FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Thursday, June 6, 2019

8:00 a.m. to 3:12 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: It is now 8:00. Please take your seats.

Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so, as we have just done up here. I would also like to identify the FDA press contact Allison Hunter. If you are present, please stand.

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

DR. FARLEY: Good morning. John Farley, deputy 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. YASINSKAYA: Good Morning. My name is Yuliya Yasinskaya. I'm a medical team leader in the Division of Anti-Infective Products, CDER, FDA.

DR. O'SHAUGHNESSY: Good morning. I'm Elizabeth O'Shaughnessy. I'm a medical officer at CDER, FDA.

DR. RUBIN: Dan Rubin, Office of Biostatistics, CDER, FDA.

DR. HILTON: Joan Hilton, professor of biostatistics, UCSF.

DR. SWAMINATHAN: Sankar Swaminathan, professor of infectious diseases, University of Utah.

DR. GOETZ: Matt Goetz, professor of clinical medicine, UCLA, infectious diseases, VA Greater Los Angeles.

DR. GRIPSHOVER: Hi. I'm Barb Gripshover, infectious disease, Case Western Reserve University, Cleveland.

DR. LoBUE: Good morning. I'm Phil LoBue.

I'm director of the Division of Tuberculosis Elimination at the Centers for Disease Control and Prevention.

DR. GHANY: Good morning. I'm Mark Ghany, an investigator in the liver diseases branch, NIDDK, NIH.

DR. WEINA: Good morning. Peter Weina. I'm an infectious disease physician, Office of the Undersecretary of Defense for health affairs, Defense Health Headquarters in DC.

LCDR BONNER: Good morning. LaToya Bonner, acting DFO for AMDAC.

DR. BADEN: Lindsay Baden, infectious diseases, Brigham and Women's Hospital, Dana Farber Cancer Institute, Harvard Medical School in Boston.

DR. LINDOR: Keith Lindor, professor of medicine of Arizona State University and Mayo Clinic, and a specialist in liver disease.

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

DR. OFOTOKUN: Igho Ofotokun, professor of

medicine, adult infectious diseases, Emory University, Atlanta.

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

MS. LUPOLE: Patricia Lupole, patient representative.

DR. WALKER: Good morning. Dr. Roblena Walker, research scientist, EMAGAHA, Inc.

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

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

DR. MOORE: Hi. Tom Moore, infectious disease physician, clinical professor of medicine at the University of Kansas in Wichita, Kansas.

DR. LE: Jennifer Le with the University of California San Diego, professor of clinical

pharmacy, pediatric infectious disease, and pharmacokinetics.

DR. KARTSONIS: Good Morning. Nicholas Kartsonis. I'm the industry rep, Merck Research Labs.

DR. BADEN: Thank you, and thank you all for making the time to join this meeting.

For topics such as those being discussed today 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 if recognized by the chairperson. We look forward to a productive meeting.

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

meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now, I'll pass it to Commander LaToya Bonner, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

LCDR BONNER: Thank you.

The Food and Drug Administration is convening today's meeting of the Antimicrobial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions 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 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves new drug application, NDA 212862, pretomanid tablets for oral administration, submitted by the Global Alliance for TB Drug Development, Incorporated, proposed as part of a combination regimen with bedaquiline and linezolid in adults for the treatment of pulmonary extensively drug-resistant and treatment-intolerant, nonresponsive multidrug-resistant tuberculosis.

This is a particular matters meeting during which specific matters related to NDA 212862 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 concerning the product at issue.

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

We would like to remind members and temporary voting members that if the discussion involved any other products, drugs, or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such

involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationship that they may have with the firm at issue. Thank you.

DR. BADEN: Thank you.

We will now proceed with the FDA's opening remarks. Dr. Yuliya Yasinskaya.

FDA Introductory Comments - Yuliya Yasinskaya

DR. YASINSKAYA: Good morning, everybody. My name is Yuliya Yasinskaya. I'm a medical team leader in the Division of Anti-Infective Products, FDA. I'll be presenting to you a brief overview of the submission and the issues that we reviewed.

The subject of today's presentation is NDA 212862 for pretomanid, for the treatment of pulmonary extensively drug-resistant and treatment-intolerant, nonresponsive multidrug-resistant tuberculosis. The application is for pretomanid tablets, 200 milligrams. The applicant supporting this application is Global Alliance for TB Drug Development.

This NDA has been granted priority review. On the slide, you can see a list of the bacterial drug currently approved for the treatment of tuberculosis to use in combination. You notice that that the majority of these drugs have been approved in the last century, with the exception bedaquiline.

The proposed indication for pretomanid is treatment of pulmonary extensively drug-resistant and treatment-intolerant, nonresponsive multidrug-resistant tuberculosis in combination with bedaquiline and linezolid.

This is a novel combination regimen, where pretomanid 200 milligrams is administered once daily. Linezolid, 1200 milligrams, is administered once daily as well, unless the patient is intolerant when the dose could be reduced to 600 and even to 300 milligrams daily. Bedaquiline is administered as a 400-milligram daily dose or days 1 through 14, and subsequently it's a 200-milligram dose 3 times a week for the remainder of the treatment period.

The applicant undertook development of pretomanid for tuberculosis; that is drug sensitive, multidrug-resistant, and extensively drug-resistant tuberculosis. The subject of today's discussion is the Nix-TB trial. It is phase 3, open-label, single-arm trial to evaluate pretomanid in combination with bedaquiline and linezolid in patients with XDR and treatment-intolerant, nonresponsive MDR tuberculosis.

The additional safety data comes from the Nix-TB trial, which is a phase 3, randomized, partially-blinded trial of different dosing regimens of linezolid that is used in combination with the bedaquiline and pretomanid.

As this is a novel combination, we need to know the contribution of the components of the combination to the effect of the whole regimen. The contribution of the components of the proposed BPaL regimen had been evaluated in nonclinical studies, and specifically in the murine model of pulmonary tuberculosis.

On this slide, you can see one of the representative studies that have been conducted to evaluate the contribution of the components. On the left hand side in the green, you can see that a triple drug regimen results in significantly improved bactericidal activity in the pulmonary tissue of mice that were treated with a different combination of the drugs here. It's significantly better than the dual combinations of bedaquiline, pretomanid, and linezolid.

The treatment regimens were administered for 1 and 2 months, 14 days after aerogenic exposures of mice to mycobacterium tuberculosis. On the right, you can see that pretomanid also contributes to sterilizing activity of the regimen, and when added to bedaquiline and linezolid, it reduced the proportion of animals that relapsed 3 months after the end of treatment when treatment was administered for 2, 3, and 4 months.

As I mentioned before, the core study in this submission, that provides efficacy and safety information, is Nix-TB trial. It's an ongoing,

phase 3, single-arm, multicenter trial to assess safety and efficacy of bedaquiline, pretomanid, and linezolid BPaL regimen as mentioned in this presentation and also in subsequent presentations by the FDA and the applicant, in patients with pulmonary XDR TB and treatment-intolerant, unresponsive multidrug-resistant tuberculosis.

The first patient in this trial was enrolled in April 2015, and enrollment concluded in November 2017. You can see the timeline of interim analyses and submissions to the FDA. Interim analyses have been conducted and every 15 subjects who completed the treatment and 6-month follow-up died or discontinued treatment.

Initially, the applicant reached agreement with the agency that the data from the first 45 subjects treated with the BPaL regimen would be submitted to support the NDA. However, by the time the NDA came to the agency, the data were available for 60 subjects in the MITT population for efficacy analysis.

The safety data cutoff that we have and

reviewed for this application is March 26, 2018. We have safety data for 109 subjects treated with the BPaL regimen; 93 of them have completed the full treatment; 10 were still receiving treatment at this interim data cutoff; and 6 died while on treatment.

You'll also hear today, in the safety presentation, additional information from the 120-day safety date, and the applicant will provide some analysis of interim data cutoff of January 18, 2019. FDA will not be discussing efficacy from this data cutoff, as we independently had not reviewed these data.

On this slide you can see the summary of efficacy for the Nix-TB trial. The more detailed presentation will be made by Dr. Daniel Rubin. The patient population in this trial is XDR tuberculosis and treatment intolerant nonresponsive MDR TB. The patients were enrolled in 3 centers in South Africa, and almost half of the patients were HIV positive.

Endpoint for this trial was favorable

outcome, defined as absence of bacteriological failure, relapse, or clinical failure, up to 6 months following end of treatment. The initial agreed-upon interim data cutoff was August 2017 with an MITT population of 45 subjects. You can see the favorable outcome was achieved in 89 percent of subjects.

Subsequently, interim data cutoff in the primary analysis population of 80 subjects MITT population, you see that the favorable outcome had not changed. It remained high at 90 percent, with a 95 percent confidence interval of 81 to 96 percent. Also, this data cutoff had information for 23 subjects that were followed to 24 months after the end of treatment. As you can see, the favorable outcome remained sustained at 83 percent.

As the trial was single arm, the applicant had proposed to use historical control to evaluate efficacy observed in Nix-TB trial. Two approaches were proposed. The first one was a literature based review of the treatment outcomes in the patient with XDR TB. Upon review of the

literature, point estimate for favorable outcome was 28 percent with an upper bound of 95 percent confidence interval of 34 percent, which is significantly less at the lower bound of 95 percent confidence interval observed in the Nix-TB trial.

The second approach was the matched historical control. The patients for this approach came from one of the trials that also enrolled patients in the Nix-TB trial, a site in South Africa. The patients with XDR and treatment intolerant nonresponsive MDR TB were matched to the 45 patients in the Nix-TB trial, and efficacy was compared. The favorable outcome for the matched-controlled subjects was 11 percent compared to 89 percent in the Nix-TB trial, which was statistically significantly better.

The safety in this submission comes from the 19 completed and ongoing trials; 3 of them, phase 3; 6 phase 2; and 10 phase 1 trials. 1168 subjects were exposed to pretomanid as monotherapy and in combination with other antibacterial drugs. 121 subjects had received pretomanid in the regimen

proposed for marketing, the BPaL regimen, for a duration of up to 9 months.

These patients come from the Nix-TB trial, 109 patients, and also from ZeNix trial, 15 subjects, with a data cutoff of March 2018. However, again as I mentioned before, the safety update provided additional data not only from the Nix-TB trial but also for the ZeNix trial, and we have a total of 61 subjects in the ZeNix trial that we evaluated and conducted the safety analysis on.

Safety of pretomanid as a monotherapy comes from the nonclinical studies and the early clinical studies. Several target toxicities have been identified in the nonclinical studies, specifically testicular toxicity, cataract formation, and neurotoxicity. This had been evaluated in clinical development, and so far data are reassuring.

Pretomanid as a monotherapy does not have QT liability in the nonclinical studies or in thorough QT studies conducted by the applicant. Although hepatotoxicity had not been a major prominent feature in nonclinical development, there were

3 cases of fatal hepatotoxicity that had been observed in early clinical trials when pretomanid was used in combination with pyrazinamide and moxifloxacin. This had been evaluated further in the BPaL regimen and other regimens by the applicant.

On this slide you can see the adverse events of special interest that were examined by the FDA in great detail. It is hepatotoxicity; pancreatitis; effect on fertility; peripheral and optic neuropathy; myelosuppression, QT prolongation; and lactic acidosis.

As for the outline of the day, my presentation will be followed by applicant's presentation, and then presentations by the FDA. Summary of efficacy will be presented by Dr. Daniel Rubin, and summary of safety will be presented by Dr. Elizabeth O'Shaughnessy.

For both the FDA and applicant's presentation, we'll have time for clarifying questions, and then we'll break out for lunch. After that, we'll have an open public hearing, and

we'll conclude with a discussion of the questions that we posed to the committee.

The question that we have for you today is to vote and discuss whether the applicant has provided substantial evidence of effectiveness and sufficient evidence of safety of pretomanid as part of the combination regimen with bedaquiline and linezolid in adult patients with extensively drug-resistant XDR tuberculosis and treatment-intolerant, nonresponsive multidrug-resistant tuberculosis.

If yes, we want you to discuss any recommendations concerning labeling, and if not, we want you to discuss whether additional studies or analyses are needed. Thank you.

DR. BADEN: Thank you.

We will now move on 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, the FDA believes

that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including 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 the sponsor, including equity interest 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 Global Alliance of TB Drug Development presentations.

Dr. Spigelman?

Applicant Presentation - Mel Spigelman

DR. SPIGELMAN: Good morning, and thank you very much. My name is Mel Spigelman, and I'm the

president and CEO of the TB Alliance. Since its inception, TB Alliance has worked on the research and development of both new drugs, but perhaps even more importantly, new multidrug, regimen-based paradigms developing new TB therapeutics.

We're very pleased to be here today to review the first novel regimen for the treatment and cure of the large majority of the most resistant and lethal forms of active TB. But first, let me just take a moment to present a brief overview both of TB and our organization.

TB kills more people than any other infectious disease in the world, and it's perhaps the quintessential disease of poverty, affecting the poorest of the poor. Worldwide, more than 2 billion people are infected with the bacterium that causes TB, and it is responsible for 1.6 million deaths annually.

Equally important in an era of mass migration and international travel, TB is transmissible through person to person contact, and the lengthy process in treating even

drug-susceptible TB, coupled with the transmissibility of all forms of active TB, has given rise to drug-resistant strains becoming more common and extremely challenging to treat. We now understand that person-to-person transmission is the greatest single source of drug-resistant TB, and to highlight the relative importance of drug-resistant TB, that drug-resistant TB is the largest single source of antimicrobial resistance globally.

The major challenges with treating extensively drug-resistant TB include the following: treatments have been too long, at least 18 months in duration; too complicated, at least 5 drugs, including some with daily injectables and no defined set regimen.

The treatments have been highly toxic, which leads to early discontinuations due to side effects that can include deafness, renal failure, and psychosis. Regimens that have poor efficacy, success rates in the population that we studied in South Africa in the pre-bedaquiline era were on the

order of 20 percent. It was actually within this context that the TB Alliance was founded.

TB Alliance is a not-for-profit product development partnership. Our goal is to discover, develop, and deliver faster-acting therapies in the long neglected field of tuberculosis. The founding of the alliance actually dates back to February of 2000 at a meeting in Cape Town, South Africa, which was organized to chart a course for improving the dire situation with TB therapy.

The meeting was convened by the Rockefeller Foundation and hosted by the Medical Research Council of South Africa; the U.S. National Institutes of Health; the Bill and Melinda Gates Foundation; the Wellcome Trust; and the UK Department for International Development. Approximately 120 representatives, mostly from academia, government agencies, nongovernmental organizations, and donors gathered to participate in this important discussion. One of the major decisions from that meeting was to form the TB Alliance.

Today we work with and leverage a global network of both public and private partners as noted on this slide. Central to our mission is to only develop products that will be adopted, available, and affordable to all in need. Based on those principles, TB Alliance has now assembled the largest pipeline ever of potential new TB drug candidates.

Now, let me turn to the issue really at hand today, which is a new drug application that has been submitted for pretomanid. Pretomanid is a new chemical entity that has been developed specifically to treat TB. The compound is a nitroimidazooxazine with novel mechanisms of action. In both nonclinical and clinical studies, pretomanid has shown anti-TB activity against both drug-susceptible and drug-resistant strains of M. tuberculosis. It also possesses excellent bactericidal and curative or sterilizing activities.

As of March, 2018, pretomanid had been studied alone or in combination in 1168 individuals

and in 19 clinical trials, and FDA has granted priority review and qualified infectious disease product and orphan drug status to the compound.

Combining pretomanid with bedaquiline and linezolid in the Nix-TB pivotal study presented a unique opportunity to evaluate a novel regimen with potentially transformative ability and utilizing the minimum number of drugs that would be acceptable for treating patients with active TB. We will refer to this 3-drug combination as the BPaL regimen.

Each drug in the regimen has demonstrated potent preclinical and clinical anti-TB activity with minimal preexisting resistance, and all 3 drugs contribute to both the bactericidal and the curative activity of the regimen as a whole. In animal models of this regimen, efficacy is even better than the standard first-line treatment for drug-susceptible TB.

The Nix-TB study demonstrated that this all oral-fixed, BPaL regimen is a breakthrough cure for extensively drug-resistant TB, treatment-tolerant,

or nonresponsive multidrug-resistant TB. We will refer to these three categories today as highly-resistant TB. We also define the term "cure" as no clinical or bacteria logic evidence of tuberculosis at 6 months after the completion of treatment.

The 6-month regimen was found to cure 90 percent of patients with highly-resistant TB. Adverse events were manageable and as expected with this combination of drugs, and the vast majority of patients were able to complete therapy and achieve therapeutic success.

When we now look at the results of the Nix-TB trial in the context of the challenges that I just described in the treatment of highly-resistant TB, our presentation today will demonstrate how pretomanid and the BPaL regimen can overcome these issues.

Specifically, we can go from now long treatment durations of more than 18 months to a 6-month regimen; from complicated combinations of 5 or more drugs that may include injectables to a

3-drug, all oral, clearly defined set regimen; from highly toxic drugs that frequently contribute to discontinuations to a regimen that has manageable tolerability and very few discontinuations; and from poor efficacies with the very low historical cure rates in comparable populations to a cure rate of 90 percent.

Based on the Nix-TB results, we're seeking approval for pretomanid as part of a combination regimen with bedaquiline and linezolid in adults for the treatment of pulmonary extensively drug-resistant, or treatment-intolerant, or nonresponsive multidrug-resistant tuberculosis.

This indication represents the select group of the most severe worst prognosis patients with XDR or MDR TB. The path to this NDA submission has not been conventional, so I do want to briefly review the regulatory history.

Nix-TB is an ongoing study that was initiated in 2015 and completed the enrollment of 109 patients in November of 2017. Based on the planned interim analysis, the FDA agreed that

safety and efficacy data on the first 45 patients would be acceptable to support an NDA submission.

The data which we will present to you today will be based on the 81 patients in the primary efficacy analysis population and the 109 patients in the safety analysis population that has been submitted in the NDA.

Additionally, we will be sharing with you the latest data from the 120-day efficacy update consisting of 104 patients for efficacy, which will demonstrate both the consistency and the durability of response. Patient follow-up is ongoing to 20 months post-end of treatment for all participants.

I would now like to outline the agenda for our presentation. Dr. Neil Schluger of the Columbia University Department of Medicine, who has spent almost three decades treating patients with highly-resistant TB, will present the unmet need for highly-resistant tuberculosis. Dr. Dan Everitt of the TB Alliance will present the Nix-TB studies, efficacy, and safety data.

Dr. Francesca Conradie of the University of

Witwatersrand in Johannesburg, South Africa, who is the principal investigator of the Nix-TB trial, will provide her clinical perspective; and finally, Dr. Everitt will return to moderate the question and answer period. We also have additional experts with us today to answer any questions that may arise, and all external experts have been reimbursed for their time and/or their expenses.

Let me now invite Dr. Schluger to present the unmet need for highly-resistant TB. Thank you all very much.

Applicant Presentation - Neil Schluger

DR. SCHLUGER: Good morning. I'm Neil Schluger, chief of the Division of Pulmonary Allergy and Critical Care Medicine at the Columbia University Medical Center in New York, and professor of medicine, epidemiology, and environmental health sciences at Columbia. I've devoted my clinical and research career to patients with tuberculosis, beginning at the height of the TB epidemic in New York City in 1992 when I directed the TB clinic at Bellevue Hospital and

continuing until today.

For 16 years, I was the chairman of the Tuberculosis Trials Consortium, which is a CDC funded group of researchers conducting clinical trials to improve TB treatment, and I remain as a principal investigator in that consortium. I was also a member of the Nix-TB data safety monitoring committee for the TB Alliance.

I'm here today because the unmet need for people infected with the most lethal forms of highly-resistant TB is great and growing. Patients face complex and extremely onerous treatment options. Cure rates are low and mortality rates are high. In fact, globally, TB is the world's leading cause of death from a single infectious agent.

In 2017, the World Health Organization estimated that 10 million people develop tuberculosis and more than 4,000 people die every day from this disease. TB is a particularly significant concern for people living with HIV. In fact, TB is the greatest killer of people with HIV.

Patients with tuberculosis have a debilitating systemic disease. Common symptoms include fever, cough, weight loss, sputum production, and hemoptysis. Because of the prolonged treatment, many patients experience profound social isolation and stigma, and the longer the patient goes without effective treatment, the higher the risk for permanent lung damage, for bacteria that spread to other organs, for transmission to others in the community, and for death.

Effectively treating tuberculosis in its simplest forms can take between 6 and 9 months, much longer than treating other types of common bacterial infections. Complex and difficult regimens present a significant challenge, especially in parts of the world where access to care is limited.

Patients who are untreated or who are treated improperly remain sick for a long period of time and may die. If drugs are taken incorrectly, the TB bacteria that is still alive may become drug

resistant.

Regardless of who is infected or how they were infected, patients with TB that is resistant to drugs have a disease that is much more difficult to treat. Multidrug-resistant TB, MDR TB, is TB that is resistant to at least two of the most powerful first-line antibiotics, isoniazid and rifampicin. Extensively drug-resistant TB, XDR TB, is TB that is resistant to isoniazid and rifampicin plus any of the fluoroquinolones and at least one of the three second-line injectable drugs.

Resistant TB can result from either transmission from one person with highly-resistant TB to another or from a failure of previous treatment for drug susceptible or a multidrug-resistant TB. In either case, antimicrobial resistance is increasing around the world, and the likelihood of an epidemic with difficult-to-treat strains is growing.

Over the past 25 to 30 years, we become aware of the growing threat of drug-resistant TB. This was recognized in New York City in the early

1990s and is now appreciated globally. XDR TB in fact has been confirmed in 127 countries around the world.

In 2017, there were about 460,000 new cases of multidrug-resistant TB globally. While about 39,000 of these were estimated to be extensively drug-resistant TB, only about 8700 of those patients were treated for their extensively drug-resistant TB. Treatment for highly-resistant TB is burdensome, prolonged, and toxic.

Typical treatment consists of up to 8 drugs, including 6 months of daily injections in many cases, followed by 12 to 18 months of 5 drugs every day. Treatment often requires hospitalization, and drugs are difficult to take because of side effects, including permanent hearing loss and kidney damage from several of the injectable drugs.

Due to these factors, as well as the lack of availability, around the world, only 20 to 25 percent of patients with MDR and XDR TB are currently being treated. Very few trials have been done to guide treatment for drug-resistant

tuberculosis. We often design treatment regimens by listing all the TB drugs on the blackboard, crossing off the ones that the bug is resistant to and giving the patient everything that's left. This is hardly ideal, but it's often the best we can do.

Recently, results of the STREAM trial were published. STREAM showed that under the best conditions, treatment could be shortened to 9 months, but this requires the administration of at least 7 drugs, including an injectable drug, and side effects were just as common as with longer treatment regimens.

This trial included patients with MDR TB but who were susceptible, by and large, to second-line injectables or a fluoroquinolone. Patients in the Nix-TB trial by definition would be ineligible for treatment with the STREAM regimen because of extensive prior treatment or resistance to quinolone and injectable drugs.

Although outcomes are better with the recent approvals of new drugs now recommended by the World

Health Organization, there are a little data available about how to use those drugs, in what combinations, and for how long. It's long past time for a new defined regimen for highly-resistant TB with little to no resistance.

The regimen should shorten treatment duration and allow patients to convert culture status quickly to interrupt the transmission process. It should simplify administration, improve tolerability and the ability to manage adverse events, and improve cure rates, including for people with HIV

Thanks very much for your attention. Now I'm pleased to invite doctor Dan Everitt to present the Nix-TB study results.

Applicant Presentation - Daniel Everitt

DR. EVERITT: Good morning. My name is Dan Everitt, and I'm the vice president and senior medical officer at TB Alliance. I've been the physician leading the Nix-TB trial since it began back in 2015, and I'm very pleased to be here today to review the Nix-TB results.

The 3-drug, all oral, 6-month regimen that combines pretomanid with bedaquiline and linezolid cures approximately 90 percent of patients with highly resistant. Patients on the BPaL regimen converted quickly to culture-negative status with a median time of less than 6 weeks. In addition, patients improved clinically with a reduction in symptoms and an overall improvement in patient reported health status.

Now, let me first describe the design of the Nix-TB trial. The Nix-TB trial is the first clinical study to develop a fully new regimen, including a new chemical entity to treat highly-resistant TB. The focus was on developing pretomanid as a new drug in the context of a specific drug regimen.

The pivotal phase 3 study was a multicenter, open-label, single-arm study, assessing the safety, the efficacy, and the tolerability of BPaL in patients with either pulmonary extensively drug-resistant TB or treatment-intolerant, or nonresponsive multidrug-resistant TB. A total of

109 patients were enrolled and treated at three centers in South Africa. While enrollment has completed, this is an ongoing study with continuing follow-up past the primary endpoint to 24 months after completion of therapy.

Pretomanid's mode of action is complex, and it requires metabolism of the drug to an active form within the tuberculosis bacterium. Pretomanid kills both replicating mycobacteria tuberculosis and bacteria that has stopped replicating due to the presence of stringent conditions such as hypoxia. Hypoxia is present in some TB lesions.

Against replicating MTB under aerobic, the main mode of action is inhibition as synthesis of a cell-wall component. Against non-replicating bacteria under hypoxic conditions, pretomanid works by releasing cell-damaging nitric oxide that leads to mycobacterial death.

Now, active tuberculosis requires a minimum of 3 drugs for effective treatment. Streptomycin was the first drug used to treat TB back in 1940s, and later, isoniazid was also tried as monotherapy,

but monotherapy quickly showed that resistant organisms developed rapidly. While trials of 2 drugs showed some success, treatment required long durations, and concerns of resistance led to a consensus that a minimum of 3 drugs is necessary to effectively treat tuberculosis.

In the Nix-TB trial, we had the opportunity to combine 3 drugs with very little preexisting resistance and which have different mechanisms of action against TB. Mouse models of TB infection are predictive of bactericidal activity and cure in humans with TB. Clinically relevant doses of BPaL in mice with TB infection gave very impressive results, strongly supporting our plan for Nix-TB.

In this model, mice were infected with TB 2 weeks before being given various treatment. Groups of mice were then euthanized at multiple time points and their lungs were cultured to quantify the TB bacteria. Some mice were euthanized immediately after treatment ended to assess bactericidal activity; other mice were euthanized 3 months after treatment to assess

curative activity.

You will see the mouse results showing that while pretomanid alone has potent bactericidal activity, the greatest activity is when the full 3-drug BPaL regimen is given. You can see here that over 8 weeks, pretomanid alone has substantial bactericidal activity.

Greater reductions among burden were seen when any two of the drugs were combined, and the greatest reduction was seen when all 3 drugs were given together. BPaL reduced the CFU significantly further than any of the 2-drug regimens, and that demonstrated that each drug independently contributed to the regimen's overall activity.

In another study where groups of mice were treated for varying durations of time and then held with no treatment for 3 months, any mouse with TB culture from the lungs was considered to have relapsed. When mice were treated for up to 4 months with bedaquiline and linezolid, almost all relapsed 3 months after ending therapy.

However, when pretomanid was added, all mice

were cured after 3 months of therapy. Furthermore, pretomanid prevented the development of resistance seen with the 2-drug bedaquiline and linezolid combination. This gives confirmation that pretomanid is critical to both the curative activity of the regimen and to preventing emergence of resistance.

In a study in humans of early bactericidal activity, each dose group had 15 patients. The amount of curable TB organisms decreased over the 14-day period, as shown here as regression curves fitted to colony-forming units on culture plates. Similar results were seen for 100- and 200-milligram groups, and we saw less activity at 50 milligrams daily.

In a different study, we saw no greater bactericidal activity with doses up to 1200 milligrams a day. This combined with results of 8-week phase 2 studies and a risk-benefit assessment led us to take the 200-milligram daily dose into phase 3 trials. We've also conducted similar studies of early bactericidal activity of

bedaquiline and linezolid alone and shown very similar results over a 2-week period in patients with newly diagnosed TB.

I'd next like to discuss the design and location for the Nix-B study. We decided on a single-arm study design for several reasons. First, patients with highly-resistant TB had limited treatment options due to their resistance profile. Second, there's no standard set regimen for patients with highly-resistant TB to have used as a comparator.

Third, there would have been multiple challenges in randomizing patients to BPaL versus the historically used ad hoc regimens that have many side effects, often poor treatment outcomes, and were long and complex, requiring at least 5 medicines.

