that it will be that way, but if it is, then that's maybe all you need.

Again, I agree that the label should be clear and reflecting that there was no clear sign of clinical benefit within the study.

DR. BADEN: So we have 12 yes; 2 no. The 12 yes themes were strong evidence of cultural negativity, safety is complex to interpret. It's a complex disease to study. Better treatments are needed. It's clearly better than background and

may allow voidance of prolonged use of background regimens that are failing.

There are many unneeded aspects of the data, including the MAI genetics and long-term clinical outcomes. The noes, no clinical data, patient-reported improvement lacking, and this is repackaging of a drug we already use with some statistical benefit but no clinical benefit.

Labeling considerations have to do the population studied in terms of salvage use for refractory disease in that hospitalizations and AEs are significantly increased and need to be attended to, and the patients need to be aware.

The extension study that is ongoing, it's unclear what that will actually tell us given the nature of the design. And if I hear everyone's comments, I think the committee would lean towards requiring future trials to define a clinically meaningful endpoint, quality of life, and address some of the issues raised.

I think that completes the discussion. Before we adjourn, any final comments from the

agency?

DR. NAMBIAR: Thank you, Dr. Baden. I just wanted to say thank you to the committee. It was a really very useful discussion, and I really appreciate the fact that you have stayed over time. We're supposed to have finished over an hour ago. I think that allowed for a very robust discussion of the issues at hand, which were very complicated, so I think this was really, really appreciated from all of us.

I would like to thank the applicant for all the work they've done on this NDA. Many things to the speakers at the open public hearing, including the patients who shared their stories, and thanks to the team and the consultants at the FDA who have done a great job with this NDA.

So thank you, and we'll see many of you, if not all of you, tomorrow morning.

Adjournment

DR. BADEN: Sorry. I would also like to thank the applicant for tremendous presentations of complex data and the agency. And the rain has now

passed, so we can adjourn. Thank you all. See some tomorrow.

(Whereupon, at 5:17 p.m., the meeting was adjourned.)