South Africa was ideal for the trial given the high prevalence of highly-resistant TB, excellent trial infrastructure and investigators, and a reliable regulatory environment. Here's the dosing for the BPaL regimen used in the trial.

Each of the drugs were given over a 26-week period: 1 tablet of pretomanid 200 milligrams once daily; plus the standard labeled dose of bedaquiline, which is 400 milligrams once daily for 2 weeks; followed by 200 milligrams 3 times a week; plus linezolid at a total daily dose of 1200 milligrams.

Because of known toxicities, the study protocol allowed the physician discretion to modify dosing in specific ways. Linezolid could be reduced after the first month or temporarily interrupted for adverse effects. If interrupted, linezolid could be restarted at the same or at a lower dose. Also, linezolid could be discontinued after the first month of treatment.

While no changes in the doses of pretomanid or bedaquiline were allowed, the full BPaL regimen could be interrupted for up to 35 consecutive days. Any missed doses would be made up to complete a full 26 weeks, 6 months of therapy.

The Nix-TB study included 6 months of the BPaL regimen, which is the same amount of time it usually takes to treat standard drug-susceptible

TB. There was an optional three 3-month extension period for patients who are culture positive between months 4 and 6. Study medication was administered with food and orally. After treatment was completed, patients had monthly follow-up visits for the first 3 months and then once every 3 months for a total of 24 months. The primary endpoint was defined as a patient status at six months after the end of treatment.

Literature on past trials have shown that the majority of relapses occur within the first 6 months finishing treatment. Nix-TB, importantly, used an ultimate clinical endpoint, and it did not rely on a biomarker or surrogate. The primary endpoint required not only culture negativity but maintaining culture negative status 6 months following the end of treatment.

Patients were categorized as having either a favorable or an unfavorable outcome. Patients could have an unfavorable outcome by having clinical or bacteriologic failure during treatment, essentially failing to convert their sputum to

negative during treatment. They could also be unfavorable if they had a relapse of their TB infection post-treatment.

Any patient who is withdrawn at any point during treatment or follow-up and require alternative treatment for their TB was also considered to have an unfavorable outcome. Death was an unfavorable outcome in the intent-to-treat analysis unless it came after a relapse or another reason for an unfavorable outcome. Patients who had a favorable outcome were considered cured.

The study enrolled patients with highly-resistant pulmonary TB who met the following key eligibility criteria: TB documented by culture or molecular probe within 3 months of enrollment and a documented history of the required drug resistance. Patients must have had a body weight of at least 30 kilograms and a chest x-ray consistent with pulmonary TB that was taken within a year prior to screening.

The key reasons patients were excluded are noted here. HIV-infected patients were allowed in

the study, but those with a CD4 count less than 50 were excluded. Patients needing certain drugs such as strong hepatic enzyme inducers or inhibitors were excluded also. And patients with low hemoglobin platelets or neutrophil counts were excluded, as were patients with elevated liver enzymes or elevated bilirubin.

In the primary efficacy analysis, we present the percent of patients with favorable outcomes and we prospectively specified that the trial would be successful if the lower bound of the 95 percent confidence interval was greater than 50 percent. We set 50 percent as a favorable rate to exceed, as that was much higher than prior experience for patients with highly-resistant TB before either bedaquiline or [indiscernible] were in use. Key secondary endpoints included time to sputum culture conversion to negative status for all patients who were culture positive at baseline; changes in TB symptoms; and patient status at 24 months after the end of treatment.

Turning next to the Nix-TB efficacy results,

93 percent of patients successfully completed treatment; 143 patients who were screened and then 109 patients were enrolled and began the BPaL regimen. This was the same number of patients that's included in the overall safety population.

Twenty-eight patients at the time of our NDA file did not yet reach the primary efficacy endpoint, so the intent-to-treat population included 81 patients. One patient who died after completing treatment but was culture negative when last seen was excluded from this modified intent-to-treat analysis as specified in our statistical analysis plan. Thus, the MITT population included 80 patients.

The mean age of the patients was 35 years. There were slightly more males than females, and most patients were black. The mean body mass index was 20.6, although we had a range down as low as 12 and up to 41. At screening, nearly two-thirds of the patients had a diagnosis of extensively drug-resistant TB.

The overall median duration of a patient's

TB infection prior to screening was 12 months with a maximum of more than 11 years. Just over half the patients were HIV positive with a mean duration since diagnosis of their HIV of about 5 years. All the HIV patients were on antiretroviral therapy.

Now of note, the majority of patients had cavities on their chest x-ray, and many with bilateral cavities, and that's known to be a risk factor for poor outcomes in patients with TB. We assume that all patients had TB isolates that would be susceptible to each drug in the BPaL regimen. During the trial, the minimum inhibitory concentrations, or the MICs, for the 3 drugs were determined on baseline isolates, although that information was not available to the clinicians at the time of enrolling and treating the patients.

Available baseline isolates showed all linezolid MIC values below or equal to the critical concentration for this drug that's recommended by the World Health Organization. Two patients had bedaquiline MIC values just above the critical concentration recommended by WHO. The range of MIC

values observed for pretomanid were all less than or equal to 1 microgram per mL, and that is our proposed breakpoint to use to determine susceptibility.

The MITT analysis was identified as the primary analysis, and per the statistical analysis plan, the MITT population excluded one patient who died nearly 6 months after completion of therapy, and he was culture negative at the last time evaluated.

The BPaL regimen resulted in 90 percent of patients having a favorable outcome. The lower bound of the 95 percent confidence interval for the proportion with a favorable outcome was 81 percent, far exceeding the 50 percent prespecified threshold for success, and these results were consistent for patients with either XDR TB or treatment-intolerant or nonresponsive TB, MDR TB.

The intent-to-treat population had very similar results; 89 percent of the ITT population had a favorable outcome, and they achieve relapse-free cured at 6 months following completion

of treatment. These results were consistent with patients also with XDR TB or the treatment-intolerant or nonresponsive MDR TB, as you can see.

We also looked at a prespecified subgroup analysis by HIV status. The primary efficacy findings were similar regardless of HIV status. Further subgroup analyses by age, sex, weight, cavitation on x-ray, and baseline bacteria load in sputum showed essentially the same results for the different subgroups.

Next, our discuss our key secondary endpoints. Shown here is the time to culture conversion. Patients With treatment-intolerant, nonresponsive MDR TB and XDR TB converted at very similar rates. Of the 68 patients with positive cultures at baseline, the median time to conversion was 5.7 weeks. The one XDR patient with a positive culture at the week 16 visit here converted within the next week.

This median time to culture conversion is very similar to what's been reported in trials of

drug-susceptible TB. Overall, patients also achieved a reduction in their TB symptoms from baseline to the end of study, and this graph shows a progressive reduction in symptoms over the course of treatment.

At baseline, 96 percent of patients experienced symptoms. By week 8, this percent decreased to 75 percent, and by the end of treatment, patients experienced TB symptoms decreased to 49 percent, and this decline is consistent with the change in disease status.

Here's a review of the incidence of bacteriologic failure or relapse at 24 months post-therapy for patients who had follow-up for the full length of the study. As a reminder, this is an ongoing study with follow-up continuing. The data support that, in general, cure at the primary endpoint is sustained over long-term follow-up. At the time the data were extracted, 23 patients reached the 24-month endpoint assessment. Of these, 3 died during treatment and one relapsed 15 months after completing the study regimen.

I'd now like to show data of the latest from our 120-day update recently submitted to the FDA. In this analysis, we have 104 of the 409 patients followed to the primary efficacy endpoint 6 months after treatment. With almost all of the patients followed at the primary endpoint, we now have an overall favorable rate of 91 percent, which is essentially the same as what I showed you from the time of our initial NDA filing.

I'd next like to review an analysis comparing a historical control group of 84 patients with XDR TB with the first 44 patients in the Nix-TB trial, which shows a benefit of the BPaL regimen. The study used individual patient data from one of the sites where the Nix-TB study was conducted prior to the start of Nix. Patients in both groups were from the same geographic area, and they were individually matched on a nearly 2 to 1 ratio in terms of age, sex, body weight, and HIV status distribution at baseline.

Patients in the control group had been treated between 2008 and 2014 with various drug

combinations, which did not include bedaquiline or linezolid, and treatment outcomes were recorded as either favorable or unfavorable. Favorable for the control group used the World Health Organization definitions of cured or completed treatment, which assesses patients' status at the end of treatment.

What we see is about 89 percent of the Nix-TB patients had favorable outcomes compared to about 11 percent of the control population. This matched comparison clearly favors the outcomes for the patients in the Nix-TB trial, and the magnitude of the difference in treatment outcomes of the two populations indicates the potential benefit of the BPaL regimen in patients with extensively drug-resistant TB.

In summary, the Nix-TB study showed that the BPaL regimen can transform the treatment of highly-resistant TB, with patients being cured by taking a short, a simplified, and an effective regimen. Ninety percent of patients with highly-resistant TB achieved relapse-free cure status 6 months after the end of treatment, with a lower bound of

patients achieving a favorable outcome far exceeding the prespecified threshold of 50 percent, and that result was the same for the half of the population who had HIV co-infection.

Furthermore, patients on the BPaL regimen converted to culture-negative status very quickly with a median time of less than 6 weeks. Ninety percent of patients remained relapse-free at 6 months after the end of treatment with preliminary data at 24 months, indicating that these patients were indeed cured.

Next, I'm going to present the safety profile of pretomanid as part of the BPaL regimen for the treatment of highly-resistant TB. Data discussed reflect the data submitted at the time of a new drug application.

The Nix-TB safety database include safety information on the 109 patients who were treated with BPaL and who will be followed for 24 months post-therapy. In this section, I'll describe overall safety, and then I'll focus adverse events of special interest.

Overall, adverse events were as expected with these 3 drugs in the BPaL regimen. As you'll see, events were generally manageable with dosing modifications, and the majority of patients were able to complete therapy. The only patients who did not complete therapy where the 6 who died and the 10 patients who were continuing treatment at the time of the NDA submission.

Beyond the Nix-TB database, the new drug application included information on over 1100 patients across 19 studies. These included trials where pretomanid was studied alone and phase 2 and 3 studies of pretomanid used in different regimens.

Now, let's take a look at the data beginning with the larger database. In the phase 1 studies, healthy volunteers were treated for up to 14 days. Shown here are the adverse events reported for the patients receiving pretomanid, 289 patients, versus placebo. Of note, the hemoglobin decreases here were due to protocol-driven blood draws in the thorough QT study, and multiple electrocardiograms in that study also resulted in contact dermatitis.

In the phase 2 studies where pretomanid alone was compared to the standard HRZE treatment for drug-susceptible TB over 14 days, some of the adverse events were similar to those in healthy volunteers. The most common adverse events for pretomanid alone were related to GI symptoms, skin, and headache. However, in this population of patients, headache was much less common than in the healthy volunteers.

Now moving to the Nix-TB trial, many of the patients were quite ill with their TB and comorbidities when they entered the trial. Not surprisingly, given the length of the time of follow-up, all participants experienced at least one adverse event. About 17 percent of patients experienced a serious adverse event, and about half the patients experienced at least one grade 3 or grade 4 adverse event.

Shown here is a list of the adverse events occurring in more than 15 percent of patients. As you can see, the most common adverse event was peripheral sensory neuropathy, and that's something

that's been well described as an adverse event for linezolid. GI events of nausea, vomiting, dyspepsia, and decreased appetite were fairly common and expected based on prior studies for each of these 3 drugs.

About a third of patients experienced anemia, another adverse event that's well described with linezolid use; also, headache was reported in about a quarter of patients. In addition to neuropathies and anemias, some of the other side effects have been described for all of the drugs in the regimen.

Despite common adverse events, the large majority of Nix-TB patients were able to tolerate therapy and complete treatment. The only patients who permanently discontinued the regimen were the 6 patients who died during the course of treatment, and I'll discuss them in a few minutes.

The entire regimen was interrupted in 20 patients due to adverse events. Other than the patients who died during therapy, all patients who were interrupted were able to complete the full

6 months of therapy or they were ongoing at the time of the NDA submission. A key factor in enabling patients to stay on treatment and complete the full regimen was the ability to modify dosing for the drugs in the regimen due to an adverse event.

Linezolid was likely responsible for most adverse events and for all the dose modifications. Fifty patients interrupted and resumed their treatment of linezolid at the same or the lower dose. Thirty-three patients permanently discontinued, with all surviving patients completing treatment. The most common reason for permanent discontinuation of linezolid was peripheral neuropathy. At the same time, 34 patients completed taking linezolid without any interruption or miss doses, although they may have had their dose reduced.

Moving now to serious adverse events, as I mentioned previously, at least one serious adverse event was reported in 17 percent of patients. The most common serious adverse events reported were

pneumonia and worsening pulmonary TB, and those were related to the underlying disease. Sepsis, hypoglycemia, and anemia were reported in 2 patients each, and all other serious adverse events were single preferred terms of unique types.

Fifty-three percent of patients reported a grade 3 or grade 4 adverse event. The most common event was peripheral sensory neuropathy, which is known to be associated with linezolid, and as just discussed, this was a common reason for modifying the dose of linezolid by either reducing the dose or temporarily stopping or discontinuing linezolid. Elevation of transaminases, including GGT, as well as amylase increases also occurred in a higher proportion to other events.

A total of 8 deaths were reported in the trial. The patients who died generally had severe TB infections and advanced underlying disease. In fact, there was information from autopsies on 5 of the first 6 patients, and 3 of them had autopsy findings of multiorgan TB infection; 5 of the 8 patients also were infected with HIV.

Six of the deaths occurred during study treatment, and these deaths were relatively early within the first 3 months. Two additional deaths occurred at least 6 months after completing the trial regimen. Patient number 7 died approximately 6 months after completing study treatment due to natural causes, which in South Africa means just death not due to violence, and this patient had negative sputum cultures at his final visit before dying.

Patient 8 was a patient who relapsed, had an unfavorable outcome, and then subsequently was successfully treated but he later died with gangrene and sepsis, all unrelated to his TB or his drug therapy, and both these patients were HIV positive.

Next, I'll review the various adverse events of special interest that we identified at the start of the trial for especially careful surveillance, and these were based on preclinical toxicology findings or known clinical areas of concern for each of the 3 drugs.

Here are the prospectively identified adverse events of special interest relative to each drug in the BPaL regimen. For pretomanid, the first 4 adverse events are based on animal toxicology findings, and hepatic toxicity is based on a preliminary clinical safety signal. In the case of bedaquiline, myopathy and pancreatitis are based on animal toxicology findings, and ECG and hepatic effects are based on the product label. For linezolid, all the listed events here are clinical observations noted in the product label.

The briefing document you received covers all adverse events in some detail, but these are the key adverse events we wanted to watch especially closely when the trial started, and I'd like to focus on a few of these now.

Hepatic safety is a signal we've been watching closely. This shows key indices of potential hepatic injury as elevations at various cutpoints in ALT and in total bilirubin. While approximately 5 percent of patients had elevations of ALT either in the 3 to 5-fold range or the 5 to

8-fold range above the upper limit of normal, only one patient had an elevation greater than 8-fold above the upper limit.

Two patients had total bilirubins greater than 2-fold above the upper limit of normal. However, many of the patients did have elevations at baseline. This column highlighted shows the much smaller number of patients who had ALT elevations in each category and had ALT within the normal range at baseline.

A standard way of evaluating liver safety is the so-called eDISH plot, which is shown here, and each point represents a single patient, and all patients from the trial are represented. You can see highlighted the two cases that met laboratory criteria as potential Hy's law cases located in the upper-right quadrant of the graph.

Both of these patients resumed treatment and completed the study with a return their enzymes and bilirubin to within or close to the normal reference range, and these patients both had a favorable outcome at the primary endpoint.

Hepatic safety has been evaluated carefully across the pretomanid development program. Here's a table of potential Hy's law cases based on ALT and bilirubin across the program by various groupings. As you can see, there were no cases meeting potential Hy's law enzyme and bilirubin elevations when pretomanid was administered alone for up to 2 weeks.

In the study of various combination regimens, including pretomanid, which usually included the anti-TB drug, pyrazinamide, there were 4 potential Hy's law cases or 0.6 percent of the total. In contrast, in the study arms treated with the standard HRZ regimen for drug-susceptible TB, there were three cases or 1.3 percent of the total. And I've already noted the two Hy's law cases in the Nix study, and they were both able to resume and complete treatment.

Next, I'll discuss adverse events potentially related to the pancreas, which we've identified as an adverse of special interest based on animal toxicology findings for bedaquiline.

Importantly, for patients who interrupted the drug regimen due to one of these events, all were able to resume therapy following resolution of the adverse events noted here.

Three patients had adverse events that coded under the category of pancreatitis or hemorrhagic pancreatitis as specified in this slide. Many of these events were considered grade 3 or 4, and two were reported as serious adverse events. However, there were no permanent withdrawals from the trial due to these events. Two patients who died had autopsy findings of pancreatitis, although all remaining patients completed drug treatment through the end of the study without withdrawing.

Finally, I'll review the adverse event well described with the use of linezolid, beginning with peripheral neuropathy, the most common adverse event in the Nix-TB study. Eighty percent of the patients reported an adverse event of peripheral neuropathy. The most frequently reported adverse events in this category were peripheral sensory neuropathy, neuropathy peripheral, parasthesia, and

hypoaesthesia. The majority of these events were grade 1 or 2, none were considered serious, and they gradually diminished after treatment was completed.

Here we see the time and days to the first linezolid dose interruption and/or dose reduction for peripheral neuropathy, and this tells us a couple of things about this toxicity. First is that the onset of peripheral neuropathy is delayed, generally occurring after the first 3 months of treatment; and second, the events were managed with dose interruptions, reductions, and in some cases discontinuation of linezolid.

With a concern about optic neuropathy from linezolid, patients had regular eye examinations for visual acuity and for color vision, and then fundus examinations if any concern was raised. In the trial, 2 patients developed optic neuropathy or optic neuritis. Both patients had symptoms of visual changes in fundus examination consistent with optic neuropathy. In both cases, linezolid was stopped permanently and their vision returned

to normal over one to several months, and the fundus exam returned to normal as well.

Myelosuppression is another risk associated with linezolid, and it was reported in about 47 percent of patients. Anemia was by far the most common event, followed by neutropenia and thrombocytopenia. While the majority were grade 1 or 2 in severity, there were 3 adverse events, one of neutropenia, and two of anemia. Overall, just 2 patients discontinued linezolid due to these adverse events, but they remained on the other 2 drugs in the regimen, and they completed the trial.

Here we see the time and days to first dose interruption and/or dose reduction of linezolid for incidences of myelosuppression. Linezolid dose interruptions and reductions due to myelosuppression were generally for cases of anemia, and they generally occurred in the first 3 months.

In conclusion, the data showed that the BPaL regimen has a manageable safety profile, which allowed the majority of patients to complete the

full 6 months of treatment. In fact, all but 6 of the enrolled patients in Nix-TB were able to complete the regimen. This type of completion rate is similar to completion rates for patients being treated for drug-susceptible TB, and it's far greater than those rates generally seen for highly-resistant TB.

The types of adverse events with BPaL were expected. These have been well characterized, and they were managed by the interrupting of the full regimen or the interrupting, reducing, or permanently discontinuing linezolid. Patients on the regimen clearly do need to be followed carefully, and knowledge of the potential toxicities of the 3 drugs can guide the clinician on whether to modify the dosing of linezolid or to interrupt the full regimen.

We're now working on details for postmarketing activities to further evaluate the efficacy and safety of the 3 drugs in the BPaL regimen. ZeNix is an ongoing phase 3 trial of the BPaL regimen that is designed to optimize the use

of linezolid, and this study is currently enrolling.

SimpliciTB as a phase 3 trial are the regimen of pretomanid combined with the bedaquiline, moxifloxacin, pyrazinamide to treat drug-susceptible TB in 4 months or drug-resistant TB in 6 months, and it's also currently enrolling. A male reproductive study is nearing initiation to evaluate parameters of sperm and semen in men with TB, treated over 6 months, to follow up on toxicology findings in rats of testicular toxicity.

We'll work with the agency to establish a pretomanid resistance surveillance study over a 5-year period in multiple geographic areas to assess the extent of development of resistance to pretomanid after market approval.

I'd now like to invite Dr. Francesca Conradie, our principal investigator in the Nix-TB trial, to the lectern to discuss her clinical perspective on the BPaL regimen.

Applicant Presentation - Francesca Conradie

DR. CONRADIE: Good morning. My name is

Francesca Conradie of the University of Witwatersrand in Johannesburg, South Africa. I've been involved in the field of clinical TB research, including its most highly drug-resistant strains for the past 10 years. Prior to my work in TB, I was involved in clinical HIV research, including as an investigator in registrational antiretroviral trials in this high HIV-prevalent region.

I'm here today, in my role as the principal investigator of the Nix-TB trial, to provide my clinical perspective on pretomanid and the BPaL regimen. I will refer to my role in caring for these patients with highly-resistant TB, many of whom were HIV co-infected. We dealt with the sickest of the sick and still had excellent results. We stand at an historic moment in the global battle to end this deadly disease.

Let me take a moment to first provide some context for the treatment of highly drug-resistant strains of TB. As we've been discussing today, tuberculosis that is extensively resistant to first- and second-line treatment has left

physicians with little choice other than trying as many of the known potentially effective drugs that a patient can tolerate in the hope of killing resistant bacteria. This could have required 2 years or more of toxic and potentially permanently debilitating treatment. It was a haphazard approach of the last resort.

While we have seen evolution in the treatment environment with new medicines being registered, resulting in a significantly better prognosis, patients still face a long and complicated treatment journey.

In the first documented outbreak of XDR TB, that occurred in Tugela Ferry in South Africa in 2009, 52 of the 53 people who acquired this disease died. From there, we moved to a success rate of 20 percent prior to 2014, and now we see about a 65 percent success rate with addition of bedaquiline and linezolid. But the treatment still requires 5 or more drugs and at least 18 months of treatment. We still continue with the approach of adding medicines in the hope that they will work.

While laboratory testing exists to establish drug susceptibility for a particular patient's TB, it is not available in many areas where TB infections occur, and even where it is, it is not reliable for all of the therapeutic options. Bottom line. It still takes a long time, and there is no proven set regimen or standard of care.

With the Nix trial, we had the opportunity to actually cure highly-resistant TB in the same amount of time that is typically used to treat standard drug-susceptible TB. Launched in 2015, we were using bedaquiline, which in 2012 became the first new anti-tuberculosis drug in 50 years to receive regulatory approval; linezolid, which is a repurposed drug used normally for other resistant infections; and pretomanid, an investigational drug developed by the TB Alliance.

The hope of this all-oral regimen was not just to put several new individual medicines into the mix but to provide evidence for how these 3 drugs could be used effectively to simplify and shorten treatment duration with a predefined

combination. The other goal was to study this regimen's ability to overcome highly drug-resistant TB in patients who were quite sick and vulnerable to treatment side effects.

Patients enrolled in the Nix trial had had their clinical TB infection for a substantial period of time. Prior to enrollment, patients had continuous known TB infection for a mean of 22 months, ranging from 2 weeks to more than 8 years, and half were HIV-coinfected.

The efficacy results greatly exceeded our expectations. The durable cure rate of nearly 90 percent is far superior to any reported cure rate for the treatment of highly-resistant TB. In fact, it is similar to the cure rate for treating drug-susceptible TB with standard therapy.

Considering safety, from the beginning, we knew what side effects to expect and counseled people from the moment that they were considering enrollment about what to monitor for and how we would address them. The most consistent side effects were weakness, numbness, and tingling in

the feet from peripheral neuropathy associated with linezolid. This side effect and other side effects known to be associated with linezolid led to more than 60 percent of patients having at least one brief treatment interruption.

A combination of regular cabinetry assessment and patient counseling allowed us to pick up side effects early and address them through dose modification, and that flexibility to modify dose in order to both manage adverse events and to maintain efficacy is a key benefit of this regimen. No surviving patient withdrew due to adverse events.

We're witnessing life-changing results. Allow me to tell you about two of the patients treated in the Nix trial who really exemplify the Nix outcome. The first was a young woman whose sister had died from XDR TB, and she had been undergoing treatment for a year before entering the trial. I will always remember the day she learned that her culture was negative, that her TB had cleared. She went into a room and began crying so

loudly that the nurse rushed in thinking that she was in some kind of distress and needed medicine, but these were actually tears of joy.

The second story is a young man who contracted XDR TB when he was 17 years old. He'd been trying to cure his infection for 6 or 7 years. He traveled from an outlying province and committed treatment and follow-up in Johannesburg. On the Nix-TB regimen, both were cured within 6 months and both continued to do well. Significantly, these patients were able to resume their lives, reenter their communities, and do so much earlier than if they had been on previous therapy for highly-resistant TB.

As I'm reflecting on my experience in South Africa, it is essential to keep in mind that TB is a highly transmissible infection. Drug-resistant TB is as infectious as drug-susceptible TB. With the world becoming a smaller place, although TB is predominantly seen in areas with fewer resources, TB is a global problem. We've seen other infectious illnesses cross borders such as H1N1

influenza, SARS, MERS, and even Ebola.

Considering all of the results presented here today and the enormous unmet need, it is my strong conclusion that the overall benefit to risk ratio of the BPaL regimen is highly positive. Sitting on the front lines of the battle against TB as I do, I see the mixed results as a watershed. In the field, people refer to the treatment environment as pre- and post-Nix, meaning that the way that we manage the treatment of highly-resistant TB has radically changed based on the Nix-TB results. Indeed, we are establishing a new standard of care.

If we wish to make the World Health Organization's goal a reality and to end TB, then we must stop the emergence and spread of drug resistance, which is a global threat to that goal. With a simplified, effective, shorter, clearly defined, and all-oral regimen, the BPaL regimen transforms the treatment for people with highly-resistant TB.

Thank you. Dr. Everitt will now return to

the lectern to moderate the Q and A.

Clarifying Questions

DR. BADEN: I would like to thank the Global Alliance, the sponsor, for efficiently presenting a tremendous amount of data on this regimen and this potential treatment for this serious disease.

To the committee, we have about 35 minutes for questions to the applicant. If you have a question, please signal myself or LaToya, and we will keep a running list. If there is a line of question that is ongoing and you wish to build on that line of question -- and I know we'll eventually get this right -- turn your card sideways so we can build on a theme.

Please don't turn your card sideways because you want to jump in and start a new line of questioning because that's not fair to the other panel members, and that way we can try a thematic development for questions. I will start with the first question while we accrue the questions from the panel.

Again, thank you for a tremendously clear

presentation of the data. I think we learn a lot from failure. It wasn't as clear from me from the presentation or the briefing document the cause of the 10 failures. And I think if I have the numbers correct from the updated document between the two groups, there were 10 failures.

Why were they failures? Is it because of death, relapse, resistance; how much resistance was seen? Can you please clarify?

DR. EVERITT: Yes. There were two patients in the modified intent-to-treat analysis, so there were essentially 6 deaths during the treatment, early in the treatment period. Those were clear failures. And then there were 2 relapses before the primary endpoint, before the 6 months after the end of treatment, 6 plus 2.

Those were the key ones. There was an additional patient who died of so-called natural causes. He was found dead at home at about the 6-month endpoint, and he was the one who had culture-negative results when last seen that we excluded from the modified intent-to-treat

analysis, but he was included in the intent-to-treat analysis. There was one patient who died, but he died after relapsing. He was the first relapse. He later died with gangrene and sepsis, unrelated causes.

DR. BADEN: So the cause of failure were 6 deaths, 2 relapses --

DR. EVERITT: And another death --

DR. BADEN: -- another death.

DR. EVERITT: -- that was excluded from the modified intent-to-treat analysis but included in the intent-to-treat analysis.

DR. BADEN: And the 2 relapses, drug resistance?

DR. EVERITT: Let me just bring up some information on those two. Basically, the 2 relapses, which are listed as patient 8 and 9 in the briefing book, they had -- let me actually ask my microbiology colleague to comment.

You're interested in their drug resistance?

DR. BADEN: Correct. I'm trying to understand failure, and failure death, as you

clarified, which may have competing risks, but also failure because of progressive infection in the context of antimicrobial resistance or regimen failure.

DR. EVERITT: Okay. So the 2 patients that relapsed before the primary endpoint, again, they had culture converted to negative, somewhat later than the average. The median culture conversion was less than 6 weeks. These two patients were -- at 12 weeks, they culture converted.

The MICs, the first one at baseline, the baseline isolate, were less than 1. They were all considered drug susceptible. That patient was the only one we had cultures from the isolate at the time of relapse, and the pretomanid and linezolid MICs were less than 1, but the bedaquiline MIC had actually increased 8-fold, from 0.5 to 4, and that was actually associated with a known genetic mutation.

The other patient had no baseline isolate that could be grown to confirm the MICs, but at relapse, all the isolates were below the MICs

considered susceptible.

DR. BADEN: Thank you. Ms. Lupole, a follow-on?

MS. LUPOLE: Yes, sir. Were these patients screened for hepatitis?

DR. EVERITT: They were not specifically screened for hepatitis on entry. The attempt was if there was a concern about hepatic enzyme changes or whatever later, that they would be worked up in most cases. They were not screened initially.

DR. BADEN: Dr. Green?

DR. GREEN: It's a follow-on to Dr. Baden's question. There are 6 patients. I think you said either 5 or 6 died and had an autopsy. We didn't hear whether or not at autopsy -- and they had autopsy, and they had evidence, I recall, of ongoing disseminated TB. Were those isolates cultured at autopsy and did they also remain susceptible, or did resistance emerge in those patients?

DR. EVERITT: Five of the six patients -- let me see if we have the slide on the

patients -- the other slide on patients who died. Five of the six had autopsies. Three of them had extensive TB. That actually was not cultured at autopsy.

Let me ask Dr. Juliano Timm, by microbiology colleague, to comment whether we had follow-up cultures on any of those patients that died. Again, they may have died somewhat proximate to the last culture.

DR. TIMM: Good morning. Juliano Timm, microbiology consultant. Per protocol, we only tested isolates at baseline and after week 16. So all patients who died before this point had not there TB bacteria further tested.

I should say that from the group of patients who died, one had an elevated MIC to bedaquiline. All the others either could not be tested because their isolates could not be regrown, or the ones who were tested were susceptible to the drug. So there is no correlation between resistance at baseline to death or relapse. We cannot establish in correlation.

DR. BADEN: Thank you. Dr. Moore?

DR. MOORE: Yes, the microbiology question. The isolates that were identified after treatment, how were you able to distinguish between relapse versus reinfection? Was there DNA testing?

DR. EVERITT: Yes. We attempted to do whole genome sequencing to test at baseline and at follow-up. Dr. Timm, our microbiologist, can speak to what information we do and don't have.

DR. TIMM: We performed whole genome sequencing, and we used the well-established criterion to separate relapse from reinfections, based on single nucleotide, all forms, number of SNPs. So any pair that had over a hundred SNPs was considered reinfection. We actually have not observed any reinfection. We only observed relapses.

I should say that in one case, we didn't have the baseline isolate, so we could not confirm it was a relapse, but per protocol, we treat it as a relapse. In the other case, it was clearly a relapse because the number of SNPs was in the 5

range. So it was confirmed a relapse.

DR. BADEN: Thank you. Dr. Daskalakis?

DR. DASKALAKIS: Just a couple questions about linezolid in the regimen. Are there any historical controls that you can provide for frequency of the common linezolid side effects? That's question one. Another question is, when linezolid was discontinued in the regimen, was it replaced with other drugs?

DR. EVERITT: Yes. Let me start with the second question; that's easy. If linezolid was discontinued, no, it wasn't replaced. We had good animal data suggesting that even 1 month of linezolid may be adequate in this regimen, so that gave us some confidence to say the clinician could do what they felt they needed to do after the first month.

The question about historic linezolid, we did an extensive literature search to look at what was known with long-term linezolid use. I'll just show you a little bit of information. When the trial was designed, again, there was relatively

little information. There was a study in South Korea of 38 patients that gave us some information.

Since then, we've looked, and there's a little bit more information. Basically, what we say are all the things that are in the product label for Zyvox, linezolid, for even just up to 28 days, what's well known as things like optic neuropathy that tend to occur with much later treatment.

But we essentially didn't see anything. I think we've characterized it in more detail than what's in the literature. What we found is a literature that did a meta-analysis of a number of different studies with a large number of patients, and found that at 1200 milligrams versus 600 milligrams, more patients at 1200 had the dose decreased, although the number discontinuing was about the same in the groups.

DR. BADEN: The table is lit up with follow-ons. My follow-on, the absence of thrombocytopenia I find striking. Can you comment on thrombocytopenia?

DR. EVERITT: I can comment a little bit. We were a bit surprised. Thrombocytopenia was one of the most described, but that often came out of healthy volunteer studies with relatively small reductions. Thrombocytes, it can be an acute phase reactant and severe infection. We just did not see much of it.

DR. BADEN: How systematically did you assess platelets?

DR. EVERITT: Well, with every CBC, platelets were assessed, and it was initially weekly, and then it moved to monthly. They were evaluated. We've shown the information for when the regimen was changed based on the judgment of the clinician, so minor fluctuations or reductions would not have been a reason to stop, given the lethal disease that was being treated.

DR. BADEN: Dr. LoBue, did you have a follow on?

DR. LoBUE: Yes, about linezolid. Was there any attempt to look at the amount of linezolid taken in association with outcome, like a certain

minimum amount of linezolid that you need for this regimen to work, or if you miss a certain amount, we start becoming worried about failures?

DR. EVERITT: Let me show you this slide that groups by linezolid discontinuations and all. While that's coming up, though, let me just say that the median amount of linezolid given was up into the 5th month, so the vast majority of patients actually got a lot of linezolid, and nobody stopped at the end of 1 month.

Do we have the box and whisker plot, the three that I think show by categories?

Let me show you this one. If you look at the patients who interrupted linezolid on the left, the patients who discontinued, and the patients who did not interrupt or discontinued, the patients who interrupted -- and that could've been for any reason -- again, the overall favorable rate of them was 97 percent.

The patients that discontinued included the 6 patients who died, and by definition discontinued. Of interest is that every patient

who discontinued who did not die had a favorable outcome. It was a hundred percent favorable. It was just the deaths that bring that down to the 78 percent. Then what you see on the Y-axis is the median time to culture conversion, which for patients who interrupted versus those who did not interrupt or discontinue was widely overlapping confidence intervals.

DR. BADEN: Dr. Goetz?

DR. GOETZ: We're hitting the linezolid fairly hard. The previous question was you answered whether they continued or discontinued. Do you have data with cumulative dose and response, to be another way of looking at that?

Then a related question, which is did you develop a protocol or algorithm for decreasing the linezolid dosage based upon either laboratory changes or peripheral neuropathy, or is that at the discretion of the investigator?

DR. EVERITT: Yes. Let me take the first one first. Essentially, the protocol when we started, it was early days of getting experience

with this. We wanted to essentially hit this disease hard with the full high dose. We pretty much left discretion to the investigator. Perhaps later, Dr. Conradie can discuss how they made the decision. We did not give any specific advice.

In the ongoing trial, we've given some suggestions. For example, with anemia, if a grade 3 hemoglobin of 8 has hit, and it's been, say, a 25 percent decrease from baseline, consider either interrupting or reducing the dose of linezolid. So we are giving some advice for the future, but in the Nix trial, it was really left to the discretion of the investigator. But we did have monthly phone calls with the investigators, where all shared their experience and advice on what they were learning.

Let me ask you to reframe your first question.

DR. GOETZ: The first question was can you relate outcomes to cumulative dose or percentage of linezolid received rather than what you showed was continuation or discontinuation as sort of a

dichotomous variable rather than a continuous variable.

DR. EVERITT: I could try to get that specific analysis after the break; we didn't do it. But one easy thing to say is, again, there were only 2 relapses, and both of those patients continued linezolid all the way through. I believe one had a decrease in dose. So with so few ends of bad outcomes, it's very difficult to do much of a formal analysis. It's fairly anecdotal.

DR. GOETZ: If I can just continue on a theme, adherence overall in this study, can you comment on that with other medications as to -- you achieved very nice results with your outcomes. I was just wondering what percentage of medications were people taking, pill counts, and other information going beyond the linezolid toxicity or side effect issue?

DR. EVERITT: We had pill counts on the 3 drugs specifically, and it was well over 80 percent when done.

Let me ask Dr. Conradie, who was there with

the patients, perhaps to comment on -- again, half of the patients had HIV. They were on 3 antiretrovirals, usually co-trimoxazole, other drug, a big burden, and many of them, especially later in the trial, were treated as outpatients.

Dr. Conradie?

DR. CONRADIE: Thanks very much. I'm Dr. Conradie from South Africa. Just as the treatment has changed of drug-resistant TB, the treatment policies have changed in South Africa. When we started on Nix-TB, all patients were admitted to hospital and were kept in hospital until they culture converted, which is an average of about 4 months. But with the burden of disease, we've adopted a more decentralized mode of care, and in all of the sites towards the end of the trial, some patients were not admitted at all.

What we did is that the treatment regime was on a simple card, pretty easy to follow. We counted pill returns. And also, when patients were enrolled on to the study, we asked them to elect a treatment body or a DRT supporter to assist. But

as Dr. Everitt said, also half of them were on antiretroviral therapy. Some of the patients were, in addition, a risk for the development of TB as diabetes, so they were on complicated regimens. But despite that, for the number of pills, we had an almost 90 percent cure rate.

DR. GOETZ: Thank you.

DR. EVERITT: Thank you.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Still on linezolid theme, it said most of the neuropathy symptoms resolved when the drug was stopped. Can you go into more detail? Did it fully resolve and over what time frame? That can be debilitating.

DR. EVERITT: Sure. It can be a pretty nasty adverse effect. Neuropathy resolves much more slowly than anemia, which resolves quickly. We do have a graph that shows one way of looking at it. Again, it's patient by patient, very particular.

Let me just show you this. This is one way of looking at it. We did use a neuropathy rating

scale, patient assessment across four different key criteria, and this was the question, are you experiencing pain, aching, or burning in your feet?

This shows the proportion of patients, so this is a mean across patients. What you can see is at about week 20 is where that score peaked the highest, which goes with neuropathy coming sort of in the last 3 months. That's around the time patients had dose reductions, or eruptions, or withdrawals, and then it gradually went down, you can see, to a 3-month follow-up period. That's kind of spanning a 6-month period there.

Let me ask Dr. Conradie, though, just to comment from her experience, with all the patients in the clinic and in the study, how she found the time course of resolution of the neuropathy.

DR. CONRADIE: I think I've noted the first thing we need to know is that 10 percent of the patients roughly had some form of peripheral neuropathy on entering the trial. Often that was HIV related. Once peripheral neuropathy was established, it has it pretty typical time course,

where patients first complained of parasthesia. If the patient was doing well on treatment and had culture converted, then we interrupted. And most of them, as you can see, had settled down towards the end of the their treatment.

DR. BADEN: Dr. Ofotokun, the final linezolid follow-up.

(Laughter.)

DR. OFOTOKUN: My question was addressed. Half of the population were HIV-infected individuals. And like was said just now, peripheral parasthesia is common in this population. I just wanted to get a sense, in terms of treatment failure or side effect, do you have a sense of whether HIV was a mitigating factor in how well people did with regards to how well they tolerated this regimen?

DR. EVERITT: Yes. Let me show you -- first of all -- again, this goes back to what I had shown. If you look at favorable status, absolutely no difference in the modified intent-to-treat analysis, no difference. We do have HIV by ways of

looking at adverse effects.

If we could bring up the adverse effect by HIV slide. This is another way of looking at it. This is HIV positive or negative, and of course everybody had an adverse event, so it's a hundred percent for both. If you look at serious adverse events, you can see it's pretty much spot-on whether patients were HIV infected or not; the proportion of the events, 19 percent versus 16 percent.

If you look at grade 3 and grade 4, again, very similar across the board, and that kind of went with individual adverse events as well. But that's probably the easiest way to look at it, somewhat surprising but perhaps reassuring.

DR. BADEN: Thank you. Dr. Green, we're at a new line of questioning.

DR. GREEN: My question was answered early on.

DR. BADEN: Great. Dr. Follmann?

DR. FOLLMANN: The main issue for me, I guess, is the 90 percent cure seems very large, and

I'm wondering what the comparison is. So if we had a randomized trial of 90 percent versus 10 percent, I don't know if we would be here.

So part of what I want to do during this discussion is imagine what would be the comparator and what would be the rate for that. You have a bar of 50 percent cure as the, I guess, threshold for success, and yet you mentioned that bedaquiline and linezolid had 65 percent cure rates, so if you had thought of data as a comparator, the bar would be different.

So implicitly, I suppose you're imagining if you had done a trial, it would be, what, the BPaL regimen versus the blackboard regimen of the remaining drugs that aren't resistant, excluding bedaquiline and linezolid? And if so, is that a trial for which one would have equipoise? Is that a fair comparison or would a fair comparator include bedaquiline and linezolid?

I'm trying to imagine the trial and what would the arm be that would make the 90 percent persuasive. I suppose this is a question also for

the FDA, because 90 is good, but what's the comparator?

DR. BADEN: The FDA will have their time shortly. We'll turn this to the sponsor.

DR. EVERITT: We were designing the trial early in 2014 to get it initiated in 2015. Bedaquiline had just been approved. There was a concern about excess deaths. There was very little information on linezolid. Bedaquiline was not approved in South Africa or most parts of the world. It was very early, and the care available was the blackboard sort of care. And for a variety of reasons, we did not feel it would be appropriate to have an arm for that standard.

Let me ask Dr. Neil Schluger for his comment as to whether he thinks it would have been either appropriate or the ethical equipoise to have done a randomized-controlled trial at that time.

DR. SCHLUGER: Hi. Neil Schluger. I think at the time the trial was conceived and initiated, there were several factors that justified the study design was used, in fact, perhaps even required the

study design that was used.

The first, as has been pointed out in 2014, really wasn't a standard of care for patients with extensively drug-resistant TB at all. And I think as recently has been appointed out in a nice paper by Patrick Phillips and Andrew Nunn, who were highly regarded clinical trials statisticians and designers in the TB TV world, in that circumstance, the use of external or historical controls maybe actually are a requirement when there really is no standard.

Second, if one wanted to say, well, in the absence of a standard, what about just optimized background regimen, you would have been in a very difficult position. I say this partly from my perspective as someone who's spent a lot of the last 27 years helping to design TB clinical trials, where you would have had one treatment arm that was 6 months long and another arm that was 24 months long. Those are extraordinarily difficult trials to try to pull off.

Third, certainly there is an urgent pressing

need I think, and the use of this trial design is probably the most efficient, rapid way to get meaningful clinical results. Finally, when one looks at what had been the historical experience with patients with XDR TB, as you've seen earlier in the presentation, particularly in South Africa where you had favorable outcome rates in the 20 percent range with those kitchen sink, blackboard kind of regimens, you now had a comparator regimen that, based on preclinical data and the early clinical experience, was expected to have a substantially increased rate of efficacy. And I think that, as you mentioned, would have created a real problem of equipoise.

As an investigator and as a clinician, I don't know that -- well, I think I do know that I would not have had equipoise about putting a patient into a trial where the historical outcome might have been a 20 percent favorable rate, and the comparator regimen would have been expected to be associated with a much, much higher rate. I think those factors, the background community

standard if you want to call it that, and rate of success is very, very low, combined with the really rigorous definition of an endpoint, culture conversion or not, and satisfies the guidelines set out in the International Conference on Harmonization for use of external or historical controls.

DR. FOLLMANN: I have a follow-on again. It's sort of related to the theme of the clinical trials. In a clinical trial, if we had run that, we'd have the same inclusion criteria for control and treatment. We'd have the same assessment schedule for control and treatment in the same follow-up and so on.

You reported a 10 percent success rate for the historical control, and I'm just wondering how similar they were assessed and followed up. For example, you mentioned the historical control would be followed up for 24 months of therapy up to that, and then you'd have six months after that to determine success or not, so that's a 30-month window.

Failure includes dropping out at any time over the 30 months, whereas in the treatment, failure is dropout over I think up to 15 months and so on. Also, I wonder if the culture schedule is the same for the two.

It would be nice if there were sensitivity analyses and so on to get at those kinds of issues to try and equalize the way you follow up and ascertain favorable or not for the two arms. For example, if you had a 30-month favorable outcome in the Nix-TB trial, that would be one way to try to equilibrate the two. But just on the sensitivity analysis going to that -- robust, the 10 percent is?

DR. EVERITT: Certainly, there were differences in the follow-up and all. Let me show you one analysis that had very hard endpoints followed different ways. We did a mortality analysis of the matched controls, as well as a very hard endpoint, actually, particularly at the recommendation of the FDA. This just is one other way of looking at it that I'll show you.

This was actually the control group, the full -- there was actually 190, and these were patients taken from Brooklyn Chest Hospital in Cape Town where the Nix-TB study was previously. This shows the number alive and who had died at the end of 12 months and at the end of 24 months. That's after the start of therapy comparing Nix-TB.

Again, this shows a very similar, big difference with the risk ratio or a 3-fold reduction in risk for the Nix-TB patients compared to the controls. That's just one other way that uses a very hard endpoint and different data cuts.

DR. BADEN: Dr Ellenberg?

DR. ELLENBERG: Yes. One of you had indicated that you didn't consider a control arm that would include bedaquiline because it had just been approved, and it had a lot of deaths, and people were worried about it, but that was part of the regimen. So I guess I don't understand why if there was worry about its safety and that not enough was known about it, why -- it just seems inconsistent to me that it couldn't have been part

of a control regimen, especially given that apparently the success rate with the bedaquiline regimen, at the basis of approval, showed pretty good results.

DR. EVERITT: Well, yes. As we had mentioned, there were a variety of reasons. We felt at the time to consider a single-arm study, and that's what the study was.

Let's go back to the previous slide I'd like to show. Just going fast forward a bit, another way of comparison I think for reference, it's helpful. Dr. Conradie had mentioned improved success now with more operational reports, not formal drug development studies, where bedaquiline and linezolid have come to be used more over the course of the evolution of the trial.

Perhaps one of the most relevant publications, again, comes out of the Cape Town experience and was published at the end of last year. I'll just show you -- and this is where one of several publications have come up with, say, an approximately 65 percent success rate.

This was Dr. Olayanju with the senior investigator, Dr. Dheda, in Cape Town, and this compared their experience in the pre-linezolid/bedaquiline era. That was essentially our control group. Here it's shown as a 13 percent sort of favorable outcome versus what now they're reporting in the bedaquiline era, and most of these patients were treated with linezolid where they had a 66 percent outcome.

So we acknowledge that, but keep in mind this was a 24-month treatment of a median of 8 drugs, and yes, it's getting close to our 90 percent, but our treatment is 3 oral drugs for 6 months with 90 percent.

DR. ELLENBERG: Let me follow up on the issue of the controls because your matched control group was matched for a number of things, but certainly not all of the inclusion criteria --

DR. EVERITT: Sure.

DR. ELLENBERG: -- that were a part of your trial. I don't have a sense for how much those additional inclusion criteria would relate to

prognosis, likelihood for success, but I assume you've done a comparison on those aspects for the matched controls versus the Nix-TB study in terms of what else they were required to have to be in the Nix-TB study.

DR. EVERITT: Yes. We could not control for everything in the inclusion criteria. This just shows the baseline characteristics for what we were able to match on. It was gender, weight, HIV status, and age, which are all important, but it's not the maximum, but it's what we had available in the individual dataset.

Let we mention, in terms of some biases, though, yes, there are possibilities that our inclusion and exclusion criteria had a little bit of a healthier population that may have done better than those. We still had a very sick population.

Two other considerations is that the patients coming into Nix had had their TB for a median of 12 months, a mean of 24 months. These were patients failing treatment coming into this study who still had a 90 percent favorable outcome.

In the control group, those were newly diagnosed patients, newly treated, so they would have stood a chance of a better outcome, even though, again, they did not have the same inclusion and exclusion criteria that we did in the trial.

DR. BADEN: Doctor Goetz?

DR. GOETZ: Just thinking about trial design, we can't undo what you did, but thinking about what could be done going forward. In the data that's been quoted a couple of times now, showing a 65-ish percent response rate to regimens including bedaquiline and linezolid, without the pretomanid, can anyone comment on what the rates -- of those 34-35 percent of people who failed, what are the rates of resistance to bedaquiline or linezolid being seen, just thinking about feasibility of different pathways and consequences affiliated with the regimen that might be close to a standard now short of what we're talking about with this application?

DR. EVERITT: Yes. I'm going to ask Dr. Juliano Timm, our microbiologist, to comment on

what's known about resistance rates to linezolid and bedaquiline. While he's coming up though -- no, I'll let him comment on that. yes.

DR. TIMM: Juliano Timm again. As said before, the baseline resistance rates for the 3 drugs are very low. I can give you more information on this slide. It summarizes what we know about preexisting or baseline resistance rates for the 3 drugs.

Published data showed resistance rates in the order of 0.5 to 2 percent for bedaquiline and 0.2 percent for linezolid. There is limited data for pretomanid, our drug, that has been published. However, we have some unpublished data, and it's of two types. We conducted surveys of strain collections and showed that pretomanid resistance rates are near 1 percent in these collections.

Perhaps more relevant, we have susceptibility data on over 700 patients included in the various TB Alliance phase 2 and phase 3 trials. We identified only one resistant isolate. In Nix-TB, we have already mentioned, we saw only

2 isolates resistant to pretomanid at baseline. So the preexisting resistant rates are very low for the 3 drugs.

Have I answered your question?

DR. GOETZ: I guess my question was more -- these are important data, but I was thinking about in people who failed bedaquiline and linezolid containing regimens; what's the rate of emergent resistance there?

DR. TIMM: We don't have this information. To my knowledge, it's not published.

DR. EVERITT: We just know that the one patient who relapsed did acquire a mutation that gave a relative increase in MIC.

DR. BADEN: It is now past 10:05. It's 10:09. We will take a 15-minute break, but I just want to note that we have about half the panel members who still have questions. So we still have a lot of information we wish to interact with the sponsor. However, we'll take our break. The agency will give their presentation, we'll question the agency, and then we'll return to completing the

questioning with the sponsor.

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 in 11 minutes at 10:20. Thank you.

(Whereupon, at 10:09, a recess was taken.)

DR. BADEN: We will now resume the meeting, and we will begin with the FDA presentations.

Dr. Rubin?

FDA Presentation - Daniel Rubin

DR. RUBIN: Thank you for the opportunity to present on the clinical efficacy assessment of pretomanid. I will discuss the design of Nix-TB, results, use of historical controls, and then provide a summary and conclusion.

The efficacy assessment in this application was based on Nix-TB, as this was the only pivotal trial evaluating the regimen and patient population under consideration. Patients had either extensively drug-resistant tuberculosis, or treatment-intolerant, or nonresponsive

multidrug-resistant tuberculosis. The study was conducted at 3 sites in South Africa.

Nix-TB was a single-arm study in which all patients were treated with the regimen of bedaquiline, pretomanid, and linezolid. The study was not intended to provide clinical evidence for the contribution of each of the 3 regimen components. Treatment was to be given for 6 to 9 months. The primary endpoint assessment was 6 months after the end of treatment.

This slide lists the dosing of the bedaquiline, pretomanid, and linezolid regimen. While the study was ongoing, the protocol amendment changed the linezolid dosing from 600 milligrams twice a day to 1200 milligrams once a day. Due to toxicity, linezolid could be discontinued, interrupted, or dose reduced while patients remained on bedaquiline and pretomanid.

The planned sample size of Nix-TB was 200 patients. However, enrollment stopped after 109 patients had been treated due to the observed efficacy results and follow-up is continuing. The

applicant and FDA initially agreed that efficacy could be evaluated based on the first 45 patients with complete primary endpoint data. The results in this presentation are based on the more recent data cutoff of June 29, 2018, with 81 patients having complete primary endpoint data. Efficacy conclusions are not sensitive to the timing of the data cutoff.

The primary efficacy endpoint in Nix-TB was bacteriologic failure, relapse, or clinical failure through follow up 6 months after the end of treatment. The primary analysis population was a modified intent-to-treat population of all treated patients. This was an historically-controlled trial in which the objective was to evaluate superiority to the predefined historical control favorable outcome rate of 50 percent.

The Code of Federal Regulations notes that historical controls are acceptable in principle for drug approval, but only under certain conditions. It states that the results of treatment with the test drug are compared with experience historically

derived from the adequately documented natural history of the disease or condition, or from the results of active treatment in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances.

Examples include studies of diseases with high predictable mortality, for example, certain malignancies, and studies in which the effect of the drug is self-evident such as general anesthetics and drug metabolism.

Similarly, the International Conference on Harmonization guidance document on the choice of a control group states that the inability to control bias restricts use of the external control design to situations in which the effect of a treatment is dramatic and the usual course of the disease highly predictable. In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and

treatment variables on the endpoint is well characterized.

There were 143 patients who signed an informed consent for Nix-TB, however, 34 were screen failures, leaving 109 treated patients. Note that screen failures are potentially more important in the historically-controlled trials than in concurrently randomized trials if they select for a less acutely ill patient population. Please also note that the number of patients signing informed consent and number of screening failures in this slide are corrected from the slightly different numbers in your background materials.

Of the treated patients, 81 were enrolled at a sufficiently early time to have expected primary outcome data by the June 2018 data cutoff. A single one of these 81 patients was excluded from the MITT primary analysis population due to non-tuberculous death. This form of exclusion is not ordinarily recommended, but the single case in this study did not affect efficacy conclusions.

This slide displays demographic characteristics of patients in Nix-TB. The two columns respectively show demographic characteristics in the safety population of all 109 treated subjects and in the MITT primary efficacy analysis population that restricted to 80 patients with sufficient follow-up to obtain primary endpoint data based on the June 2018 data cutoff. The average age was approximately 35 years old. Approximately half of patients were female. All patients were enrolled in Johannesburg, Cape Town, or Durban, South Africa.

Approximately half of patients were HIV positive at baseline. About two-thirds of patients had extensively drug-resistant tuberculosis, with the remaining having treatment nonresponsive or treatment-intolerant, multidrug-resistant tuberculosis. Most patients had unilateral or bilateral pulmonary cavities.

As shown in bold, the rate of favorable outcomes for the primary endpoint 6 months after the end of treatment in the primary analysis

population was 72 out of 80, or 90 percent. Also shown in bold, the 95 percent confidence interval for the favorable outcome rate ranged from 81 percent to 96 percent. Because the lower limit of 81 percent greatly exceeded the predefined historical control rate of 50 percent, Nix-TB met the predefined criteria for declaring efficacy. High favorable outcome rates of approximately 90 percent were also seen in both the extensively drug-resistant and multidrug-resistant subgroups.

The Nix-TB results provided statistical evidence that the rate of favorable outcomes with the BPaL regimen exceeded 50 percent. This conclusion was robust to premature study termination, as a conservative adjustment for interim analysis still yielded a lower confidence limit greatly exceeding 50 percent.

The conclusion was also robust to the handling in the analysis of the 34 screen failures and one subject excluded from the primary analysis population by the applicant for non-TB death, as a conservative imputation of treatment failure for

these subjects still yielded a lower confidence bound exceeding 50 percent.

Please note that the confidence interval for this imputed success rate is corrected from a slightly different interval in the meeting background materials.

Favorable outcome rates were consistently high across baseline subgroups defined by demographics and disease characteristics. In particular, the favorable outcome rate was approximately 90 percent for patients who were HIV negative at baseline and also for those who were HIV positive at baseline.

As will be discussed in more detail in the safety presentation, there was a high degree of linezolid intolerance in Nix-TB. Linezolid toxicity did not adversely affect efficacy with the monitoring in this clinical trial setting. Favorable outcome rates were high in subgroups defined by initial linezolid dose and in post-baseline defined by linezolid termination, interruption, or dose reduction.

Based on the time of enrollment, only 23 patients were expected to have data for the secondary endpoint of treatment outcome 24 months after the end of treatment. Favorable outcomes were observed in 19 out of the 23 patients. Thus, there did not appear to be an efficacy fall off with longer-term follow up.

Another secondary endpoint was time to sputum culture negative status. Aside from the cases of death, virtually all assessable patients were culture negative 16 weeks after enrollment. An additional secondary endpoint was changed from baseline weight. The patients reported a modest weight gain with a median gain of 3 kilograms by 6 months after the end of treatment.

Because this was a historically-controlled trial, it was important to assess the appropriateness of the predefined 50 percent historical control favorable outcome rate. The applicant provided two sets of analyses to address this issue. These were a literature review and also a match to historically-controlled comparison

which I will now discuss in turn.

In the literature review, there were 18 studies with 1,731 patients meeting search criteria for reporting results with extensively drug-resistant tuberculosis treated without components of the BPaL regimen. We excluded two studies in which response rates could only be estimated. The literature review used World Health Organization outcome definitions for XDR TB, with success based on judgment of cure or completion of therapy.

Studies were highly variable with respect to response rates, mortality rates, timing of reported assessments, geographic location, and calendar time of treatment. It is also well known that prospective clinical trials often select for less severely ill patient populations than literature-based observational studies.

Here are the results from studies in the literature review. Starting with the left most column, the table displays the author and year of publication; the calendar time of the study; the

percentage of patients HIV positive at baseline; the study location; and the all-cause mortality rate. These mortality rates were difficult to interpret due to differences in assessment times.

From the right-most column, you can see that favorable outcome rates have been relatively low in previous published literature on extensively drug-resistant tuberculosis. In particular, historical success rates were generally lower than the 50 percent historical control rate specified for Nix-TB and much lower than the success rates under the BPaL regimen in Nix-TB.

A DerSermonian and Laird random effects meta-analysis of the preceding 16 studies yielded an estimated treatment success rate of 28 percent, with a confidence interval from 21 percent to 34 percent. Moreover, historical success rates have previously been very low in South Africa, where Nix-TB was conducted. All 6 South African studies in the literature review reported success rates no higher than 22 percent.

In addition to the literature review, the

applicant conducted a matched historically-controlled comparison. We do not have patient-level data submitted from this analysis. The Nix-TB group was based on the first 45 patients with primary outcome data. The highest enrolling study site in Nix-TB was Brooklyn Chest Hospital in Cape Town, South Africa. Recall that the primary endpoint was defined 6 months after the end of 6 to 9 months of treatment.

The historical controls were drawn from 202 patients treated at this hospital without any of the bedaquiline, linezolid, pretomanid component, or delamanid, which was in the same class as pretomanid, between 2008 and 2014. The primary endpoint for this group was defined 24 months after the start of treatment, and treatment was planned for 18 months or longer.

Patients in Nix-TB and the historical group were individually matched based on propensity scores derived from the covariates of age, sex, body weight, and baseline HIV status. Each Nix-TB patient was to be matched with two historical

control patients, although in some cases it was not possible to identify exactly two matches.

The statistician responsible for matching was to be kept blinded to treatment outcomes throughout the matching process. The baseline characteristics of sex, age, weight, and HIV status were very well balanced between the BPaL group in Nix-TB and the matched historical controls.

From this table, you can see that the BPaL group in Nix-TB had much more favorable outcomes than the match historical controls. Rates of favorable outcomes with the BPaL regimen were 89 percent in Nix-TB, while only 11 percent of matched patients in the historical control group had favorable outcomes. This difference was highly statistically significant.

Results were not an artifact of the shorter follow-up times in Nix-TB. As previously noted in the discussion of secondary endpoint results, patients in Nix-TB had similarly high success rates 24 months after the end of treatment. Rates of death 12 months after the start of treatment were

also significantly lower in the BPaL group than in Nix-TB, in Nix-TB than in the matched historical controls. Death rates were 9 percent in Nix-TB and 34 percent in the matched historical control group.

Now it is possible that there were unmeasured differences between the two groups. The historical control group included only patients with newly diagnosed, extensively drug-resistant tuberculosis, while the BPaL group in Nix-TB also included prior treatment failures and treatment-intolerant or nonresponsive multidrug-resistant TB.

The rate of patients screened for Nix-TB at the Brooklyn Chest Hospital during the study period was also lower than the rate of patients treated for extensively drug-resistant tuberculosis at this hospital in the historical control period; thus, Nix-TB may not have screened for the entire target population at this hospital.

In summary, the favorable outcome rate for the BPaL regimen in Nix-TB was higher than the predefined historical control rate of 50 percent.

This threshold was supported by a literature review, which found lower success rates in previous studies of extensively drug-resistant tuberculosis.

Efficacy was also supported by a matched comparison with historical controls in which much higher success rates and lower mortality rates were reported for those treated with the BPaL regimen than in a matched group from Brooklyn Chest Hospital in Cape Town South Africa.

Because there was no randomized control group in Nix-TB, there remains the possibility that efficacy comparisons were confounded. However, this may be a setting in which historical controls can be used to provide a reliable efficacy assessment of the regimen. Thank you.

DR. BADEN: Thank you.

Dr. O'Shaughnessy?

FDA Presentation - Elizabeth O'Shaughnessy

DR. O'SHAUGHNESSY: Good morning. I would like to present the safety presentation for pretomanid as part of 3-drug regimen containing bedaquiline and linezolid for the treatment of

patients with XDR TB and treatment-intolerant and nonresponsive MDR TB, and throughout the presentation, I'll refer to the regimen as BPaL. Before I start, I'd just like to acknowledge Peter Glass, Rui Li, and Scott Runyan, in the Office of Computational Science, for their work on the safety analyses for this NDA.

This presentation will include safety findings for pretomanid alone in animal toxicology studies and in 2 pooled phase 2 EBA studies; a summary of adverse reactions known to be associated with bedaquiline and linezolid; and then the focus of the safety review will be on the Nix-TB trial. Common treatment-emergent adverse events, serious adverse events, and adverse events of special interest will be discussed.

I should say our safety findings are very similar to that of the applicant, so I will skip through some of the slides. I will also present some preliminary data on adverse events from the ongoing ZeNix trial, and the final slide will summarize our conclusions about the safety of the

BPaL regimen.

Before I begin with the safety per se, this is just a high-level summary of the PK characteristics of pretomanid. I just want to point out some features in the various sections. In the absorption section, under food effect, we see that exposure to pretomanid increases following administration with a high calorie/high fat meal.

In the metabolism section, we see that pretomanid is extensively metabolized without an identified major pathway, and CYP3A4 plays a minor role in the metabolism of pretomanid. Under the excretion section, the half-life for pretomanid following a single- and multiple-dose administration was 17 and 16 hours, respectively. Finally, the effect of renal or hepatic impairment on the PK of pretomanid is unknown at this time, and there are no clinically significant differences in the PK of pretomanid based on sex, body weight, race, or HIV status.

In this table, the safety findings for pretomanid alone in animal toxicology studies and

the relevant findings in clinical studies are summarized. Safety signals identified in animal toxicology studies in the left column include neurotoxicity, cataract formation, infertility in male animals, QT prolongation, and hepatotoxicity.

With regard to neurotoxicity, central nervous system effects manifested as convulsions, and ataxia were identified in monkeys who received 5 times the human exposure for pretomanid. In the clinical development program, there were 2 subjects who had seizures in the Nix-TB trial, and both of them had risk factors for seizures. One patient had a history of seizures and the other patient had a tuberculoma in the right temporal lobe. When the tuberculoma was removed, the patient had no further seizures in the 6-month follow-up post-neurosurgery.

With regard to cataracts, they were observed in rats and monkeys at 7 times human exposure for pretomanid. No cataracts were seen as lower exposure multiples. Since 2009, patients who have been exposed to pretomanid in phase 2 and 3 trials,

including the Nix-TB trial, have been evaluated for cataracts, and no clinically significant effects on the lens have been found at the doses and durations of pretomanid that were tested. Our FDA ophthalmology consultants reviewed these data and concurred with those results.

From animals, we do know that pretomanid causes spermatocyte degeneration and infertility in male rats at 1.5 times human exposure. In human trials, results showed that male hormone levels were generally within the normal ranges in patients taking pretomanid as part of TB drug regimens, and these data were reviewed by our consultant urologist within FDA, and they recommended that the applicant conduct a human semen analysis study; and as you heard, this study is about to be initiated. This study should provide evidence to determine whether pretomanid can indeed cause testicular toxicity in humans.

There was minimal QT prolongation in animal studies, and there was no clinically significant QT prolongation in a thorough QT study of pretomanid.

Consultants in the FDA and the review team for QT studies concluded from their review the data that pretomanid has a lower risk to prolong the QT interval at therapeutic exposures.

In the Nix-TB trial, no patient had a QT interval longer than 480 milliseconds and one subject had a post-baseline increase in QT of greater than 60 milliseconds. Finally, with regard to hepatotoxicity, hepatotoxicity was observed in mice, rats, and monkeys. Elevated transaminases and increase in liver weights were observed. In human trials, elevated transaminases were reported, and there were deaths in earlier trials in a regimen containing pretomanid, moxifloxacin, and pyrazinamide. Cases of hepatotoxicity in the clinical development program were reviewed by consultant hepatologists at the FDA.

To begin with, we wanted to look at safety at pretomanid alone, so we were able to look at safety in two phase 2 early bactericidal activities studies, in those studies, patients received pretomanid for up to 14 days. 122 patients

received pretomanid alone, and 16 received HRZE.

The doses ranged from 50 milligrams up to 1,200 milligrams, and the mean number of days on treatment was 13.7; 47 or 39 percent of subjects in the pretomanid group experienced adverse events versus 7 or 44 percent in the comparator group of isoniazid, rifampin, pyrazinamide, and ethambutol, which is standard of care.

The most frequent adverse events were skin and subcutaneous tissues disorders, which included pruritus, rash, and urticaria, and gastrointestinal which included nausea, vomiting, and abdominal pain. In that study, peripheral neuropathy, decreases in hemoglobin, increases in hepatic transaminases, and emanated and QT prolongation occurred in one patient each.

In this slide and the next one, I'll just cover very quickly the adverse reactions known to be associated with the two other drugs in the regimen, bedaquiline and linezolid. As we know, bedaquiline is indicated for the treatment of MDR TB, and the recommended dose was used in the

BPaL regimen.

In the bedaquiline prescribing information, there are warnings and precautions for QT prolongation, hepatotoxicity, and drug interactions with CYP3A4 inducers, and in one study, in patients with MDR TB, there was an unexplained mortality imbalance in the bedaquiline arm.

The warnings and precautions section of the linezolid label include myelosuppression, which is manifested as anemia; leukopenia; thrombocytopenia and pancytopenia; peripheral neuropathy and optic neuropathy; serotonin syndrome with serotonergic drugs; elevation of blood pressure; hypoglycemia; seizures; and lactic acidosis. A mortality imbalance unfavorable to linezolid also occurred in one study.

Hypoglycemia occurred in patients who were taking glucose-lowering drugs, and seizures occurred in patients with a history of seizures. Most of these adverse events were associated with therapy longer than 4 weeks.

Finally, the safety database for pretomanid

included 1,507 subjects at the March 26, 2018 data cutoff date listed above. Among the 1,168 subjects who received pretomanid alone or as part of a combination, a very small proportion of these, 109 or 9 percent, were exposed to the BPaL regimen. Safety data on 15 subjects from the ongoing ZeNix trial was also submitted.

The other phase 2 and 3 trials investigated other combinations of pretomanid with moxifloxacin, pyrazinamide, and drug bedaquiline in patients with drug sensitive and MDR TB. In the phase 1 trials that we saw, there was 289 healthy subjects exposed to pretomanid alone or in combination with other drugs.

The safety data from the phase 1 trials didn't identify any additional new adverse events and won't be discussed in this presentation. As we heard before, the safety database for the Nix-TB trial is 109 patients, and 93 patients had completed the 6 months of therapy by the March 26, 2018 data cutoff date. I'll represent some updated safety for the ZeNix trial later, which includes 61

patients, and there's a later cutoff date, and the 15 subjects I mentioned earlier are included in that 61.

This is a review of the treatment-emergent adverse events in the Nix-TB trial. Adverse events occurred in all patients, as heard, and serious adverse events occurred in 19 or 17 percent of the patients. Life threatening and severe adverse events occurred in over half of the patients.

Adverse events leading to the discontinuation of any drug occurred in 30 percent of the patients, and linezolid was discontinued in 27 or 25 percent. In the last two rows, we see that the 6 patients who discontinued the BPaL regimen are the same 6 patients who died during the treatment period.

This slide describes the deaths in the Nix-TB trial, and I think they've all been discussed at length in the former presentations, so I'm not going to comment on them at this time.

With regard to serious adverse events, as I mentioned, they were 19 patients or 17 percent of

the study population. Six patients had serious adverse events leading to death, and they have been discussed previously. Thirteen patients had resolved their serious adverse event at the data cutoff date.

Serious adverse events occurring in 2 or more patients included pneumonia, sepsis, anemia, hypoglycemia, pancreatitis, optic neuropathy, seizure, or hematemesis. Adverse events considered to be related to the BPaL regimen are discussed later.

The treatment-emergent adverse events in the Nix-TB trial are summarized in the following graph. Really, the main point of the graph is to show that peripheral neuropathy was by far the most common adverse event occurring in 87 or 80 percent of the patients. We've grouped several terms in there, including peripheral sensory neuropathy, hypoaesthesia, paresthesia, et cetera. Anemia, nausea, vomiting, and headache were the next most common adverse events.

This is just a different way of showing

selected treatment-emergent adverse events leading to discontinuations, dosing interruptions, and dose reductions of linezolid, or dosing interruptions of the entire BPaL regimen. The orange, gray, and blue bars refer to dosing interruptions, dose reductions, and discontinuations of linezolid.

There is overlap among these three groups. For example, many of the patients who had dosing interruptions also had a reduction in their dose after they restarted linezolid. The navy colored bar refers to the interruptions of the BPaL regimen. There is no overlap between the BPaL interruptions and linezolid dosing interruptions.

Again, peripheral sensory neuropathy and hematopoietic cytopenias such as anemia were the main reasons for dosing interruptions or dose reductions of linezolid, and other reasons included optic neuropathy, pancreatitis, lactic acidosis, and increases in hepatic transaminases.

The range of dose interruptions of linezolid increased over time -- this is not on the graph -- with a median time to a first-dose

interruption of 110 days or 15 weeks. Increases in hepatic transaminases was the main reason for the interruptions of the entire BPaL regimen, and again, the 6 patients who died were the only group who actually permanently discontinued the regimen.

These are adverse events with special interest associated with the regimen, which include peripheral neuropathy; optic neuropathy; myelosuppression; hepatic enzyme abnormalities; pancreatitis; and lactic acidosis. Results for these adverse events were represented by HIV status, as shown in the next few slides.

This is peripheral neuropathy. The frequency of adverse events associated with peripheral neuropathy was similar among HIV-negative and HIV-positive patients at 81 percent and 79 percent, respectively. The adverse events, as I said, were experienced by a total of 87 or 80 percent. However, 75 of these were peripheral sensory neuropathy. The onset of neuropathy, as I said, increased over time, and the majority occurring in week 9 and week 26.

Most of the treatment-emergent adverse events associated with peripheral neuropathy were recovering at the data cutoff date of March 26, 2018. However, there were 31 adverse events that had not resolved, and the outcomes for 19 of these events were unknown or were not reported.

With regard to optic neuropathy manifested by visual changes and changes in the optic disc on examination, these were reported in 13 or 12 percent of subjects. These adverse events led to linezolid being discontinued in the patients who experienced optic neuropathy, optic neuritis, and reduced visual acuity. Fortunately, these adverse events were reversible, and most of these events associated with optic nerve disorders were recovered or recovering at the data cutoff date in March 2018.

Hemaopoietic cytopenias were observed in 51 or 47 percent of patients in the Nix-TB trial. As we heard, anemia was the most common adverse event. Anemia, neutropenia, thrombocytopenia occurred in 37 percent, 8 percent, and 5 percent of patients,

respectively. Anemia occurred more frequently in the HIV-positive group. The patients recovered once the dosing of linezolid was interrupted or the dose was reduced.

The onset of events were reported beyond 2 weeks and mostly around the third month. Most of these events, again, resolved or were resolving at the data cutoff date. Three events had not resolved and the outcome for two of these events were unknown.

Hepatic adverse events were experienced by 39 or 36 percent of patients, and elevated hepatic transaminases were the most common adverse event. More patients in the HIV-positive group had hepatic enzyme abnormalities as compared to the HIV-negative group, and this was driven by the 16 subjects in the HIV-positive group who had elevated gamma GT levels.

Two patients were reported to have drug-induced liver injury. They developed elevated transaminases greater than 3 times the upper limit of normal and elevated bilirubin levels greater

than 2 times the upper limit of normal on treatment and were potential Hy's law cases.

This table summarizes shifts in ALT levels from baseline to post-baseline, and the baseline level categories are on the far left. Among those patients who had normal ALT levels at baseline, 2 patients experienced ALT elevations greater than 3 times the upper limit of normal and 3 had ALT levels greater than 5 times the upper limit of normal. There were 12 patients overall who experienced elevations in ALT greater than 3 times the upper limit of normal post-baseline.

No patient had to discontinue the study drugs due to elevated hepatic transaminases. However, they did lead to interruptions of linezolid or interruptions of the entire regimen in 8 patients.

This table summarizes shifts in total bilirubin levels from baseline to post-baseline. These are the same two patients which are the potential Hy's law cases. There were 2 patients whose levels were 2 times the upper limit of normal

post-baseline.

I'm going to describe briefly the 2 cases, which were potential Hy's law cases. Case 1 was a 25-year-old man with XDR TB who was HIV negative. His ALT and total bilirubin levels peaked around week 8, around 6 times the upper limit of normal for the ALT and 2.2 times the upper limit of normal for the bilirubin, and then they rapidly decreased during week 12, and then came back to normal at week 20.

Investigation showed the patient was negative for hepatitis B, hepatitis C, and a urine toxicology screen was negative. The patient had denied using alcohol or herbal medications. His concomitant medications included, metoclopramide, morphine, and paradoxine, and chloromycetin eye ointment.

The BPaL regimen was interrupted for 3 weeks. The ALT and total bilirubin levels declined toward the normal range, as I mentioned. They continued to decline after the patient was rechallenged with the regimen, and he successfully

completed 26 weeks of treatment.

The second case is a 36-year-old female who had XDR TB and was HIV negative, and her ALT and total bilirubin peaked around week 11. She also had an elevated alkaline phosphatase level. She reported drinking alcohol during the trial. I did not see a workup to rule out other causes of hepatotoxicity. Her concomitant medications at the time included lansoprazole, paracetamol, and cyclizine for suspected severe gastritis.

The regimen was interrupted for 2 weeks. ALT and total bilirubin levels declined to the normal range. She had a further blip around week 20, but they again declined, and she completed her treatment with 2 drugs at week 34 because linezolid had been discontinued around week 26 for worsening peripheral neuropathy.

This just looks at the pancreatitis cases. This is treatment-emergent adverse events. We had 3 patients with pancreatitis, and there's a minor error in the table in your background document. Two of the patients who had hemorrhagic

pancreatitis were HIV positive, and the other patient with the acute pancreatitis was HIV negative. The number of patients in the HIV-positive group experiencing any treatment-emergent event under this heading is 14, not 15, so it makes a total of 22.

The risk factors for patients who had pancreatitis and also increases in lipase levels included HIV, antiretroviral therapy, and alcohol use. They did lead to dosing interruptions of the study drugs.

This table summarizes shifts in lipase levels from baseline to post-baseline. Among the patients with normal levels at baseline, 3 had elevations greater than 2 times the upper limit of normal, and one had an elevation greater than 3 times the upper limit of normal. Most patients were in the grade 1 or 2 category, which were less than 2 times the upper limit of normal.

Finally, there were 8 patients who reported treatment-emergent adverse events associated with lactic acidosis. All of these had resolved except

for one, which was a case described as hyperlactacidemia in a patient who died of pneumonia and sepsis. As far as I know -- and I can stand corrected from the sponsor -- lactic acidosis has not being reported in any of the other clinical trials.

Finally, just a quick update on the ongoing ZeNix trial, we have data for 61 patients, and we had a quick look at the treatment-emergent adverse events, and these are presented in this table. There are 51 or 84 percent of the patients who experienced at least one treatment-emergent adverse event, and the most common adverse events were peripheral sensory neuropathy, increases in ALT, vomiting, anemia, and skin rash, and just to point out that these types of adverse events are very similar to those reported in the Nix-TB trial.

In summary, there is a limited safety database for the BPaL regimen. There were 8 deaths in the trial and 6 patients died during treatment. Adverse events leading to death included pneumonia, TB progression, sepsis, acute pancreatitis, upper

GI bleed, and multiorgan dysfunction, peripheral sensory neuropathy, anemia, nausea, vomiting, headache, and increased transaminases were the most common treatment-emergent adverse events.

There were two potential Hy's law cases, however, no patient progressed to serious liver injury. The neurologic, hematologic, and hepatic adverse events associated with the regimen where managed using dosing interruptions, dose reductions, or discontinuation of the study drugs.

As I said, the discontinuations of the entire regimen only occurred in the patients who died. Most of the adverse events were reversible using this approach. However, we don't have data, at this time, on the peripheral neuropathy cases who were still ongoing, and it's not clear if some of those were irreversible or not.

I'll also say that safety findings were similar among the HIV-negative and HIV-positive group, except that a greater proportion of HIV-positive patients had anemia and hepatic adverse events as compared to the HIV-negative

group, which would be expected.

Finally, going forward, if pretomanid is approved, regular monitoring of patients on the regimen for development of optic and peripheral neuropathy, myelosuppression, QT prolongation, as it is associated with bedaquiline, and hepatotoxicity would be important for patients' safety.

This concludes the safety presentation. Thank you for your attention.

Clarifying Questions

DR. BADEN: Thank you, Dr. Rubin and Dr. O'Shaughnessy for terrific presentations, reviewing the applicant's folder.

We will now proceed with clarifying questions to the agency. After we've completed those clarifying questions, if there still is time before lunch, we will go back to the applicant to continue our clarifying question process. Please remember to state your name for the record before you speak. If you can, please direct your questions to a specific presenter.

Questions? Dr. Ellenberg?

DR. ELLENBERG: The data that we have seen all show data for this 3-drug regimen compared to various historical control groups, but I haven't seen anything that demonstrates the contribution of pretomanid, which is what we're asked to evaluate for approval, specifically, just as part of this regimen. The only data that we've been shown was from a mouse study.

Are there data that we should be aware of, clinical data, that supports the contribution of pretomanid to this regimen?

DR. RUBIN: You're right. There aren't clinical data per se, at least not from Nix-TB, that show a pretomanid contribution. The study was really designed to show that this 3-drug regimen was superior to the standard of care that was used before any of those regimen components entered practice.

There are some literature that had been alluded to showing that bedaquiline and linezolid regimens may achieve success rates in the range of

65 to 80 percent, which is lower than the 90 percent rate in Nix-TB, but maybe not a large enough difference that you wouldn't be concerned about confounding. So I think that the evidence for the contribution is mainly based on the data from the mice.

I'll ask if my colleagues have any other comments on this.

DR. BADEN: A clarifying question to the agency. Is the question to us pretomanid or is the question to us the triple-drug regimen?

DR. NAMBIAR: This is Sumathi. As Dr. Yasinskaya presented, the question to the committee is about the use of pretomanid in combination with bedaquiline and linezolid.

DR. BADEN: So it's the regimen. It's the 3 for 6 months is the question to us.

DR. NAMBIAR: Yes, that's correct.

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

DR. WEINA: Yes, it is. While the question may be for the 3 drugs, the problem is that this

isn't a fixed-drug combination. So if approved, it can be used off label and combined with almost anything, and there are a lot of other drugs out there.

So I think it's a valid question that, in general, the single drug, even though we're being asked about the combination --

DR. BADEN: I was not questioning the validity of the question or the importance of the matter. The challenge is the question asked of the committee. There are 101 other questions that we're all incredibly interested in as our list of questions denotes. So I think that we are all interested in that, but we also need to keep our eye on the way in which the studies were done, the data are presented, and the issue before the agency that they're asking us for advice on.

I think Dr. Le, you have a new line of questioning.

DR. LE: I have several questions related to the pharmacokinetics. In the studies, it showed that between fasting and fed patients, there were

differences in exposure, drug exposure. What is the recommendation, and how was the clinical trial set up? How did the patients take it during the clinical trial, fed or unfed state, and what would be the recommendation going forward?

DR. SOMANI: Thank you for the question. This is Amit Somani. I am the clinical pharmacology reviewer along with my colleague, Sonia Pahwa, for this application. Regarding the administration of pretomanid or the regimen, it was all administered with food.

Regarding the exposure differences between fasted and fed condition, there was a dedicated study that was done to assess the food effect for the 200-milligram dose. I can speak on the exact numbers for AUC and Cmax differences if there's an interest in that.

DR. LE: Yes, a doubling.

DR. SOMANI: So it's about doubled, but it's like 70 percent something, and then 80 percent something, and that's captured in the briefing package. But just for the record, they are --

DR. LE: So that would be the recommendation going forward.

DR. SOMANI: Yes. The final recommendation is to be administered with food because the Nix-TB trial is a pivotal clinical study. The Nix-TB trial is done when the regimen is administered with food, and the bedaquiline labeling also recommends bedaquiline be administered with food.

DR. LE: In that same study that you have, I think, were the same patients fed, fasting and fed, or --

DR. SOMANI: That's a healthy volunteer study. When you do a food effect study, those are all healthy volunteers in which the food effect was assessed.

DR. LE: Right. The question why I asked that is because I'm trying to figure out why both the volume and the clearance were decreased by half in the fed versus the fasting state. So I'm trying to see if it was the same patient or try to figure out what the explanation for that is.

DR. SOMANI: That's an apparent volume of

distribution, by the way, so there is the bioavailability, which is also factored in. So are you talking about the dedicated food effect study results table that was provided?

DR. LE: Yes, the table that was provided.

DR. SOMANI: In that, you have the Vd and clearance. For the fasted subjects, the apparent clearance is 7.6 in the fasted subjects versus 3.9 in the fed subjects. Basically, you have then, again, an increase for the Vd, apparent volume of distribution, 180, and then 97 in the fed subjects, and that's expected.

DR. LE: Okay.

DR. SOMANI: Because it's an apparent volume of distribution, an apparent clearance that you have, and there is a difference.

DR. LE: Okay.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Thank you.

DR. SOMANI: Do you have a follow-up question on the PK?

DR. LE: Maybe one --

DR. BADEN: Did you have a follow-on? I'm sorry. Dr. Le?

DR. LE: Yes. Well, I had one more, but that's related more to the metabolism of that.

DR. SOMANI: Okay.

DR. LE: I don't know if that's you who's going to address that. I think it was presented in the package that there was an OAT3 changes with this. Can you elaborate on that?

DR. SOMANI: Let me go to the relevant study here. Regarding the OAT3 transporter -- that you were referring to -- those are primarily based on in vitro studies, and in the in vitro studies, pretomanid inhibited OAT3, substrates of OAT3.

Let me just read it here. Hold on.

"Pretomanid was found to be an in vitro inhibitor of OAT3 at the clinically relevant concentrations." Then our recommendation was presented there, which is you have to avoid the administration of pretomanid with the substrates of OAT3 just because of the unknown in vivo liability.

DR. LE: Right. But there's racial and

ethnic differences with the OAT3. I'm just wondering if there were plans to evaluate that further because right now I think only methotrexate was listed there, but there are other substrates as well.

DR. SOMANI: Yes. We have looked into that, but we were -- like we have to go again and look into the other labeling because we didn't want to put any additional examples for which you could not directly have a meaningful clinical implication if you were to use that as a substrate of OAT3.

We used the FDA's website to provide one of the examples there, but that's just one of the examples. But clearly, we are making this extrapolation into recommendation that we have for the OAT3 substrate. It's all driven by the in vitro studies.

DR. LE: Okay.

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

DR. SWAMINATHAN: I wanted to ask about this fairly significant effect of high-calorie meal.

DR. BADEN: Please speak into the

microphone.

DR. SWAMINATHAN: I wanted to ask about the effect of this fairly significant effect of the high-calorie meal on the serum levels. I understand that the dose of 200 milligrams is partly based on the fact that the dose response sort of plateaus at that point.

That seems to be fairly important. I just want to make this clear because there's been concern raised about bedaquiline resistance emerging fairly quickly, and the co-administration of adequate levels of sterilizing cidal drugs would be important.

Do we have good pharmacokinetic data from actual patients as opposed to healthy, fed volunteers for this dose response?

DR. SOMANI: Just to further understand your question, your question is that when you gave it with food, you have almost a double increase in exposure. What is the underlying final question that you're asking? Is it apparently for pretomanid dose selection that's then further taken

into the pivotal study?

DR. SWAMINATHAN: Very concisely, do we have data from patients in this study as to what the serum levels achieved after the 200-milligram dose, and are those comparable to the pharmacokinetic studies done in healthy, fed patients?

DR. SOMANI: Okay. I can also have my colleague, Eliford, who can speak about any differences if what you are getting to are differences in patients versus healthy subjects, when pretomanid or the regimen is given -- pretomanid primarily is given with food. Eliford Kitabi is the pharmacometrics reviewer, and he'll provide his response on that.

DR. KITABI: Again, Eliford Kitabi, the pharmacometrics reviewer. There is a difference between healthy subjects and patients that get exposure, but the difference is clinically significant. It's very minor.

DR. SWAMINATHAN: I'm not sure what the basis for saying it's not clinically significant is because we don't know if a slightly lower or lower

exposure to pretomanid may or may not lead to more rapid emergence of resistance, to bedaquiline, for example.

DR. KITABI: The healthy subjects have relatively higher exposure.

DR. SWAMINATHAN: How much higher?

DR. KITABI: Sorry. Can I refer to my --

DR. BADEN: Of course.

DR. NAMBIAR: Dr. Baden?

DR. BADEN: Yes?

DR. NAMBIAR: I think while we're waiting, if the applicant has information that's readily available and they're willing to share, I think that would be helpful.

DR. BADEN: Does the applicant have the information?

DR. EVERITT: Just quickly, let me call on Jerry Nedelman. Do you want it now or later?

DR. BADEN: No. If you have the information readily available, please.

DR. EVERITT: Yes. Our pharmacometrician is Jerry Nedelman. I think it's both the dose

response effectiveness around the concern of food and then also in patients.

Jerry? You may want to just clarify the question if you're not sure.

DR. BADEN: I think the question was the PK is impacted by diet, and that was seen in the phase 1 in healthy volunteers. In the Nix study, was there a difference in PK compared to in the healthy volunteers?

DR. EVERITT: Could he come up here for a minute?

DR. BADEN: Of course. Just use the other microphone.

DR. NEDELMAN: Jerry Nedelman, from TB Alliance. Quickly, this is a slide that shows data we've assembled from across studies, including Nix-TB on the bottom, which shows a steady-state PK of pretomanid under different food conditions.

At the top half of the slide, you see data collected from studies where pretomanid was administered fasted; the bottom slide where pretomanid was administered fed again. These are

all patients with PK at steady state.

On the far right-hand column, you can see mean areas under the curve. Looking at the top half of the slide, you can see they range from 28 to 40 microgram hours per milliliter. At the bottom half of the slide, you can see they range from 55 to 80 microgram hours per milliliter, and there's Nix-TB at 56.

So the food effect seems to be robust across both healthy volunteers and patients and across studies, including Nix-TB.

DR. BADEN: Thank you.

Back to the agency. Dr. Ofotokun, a follow-on?

DR. OFOTOKUN: Yes, still on the issue of pharmacokinetics, metabolism, my other concern is the impact of the drug on the transporter, especially how that affects the metabolism of the antiretroviral drugs. Many of the nucleoside analog studies used along with the antiretroviral drugs are also substrate of the drug transporters.

Do we have a sense of the impact of this

product on concomitantly administered HIV medicine in this patient population?

DR. PAHWA: Sonia Pahwa, clin pharm reviewer. There is a DDI study where the antiretroviral drugs like ritonavir boosted lopinavir has been tested with pretomanid, and also efavirenz co-administration with pretomanid has been tested. With the ritonavir boosted lopinavir, when it is co-administered with pretomanid, there was no clinically significant DDI observed, so the exposure of pretomanid is not altered. Also, the exposure of lopinavir is not altered.

With efavirenz, there was some decrease in the exposure of pretomanid observed, and also based upon the label of bedaquiline, efavirenz should be avoided with bedaquiline, so this has been excluded in the trial, and also should not be given with this combination. Other than that, these two were evaluated.

With respect to transporter, there is no liability except OAT3, which has been discussed by my colleague. That is based upon the in vitro

interactions, and there is no clinical study done.

DR. OFOTOKUN: The ones I'm really even more concerned about is the background regimen, the nucleoside analog like tenofovir that is widely used along with -- that is almost used in our HIV regimen.

DR. SOMANI: Our recommendation is for OAT3 class of drugs, so any drug that would fall under that OAT3 substrate, that would have to be factored in, whether there is a likelihood of a clinically relevant interaction. Then if there is a recommendation in that labeling, then we are asking to avoid or monitor, or dose adjust, based on the approved labeling for the OAT3 substrate drug that would be of concern.

If the applicant wants to add further on that, we would welcome them to add further on the concern that you have raised or the question that you have raised for OAT3 substrate ability with HIV drug.

DR. BADEN: I'll ask the applicant to save that for when we resume with the applicant.

Dr. Goetz, a follow-on?

DR. GOETZ: My question, maybe it's the applicant who can answer this better. You commented that the weight distribution was something like a BMI of 17 to 41, which is going to correlate with a great difference in poundage as well. I'm interested in -- two questions -- the variability of levels in the patient population and getting a fixed-level dose.

You presented data on the AUC over 24 hours of your dose, but do you know what the critical pharmacodynamic variable is for effectiveness in terms of whether it's AUC peak or Cmin?

DR. BADEN: I'll ask the applicant to put that on the list of questions to address when we returned to you.

Dr. Ghany?

DR. GHANY: Yes. Thank you. Mark Ghany. My question is directed to Dr. O'Shaughnessy. I do have a few questions about the hepatotoxicity associated with this regimen. In reviewing the data that was given to us, there were 4 deaths

associated with the use of pretomanid in another regimen.

Can you tell us a little bit about those deaths. Is there liver histology available on what the description was?

My second question is there seems to be absence of data of hepatotoxicity in patients with underlying chronic liver disease or even cirrhosis, and I wanted to hear what the agency's views were on this because, honestly, there's the potential for increased hepatotoxicity in these populations.

DR. O'SHAUGHNESSY: As I recall, the 3 deaths that occurred in 2015 in the STAND trial occurred with a regimen containing pretomanid moxifloxacin and pyrazinamide. As far as I remember, they were drug-sensitive TB patients. They were young patients. The elevations happened and were detected around week 4 of therapy, however, the patients seemed to have pretty normal liver function around week 2, so they happened early on in the course of the treatment with that regimen.

There were some issues with regard to the patients being seen at outside clinics and not seen at the study center, so the regimen was probably not stopped as quickly as it should have been when the elevations were seen and ended up in liver deaths. It's been a while since I've reviewed those cases, but that's my recollection of those 3 cases.

DR. GHANY: The second part of my question about safety in patients with chronic liver disease and cirrhosis?

DR. O'SHAUGHNESSY: We have I guess not really looked at the current regimen, the BPaL with patients with severe liver disease.

DR. BADEN: I think a colleague of yours -- please.

DR. O'SHAUGHNESSY: Oh, I'm sorry. Dr. Avigan.

DR. AVIGAN: Hi. Mark Avigan. I'm a hepatologist, and I'm actually tracking some of these issues. I just want to mention that Dr. John Senior, who is my colleague, was also a reviewer

for this particular phase of the development program. But we did look actually at an earlier set of data around the other combination that you mentioned, pyrazinamide and moxifloxacin, and there was in fact a quite extraordinary, startling cluster of 3 cases in the STAND trial of acute liver failure, which occurred approximately 4 weeks into the treatment program.

These were looked at by the sponsor. They might want to talk about it. They had their own consultant looking at these cases, and they concluded these were probably causally linked to the regimen. There was some question and discussion about what is the underlying mechanism of this since it's a combination, in fact, with pyrazinamide.

The conclusion was that perhaps there was an interaction with pyrazinamide and this new study drug pretomanid, but the nature of that interaction wasn't totally clear. But the frequency of these events was much higher than you might see with pyrazinamide alone, which is also known to be

hepatotoxic.

I think the new combination that we're seeing here has the absence of such dramatic cases of severity, where we see a liver signal but without the liver failure effects, but in a very small study population. I think that's what we're left with, a small study population with a few cases of potential liver toxicity, but in complex patients who may have other effects going on.

DR. BADEN: Dr. Lindor?

DR. LINDOR: Keith Lindor. I wanted to get some clarification about the transaminase elevations at baseline. In the material that came from the sponsor, the exclusion criteria lists transaminase elevations, but in the other document, it looks as if patients with transaminases, either ALT or AST, greater than 3 times the upper limit of normal are to be excluded.

In the data that you showed, there were several patients who had had transaminase over that 3-fold upper limit of normal at baseline. Was that a true exclusion? And if so, how did so many of

those patients get included in this study?

DR. O'SHAUGHNESSY: The tables I presented were presented based on the laboratory data, so I think they're correct. I do know some of the patients, at least one of the patients who had an ALT level greater than 5 times the upper limit of normal at baseline, I noticed when I looked at his ALT levels, he actually had transaminitis previously, associated with other TB regimens he had been on.

When he came into the trial, he had high levels of ALT, and actually his levels went down while he was on treatment. So that's the one I remember, and the other ones, again, they're based on laboratory data. I don't know their actual cases, specifically.

DR. BADEN: I'll ask the sponsor to also have that as another clarification.

Dr. Hilton?

DR. HILTON: This is probably for the sponsor, so I could hold. But just briefly, you mentioned that you're concerned about male

infertility, but I didn't hear mention of examination of effects on female infertility.

DR. BADEN: If the agency has any knowledge of the impact on female fertility or toxicity or if you're aware of any such data.

DR. McMASTER: I'm Owen McMaster, the pharmacology-toxicology reviewer. We did fertility studies, and it was clear that pretomanid affects male fertility. When we dosed females with pretomanid and used healthy males, there was no effect on fertility.

DR. HILTON: What outcome did you use?

DR. McMASTER: We looked at pregnancy, pregnancy rates.

DR. HILTON: For example, hormones such as anti-mullerian hormone might give a signal.

DR. McMASTER: We looked at inhibin. We looked at LSH, FSH. There was no impact on testosterone, but I think there was a reduction in inhibin, and I think there might have been an effect on FSH as well. However, clinical probably has data on hormones.

DR. O'SHAUGHNESSY: Actually, I might ask the urologist to speak to the male hormone levels.

DR. McMASTER: There was no impact on the female fertility, based on the animal data.

DR. BADEN: Will the urologist please introduce yourself and your relationship to this effort?

DR. DIMITRAKOFF: I am Jordan Dimitrakoff. I'm a medical reviewer in the Division of Bone, Reproductive, and Urologic Products. I can only speak to the male data, since that's what was presented to us. As was mentioned by Dr. O'Shaughnessy, there were 3 studies that we reviewed, and only one of those studies, NC-005, actually had adequate data to examine the relationship.

There was a signal from the preclinical data, but we didn't actually detect a definitive signal in the human data, and we have recommended a semen study to definitively evaluate the effect on male fertility.

DR. HILTON: There seems to be a gap.

DR. BADEN: For the applicant, another issue just to comment on as to whatever data may or may not be available.

Dr. Swaminathan?

DR. SWAMINATHAN: The incidence of lactic acidosis with linezolid may be related to the duration of therapy. Is the plan to recommend serial monitoring of serum lactate levels?

DR. O'SHAUGHNESSY: We haven't made any such recommendation, no.

DR. BADEN: Dr. Nambiar?

DR. NAMBIAR: Just to comment, Dr. Swaminathan, if you do have any recommendations going forward, I think that will be part of the question, and we would love to hear from you because the NDA is still under review.

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

Dr. Follmann?

DR. FOLLMANN: Thanks. This has to do with the meta-analysis. There's a lot of heterogeneity in the success rates, ranging from 10 percent to 60

percent in the meta-analysis. This was all, I guess, in the pre-bedaquiline, pre-linezolid era.

If you could comment on the definition of success for those studies; I know it might be hard to discern that from the reports, but if you'd comment on how they define that. Then I have a follow-up question.

DR. RUBIN: Success for the meta-analysis, the attempt was to use WHO definitions based on, basically, investigator judgment of cure or completion of therapy, but it may not have been possible to have that completely standardized over all of those different studies. One aspect that was not standardized was the timing of the assessment of cure. So there definitely was heterogeneity. That was a limitation of the literature review and meta-analysis.

DR. FOLLMANN: Then another comment. There are two flavors of meta-analysis, one called a fix effects meta-analysis and another, a random effects meta-analysis, which you did, which properly reflects the heterogeneity. But to my mind, if you

do a random effects meta-analysis, you can come up with a different bar or threshold for what's going on.

You can think of a simple example. Say you have a large number of studies that have a 10 percent success rate and a large number of studies that have a 60 percent success rate, so half are 10 percent and half are 60 percent. On average, the success rate is 35 percent, but that's not a really satisfying bar because if you had a new study that at a 50 percent rate, it might be a lot larger than 35, but it's not a lot better than 60, which half the studies were.

So I think when there's a lot of heterogeneity in the meta-analysis, another bar would be to say, what is the range of success rates that fall in the meta-analysis? And there are different ways to calculate that, including from the DerSermonian-Laird approach. But the bar of 35 might be too small I would think. If we take into account the heterogeneity, maybe a bar like 60 percent would be more relevant because the studies

are so different.

DR. RUBIN: Thank you. That's an interesting suggestion, and we didn't look at whether the outcomes had that kind of bi-modal structure. I will say that I believe only two of the studies had success rates of over 50 percent, and one was a very small study in Israel with 12 subjects. Then the range, I think the highest success rate was 60 percent or below the 90 percent in Nix-TB, which gave us some confidence. Then we had the much lower success rates in the studies in South Africa.

DR. FOLLMANN: Well, the South Africa I think is the most relevant for our question. Our study was done -- or the Nix-TB study was done in South Africa. You said there, I think, the success rates were all like 22 percent or less, something like that.

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

DR. LE: Yes. I want to piggyback on Dr Hilton's comment regarding -- at least to me, there are clear signals from preclinical animal data for

not only maternal but fetal effects as well as lactation. I wanted to see if there was any -- one of the reasons why we couldn't see in the trials is because all pregnant women were excluded. I wanted to see what the plans were and the recommendations were from falling through and following up, to get more data in that area.

DR. NAMBIAR: Just to make sure I understand your question, are you asking the plans for studies postmarketing? What might be the intention?

DR. LE: Yes.

DR. NAMBIAR: As I said, the application is still under review, so as part of your appraisal of the scientific data provided, if you have any recommendations or suggestions for what might be studies that need to be done, we would like to hear from you. We still haven't made a decision.

DR. BADEN: What I think I'd like to do, since we've concluded with all of the clarifying questions for the agency, is to return to the sponsor because I think, Dr. Le, your question may best be asked of the sponsor as to their plan.

Dr. Everitt, if we may -- and I assume from the committee, I've read the committee correctly, that there are no further clarifying questions to the agency, although we still can ask them in the combined discussion. But at this point, there are many questions for the sponsor. Let's start with Dr Le's regarding the female reproductive tox and your thoughts on how to go forward with assessment of that, given the limited data.

DR. EVERITT: Thank you. First, let's clarify what we have done and what we know from reproductive toxicology studies, and a full battery have been done. I'd like to ask my colleague, TJ Yang, just to briefly summarize what we know about any reproductive effects from the studies, and then we can talk about clinical studies after that.

DR. YANG: Thank you. My name is Tian Yang, director of preclinical drug evaluation. Can I have slide 106?

This slide is showing segmented 1 fertility study in rats. Remember, we observed the male reproductive toxicity test at a relatively low

level. In this study, the first male dose was for 10 weeks and the female dose for 2 weeks. You have it for 3 weeks. So that's why you see the male dose is 10 weeks and plus 3 weeks cohabitated. The female was dosed for 2 weeks, and then cohabited for continued dosing.

If you see the control is 92 percent fertility and a 10 milligram per kilogram is the same as control, when the dose goes high to 30 milligram per kilogram, you get fertility at 64 percent. The male continues dose 4 additional weeks in the middle column, so a total dose of 14 weeks and paired with naive female. The fertility in this group still contains 64 percent.

This is indirect evidence, which means this group of males versus females, and female dosed or without dose in the fertility index is the same. The female is given 10 weeks of recovery and paired with naive female in the last column, compared to control. At 30 milligram per kilogram, you still see the fertility index as lower, but compared before the recovery, it's somewhat recovered.

Simply, I want to point out if you look at the medium column, male paired with naive female versus the first column paired with dose to female, the fertility index is about the same. This may indirectly suggest the female is not affected by the fertility.

Also, we had done segment 2, which involved a prenatal development study and also the segment 3 post hoc study, which was for pre- and post-natal development study. There is no teratogenic or development issue. When you give a higher dose to female, like 100 milligram per kilogram, it's general toxicity because with food consumption, the body weight is reduced, which makes the animals unhealthy. At that high dose in the female rat, you see a slight interest [indiscernible] extended, from 5 days to 6 days of [indiscernible] cycline increased to one day in some animals, but it's a really high dose relevant to the healthy condition.

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

DR. HILTON: Yes. Thank you. Could we discuss that slide further?

DR. YANG: The fertility slide?

DR. HILTON: Yes.

DR. YANG: Slide 106.

DR. HILTON: It could be that the first column with male dosing of 10 weeks and female dosing of 2 weeks is not sufficiently different from the middle column of male dosing for 14 and female dosing for none. It's not very representative of the treatment duration. Just because the data in those two columns are similar, I don't think that I can agree with you that that suggests that fertility's only affecting the males. I don't think that you've adequately dosed the female rats in order to study this question.

DR. YANG: I agree it's not conclusive directly. Just to clarify, the female in the first column, actually, the total dose is 6 weeks because there are 2 weeks at 3 dose, and the 3 weeks, continue during the pairing, and an additional one week from the GD7 [ph].

DR. HILTON: Okay. It's still about half of the male dosing, so I don't find it conclusive

myself.

DR. BADEN: So it seems that future monitoring of this, particularly in patients treated, may be important data to generate.

DR. HILTON: Sure, but preclinical studies as well.

DR. BADEN: Of course, and patients treated; so yes.

From the prior discussion with the agency, the issue of hepatotoxicity and potential use going forward as raised by Dr. Ghany, any comments on that line of discussion from the agency discussion?

DR. EVERITT: Just coming back, was there a specific question to comment on?

DR. BADEN: Dr. Ghany?

DR. GHANY: Yes. Just to follow up on the line of questioning with the FDA, can you comment, was there any signal that identified hepatotoxicity in the patient? For example, the trial was extended up to 9 months. Was longer duration associated
with increased risk of toxicity, or older age,

gender, race, other agents used in the regimen?

I have a second question, but I'll let you answer that first.

DR. EVERITT: Just one comment is only 2 patients extended for 9 months extended by the 3 months, and those patients, there was not any particular hepatotoxicity concern.

I guess your question is, is there anything we identified that may have predicted patients who had ALT elevations or Hy's law?

DR. GHANY: It's not predicted; it's make them at greater risk for.

DR. EVERITT: Let me ask Dr. Jim Freston, our drug-induced liver toxicity expert who's reviewed all the cases and done adjudications.

Could you maybe comment specifically on that question; in the overall review, are there any factors to identify the patients at higher risk of toxicity?

DR. FRESTON: Good morning. I'm James Freston, emeritus professor of medicine and clinical pharmacology at the University of

Connecticut. As you mentioned, I did have a chance to review all these cases along with another external consultant. We couldn't identify any condition, either going into the study or during the study, that predisposed to generating an hepatic signal.

Just to comment about -- there's been much discussion in the DILI, drug-induced liver injury, community about whether or not preexisting liver disease predisposes to DILI. Results are mixed, but the general consensus is there's little evidence that it does. It may make DILI worse.

DR. EVERITT: I will mention we do have an ongoing hepatic impairment study. That's a phase 1 PK study being conducted by NIH. Clearly, that won't speak to long-term administration to patients with underlying liver disease, but that will give pharmacokinetic and at least single-dose safety information.

DR. BADEN: Dr. Ghany?

DR. GHANY: Yes, a follow-up question. Can you tell us a little bit about the pattern of ALT

resolution? Was it quick? Did it take a long time? Because this would obviously be important for how you monitor these patients for resolution. Then also, I think there was some date on rechallenge, and it seems that there was no increased ALT or AST. If you could just confirm that that indeed was the case.

DR. EVERITT: First, all of the patients, the 8 patients that had their regimen interrupted because of any hepatic abnormality, they all went on to finish out the full 26 weeks of therapy with rechallenge.

Let me just show you. Here are the patients that interrupted. It's 8 individual patients; there are 9 interruptions. One of the Hy's law patients -- potential Hy's law patients -- interrupted twice. This shows the number of days they were interrupted. Now, that was at the discretion of the investigator, but in general, the rechallenge would not happen until the liver enzymes approached back to baseline levels.

You can see that most of them were

essentially within about 2 weeks. There was one patient that interrupted for a total of 30 days. Everybody else was up to, say, 18 days before they were reintroduced, and then successfully finished out the full 26 weeks of treatment without any further interruptions.

DR. GHANY: One? Sorry.

DR. BADEN: Please.

DR. GHANY: Just to clarify, did the transaminases return back to normal or the patient's baseline?

DR. EVERITT: Yes. Right. You saw that some came in with elevations. We allowed up to 3-fold elevations coming into the study. But yes, returning to baseline or near baseline.

DR. GHANY: Thank you.

DR. BADEN: Dr. Gripshover? Microphone, please.

DR. GRIPSHOVER: Sorry. Actually, two questions, one actually on that last slide. Do we know when -- how long into their study treatment these happened? Is there any time course for the

hepatotoxicity or is it totally random?

DR. EVERITT: The amount of time into treatment before these elevations were -- I don't think -- we don't have a slide on that specifically. That's something we could try to get you after the break and show after lunch, specifically the time to increases in elevations or at least a decision being made to interrupt. We can get that.

DR. BADEN: Dr. Goetz?

DR. GRIPSHOVER: I had --

DR. BADEN: Oh. I'm sorry. Dr. Gripshover?

DR. GRIPSHOVER: I know the FDA had said that they thought the STAND hepatotoxicity might have been that interaction with PZA, but SimpliciTB on the ongoing trial using it, pretomanid with PZA now?

DR. EVERITT: We've had several different phase 2 trials and then a phase 3 trial where pyrazinamide has been part of the regimen generally with moxifloxacin, and then we have an ongoing study where bedaquiline is part of it. So that

raised concern that was referred to, we call the STAND trial, and that was pretomanid, pyrazinamide, and moxifloxacin, and that's where there were 3 patients who died with liver failure, and that was discussed by the FDA representative.

At the time, and it still stands, we did an analysis across our program. There also was a patient randomized to HRZE, a drug-susceptible patient who died with liver failure, the common thing being pyrazinamide in both of them. And actually, across our program, the actual deaths from liver failure have essentially been in the same ratio as the numbers randomized to pretomanid containing regimens versus the standard of care, HRZE, 1 HRZE, 3 pretomanid.

DR. GRIPSHOVER: Can I follow on?

DR. BADEN: Yes.

DR. GRIPSHOVER: We didn't actually get to see the data from STAND. Did you have a lot that also had elevated transaminases that we should maybe know more about?

DR. EVERITT: Let me ask if we have a slide

that STAND is specific about transaminase elevations, where there is the HRZE control arm. We could try to show that after the break. We have it. We're just aren't quite ready to project

DR. BADEN: Great. We'll look at that after the break.

Dr. Goetz?

DR. GOETZ: I think you said this before, but if you go back to that liver slide where you showed the times of discontinuation, you commented that the patients were resumed on therapy. If I read the materials properly that were sent out and heard perhaps what you said earlier, the intervention that was made when people were put back on therapy was that if any changes were made in therapy, it was the linezolid that was dropped rather than the pretomanid.

In other words, on those, of the people who resumed therapy, what components of therapy were resumed or changed?

DR. EVERITT: In general, across a study when the regimen was interrupted, say, for a

hepatic concern, all 3 drugs had to be interrupted. You couldn't just label linezolid on as unopposed monotherapy. In general, all 3 drugs were resumed. The investigators were not thinking of linezolid as much hepatotoxicity concern.

For these particular 8 cases, again, that's something I could get you after the break. I don't have the exact detail as to how many did or did not resume on linezolid.

DR. GOETZ: What dose of linezolid, would be the other question.

DR. BADEN: Great. Dr. Le, did you have a follow-on?

Dr. Weina?

DR. WEINA: New question, right?

DR. BADEN: Yes, please.

DR. WEINA: Thank you. I know we're focusing on the Nix-TB in the discussion, but can you clearly state the outcomes of the other clinical trials in regards to efficacy and safety? I asked this because this isn't a fixed-drug combination. Although we're being asked to have a

discussion about the combination of these 3 drugs, the reality is that in the real world, if this is approved, it's going to be available out there as a single drug, which can be combined in any possible way that's available out there. There's a lot of data out there, NC1 through NC6, that you have data on both safety and efficacy, and it would be nice to have that clearly presented.

DR. EVERITT: Let me just quickly show a few things. The purest thing, does pretomanid have an effect, can come from only a maximum of 14 days, and I showed that in the core presentation, the early bactericidal activity study.

After 14 days, it's not ethical or clinically possible, really, to treat somebody with just one single drug; they have to go on a regimen. As I said, we've shown that for both bedaquiline and linezolid, that over 14 days, one gets over a log reduction in CFUs. We've then done studies with other regimens, where again, it's always in combination.

Let me maybe show the results from NC-005,

is one that was a 2-month study looking at changes at culture conversion, as well as -- culture conversion not to the ultimate clinical outcome, but an 8-week study following serial measurements; see if we can get that.

NC-005 was a little bit of a complex design. Basically, drug-susceptible patients were randomized to pretomanid, pyrazinamide, and then either bedaquiline added on, or for the drug-resistant patients, it was pyrazinamide, moxifloxacin, and -- moxifloxacin, pretomanid, pyrazinamide, and bedaquiline.

Again, it's maybe a little bit complicated to look at, but what we have here are hazard ratios of the time-to-culture conversion. Wait. First, let me just quickly show you first the study design and try to keep this succinct.

This was the NC-005 study. Drug-susceptible patients were randomized either to bedaquiline at the standard registered dose with pyrazinamide 200 milligrams or -- pretomanid 200 milligrams or pyrazinamide, or to bedaquiline at a 200-milligram

daily dose. We're testing a daily dose of bedaquiline, pretomanid, and pyrazinamide, or Riferfor is the brand name for the standard HRZE for 8 eight weeks. Drug-resistant patients were not randomized; they were just given bedaquiline, pretomanid, pyrazinamide, moxifloxacin, and followed up for 8 weeks.

Now, let me go back to the hazard ratios, which is one way of looking at it, and this is relative to HRZE. The bedaquiline loading dose with pretomanid and pyrazinamide versus HRZE, you had a 1.7 statistically significant hazard ratio for an improved time to conversion to negative. With the bedaquiline at a 200-milligram daily dose -- and that's what we're taking forward actually in our ongoing studies -- with pretomanid at the 200-milligram dose and pyrazinamide, a hazard ratio of 2.

When we looked at the drug-resistant patients given moxifloxacin, pretomanid, bedaquiline, and pyrazinamide, we actually had a hazard ratio of 3.3; again, highly statistically

significant. That's about the best hazard ratio that's ever been reported in a TB study of a new regimen relative to the standard that I would get if I had drug-susceptible TB and was treated here.

So that's one of the studies. Just quickly, let me just show you also a simple way of looking at it is how many patients were culture negative at 2 months? You can see the HRZE control was only 51 percent were culture negative and liquid culture at 2 months versus the various pretomanid-containing regimens, ranged from 67 to 96 percent.

So that's one of the studies. We could probably take more time than we have to go through others, but if that helps.

DR. WEINA: And just a follow-on to that, besides what we've already seen with the pyrazinamide combination and the concern for that combination, are there any other combinations that are potentially concerning that maybe some signal came out of the other trials?

DR. EVERITT: I would say no. Most of our trials have included pyrazinamide. Until we got to

the BPaL regimen, the others have just been short exploratory trial of, say, 2-drug combinations to look at 14-day early bactericidal activity.

DR. BADEN: The efficacy data for the Nix trial that you presented, what was your censor date for those data?

DR. EVERITT: The 120-day update was Jay in January.

DR. BADEN: So the data were through January or through April?

DR. EVERITT: Through January of this year, right.

DR. BADEN: Got It. We're about to go to break, but I wanted to pose something that you can think about at break.

Do you have the 6-month follow-up on the Nix trial if there are more failures, and whether or not you can comment on that after the break?

DR. EVERITT: I can say right now, in the follow-up -- and it may have been shown on one slide -- there's only one relapse after the primary endpoint of patient.

DR. BADEN: So up through June 1st of 2019, there's one more failure? I'm harping on the data censoring.

DR. EVERITT: Not before the primary endpoint.

DR. BADEN: I just want to make sure that we have the most current data on failures for the primary endpoint --

DR. EVERITT: Right.

DR. BADEN: -- because if there were a lot of failures after the censorship date, and we're not aware of that, that might lead to some misunderstanding.

DR. EVERITT: Let me just show this slide of the 120-day update where we stand.

DR. BADEN: I still don't understand when does the 120-day update end?

DR. EVERITT: In January.

DR. BADEN: So it's data through January.

DR. EVERITT: Data through January.

DR. BADEN: You have data through June 1st.

DR. EVERITT: Yes.

DR. BADEN: Okay.

DR. EVERITT: So now we have follow-up on 38 patients. Do we have that slide, 38 patients through 24 months? This is giving the further update.

DR. BADEN: That's still not my question.

DR. EVERITT: No.

DR. BADEN: You have 109 patients.

DR. EVERITT: Yes.

DR. BADEN: The 109 patients minus the 8 who have died is 101 patients. The 101 patients, do you know through June 1, 2019 if any of them have subsequently failed? So it's not just through the 24 months. There may be people who are at 18 months.

I just want to make sure the committee is aware. And the reason I raised this wasn't necessarily for you to answer right now. If over lunch, you need to look at these data, my own view is if you happen to have 6 failures in May of 2019, but they're not in the data presented, that would be important for us to know. If the answer is

there are no further failures, that is incredibly reassuring.

DR. EVERITT: Yes. I can answer you quickly right now. Let me just show you very specifically, in the 120-day update, there are 38 patients that have been followed through 24 months. Patients that were enrolled with the ability to have 24 months follow-up, 4 deaths in that group, one relapse.

Now let me tell you, in the entire knowledge we have now, there is still just the 6 deaths during treatment plus the one who died of unrelated causes that we took out of the MITT analysis; 2 patients that relapsed before the primary endpoint; only one additional patient that has relapsed after the primary point, and he relapsed at month 15; and no other relapses.

If I can ask the agency's permission, right up to today, we now have the final culture results at the primary endpoint for the 109th patient, the last two that were -- may I just mention what -- they were culture negative, so no more

relapses.

Does that clarify it?

DR. BADEN: Yes. I was looking for a very crisp answer, which was you presented us the failures, and you're not aware of any other failures.

DR. EVERITT: There are no more failures.

DR. BADEN: As opposed to getting lost in data cutoff dates.

It is 12:07. Our time is limited. We will break for lunch. We will resume at 1:00 sharp for the OPH session. Please take all your belongings you may want to take with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, the press, or with any member of the audience. Thank you. We'll resume 1:00 sharp here.

(Whereupon, at 12:07 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:00, and we should resume. This is now the open public hearing session.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee 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 statements, to advise the committee of any financial relationship that you have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA

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

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

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every patient 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 as well.

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.

DR. REICHMAN: Good afternoon. I'm Lee Reichman. I'm a retired professor of medicine and preventive medicine and community health at Rutgers New Jersey Medical School. I'm the founding executive director of the Rutgers Global Tuberculosis Institute, which recently celebrated its 25th anniversary. It's one of only four federally funded centers of excellence in tuberculosis, all of which are funded by CDC.

Early on, I was director of the Bureau of Tuberculosis Control for the city of New York. I support the pretomanid combination regimen for extensively drug-resistant and treatment-intolerant, nonresponsive multidrug-resistant tuberculosis. Based on my review of the data, it's a simpler, shorter, and better tolerated treatment for these adult patients.

I'm appearing here on my own behalf. TB Alliance has reimbursed my travel expenses from New Jersey to be here today, but I'm certainly not

being compensated for my time. Frankly. I'm pleased to see the Alliance is here to discuss its treatment regimen for these challenging forms of tuberculosis. I was a board member of the Alliance back in the early 2000s, as well as a continuing member of the stakeholders' association.

In my 50-year career, I've had the opportunity to know and directly care for or consult on thousands of patients with tuberculosis, including a significant number with multiple drug-resistant tuberculosis and a few with extensively drug-resistant tuberculosis. I've also been responsible for training thousands of medical students and clinicians and healthcare workers in all aspects of prevention, treatment of drug-resistant and drug-sensitive TB.

I'm co-editor of two editions of a very widely cited textbook on TB and a popular book. I've also authored or co-authored more than 250 peer-reviewed medical articles, most on aspects of TB care, control, and treatment. I wanted to speak here today because TB remains the largest killer of

any single infection.

This is a tragic paradox because modalities exists to prevent, treat, and control it. However, treatments and therefore effective control measures have increasingly failed in their role because of the advent of multiple drug-resistant TB and extensively drug-resistant TB.

According to WHO, these resistant forms now account for over half a million estimated cases each year. Unfortunately, as I pointed out in my book, Timebomb: The Global Epidemic of Multidrug-Resistant Tuberculosis. TB was and still is perceived to affect mainly poor people and minority groups, and therefore has little financial incentive for big pharma to develop treatments for it.

The solution to the paradox, as described in Timebomb, was the advent of the Global Alliance for TB Drug Development as a model of a public-private partnership. It pioneered the initiative of testing new complete regimens rather than single new drugs for TB, resulting in the drug pretomanid

as part of an oral regimen, including bedaquiline and linezolid.

As a long-time clinician educator, I'm convinced by the evidence that we've heard today because I know of the challenging disease this is and how difficult it is to endure the standard that is and was of care when this trial began, and I believe pretomanid fulfills this urgent need.

Before the advent of the pretomanid- and bedaquiline-containing regimen, we fought multiple and extensively drug-resistant TB using a draconian 24-month regimen of very difficult-to-tolerate drugs, including 6 or more months of a painful injectable with numerous side effects, with only about half the patients being cured.

So here we are assessing an oral 6-month regimen anchored by pretomanid. The regimen cures about 9 out of 10 patients in 6 months, with the most resistant cases being cured. I wish I had this regimen option for my appropriate patients before I retired.

I hope the regimen is approved. We have

enough data to have confidence that it will give clinicians a new and effective tool that is simpler than what we have now, shorter on treatment duration than our current options, and far better tolerated. These features are what we need now in these patients. Thank you very much.

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.

MR. RANA: Good afternoon. My name is Nauman Rana, and I am a multiple drug-resistant tuberculosis survivor. I'd like to point out that I have no financial relationship to the sponsor, but they did cover my transportation and accommodation last night in the lovely Sheraton here in silver spring. I'm here representing only myself, however.

I am thankful to the FDA for letting me share my story. I know you're here to discuss a new treatment for XDR and nonresponsive MDR B, but I believe my journey with MDR TB might be helpful.

I was initially diagnosed with MDR TB back in 2013, and my treatment lasted for almost two years. Looking back, I can honestly say that those two years were the most difficult and challenging of my life, both physically and mentally.

I was diagnosed with TB when I was 32 years old, living in New York City. At the time, I was a very healthy individual overall, hardworking, most of the time followed a good diet, and I exercised. It took nearly 8 months to get correctly diagnosed. Once I was, I was given medication and was told it would last 6 to 9 months. However, 2 months later, I found out that INH and rifampin, the strongest first-line drugs, were not working on me, and I was diagnosed with MDR TB.

I was told other drugs I had to take with the treatment would last almost two years. I felt angry, confused, more hopeless, depressed, and fearful for my life. I began treatment for MDR TB in November of 2013 and completed it by May of 2015. Luckily, I was cured. However, getting through each day during the treatment period was a

physical and mental battle for me because the side effects from the drugs were so strong. I took 9 to 10 pills each day for almost two years, along with an injection for 6 months; and thank God it was only for 6 months, that injection, because it was the most toxic of them all.

This daily regimen of drugs made me feel physically and mentally exhausted. I never had much of an appetite or energy to do exercise, be social, or any real work. Most of the time, I suffered from a bad case of acid reflux from taking all of the pills. I also suffered from some hearing loss as a side effect from the injection.

The worst for me was the deep state of depression that I fell into. I noticed every day got worse. Since the treatment was so long, it got worse and worse over time. First, the stigma that comes with the disease isolates you and then mentally paralyzes you. Even after I finished the treatment, the depression had gotten so bad to the point I had to see a therapist and get on medication.

I believe the whole TB experience for me was a traumatic one, and it is also the case for many TB patients out there. We need more and better alternatives to treat TB. There's a reason why this disease is the number one infectious disease killer in the world. The current drugs and regimen offered at the mass level is just not good enough.

As an MDR TB survivor, I understand and know what I want to see in an improved regimen for these patients, and pretomanid meets those needs. Better diagnostic tools need to be made available so we can detect MDR and XDR TB much sooner. Patients urgently need a shorter, more effective treatment regimen because two years is just too long; 9 months is even too long.

I pray you never have to know what it's like to undergo treatment for this disease, but I can tell you that it was extremely difficult for me, and I had been a 32-year old strong individual when I got sick, and with taking nearly a dozen pills, plus the injections, and the side effects made every single day of treatment very hard, almost to

the point where I felt like giving up.

Lastly, I do want to say that TB is curable, but the stigma isn't, so we also need more dialogue around the suffering and mental impact due not only to the disease but also because of the long and painful treatment. As a survivor and advocate, I'm very passionate about sharing my experience so that it may help in bringing more awareness and eradicating this disease globally. I hope to see that in my lifetime. Thank you.

DR. BADEN: Thank you. Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. GOOSBY: Thank you very much. It's an honor to present to the committee today. My name is Dr. Eric Goosby, UN secretary general, special envoy for tuberculosis, and professor of medicine, and director of the Global Health Delivery and Diplomacy Institute at the University of California, San Francisco.

I have been asked by Dr. Ken Castro to read

his testimony, who had a last minute change and a conflict and could not be here today. I will then follow that reading with my own presentation.

"Good afternoon. My name is Kenneth Castro. This testimony is provided on my behalf as part of the open public hearing portion of the June 6 AMDAC meeting to discuss the new drug application for pretomanid.

"I'm a professional subject matter expert, cognizant of the unmet treatment needs in people afflicted with multidrug-resistant tuberculosis and XDR TB around the globe. I hold the rank of professor of Global Health and Epidemiology at Rollins School of Public Health, Emory university, and remain a fellow of Infectious Diseases Society of America, FDSA [sic].

"Before accepting my present full time academic appointment, I served as an officer in the Commissioned Corps, U.S. public service and attained the rank of Rear Admiral. My professional career at the Center for Disease Control and Prevention included serving as director of the

Division of TB Elimination from January 1993 to July 2013. I'm testifying here today in support of the approval of pretomanid to be used as part of a regimen with bedaquiline and linezolid for the treatment of adult diagnosed with XDR TB, not responsive to therapy for MDR TB.

"These are life-threatening conditions and the FDA's accelerated approval process to expedite access for promising therapies to treat a serious life-threatening condition and provide therapeutic benefit over available therapies. This is a critical need now for the safe and effective treatments such as this regimen containing pretomanid to treat these extremely challenging forms of disease.

"The proposed use of pretomanid as part of the combination regimen with bedaquiline and linezolid in adults for the treatment of pulmonary TB and treatment intolerant to the nonresponsive MDR TB could help reverse the disturbing course of the disease that began to take shape in the 1980s with the global emergence of resistant forms, and

resistance has now become increasingly difficult to treat, to the point where some patients have little chance of achieving a cure.

"How do we get there? From 1985 to '92, the U.S. experience was an unprecedented reversal of longstanding declines in TB incidence rates by 20 percent in the context of widespread occurrence of MDR TB, associated with the emergence of HIV. At CDC, we coordinated a national and multi-agency response to the alarming trend. Our response included training, testing, conducting research to identify new tools for the diagnosis, treatment, and prevention of TB, with an emphasis on the systematic and rapid identification of drug resistance.

"Our full-course press against TB had an effect. The TB incidence in the United States declined from '83 to 2018, but the cost of the disease have been enormous. The human toll is incalculable, but CDC did calculate costs associated with averted TB cases. In New York City alone, it was estimated that it cost $1 billion to

recover from this resurgence.

"In addition to the life-threatening nature of MXDR TB, CDC has estimated the exorbitant costs of treatment, ranging from $260,000 per person for MDR to $554,000 per person for XDR TB treatment. In contrast, the cost of treatment for people with drug-susceptible TV averages in the United States about $17,000 per person.

"But there is a reason for optimism. We calculated averted TB cases and costs for the years '95 to 2014 by nationwide improvements against tuberculosis using two different scenarios and statistical modeling. Averted TB cases ranged from 140,000 to 319,000. The societal benefits of averted TB cases ranged from 3.1 to $6.7 billion, excluding deaths, and from U.S.6.7 to U.S. $14.5 billion, including deaths.

"Despite all of our efforts and our successes in fighting drug-susceptible and drug-resistant TB, we still have thousands of cases of TB every year in the United States and globally. MDR TB at 558,000 persons in 217 [indiscernible]

remains the challenge. Added to this is the fact that TB is an airborne disease in our increasingly rapid paced and fluid society.

"In closing, I disclose that I have no conflicts of interest in, and I do have an intergovernmental professional personnel act, IPA agreement, but I am not being reimbursed for this effort. I in closing want to just emphasize that we need better treatments for this patient population. in this setting, pretomanid and other drugs with demonstrated safety and efficacy profiles must be made available."

Thank you for Dr. Castro's statement.

Now I want to make just a brief statement myself. I am Eric Goosby, infectious disease professor of medicine and a director of the Institute for Global Health Delivery at UCSF. I served as the U.S. Global AIDS Coordinator for the president's emergency plan for AIDS relief and as the UN Secretary General Special Envoy on tuberculosis.

I have over 35 years of experience in

tuberculosis, mostly in the context of HIV in the United States and globally. My travel here to appear today was sponsored by TB Alliance, however, I am not receiving reimbursement compensation for my time. My views are entirely my own.

I'm here to support the NDA for pretomanid in combination with bedaquiline and linezolid to treat XDR treatment-intolerant and nonresponsive XDR-MDR TB. Your decisions today are very important for both the current and future XDR treatment-intolerant and nonresponsive. This specific patient population, which evolved out of resistance to other TB medications, including many still in use today, is rapidly growing as resistance continues to increase.

Despite the limited and treatment advances, the XDR treatment-intolerant and nonresponsive MDR TB patient population overall continues to have a high probability of death. You've heard the speaker before me very eloquently stating the frustrations and challenges he faced in his own treatment course, and I am hopeful that this

committee understands that that is amplified by the 10 million new infections that occur annually. The 550,000 multidrug-resistant cases that come forward remain the challenge of our time, and I'm hopeful that along with FDA partners, we'll help change this bleak picture.

BPaL has a cure rate of 90 percent in the same challenging patient population, and it does so with fewer drugs without the injectables and more manageable side effect profiles. As a clinician, I have seen XDR treatment-intolerant and nonresponsive MDR patients who suffer for months and months of treatment with toxic drugs that fail often to cure their disease. Even if cure is achieved, there can be lasting impacts from the medications and the treatment course.

The example that we just had, I think really illustrated the clear, personal challenge that it gives to an individual, both in accepting the fact that they have this disease, tuberculosis, which carries a stronger stigma than HIV does in my experience, and has given a challenge to medical

delivery systems to make these systems available and responsive to the patient's needs to deliver medications that do not challenge or cause morbidity and mortality in and of themselves.

This new opportunity is in front of us, but also is an opportunity for us to address I think the challenge of universal health coverage. Without an effective response to tuberculosis as a leading killer, the leading infectious disease killer, on the planet, we will not be able to pivot into an expansion of our service platforms to incorporate the added diseases of NCDs, and make a responsive, effective delivery system that includes infectious diseases, NCDs, and allows us to really make medical care available to the planet.

Tuberculosis needs to be engaged and receded if we are going to be successful with that. I believe this treatment affords the best opportunity we've seen in bringing the MDR-XDR populations into an expectation of cure, and to allow them to reenter and continue to contribute in society.

I ask the committee to support the approval

of the TB Alliance's new drug application for pretomanid to be used in a regimen with bedaquiline and in combination with linezolid and to thank the committee for giving me an opportunity to state my position. 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.

MS. CARTER: Thank you very much for the opportunity to provide input today. My name's Joanne Carter, and I'm the executive director of the nonprofit organization RESULTS and RESULTS Educational Fund, and I'm representing RESULTS and RESULTS educational Fund today. I've served in the capacity of executive director since 2008. I also serve as vice chair of the Stop TB Partnership Coordinating Board, a partnership of more than a thousand organizations globally, and I've been in that role for almost six years.

RESULTS Educational Fund is a nonprofit organization that educates and mobilizes the

public, policymakers, and the media to address the causes and consequences of poverty, and we have been working for over two decades on the issue of tuberculosis, both as an urgent public health crisis and an issue of equity.

TB Alliance has been a financial sponsor of their annual international conference but does not provide any other financial support to our organization, and I was not reimbursed by TB Alliance for my travel for this meeting or compensated in any other way. I'm here today to express support for TB Alliance's new drug application for pretomanid.

Patients urgently need new options for treatment of unresponsive, multidrug-resistant TB and extensively drug-resistant TB. The use of pretomanid as part of a combination regimen with bedaquiline and linezolid offers new hope for adult patients with these forms of TB, not only at much higher cure rates but also significant additional benefits of shorter all-oral treatments.

TB is the leading contributor to

antimicrobial resistance, and a third of deaths from AMR are due to drug-resistant TB. As you heard from Ken Castro's testimony, in U.S., due to the high cost of treatment and intensive healthcare resources, treatment costs for MDR TB can be between a $100,000 and $300,000 per case, and for XDR have reached $1 million. These costs can outstrip state and local public health department budgets. Between 2005 and 2016, the U.S. had 1292 cases of MDR TB and 32 cases of XDR.

Globally, in this national plan for combating MDR TB, the U.S. government has set a goal for 2020 of initiating appropriate treatment for 50 percent of patients with MDR TB in the 10 countries with the highest burdens of TB.

Following last year's UN high-level meeting, UN member states endorsed the target of reaching 40 million people with quality treatment by the end of 2022, and that includes 1.5 million people with MDR TB, in effect trying to reach nearly everyone. Among the greatest challenges we face in this effort are the patients with the most resistant

forms of TB.

Despite improvements in the treatment landscape and guidelines over the past few years, the currently available treatment for the XDR for treatment-intolerant and nonresponsive MDR populations remains complex, toxic, and up to two years in length, achieving only cure rates of 34 percent in XDR and 55 percent in MDR and nonresponsive and treatment-intolerant MDR, according to recent studies.

While the latest anecdotal data out of South Africa shows that favorable rates with the use of bedaquiline and linezolid may now be up to approximately 65 percent, that treatment still has multiple drugs and at least 18 months long.

The data submitted in the new drug application from the Nix-TB trial shows 90 percent cure rates in XDR treatment-intolerant and nonresponsive MDR populations with this 3-drug all-oral 6-month treatment. Given that context, we strongly support TB Alliance's new drug application for pretomanid as part of that new regimen in

combination with bedaquiline and linezolid.

Because we feel like this regimen could have a transformative impact in the treatment of these worst forms of TB, an FDA approval of pretomanid and the BPaL regimen for this specific patient population can help save many lives for patients who would otherwise have much poorer treatment options. Thank you.

DR. BADEN: Thank you. Will speaker number 6 step up to the podium, introduce yourself? Please state your name and any organization you're representing for the record.

MS. SALZWEDEL: Hi. My name is Jessica Salzwedel. I have no financial relationship and was not compensated in any way to be here today. For the last six years, I've worked at AVAC, a nonprofit based in New York City that works to accelerate the ethical development and global delivery of prevention and treatment options for HIV, as well as related co-infections, including tuberculosis.

At AVAC, I focus on advancing the uptake and

dissemination of the good participatory practice guidelines, a guidance document for conducting stakeholder engagement throughout the research process, and I've worked with many research organizations, including TB alliance, translating these guidelines into practice, and have seen the importance and value community voices add to the research and regulatory process firsthand. This is why I'm excited and honored to read the testimony of two former participants who could not attend the meeting today but still wanted to be heard.

The first testimony from a Nix patient I want to read is from Alefe [ph] from Soweto, South Africa. She was admitted to the Sizwe Tropical Disease Hospital in 2016 sick from TB. She went through treatment only to have it fail her.

After months and months of treatment, she was still sick with all the same symptoms she had before undergoing treatment, and that's when she was diagnosed with the nonresponsive MDR TB and found her way into the Nix trial for the BPaL regimen for patients with these severe forms of MDR

and XDR TB. Here are her words.

She asks, "Why would I want to be in this trial for a new treatment for TB? I was desperate and couldn't face another two years of treatment the hospital was giving us patients with MDR. Imagine taking 18 to 20 pills in the morning, and the side effects of all of these pills taken daily would drive a normal person insane, and that is what I went through before getting in this trial, and I wasn't cured.

"In this trial, I could stop taking a handful of pills. Instead, I took 3 medicines. It's still a lot, but it's easier than what I had experienced already in the hospital. And the staff explained there would be some discomfort from the side effects, but they were worth that, however, because I was cured."

I'm also pleased to read the testimony of Boingeeswa [ph] from a small town near Johannesburg, South Africa. She goes by the name of Boingee [ph], and here's what she asked me to say to you today.

"I'm an XDR TB survivor, and I was in a clinical research study you are discussing. Being told that you have TB is painful, but being told that you have XDR TB is even worse. It is one of the most dreaded diseases and is said to be very hard to treat, and I know people who have died from it.

"My mother cried when I told her I had XDR TB. We all knew what it could mean, but I thank God every day that I had the opportunity to be part of this research study. The treatment worked for me.

"If only this treatment was made available for all patients of this form of MDR and XDR TB, I'm certain that the TB statistics would drop like water in the water fountain in our country. And I'm living testimony that XDR TB is curable, and I was cured in only 6 months, and my treatment side effects were manageable; and I'm now free to live my life again, out of the hospital and out of danger.

"So many are not this lucky. And for their

sakes and for those who are sick and suffering for months and months undergoing very difficult treatment, I ask that you support the Nix research trial regimen."

As an advocate, I'm humbled I was able to share the experience of these two women. The patient-focused drug development process shows the importance participants and patient voices play in the regulatory process and the FDA's commitment to including these perspectives. At AVAC, we know the value community support can play in product acceptance and uptake if approved.

While regulatory approval would be just one step in the process to make this new regimen available to the many who need it, community and participants play an important role in all the steps that follow to ensure accessibility and affordability. I appreciate your consideration of these comments, and thank you for your time today.

DR. BADEN: Thank you. Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization you're

representing for the record.

DR. FURIN: Good afternoon. My name is Dr. Jennifer Furin, and I have no financial interests or relationships with the drug developer, and I got here on my own.

First, I would like to thank the members of the FDA advisory panel for allowing me to speak with you today. I come to you in my capacity as an MDR TB clinician with 25 years of experience treating this disease all over the world, including in the bedaquiline era. In fact, MDR TB was the first disease I ever treated when I began as an enthusiastic first-year medical student, working in the slums of Lima, Peru back in 1995. In this way, MDR TB is forever linked with the foundation of medical science and practice for me.

I have personally witnessed untold suffering of thousands of individuals with MDR TB, and much of their suffering is due to the treatment regimens that they receive, which were not rigorously assessed, were long and highly toxic, and in all truth, were not that effective.

Our fellow humans with MDR TB are desperate for better care, as you've heard from most of the speakers today and in many of the public comments, and we their providers are desperate to give it to them. Our dreams are big. Why not a 1-month regimen? Why not a 1-week regimen with one pill?

These are our ambitions, but wishing for them does not make them so. In fact, as I learned that same first year of medical school, we can become blinded by desperation and more prone to believing unsupported conclusions.

Because the stakes are so high, the field of medicine has developed tools to protect the safety of those in our care. Our members of the medical team have a crucial role to play in this, and as a stringent regulatory authority, you have a role to play as well.

So I would invite you to take part with me in a practice known as the time out. It is precisely when we are engaged with the heady promises of potential that we must ensure we do not overlook the basics.

The time out is a mindful pause that protects patients but also protects individuals involved in the life and death decisions that are part of medical care. During this time out, I would ask the members of the advisory panel to consider five issues that are core components in the evaluation of the novel chemical entity pretomanid for MDR and XDR TB.

These are, number 1, the current context for treatment of MDR TB and XDR TB. Using the 50 percent historical success rate to assess the efficacy of the Nix regimen is setting the bar too low. It was based on cohorts treated before 2012 and excluded patients who got bedaquiline, linezolid, or delamanid.

The landscape for treating MDR has radically changed since 2012, and cure rates of above 80 percent have been reported in patients who just got bedaquiline and linezolid, including published data from South Africa, showing a 4-fold reduction in mortality among XDR patients treated with bedaquiline compared to those who were not.

Relying on historical data from prior to 2012 is misleading.

Number 2, the evidence that is available on the effectiveness of pretomanid. The FDA briefing documents note that the efficacy conclusions depend on whether 50 percent was a reasonable benchmark. I would suggest that it is not. While appreciating the need for testing shorter whole regimens in MDR TB, this can and is being done in more than 10 randomized clinical trials that included control groups, even though they were shortening the regimens.

Number 3, the safety of pretomanid especially with regards to liver toxicity and testicular toxicity, the FDA and this advisory panel are the only people who have access to the full safety dataset, and we are relying on you to play a role that no other member of the medical team can.

Number 4, the safety of the Nix regimen as a whole; so high where the rates of adverse events seen in the Nix-TB trial that they actually changed

the dosing strategy of linezolid partway through. There are multiple ongoing randomized-controlled trials with control groups who are assessing linezolid safety and dosing, and I would suggest it's premature at this point to recommend the current dose used in the Nix study.

Finally, I would ask you to consider the impact of pretomanid approval on the growing field of MDR TB clinical trials and clinical science. We know the best data comes from randomized-controlled trials. If a novel chemical entity can be approved by the FDA without appropriate controls, what would be the impetus of conducting such controlled trials in the future, and how could we ask patients to be part of such studies if new drugs can be approved without them?

In closing, I think the members of the advisory panel for taking this brief time out with me. All of us working in the field of MDR TB are in complete agreement that we are badly in need of new drugs and shorter regimens, but we are also badly in need of solid science to support the care

of individuals living with the disease.

Are we convinced the best science was used in the best data available to approve the novel chemical entity pretomanid? The FDA and this advisory panel are a stringent regulatory authority that has a key role to play in answering this question, as we all engage in the serious business of life and death. I have but one humble request to you all. Please be stringent. Thank you.

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. FOX-RAWLINGS: Thank you for the opportunity to speak today. On behalf of the National Center for Health Research, I am Dr. Stephanie Fox-Rawlings. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We can all agree that there is a need for new treatments for highly-resistant TB that are more effective, safer, and easier to use. But the law and the mission of the FDA requires that new drugs be scientifically proven to work and have a well-characterized safety profile before they are approved by the FDA.

We don't have that -- the clinical evidence provided for pretomanid, combined with two other drugs in a single-arm study. There is no randomized control group, so all we have are the results of a 3-drug combination. That makes it impossible to scientifically determine pretomanid's contribution to the patient's outcomes.

To put this in historical context, the first U.S. randomized-controlled trial, testing a new drug for TB, was published in 1948, and it was demonstrated that streptomycin was better than bed rest. The author stated it had become obvious that in the future, conclusions regarding the clinical effect of new chemotherapeutic agents in tuberculosis could only be considered valid only if

based on an adequately controlled clinical trials.

In other words, over 70 years ago, clinicians and researchers understood that there were many factors that could affect the health impact of TB treatments and that randomized-controlled studies were necessary to demonstrate if specific septic treatment worked.

As recently as 2014, FDA argued for the need for randomized-controlled clinical trials for new drugs to treat Ebola in an article in the New England Journal of Medicine. Despite the Ebola crisis, the FDA author stated that since the use of historical controls cannot reliably identify effective treatments, there use could have tragic consequences. If historical comparisons falsely suggest a benefit or fail to detect modest but meaningful clinical effectiveness, the investigational drug might be erroneously adopted as effective or discarded as ineffective.

FDA and industry have agreed on the need for an internal control group. For example, the ICH E10 choice of control group in clinical trials

states, "Inability to control bias is the major and well-recognized limitation of externally-controlled trials and is sufficient in many cases to make the design unsuitable."

It is always difficult, and in many cases impossible to establish compatibility of the treatment and control groups, and thus, to fulfill the major purpose of a control group. The groups can be dissimilar with respect to a wide range of factors other than the use of study treatment that could affect outcome, and such dissimilarities can include important but unrecognized prognostic factors that have not been measured.

Patients in the Nix-TB trial were compared to similar patients previously treated at one of the same clinics used in the trial to try to demonstrate that this drug combination was superior to combinations without any of these drugs. These patients were treated with typical care. If they had been enrolled in the trial and randomized to treatment, we might know if this drug combination led to better outcomes for the patients or not.

It is important to note that bedaquiline was approved for MDR TB, based on a trial that had a success rate of 78 percent when it was added to older drugs, which was significantly better than the success rate of the older drugs combined with placebo. However, this bedaquiline trial also reported more deaths in the new drug group. This possible increased risk would not have been found without a comparator group.

The increased risk for deaths also highlights the problem of the use of surrogate endpoints, sputum cultures in this case. Unless sputum cultures can predict survival or other endpoints that are meaningful to patients, they should not be used to justify FDA approval.

In summary, while new treatments are needed, it is impossible to accurately determine the risks or benefits of a new TB treatment without randomized trials or even matched control groups within a trial. As clinicians and patients, you deserve to know the benefits and risks before deciding which treatment to use. This information

is needed before approval, not years later. Thank you.

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.

MR. HARRINGTON: Hi. Good afternoon. My name is Mark Harrington, and I'm from the Treatment Action Group in New York, and I'm also affiliated with a global community, tuberculosis community advisory board. I have a disclosure to make, which is when we had a meeting with the sponsor regarding this NDA, they provided us with Dasani bottled water. We provided our own transportation and lodging.

As a long term member of the HIV and TB advocacy community, it's an exciting and a little bit of a daunting occasion today. It's been seven years since we last reviewed a TB drug at this group, and I would hope it wouldn't be seven more years before another TV drug or combination comes to this group.

I'm also concerned that in some ways, the results of this NDA are exciting, but as the previous couple speakers indicated, it's also kind of hard to interpret them, given the rapidly evolving treatment landscape. I think everyone in the room agrees that we urgently need new and better treatments for all forms of TB.

With that said, and as the previous speaker indicated, the whole advances in tuberculosis treatment since 1948 have been built on a foundation of rigorous and randomized-controlled trials, going back to streptomycin. Back in the mid '90s when we had an advance in the treatment of HIV -- which I guess that slide didn't make it on -- no one would have brought a protease inhibitor to the FDA in 1987 and used an historical comparator to how HIV was being treated in 1987 without rigorous and randomized-controlled trials.

I think some of the questions that the community have been really trying to think about is how do we determine the contribution of pretomanid to this regimen? That question's come up several

times before.

Do we have a rigorous sense of what was happening in the non-Nix trials that included pretomanid? We didn't really get a complete readout of the results from the STAND trial, which was in DSTB and where there were some excess early deaths, and where one of the background documents stated that noninferiority was not shown. So I'm a little concerned that we didn't see the whole dossier for the drug and how people did in the other studies.

We were also concerned about some of the other issues that you can see up there that I'm not going to read aloud, but I think the historical control issue is one of the most concerning because, as a couple of previous speakers indicated, the treatment for M and XDR TB results have improved over the last 10 years. When Gandhi et al. reported on XDR TB in South Africa in 2006, the death rate was 100 percent and now it's gone down quite significantly.

So it's not clear to us that the -- the cure

rates are really impressive in the Nix regimen, but they're also really impressive in the Belarus study that was shown at the union last year, about 87 percent completed treatment. It was impressive in a couple of the recent studies from South Africa, in programmatic settings where they're using bedaquiline and linezolid.

I think one of the hardest things to figure out is the duration because the duration was very, very impressive in this study. The other studies didn't look at short durations of TB treatment. But I think some of the really key questions for us all to think about are how are we going to move forward in understanding better how to use these drugs and what would be the role of pretomanid in a country regimen, given that, for example, another drug in the same class is already approved in some places; delamanid.

We have no idea whether there's any difference between those two drugs. It would be very important to find out for all those indications. We still don't really know the right

dose and duration of linezolid. We need to know about how to use pretomanid in combinations in children.

Think about how we're going to use this drug in the U.S., where there's really not that many cases of XDR TB. We still would like to have more options for the treatment of hard-to-treat cases of drug-resistant TB in the U.S. It would be nice if the FDA would ask Otsuka to come back and bring some more delamanid data. It would be interesting to see what would happen if they asked Johnson to come back and bring some updated data on bedaquiline.

Certainly, it would be interesting to think of what would happen if they asked Pfizer or somebody else to come back with some data about linezolid because we're being asked to approve all these drugs, but really we're being asked to approve one drug, and it's the one drug about which we have the least information.

So in closing, I would just suggest that we hope this isn't a precedent to abandoned

randomization and controls in the treatment of all forms of tuberculosis. Thank you very much.

Clarifying Questions (continued)

DR. BADEN: Thank you, and I'd like to thank all of the open public hearing speakers for their comments, as the committee takes your input quite seriously.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will continue with our discussion from before lunch. We'll start with -- I know the agency had a clarification they wanted to provide.

DR. McMASTER: Hi. I'm Owen McMaster, the pharm-tox reviewer for pretomanid, and I just wanted to add a clarification regarding the question Dr. Hilton asked earlier. We expect that the applicants conduct reproductive toxicology assessments consistent with ICH guidelines, and in

this case, the applicant has conducted the studies requested under the ICH.

In this case, the ICH guideline is ICH S5(R2). The duration of the pre-mating dosing in males is predicated on the information that the sperm maturation cycle last 63 days. On the other hand, the estrous cycle lasts 4 days in rats. That drives, in this case, the sponsor's study design, which was to dose the male rats for 70 days prior to meeting, whereas the female rats were only dosed for 2 weeks prior to mating.

So I just wanted to clarify that -- and I will quote ICH here -- "provided no effects have been found to preclude this, a pre-mating treatment interval of 2 weeks for females can be used." I just wanted to clarify that the applicant has, in this case, performed the studies consistent with ICH guidelines. Thank you.

DR. BADEN: Thank you. We'll resume with discussion with the applicant, Dr. Everitt. I will start by allowing you to provide any follow-up from the morning's discussion that can clarify things

for the committee.

DR. EVERITT: Yes. Thank you. I think most of these focus on some of the hepatic discussions, and then if I've missed something, let me know.

One quick clarification was there was one about a patient that had ALT elevation over 3-fold at baseline and why was that patient let in. We checked back on that, and there was a patient who at screening fulfilled the enrollment criteria, ALT and AST, less than 3-fold, but then at baseline actually had an ALT of 6-fold, the upper limit of normal, and an AST of 4.4. So again, it was a difference between screening and baseline.

Let me show slide AA-2, and this had to do with patients interrupting the regimen. First of all, just let me remind you the choices and the way it was. Eight patients interrupted the regimen based on hepatic adverse events. When they interrupted, they had to interrupt all 3 drugs, and then when they resumed, they essentially had to resume bedaquiline and pretomanid at the same dose. No dose adjustments were allowed at all for

bedaquiline and pretomanid, and then they may or may not resume linezolid. Then there was a question of how long into the dosing were the interruptions, so let me show you here.

This is an addition to a slide I showed. The first column is the duration of days interrupted. You saw that before. We've reordered it now by on what study day did they first interrupt dosing for hepatic adverse event? The minimum was 14, and it's ordered up to 124. So it's distributed quite a bit through the 6 months, the 26 weeks of dosing.

The two highlighted slides are the same patient, so it was 9 interruptions in 8 patients. The one had another interruption at day 124. When they resumed, there were only 2 that actually resumed with a lower dose of linezolid, which may have been because of a neuropathy or an anemia, but everybody resumed with the full 3-drug regimen, and again, everybody was able to finish a complete 26 weeks of at least the bedaquiline and the pretomanid, to complete in spite of these

interruptions.

Then there was a question about I think the STAND study relative to our whole safety database. Again, let me remind you, STAND was a study of the pretomanid with moxifloxacin and pyrazinamide regimen, so it had pyrazinamide, where as the BPaL regimen didn't.

That study was the first time that we really saw a signal of concern for ALT elevations or any hepatic events, and we did do a thorough review of the whole program and reviewed it with a data safety monitoring committee and the FDA. I think you were interested in seeing ALT and liver function data specifically in STAND.

I'll show you the so-called PAMZ regimens in STAND since you asked about it, ALT values, AST, and total bilirubin, at know, different cutpoints, 3 to 5-fold, 5 to 8-fold, and greater than 8-fold at the upper limit of the reference range ALT, AST, and bilirubin.

During that study and continuing, we really looked broadly across our whole development program

to be very careful, and we continue to monitor hepatic safety very carefully and would propose that going forward, just as the bedaquiline label requires hepatic safety to be monitored.

Let me go back, again, to this slide, which, again, was in my main presentation. This looks across the whole program at the most concerning cases of the potential so-called Hy's law cases. These are the elevations of ALT or AST greater than 3-fold the upper limit of normal and total bilirubin greater than 2-fold the upper limit of normal, which has been known to raise concern for severe subsequent liver disease.

So again, in the pretomanid alone groups for only 2 weeks, but up to 2 weeks, there were no cases. The pretomanid combinations include the STAND patients. There were 4 patients out of 633, or 0.6, with 124 patient-years of exposure, a lot of exposure, compared to, then, patients randomized to HRZE drug-susceptible patients with somewhat fewer patient years of exposure. 50, where we had Hy's law cases or 1.3 percent of the total.

In Nix-TB, we've talked about the two potential Hy's law cases, which that's the regimen we're considering here. And under adjudication by our external experts, they felt one was not truly a Hy's law case and one was a potential, and that was in 52 patient-years of exposure. So that's kind of the picture across the trial.

I believe of the clarification questions, that was the new information I had to provide. So I'll stop at that and see if there are other questions.

DR. BADEN: Thank you.

We have a series of panel members who indicated questions from this morning. I will go down the list. If your questions have been answered or are no longer pressing, we can move efficiently. I want everyone to be mindful of time so that we can ask questions succinctly and get succinct answers to get all the information we need. We ended with Dr. LoBue.

DR. LoBUE: My question was about drug susceptibility testing. You gave some preliminary

information about where you thought the cutpoint should be. Is there a plan on how this would be standardized if this were approved? Because it's going to be critical for labs to know; and then availability of the testing materials.

I believe in the meeting materials, there's some information about plates that might be available or an appropriate formulation of the drug that can be used for drug susceptibility testing.

DR. EVERITT: Yes. What we validated across multiple labs is testing using liquid culture, the MGIT, the Becton Dickinson MGIT approach looking at MICs, and we're proposing a cutpoint of 1 microgram per mL; That would be in the MGIT.

Let me turn to Dr. Juliano Timm, our microbiologist, to say a word about plans going forward, how we might provide labs with material using that cutpoint if the agency agrees that's the appropriate cutpoint.

DR. TIMM: Juliano Timm again. Yes. As Dr. Everitt has just said, we used the metric system, and as you probably know, it's a system

that has been used in many countries. Basically, the drug just has to be diluted and added to tube, MGIT tube, and a battery of concentrations tested.

That's our plan forward, and we haven't discussed the details of the surveillance program with the agency, so I cannot go into the details of how many countries or how many isolates, but the duration will be 5 years.

DR. EVERITT: And we'll be making plans for how to provide the material. Again, you don't need multiple dilutions. If it's agreed on one cutpoint, albeit in surveillance labs, we'll do MICs.

DR. LoBUE: Most labs do not do MITs, typically, TB labs, for this maybe because they're specialized labs. We've had some issues with being able to get the actual preparation of the drug that's easy to use. My lab people say they don't want to be crushing pills or breaking open capsules.

DR. EVERITT: We'll address that carefully.

DR. LoBUE: So it's a problem.

DR. EVERITT: Sure.

DR. BADEN: Thank you. Dr. Gripshover?

DR. GRIPSHOVER: [Inaudible - off mic] -- mine has been answered.

DR. BADEN: Dr. Kartsonis?

DR. KARTSONIS: [Inaudible - off mic].

DR. BADEN: You have been silenced.

DR. KARTSONIS: I had two quick questions for the sponsor. The first was I was intrigued to see that it took you 2 and a half years to enroll basically a hundred patients into the clinical trial. Was that consistent with your expectations or was that more than you expected?

My second question to you is, I thought it was also fascinating to see that all the susceptibility results for the 3 drugs, from the patients that were included in the study, there was only 2 subjects who had elevations in bedaquiline that were above the MIC of 1, and I was just curious if those two patients succeeded or not.

DR. EVERITT: Yes. We were pleased with the enrollment. We weren't quite sure. We did find

early on, again, with the desperately poor outcomes that were available, the investigators and patients were anxious to participate in a new trial with something with a lot more hope. So it moved along relatively well, and the third site was added on somewhat late. As you saw, it only contributed 12 patients.

Yes. The 2 patients, the patient that had an MIC for bedaquiline at baseline of 4 micrograms per mL, was successful, had a favorable outcome. The one at 2 was a patient who, unfortunately, died early. She actually had severe COPD and a lot of other underlying problems, and developed a pneumonia and died.

DR. BADEN: Thank you.

Ms. Lupole, do you have a question from this morning?

MS. LUPOLE: [Inaudible - off mic].

DR. BADEN: I think we have -- I'll go with the microphones that are lit, Dr. Le and then Dr. Moore with questions.

Dr. Le, do you have a question?

DR. LE: I don't have anything.

DR. BADEN: Good. Dr. Goetz?

DR. GOETZ: I don't have a question. I think all my questions have been answered with satisfaction.

DR. BADEN: Dr. Ellenberg, a question from this morning. Great. Dr. Ofotokun?

DR. OFOTOKUN: Just some clarification about the resistance profile of pretomanid. I know from the clinical data, only 2 individuals actually developed a slightly higher MIC following exposure. I was wondering if you have either in vitro or animal studies of resistant profile of this drug.

How quickly does TB develop resistance to this drug? Do we have any in vitro data of that, that is the genetic barrier to resistance for this drug?

DR. EVERITT: Yes. First, just to clarify, actually no patients in Nix developed resistance to pretomanid itself or had baseline resistance. It was just the one who developed a resistance to bedaquiline. But speaking to the preclinical, let

me call on Dr. Anna Upton, who is closest to our preclinical information, to speak about potential for resistance developing in animal studies, what we know about that.

DR. UPTON: Sure. Hello. I'm Anna Upton. I'm the senior director of biology at TB Alliance. First, to the question about in vitro data, there have been a number of studies conducted to look at frequencies of resistance and the underlying rate of resistance in vitro to pretomanid.

The range of values for the frequencies of resistance are in the order of 10 to the minus 7 to 10 to the minus 5, which is in the same range as that of isoniazid. In studies where both of the drugs were looked at, at the same time with the same methodology, we saw that for pretomanid, the rate of persistence was 5 times 10 to the minus 7, and isoniazid was about 4.5 times 10 to the minus 7. So isoniazid has a little bit higher rate of resistance just to give you some context. Rifampicin and bedaquiline, for example, have a little bit of a lower rate of resistance as does

linezolid from the literature.

In animals, we have looked in mouse models, where we have around 10 to the 8 CFU in the lung at the beginning of treatment. For pretomanid, as for bedaquiline and isoniazid in similar studies, it is certainly the case that after 8 weeks of monotherapy treatment, we observed that the CFU remaining in the lung do contain a substantial proportion of resistant colony bacteria.

However, that is the case sometimes when a combination of only 2 drugs are given together for 8 weeks, for example. But in the case of the BPaL regimen, when we dose those 3 drugs together for 3 months to the mice, we saw permanent cure, and we did not observe any resistance emerging to any of the 3 drugs given.

DR. BADEN: Thank you. Dr. Green?

DR. GREEN: During the public comment period, we heard about newer data in terms of successful trials for XDR and MDR, so thought I'd go to the agency, but I could also go to the sponsor. We have the literature review, which

includes articles as recently as I think about 2016, none of which seemed to get those high rates.

So are there published data that validate the public comments, talking about high rates of success with the newer drug regimens but not including the drug under question today or all three of the drugs combined, as we're being proposed to offer opinion on?

DR. EVERITT: The literature review specifically excluded results from patients treated with bedaquiline or linezolid, so that's why you don't see some of those newer data there. There are some smaller published studies, for instance -- I'm not sure how to pronounce the author's name, but the 2018 article from which the matched historical controls were drawn had a case series of patients treated with pretomanid or linezolid, as you saw, a fairly high success rate of 65 percent, and then there are two others smaller articles of linezolid, where you're again seeing success rates, [indiscernible] regimens in the 65 to 80 percent range; so higher success rates

with bedaquiline or linezolid, but without pretomanid.

DR. GREEN: Can you clarify the background additional drugs in terms of number of drugs and the duration of therapy, and whether or not those included injectable forms as part of their regimens?

DR. EVERITT: Right. I don't have that information in front of me or readily accessible, other than to say, kind of in general terms, that it was given for a lot longer than 6 months. I can actually show that again. This was the one I think you're referring to, if we're allowed to put it up. This was out of Cape Town, again, the same place that was our highest enrolling site, where it compared the pre-bedaquiline era to the post-bedaquiline era, and that showed the 66 percent favorable outcome versus the 13 percent previously.

You can see it was a median at 8 drugs, a lot of the older drugs. But with bedaquiline, they all got bedaquiline; 81 percent got levofloxacin,

and it was done over a 24-month time period, and these were all newly diagnosed patients.

Dr. Conradie actually was co-author of another article coming out of South Africa showing fairly high favorable rates and actually much lower mortality in the post-bedaquiline versus -- maybe just comment on this relative to the Nix-TB results.

DR. CONRADIE: The first thing I'd like to say is I am not aware of any randomized-controlled trials for the treatment of extensively drug-resistant TB. While there are ongoing clinical trials for MDR, there are no trials that are currently -- in fact, most patients are excluded once the diagnosis of XDR is made. In South Africa, about a third of patients with rifampicin resistance have resistance to quinolones as well.

In terms of our published data, we have seen impact of bedaquiline on the mortality rate in patients given it as a drug. We started off with original trials that were presented with a

mortality imbalance, and we had a slow compassionate access program, and now bedaquiline is given to all patients who have resistance to rifampicin, irrespective of their quinolone or even their INH status.

We've seen a reduction in mortality, and it's published in the Lancet respiratory journal under the name Enjaka [ph]. He's the head of our MDR directorate. We've seen a reduction between 40 to 60 percent in mortality, which is a pretty hard endpoint. So while I agree with the other people who've addressed the stage, the treatment of MDR and XDR is getting better. This is still an outlier. It's still better than that.

DR. EVERITT: Again, this is a 3-drug, 6-month, all-oral regimen.

DR. BADEN: So we have a technical difficulty, and the microphones are going to need to be reset. While the microphones are reset, we will use the old fashioned microphone. I see Dr. Goetz and Dr. Ghany both have follow-on questions.

DR. GHANY: Thank you. Mark Ghany. Just to continue along this line of questioning because I think this is really critical data for the committee when we come to make a decision. Can someone really please provide what is the expected cure rate now with an bedaquiline [indiscernible] linezolid --

DR. BADEN: Linezolid.

DR. GHANY: -- linezolid regimen, since that's now the current recommendation in the latest WHO guidelines? Can someone please let us know? This is really important because we need to know what can be achieved currently, not from historical data.

DR. EVERITT: No. I would refer to the article that was just shown. That's the most recent and most relevant. It's in the same location, same place, same kind of treatments, showing 66 percent. But again, that's a 24-month treatment with a median of 8 drugs

DR. GHANY: But what we've heard from the testimonials that there have been response rates of

80 percent or more. Is that correct?

DR. EVERITT: I would disagree with that, certainly for XDR TB in a rigorously evaluated trial.

Let me ask Dr. Neil Schluger, who is familiar with a lot of the most recent research and separate from the TB Alliance, to respond.

DR. SCHLUGER: Hi. I'm Neil Schluger. I think perhaps some of the -- I don't want to say confusion; maybe it's too strong a word. Let me try and clear this up. The most recent large MDR TB trial that was published was the so-called STREAM trial in which patients with multidrug-resistant TB were randomized to the WHO recommended, 18 to 24-month regimen versus the so-called Bangladesh regimen, which is a 9-month regimen for the treatment of MDR TB.

That regimen relies quite heavily on a quinolone and includes an injectable. In that trial, both arms -- 79 percent -- [inaudible - mic fades]. However, as we pointed out this morning, remember that by definition, the patients we're

talking about in the Nix-TB trial would not have been treated with those regimens because they are resistant to quinolones and injectables. So those are our good results for MDR TB, but those patients are different from the patients that were in the Nix-TB trial.

DR. EVERITT: That's the most recent large randomized clinical trial. As Dr. Conradie said, there are none for XDR TB.

DR. BADEN: Thank you. Does the agency have any thoughts on this comparator issue given the bedaquiline issue raised?

DR. NAMBIAR: I think, as was mentioned in the morning, the trial was designed many years ago, and we've tried to put together -- the applicant has put together a summary of the available information. So I think what we're asking for is really your opinion based on the information we've provided in the meeting background packages.

DR. BADEN: Thank you. Dr. LoBue?

DR. LoBUE: I think for the U.S. this is a difficult question because we have so few XDR TB

patients, and programmatic data is not the same as clinical trials. From what I can tell from our programmatic data, I would say I think it's reasonable to say that probably that 65-70 percent outcome is attainable in the U.S. with the best treatment available for XDR TB. I don't think 90 percent probably is.

DR. BADEN: Thank you. Dr. Goetz, did you have a follow-on?

DR. GOETZ: Not on to this particular topic, but on to a previous topic.

DR. BADEN: Please.

DR. GOETZ: The discussion of the animal sterilization data prompted me to remember something. The dosage in the animals I believe, provided in the background materials, was a hundred milligrams per kilogram, which is -- obviously we dose animals differently than we do dose people. But what do we know about serum levels in those animals? The relevance of those data would obviously depend upon what drug concentrations are being achieved, and I wonder if that issue can be

addressed.

DR. EVERITT: Yes, we do have something we can show for that; Dr. Anna Upton who works with our animal data.

DR. UPTON: Thank you. Anna Upton, senior director of biology at TB Alliance. For the most pertinent studies, which are the ones presented today where pretomanid has demonstrated contribution to the regimen, we chose two different doses to study, where we considered the mouse PK, the human PK, and also what we know about the PKPD, the driver of efficacy, and put that together to try, as best we could, to match the doses to make them as relevant as possible to the 200-milligram dose that's used in Nix-TB.

If I could show the slides, first of all, with the two efficacy studies? Thank you. I want to let you know that in addition to the slide on the left-hand panel -- sorry, the graph on the left-hand panel there, which Dr. Everitt showed earlier, where pretomanid was tested at a hundred milligrams per kilogram and at both the 4- and

8-week time points there, the CFU in the lungs have been reduced significantly further than any of together 2-drug regimens shown.

We also tested the regimen with pretomanid at 50 milligrams per kilogram, a half dose on the right-hand panel. Under the 8-week time point there, the difference between the 3-drug and 2-drug regimens is also significant. Those are the two doses that I'll talk about when mentioning the PK.

We had conducted, several years previously, a PK study in same mouse model and were able to show that percent time over MIC [inaudible - mic fades] in the plasma was the most important driver of efficacy with the AUC over MIC being the second most important. We considered those parameters when we were looking to match to the clinical dose.

What I'd like to show you here is a summary in humans at 200 milligrams under fed conditions. Those are the conditions of Nix-TB trial. The percent time over MIC was actually about a hundred percent under those conditions in the clinic, and the [inaudible - mic fades] being the AUC over 24

hours was 2.4 micrograms per mL.

In the mice, we actually dosed 5 days out of 7 per week for practical reasons. In the table, you see the 2 doses where we demonstrated the [inaudible]. If we average over 7 days with dosing for the first 5, the average is 2.3 or 4.7 for those 2 doses. But the time over MIC actually didn't achieve what we achieved in the clinic.

We weren't able to perfectly match both because the curve shapes are different in mice and humans, as you alluded to, but we felt this was a reasonable match to the clinical dose, and we do see a contribution at both of those doses.

DR. BADEN: Thank you. Dr. Follmann?

DR. FOLLMANN: This is sort of an add-on to what was discussed earlier about the comparator group; should we be thinking of a bedaquiline-linezolid comparator or a non-bedaquiline non-linezolid comparator? One thing the sponsor said was that when the study was being designed, the bedaquiline and linezolid was not really in play as a comparator for a randomized

trial had they chosen to do one.

So had they chosen to do a randomized trial, it would be the triple therapy we see versus a non-bedaquiline non-linezolid comparator. Would we be wondering about what the right comparator would be under that scenario? Should we change our minds about the right comparator as new drugs come on board and say that study is old and the comparator was bad, so we're going to discount the randomized study?

Maybe it's a fair question, but it's not, to my mind, such an easy one to say that we should automatically have bedaquiline-linezolid as the comparator.

Questions to the Committee and Discussion

DR. BADEN: Seeing no further questions, then we can move to the question at hand and any discussion among the committee, which to some degree, Dr. Follmann, you were posing, as to how to think about the challenge before us.

So we'll now proceed with the questions to the committee. I'd like to remind the public

observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. I also do want to thank the agency support staff for correcting the microphone and voting problem in mid-flight, and that's appreciated; so thank you.

Before we go to the voting, are there issues for discussion amongst the committee about data and information presented to us that are not clear, that we can help each other weigh the uncertainty? Dr. Follmann?

DR. FOLLMANN: This is more a question I guess to the FDA, but it has to do with the design and the evolution of this study. This was designed as a one-arm study, and I guess it was designed to have a 50 percent bar based on a meta-analysis perhaps. Then what is the role of the matched control comparator that the sponsor talked about? Was that an integral part of the design or was it more one arm that was going to use the 50 percent bar?

That's part of what I had to say, the fundamental design. Then also, it seemed as -- the FDA mentioned that the design was intended to enroll 200 patients, then switch to a hundred, and what was the thinking behind that? Usually in trials, we don't say things look good, so let's quit.

So anyway, just a little more about the fundamental design and then how the change in design evolved.

DR. RUBIN: I'll take a shot at trying to answer this. I wasn't involved at the design stage, so maybe my colleagues can correct me if I'm wrong. But my understanding is that the comparison with the 50 percent threshold came first, and then later the matched historical comparison was added as a supplemental analysis that the applicant could provide to shed more insight into efficacy.

Now, on the early stopping issue, it was designed as a 200-patient trial. The statistical analysis plan did have built-in stopping for futility, but it didn't have any built-in stopping

rules for efficacy. My understanding here is that it was nevertheless stopped due to the applicant's view that the success rates were so overwhelmingly high, that efficacy had been demonstrated, and that patients shouldn't instead continue in Nix-TB, and future patients should be studied in ZeNix to refine the linezolid dosing.

DR. BADEN: And that was done with the DSMB?

DR. RUBIN: There was a DSMB.

DR. BADEN: The DSMB gave recommendations in accordance with what Dr. Rubin just described?

DR. EVERITT: Just to clarify, the DSMB was really watching over safety, not making a decision of making a change for efficacy. As Dr. Rubin had said, when the agency agreed we had such -- well, with the data we had, which we saw overwhelming efficacy, that we would file a new drug application, once the ZeNix trial was ready to enroll, we switched to enroll in that. It happened to be we were at 109 patients then to direct future patients --

DR. BADEN: How did the DSMB weigh in on

this issue?

DR. EVERITT: On the issue of?

DR. BADEN: Stopping for efficacy. And it may be that they had no way in. I'm okay if -- I'm just trying to understand --

DR. EVERITT: They really didn't -- no, they didn't weigh in. They did raise any safety concerns. They were being very --

(Crosstalk.)

DR. BADEN: So they commented only on safety, not on efficacy.

DR. EVERITT: They really commented only on safety.

DR. BADEN: That's what I was trying to understand. Thank you.

Dr. Moore?

DR. MOORE: I'm just going to mention, I think, if I'm not mistaken -- and maybe the agency can help me with my recollection on this. But several years ago, this committee was tasked with -- was asked the question about whether trials of XDR TB drugs should be held at the same standard

as previous -- held to the original standard, which was relatively a short follow-up knowing full well that these patients have to be treated for two years, and you don't really know whether they're going to relapse for quite some time. So I think that played a significant in the trial design for this drug, and that may explain one of the things they were seeing.

I guess that's really all. The only other issue really that came up with that particular discussion was the ethics regarding doing trials with this particular agent, this particular organism, because the analogy of things like Rocky Mountain spotted fever, we know that doxycycline is curative, and we also know that it's a highly fatal disease.

So how do you come up with ethically designed trials with good comparator arms? It's something that just simply can't be done.

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

DR. GRIPSHOVER: I was just going to ask, is

that how the 45-patient cutoff also came? Is that when you first saw advocacy and then went to the FDA to agree? Because that also seemed -- you went from 200 to 109, but at 45 already, that was the first data cut for efficacy.

DR. EVERITT: We had prespecified to do an assessment actually every 15 patients, so it was about when we had the full data on 30 patients, we discussed with the FDA and made the decision we would move forward with what would be at least 45 patients for the initial and NDA. By the time we got the whole NDA together, we were able to write an addendum report which had the 81 patients that were followed to the primary endpoint.

DR. BADEN: Thank you. Any other discussion?

DR. ELLENBERG: I have a question for the FDA. If there is another promising new agent that looks like it might be useful in XDR TB, what do you think would be the optimal way to evaluate that for a possible drug approval? What would you do with a new drug?

DR. NAMBIAR: Let me try to answer that hypothetical. It really depends. If one can come up with a reasonable comparator regimen and one can demonstrate superiority, that's great. If the comparator regimen that we decide is one that has shown a large treatment benefit, then potentially one could design a noninferiority trial with appropriate margins. It would really depend on what is available at hand at that time.

DR. ELLENBERG: But you would be thinking of having a randomized control group.

DR. NAMBIAR: There's no question about that. We would always like a randomized-controlled trial. If that's doable, I think that's always the preferred option. I think one has to go back to when the study was conceived and thought about 4 or 5 years ago. At that time, this was designed as a single-arm trial, and then over time, the results became available, and it showed it could offer benefit to patients where there is really an unmet need. I think we came to this decision that we might be able to look at data, even if it's got its

limitations.

If we are designing a trial from the get-go, yes, we would do our best to design a randomized controlled trial. But coming up with a comparator arm at that time in a treatment population, which is XDR treatment intolerant and treatment refractory, I think it was very difficult. So that's how the single-arm trial was designed.

DR. ELLENBERG: You had [inaudible - off mic].

DR. BADEN: Your microphone's not on. Now you're on.

DR. NAMBIAR: Bedaquiline was approved I think in 2012.

DR. ELLENBERG: 2012, and this study was begun in 2014.

DR. NAMBIAR: Right, but there's one thing about when the product is approved, and when there is an uptick, and when it becomes part of treatment guidelines. So it's just in the last -- I don't know when. I may not have the dates correctly, but it's in the last few years that there has been

increase.

It was mentioned by the TB expert from South Africa how it has become a lot more part of the standard of care. There are a lot of issues around concerns with bedaquiline and increased mortality that was in the randomized-controlled trial.

The WHO treatment guidelines, was it 2018, I think, when the revised treatment guidelines included bedaquiline. This is something that we struggle with, not just in the field of TB. Treatment guidelines, when they've made these recommendations, they're also not based on very sound data. It's based on a lot of observation studies, and then that becomes the standard of care.

So as was mentioned, really, the most recent randomized-controlled trial that we have any information is on the STREAM trial, which is part 1. The rest of the STREAM trial is still underway.

DR. BADEN: Dr. LoBue?

DR. LoBUE: This is kind of really the crux of the question because bedaquiline, we're now all

pointing to as this is now standard and it gives these good results. As I recall, at the time bedaquiline was approved, the trials were randomized, but I believe they were phase 2, and we didn't have patient outcomes, it was all about culture conversion while on treatment, and there was greater mortality in the bedaquiline arm. So it seems like what is the standard that we're really looking at here?

DR. BADEN: My memory is similar to yours, that it was quite controversial in the first few years of bedaquiline emerging, with different camps believing and not believing. So it wasn't an even standard, even at the time of approval.

DR. NAMBIAR: The approval of bedaquiline is under subpart H. It was an accelerated approval based on the surrogate endpoint, a sputum culture conversion. And the final confirmatory trial is still underway.

DR. BADEN: Dr. Goetz, was that your comment?

DR. GOETZ: That was exactly the comment I

was going to make I think in the room at the time.

DR. BADEN: Great. Dr. Moore, I think you're just signaling me with your card, unintentionally.

DR. MOORE: [Inaudible - off mic].

DR. BADEN: Yes.

Since I think I see all discussion that I'm aware of has occurred, we can now move to the question.

We will be using an electronic voting system for this meeting. Once we begin to 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 our vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote 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 questions have been answered or discussed.

We have one question. I will read the question. We'll then see if there needs to be any clarifications, and if not, we'll then proceed to vote.

Has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of pretomanid as part of a combination regimen with bedaquiline and linezolid in adults for the treatment of pulmonary extensively drug-resistant XDR or treatment-intolerant or nonresponsive multidrug-resistant MDR tuberculosis. If yes, please provide any recommendations concerning labeling. If no, what additional studies/analyses are needed?

Are there any questions about the question?

(No response.)

DR. BADEN: Then let's proceed to voting.

(Pause.)

DR. BADEN: They're missing one vote. Everyone please just re-enter your vote.

(Voting.)

LCDR BONNER: For the record, 14 yes; 4 no; zero abstain.

DR. BADEN: We will start with Dr. Le. Please state your name, your vote, and any response to the follow-on information for the agency.

DR. LE: My name is Jennifer Le. I voted yes for

this. While the study design lacked both robust control and randomization, the condensing outcomes data demonstrated efficacy with some toxicity there. As such, I voted yes for the combined 3-drug regimen for the management of XDR and MDR TB

I have one recommendation for the labeling. While the presented data were consistent with the ICH guideline, there still appears to be some preclinical data suggesting potential harm on female fertility, effects on the embryo, fetus, and

lactation. So I highly recommend improve, though, in the preclinical studies as well as initiating clinical studies pertaining to this.

Other recommendations relate to future studies that I would recommend. The Nix-TB study related to approval conducted in South Africa, and it lacked evaluation of Asian populations. Based on WHO 2016 data, at least one-third of all MDR TB cases are from Southeast Asia. If not in a formal clinical trial, I recommend at least evaluation of some clinical experience in real-world situations.

Related to this data from Asian population, it may shed some light on the clinical implication of OAT3 transporters, as Asians appear to have low-frequency, reduced function polymorphism, resulting in reduced drug clearance of the substrate drugs. Also, I agree with the statement from the treatment action group that more clinical data, especially for pediatrics and pregnant woman, would be needed in this area.

DR. MOORE: I don't have a whole lot to add. As stated before, the decision regarding

bedaquiline approval was contentious and a very difficult decision to make because there was a real dearth of clinical data. We have that here. It's not perfect because it's mixed in with other -- the drug is mixed in with other drugs, and as Dr. Weina said earlier, there are sufficient concerns about off-label use as there were with bedaquiline, specifically for non-tuberculous mycobacteria.

Given the extreme need, the high mortality, and the lack of available treatment options, I think it's reasonable to -- I voted yes because I believe that the sponsor did in fact demonstrate what was available to demonstrate efficacy and reasonably safety.

My only recommendation for this drug, which would be the same that I made with bedaquiline, is just, as a caveat, that it can only be used in combination with other drugs, with those other drugs, and only for XDR TB patients until other clinical data are available. That was the same recommendation that was made for bedaquiline, and that stuck.

DR. BADEN: Dr. Moore, please state your name.

(Laughter.)

DR. MOORE: I think you just did it for me.

DR. BADEN: Please state your name.

DR. MOORE: Sorry. This is Dr. Tom Moore.

DR. BADEN: Dr. Green?

DR. GREEN: Michael Green. I voted yes. While design limitations, particularly the absence of concurrent controls, could potentially impact the levels of confidence in the data, the dramatic success achieved with the proposed regimen, including those on reduced or discontinued linezolid, in my assessment, this situation meets regulatory rules for exceptions from concurrent prospective controls and overcomes any hesitancy I might have.

Said succinctly, 81 to 95 percent cure rate for XDR warrants expedited approval as does the durability of cure demonstrated in the follow-up to date. While other regimens using linezolid and bedaquiline and may be improving outcome, these are

done in combination with many drugs for longer periods, with potential exposure to worse toxicity.

I'm about to emphasize my disappointment with the lack of cultures on autopsies for patients on trial, as this limits our understanding on the likelihood of emergence of resistance when used in this setting and the impact of that resistance on clinical outcomes. This would be especially true for those patients left on 2 drugs when linezolid is discontinued or when its dose is reduced.

The safety signal seems acceptable and appears mostly attributable to linezolid. This is especially true given the outcome of these patients and the side effect profiles of current nonsatisfactory regimens.

I do have concerns about potential off-label use in other combinations and for other indications, and would encourage the label to emphasize this, in addition to mentioning appropriate laboratory and clinical screening, as well as limitations to the use of pretomanid to combination therapy with linezolid and bedaquiline

for XDR and I guess the equivalent.

Postmarketing studies should work to determine the potential emergence of resistance in clinical failures, including relapses in those who die, as well as moving studies into the pediatric population. Thank you.

DR. BADEN: Dr. Ellenberg?

DR. ELLENBERG: Susan Ellenberg. I voted no. As I read this question, it says we are asked whether the applicant has provided substantial evidence of the effectiveness and sufficient evidence of the safety of pretomanid as part of the combination regimen. I have no idea what pretomanid contributes to this regimen. The only evidence that I have seen is study in mice.

If we only could approve regimens, drugs, based on mouse studies, we would have many thousands of treatments on the market now, most of which would not work because we know the vast majority of drugs that go into phase 1 on the basis of promising preclinical data never show effectiveness and never get approved.

So I'm very disappointed that there was an agreement to consider this drug on the basis of a 45-patient, single-arm trial. I think there is certainly a desperate need for new drugs, and it's wonderful to have shorter regimens instead of longer regimens. and less toxic regimens instead of more toxic regimens, and it's wonderful to have things that cost less. Those are all great.

I think people in these desperate situations are every bit as entitled, if not more entitled, to have drugs where there is a definitive evidence that they are going to work, and I really worry about going down the road of adding more drugs where we don't have information about whether they actually work, and ending up with people taking combinations where some of the drugs, which may get more and more expensive, may not contribute anything.

DR. BADEN: Thank you. Dr. Walker?

DR. WALKER: Hello. Dr. Roblena Walker. I voted yes. It's some heat coming from Dr. Susan here.

(Laughter.)

DR. WALKER: As I sat here and listened, I can see both sides of it. I did vote yes because, as we all know, as researchers and medical scientists, conducting any study, of course there are always things that we can go back and do. But I do believe that the sponsors did a great job of presenting the information that they found.

I think what did it for me was hearing the testaments from the public hearing and the young man that stated he was 32. So trying to put myself in his shoes as a late 30 something year old African American woman, I couldn't even imagine what not only he had to go through, but his family and his friends.

If there is this drug here in combination that could provide some type of relief to those individuals, that's where I base my vote on. However, I do agree with Dr. Le that future studies need to be conducted to see what effects they have on infertility in women, as well as in children. But overall, good job.

DR. BADEN: Thank you. Ms. Lupole, you're on.

MS. LUPOLE: Patricia Lupole. I voted yes. I have a lot of concerns about this drug, but to me, the need is outweighing those concerns a bit. I would like to see the label address the hepatic function in patients prior to starting this drug. It appears to me to be quite a bit of risk there; nothing substantiated, but just some of the data isn't jiving. So that's my recommendation.

DR. BADEN: Thank you. Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis, and I voted yes. Looking back at the indications for looking at a drug with a historical control, I think that XDR TB actually is one of those conditions that meets that need. So from my perspective, though this is not a randomized-controlled study, and it's not a perfect design nor do we have perfect data, I think that the condition merits, in this situation, a drug being looked at with such a historical control, further supplemented by the match. I think the two

different methodologies, I think for me, demonstrated substantial evidence for a very, very serious disease, that this drug does have a role potentially in the armamentarium.

I would like to echo concern that we don't really know everything we need to know about fertility, both the men and women, and that we really need to get a better sense of the role of the drug in pediatrics. So I think that from the perspective of further studies, it's really important that those are pursued.

From the perspective of labeling as well, I think that it needs to be clear that we voted for a regimen and not for a single drug. This regimen seems, based on our criteria for XDR, to actually achieve the goal on having efficacy, and I'm approving ideally this for a regimen and not just a single drug.

DR. BADEN: Thank you. Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun. I voted no. I'm fully aware of the need for more drugs for XDR and the fact that this is a very deadly, serious

condition. But the question was whether the sponsor has provided substantial evidence of efficacy and safety. At best, I am impressed with the evidence and the data that were presented. At the best, to me, they were preliminary data. You couldn't make such a significant leap from data that is generated from 45 individuals that have completed the study, 109 in total.

I have no problem with the design. I would have loved to see more people for the study to have continued or the 200 originally planned patient population had completed the study, and we have more robust data to be able to assess not just the efficacy but also the safety. So those were my big concerns.

The other concern was it's also a single-country study. All the 3 sites where the study was conducted was in South Africa. Extended drug-resistant TB is global; it's in different parts of the world. We couldn't generalize from a study from just one single country, and then a number of the other concerns that have been raised

regarding the fertility concerns of these drugs, or the toxicity that is so difficult to access just from exposure of the product to just 109 individuals. Many of them are still being followed. We don't even know the complete outcome yet of this study.

I'm definitely impressed with the outcome, the efficacy data from the 45 individuals that have completed the study, but I think, at best, they are just preliminary data. It's not enough for me to be able to conclude that this is substantial evidence of safety or efficacy.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: This is Dean Follmann. I voted no. I had a very hard time on this question, but ultimately I voted no. The reason is -- here's my thinking. If you're going to do a 1-arm study, it has to be super solid. I accept this is an environment where potentially a 1-arm study would suffice, but then when I drill down into all the details of this, there are different things that are troubling to me.

First of all, the bar of 50 percent based on this meta-analysis, if you look at the heterogeneity in those studies and you do an interval for the true success rates that lie between 8 percent and 63 percent, if you do a DerSermonian and Laird confidence interval for the distribution of true treatment effects, this is more inside baseball. But anyway, I think there's a lot of heterogeneity there, and I think the bar of 50 percent is maybe not conservative enough.

Now, Dan and others did mention that in South Africa, it's 22 percent, but I kind of don't like that. You design the study, say here's the bar, and then post facto say, "Well, if we look at the bar this way, it's even better, so don't worry about it."

The matched case control or the matched cohort study, I have some reservations about that as well. Primarily, I think in terms of defining the endpoint, the follow-up would be so different for an endpoint that's ascertained over 30 months in a control group and over maybe 12 or 15 months

in the trial we looked at. That leads to a lot of potential, and gee, what would the success rate really be? They're evaluated differently, so I was skeptical of that.

The sponsor did point out that the death rate was substantially better with the triple therapy as opposed to the historical control, and that I thought was very solid, especially because it was relative to treatment initiation. But then again, I'm thinking, well, yeah, but the thing you looked at, which was favorable or unfavorable, was kind of complicated, so then we looked at death, which is solid, but it's like looking at the second thing. For an 1-arm study, I would want no concerns about any of that, and just say here's what we did; it's super solid; we meet our mark.

Also, it seemed a little, I don't know, unconventional to say that the success rate is so great. Let's stop the study, and that's convincing to us. That was another thing that I thought was a little unconventional and weakened the evidence for it. But like I said, I had a real hard time with

it, and anyway, that's my thinking that ultimately made me tip to no.

DR. BADEN: Dr. Lindor?

DR. LINDOR: Keith Lindor. I voted yes. First, I was pleased that the agency endorsed this type of approach using historical controls for an unusual condition that had a great deal of severity and life-threatening aspects to it. I was convinced about the efficacy of the treatment trial. I think the hepatotoxicity is a potential concern as it always is in new drugs. I was reassured that the elevations in transaminases disappeared when drug was stopped and didn't return when drug was reinstituted.

So I do think that this will be an area of continued follow-up, and as far as labeling, I think it would be important to indicate that the drug was really only tested in patients whose transaminases did not exceed 3-fold the upper limit of normal.

DR. BADEN: Lindsey Baden. I voted yes. I share many of the concerns already raised. I think

that it's easy to look back and say, a different design, these are the data we have, not necessarily the study I'd want. The data are compelling about efficacy. There are many, many, many questions that need to be addressed regarding populations, drug interactions, understanding failures, resistance, susceptibility, fertility, toxicity, and those all need to be systematically looked at, and I'm hopeful that the Global Alliance will systematically generate those data.

I think there are aspects of the study design and study conduct that should be reflected on for future studies that could make the design stronger and the evidence stronger, but overall, I thought the data were compelling about efficacy for a condition for which there are truly limited options.

The retrospectoscope on bedaquiline, it was quite controversial at the time it was approved. There are some who still think that the mortality excess is a concern, so it's difficult to then indict the design about not using that when there

is still controversy in some sectors of the field over the years. So the design can be reflected on, but it made sense at the time that it emerged, given the nature of the condition and the evidence in hand for the therapies available. So I voted yes.

Dr. Weina?

DR. WEINA: This is Peter Weina. I voted no. Always use a drug when it's new. That's when it's going to have its highest efficacy and its lowest side effect profile. Only the clarity of hindsight is going to provide us the perspective we need to allow an understanding of how this drug is actually going to be used or misused if it becomes available to the general medical profession.

Given the potential cost of three new and therefore expensive drugs, there's going to be a temptation to use this off label with other combinations that haven't been studied just because they're available or cheaper.

New drugs are certainly needed. We're teetering on the doorstep of the post-antibiotic

era, but we don't need to rush headlong into potential disaster by adding a new drug to the hit list of XDR TB by not having a good understanding of what we're adding to the arsenal against TB.

The issue to me is the substantial evidence of effectiveness and sufficient evidence of safety of the drug and less the issue as part of a combination regime. I would be more enthusiastic about it if it were a fixed-drug combination than a new drug. That in my mind is camouflaged behind a treatment regime that may or may not be followed if approved.

Lots of new literature available that wasn't even discussed with bedaquiline, even though the combination in the Nix-TB study still seems to perform better than I was able to find even with a cursory PubMed search. As far as additional studies, we need to have a better understanding of how the drug works with TB drugs unless this is actually brought forward as a fixed-drug combination, and for that reason, I voted no.

DR. BADEN: Dr. Ghany?

DR. GHANY: I'm Mark Ghany. I voted yes, mostly for some of the reasons that have already been articulated. This was a challenging decision for me, but I'll tell you my thinking at how I arrived at my decision.

Based on the evidence that was presented, I think the efficacy data and the durability of this regimen in a population that has a high mortality and doesn't have many options, I think that weighed in favor against the risks or the safety concerns. What was somewhat comforting to me was that the ALT elevations do improve over time and that there was no increased signal with a rechallenge.

I do have some recommendations for the agency on moving forward. Some have already been articulated, but I think it's worth mentioning them again. We do need data in other populations, particularly children, pregnant woman, other races. We need toxicity data from patients with underlying liver disease. Many of these patients I'm sure have underlying liver disease, particularly cirrhosis. I didn't hear any evidence of data

regarding safety in these populations, so this is something I think the agency should ask the sponsor to collect.

Another big issue is how to manage liver toxicity in the patients once the drug is initiated. I think the agency is going to have to be very thoughtful in crafting a way to manage liver toxicity. We've heard from the agency that perhaps not recognizing liver toxicity early and allowing the drugs to continue may have contributed to the cases of mortality from hepatotoxicity. So that's I think something that's going to have to be really carefully, thoughtfully articulated in the label.

The concern, obviously, is that these individuals and regions aren't going to have access to health care as we do here, and cases of increased ALT enzyme elevations will go unnoticed, and we might see more cases of hepatotoxicity.

Again, my final recommendation is that because of this and the concerns that others have raised about if this drug is approved and it's used

off label, that there could be concern for additional hepatotoxicity. So I would also recommend that it be put on the label that this drug not be used with other medications until there's more data available. It should only be used as
was tested.

DR. BADEN: Dr. LoBue?

DR. LoBUE: Philip LoBue. I voted yes. I think given the very limited options and difficult options that exist for treatment of XDR TB, the data at this point are sufficient to recommend in favor. Even if the outcomes are better now with the quote/unquote "newer drugs" that was presented with the historical data, what it takes to get those outcomes with the current treatment, which often involves 8 or 9 drugs, multiple injections, is really difficult for patients. So having a 3-drug only-oral regimen I think will be of benefit to both clinicians and the patients.

While safety is a concern, and it's always a concern, I would say there is no such thing as a

safe regimen for the treatment of XDR TB, and any patients being treated with this, whether it be with this regimen or other regimens, has to be very carefully monitored and only be treated by experts in the field.

In terms of labeling, I think it needs to be very clear as people have already said. This drug should only be used as part of this regimen, and there has to be careful monitoring around the toxicities, which have been either demonstrated or potential from the animal studies.

DR. BADEN: Dr Gripshover?

DR. GRIPSHOVER: Hi. I'm Barb Gripshover, and I voted yes. I voted yes because I thought the bedaquiline, pretomanid, and linezolid regimen showed clear efficacy compared to the historical controls. The response rate of 90 percent is at least comparable to some of the more recent post-bedaquiline era longer regimen studies that we've seen, even though it wasn't compared to the data presented by the sponsor.

The specific role of pretomanid in the

regimen is not clear, and I think the label should be very clear that the full regimen is what was studied and studied only for highly-resistant TB; furthermore, used outside of this indication to be in research only until further data on the efficacy and safety of pretomanid with other agents is known.

Regarding things for the label, I think that we need to make sure they note regular monitoring of CBC and LFTs. It should be recommended with guidance included for management of the peripheral neuropathy and cytopenias with linezolid dose reduction. I also think that we need to include guidance for how to deal with transaminitis as well because we don't want to have more people dying. I think maybe a postmarketing registry of adverse hepatotoxicity events should be established as well.

DR. BADEN: Dr. Goetz?

DR. GOETZ: Hi. This is Matthew Goetz. I voted yes. Maybe I'm reading a lot into the words, but I looked at this as substantial evidence of

efficacy and safety, not definitive evidence. I certainly saw substantial evidence of effectiveness here. If we look at the results, whether we look at the full data set or the hundred 120-update, we have 95 percent confidence intervals on outcomes that range from 81 to 96 percent. And I asked myself -- I'm not a statistician, but taking a quasi Bayesian perspective and what I know, I would never have expected that effectiveness.

That effectiveness, when we compare it to the 66 percent -- and this is not a formal analysis with a back of the envelope on my part -- that shows substantial efficacy and warrants my vote. There have been many comments about the safety, the issues about hepatic safety. I'm comfortable that we have sound data. Monitoring needs to be done. We certainly need more studies in people with end-stage liver disease or cirrhosis. We need studies in people with end-stage kidney disease.

We certainly need data -- the package label needs to include information as to how to monitor and dose adjust, and I very much look forward to

the studies which are being done, the ZeNix studies, to give us more definitive data about how to manage linezolid dosage modification and avoid peripheral neuropathy, but in the interim, the field definitely needs guidance. Again, to echo what has been said, I'm voting in favor of a regimen, not in favor of a drug, and I think the package label needs to be very clear about this.

Finally, the regimen, 6 months, it's an advantage to the patient in terms of getting through treatment. It's an advantage of society in decreasing infectivity of the patient and potential transmission of tuberculosis. It's an advantage to the healthcare system in terms of the bandwidth that we have to treat large numbers of patients.

Also, by taking this step, I hope it also affects the bandwidth of industry and other sponsors to conduct studies that build upon what we know now. So for all those reasons, I voted yes.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: I voted yes. I agree with this. I try not to let the perfect be the enemy of

the good, and I think there is substantive evidence of efficacy here. I don't think that the comparisons -- the comparisons are being made to other potential treatment regimens as if those were highly established, validated, universally accepted guidelines.

I find the current guidelines to be not particularly helpful because the disease is uncommon. As someone who's actually helped to treat a couple of these types of patients, it's extremely difficult both for the patient and for the physician who feels helpless. I think while we don't have clear evidence of the role of pretomanid in this regimen, it nevertheless I think now gives one a basis to do randomized-controlled trials. That was one of the problems when this trial was begun, was that the goalpost kept moving.

I have some suggestions. I still have some concerns about what the pharmacokinetics are in actual clinical practice. It's clear that the food intake and so on effects blood levels. As to how this compared with the levels that were seen in the

phase 1 studies, it wasn't completely clear to me. I think that if in fact the multi-agent regimen prevents the development of particularly bedaquiline resistance, it would be important to know what the real-world levels are.

I also think that a large part of the toxicity that I saw here, that would need to be monitored for, may derive from linezolid, and we really don't know what the synergistic effect of the regimen is going to be on the known toxicities of linezolid. Some of that monitoring, particularly for cardiac abnormalities with bedaquiline, is going to be difficult in limited resource settings.

I think, again, some of these things that are not overly emphasized in linezolid is not really used for 6 months in general practice, routinely anyway. So that may be another aspect for peripheral neuropathy, and lactic acidosis, and so on, that needs to be particularly carefully monitored for.

I really think that with a small number of

patients and a rare disease in this country, postmarketing surveillance is going to be critical because I don't think we're going to have the kind of security in the safety of this drug with pre-approval limited studies.

DR. BADEN: Dr. Hilton?

DR. HILTON: I'm Joan Hilton. I voted yes because I think that it's possible to die from a treatment or it's possible to die from a disease. I think given that TB is the greatest killer of people from infectious diseases, this is a compelling treatment. The absolute effectiveness of 89 percent and the observed death rate of 9 percent were both really persuasive to me, in the light that every participant was able to tolerate the regimen enough that they completed it.

Several people have talked about thinking of this as a single regimen, but we had a lot of evidence that there were interruptions of individual components of the regimen, so I think the language around that has to be very clear. It can't be one pill because these have to be, as

someone said, titrated.

I also, in terms of safety, noticed that 101 out of 104 participants had moderate or greater adverse events. So again, it comes down to is the treatment killing you or is the disease killing you? But I think that the short-term nature of this -- I mean, it was within about 3 months that the really strong effects were seen. I just found this a really compelling, effective drug and a new standard against which other combinations can be evaluated.

Lastly, regarding the reply about the fertility in women, of course, if your outcome variable is overactive in the current menstrual cycle, that's one way to evaluate it. But as someone who works in examining infertility in women caused by cancer treatments, thinking more about the whole woman instead of just the immediate menstrual cycle is the way to go. Some of the terms that are used in this field are ovarian reserve and ovarian recovery, and perhaps that will help you look to different methods of evaluating

infertility in women. Thank you.

DR. BADEN: Thank you. So 14 yes, 4 no. Much of the discussion was overlapping. In synthesizing what I heard, this is not an endorsement of not doing RCTs at all. However, in this unique circumstance with a highly morbid illness, the design made sense to the majority of the committee, though the dissenting voices are heard loud and clear in the preliminary nature of the data, which requires careful follow-up in subsequent studies and use, both for toxicity as well as the many other issues that were raised by the committee.

That concludes the committee's work. Any final comments from the agency?

DR. NAMBIAR: Yes. Thank you, Dr. Baden.

On behalf of the office and the division, we want to thank the committee for their participation in today's meeting and for providing very valuable input. These discussions are extremely helpful to us as we continue the review of the NDA.

I also wanted to thank the applicant for all

the work they have done on this application and also our thanks to the speakers at the open public hearing for sharing their thoughts and experiences. Finally, I would like to extend my sincere thanks to the FDA review team and all the consultants who helped us on this challenging application.

Safe travels, and I think we'll be seeing some of you soon. Thank you.

Adjournment

DR. BADEN: Thank you, and thank everyone for their participation and the information shared. The meeting is now concluded.

(Whereupon, at 3:12 p.m., the meeting was adjourned.)