U.S. FOOD AND DRUG ADMINISTRATION

FDA PUBLIC WORKSHOP

DEVELOPMENT OF ANTIBACTERIAL DRUGS FOR TREATMENT OF NONTUBERCULOUS MYCOBACTERIAL DISEASE

April 8, 2019

7:30 a.m. to 5:15 p.m.

FDA White Oak Campus,

10903 New Hampshire Ave.,

Building 31 Great Room,

Silver Spring, MD 20993

JOB No.: 3389708

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PROCEEDINGS

INTRODUCTORY REMARKS AND PANEL INTRODUCTION

MR. COX: Good morning, everybody. We're at 8:30, so we thought we'd go ahead and get started. And first of all, I'd just like to welcome everybody to today's Workshop on the Development of Antibacterial Drugs for Treatment of Nontuberculous Mycobacterial Disease. I'm Ed Cox. I'm the Director of the Office of Antimicrobial Products.

And we greatly appreciate everybody joining us here today. We've got a diverse group of stakeholders and we think that's really important. We're grateful for all the academics, the clinical investigators, the practitioners, folks who are representing patients, patient groups, regulatory colleagues, folks involved in research in this area, and all of you for joining us here today, both here in person and also on the web. Now there's a number of folks that are watching via the webcast too.

In general, we do workshops and we face particularly challenging issues with regards to drug development clinical trial design and development of

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drugs for treatment of patients with nontuberculous mycobacterial disease is certainly a challenging area. The workshops -- current knowledge and how we might address the evidence gaps that we face in order to improve what we do in the future. And really the ultimate goal here is to improve the care of patients affected with the NTM disease.

The workshops bring the community together and they help us to both prioritize and focus our efforts. There's always a large number of different possible exercises or activities that can be undertaken to try and address some of the gaps in a particular area. The question is always, which are the ones that are most important for us to address right off the bat in order to move things forward most quickly. Generating quality evidence can be challenging, but it really is essential to the care of patients. Physicians can use it to guide the care of their patients; clinician investigators can use it, that is quality evidence, to evaluate products to identify appropriate endpoints for clinical trials and when to measure such endpoints. And ultimately,

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patients benefit from the improved care that the knowledge generated leads to.

Understanding the disease, what works, how much it works, what it does, what it doesn't do, can help us to understand a disease and lead to the identification of interventions or a combination of interventions that are best able to benefit patients.

So we've got a fairly full day. You've noticed we've divvied it up into essentially three main sections, where we talk about NTM disease. And we'll hear some -- from what we've learned from our experiences to date with clinical trials that have been reformed so far. And then we'll have an opportunity to go through some case studies.

And the case studies are meant to be essentially hypothetical situations to try and help us to identify some of what we know, some of what we could benefit from, from additional learnings and, you know, how we can essentially move forward in the field.

I would encourage people to keep in mind a few thoughts as we work through the discussions over

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the course of the day. You might, as you're thinking about this, frame things in the following way: What do we understand that's supported by evidence? What are the gaps in our understanding? How can we address these gaps? Are the designs that are durable despite these knowledge gaps? In essence, ideas and what could be done today to help us understand what interventions help patients?

So I want to thank you for your attention to my brief remarks here. And we look forward to a productive day. And I think what we'll do now is we'll also go around the table and have folks introduce themselves. And if you'll state your name, your affiliation and any conflicts of interests that you'd like to bring to the attention of the group. And typically, our conflicts of interests are also available on the written materials.

And I'll turn to Erica Brittain, on the far side, to start us out. Erica?

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

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MR. COX: And Erica, we might need you to get a little closer to the microphone. Give us one more.
MS. BRITTAIN: Shall I try it again? Is that better?
MR. COX: Yeah, just because there's folks on the web. So it really is important that we -- we use the microphone.
MS. BRITTAIN: Okay.
MR. COX: There you go, thanks.
MS. BRITTAIN: All right, good. Erica Brittain, I'm a statistician at National Institute of Allergy and Infectious Diseases, NIH.
MS. DIXON: Cheryl Dixon, statistician with the FDA. I work with the division of anti-infectives.
MS. TALLEY: Angela Talley, I'm Vice President of Clinical Development at Spero Therapeutics.
MR. SULLIVAN: Hi, my name is Gene Sullivan. I'm the Chief Product Strategy Officer at Insmed.
MR. GRIFFITH: David Griffith, with University of Texas Health Science Center at Tyler. I am a participant in multiple clinical trials with

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companies who are represented here.
MS. KASPERBAUER: Shannon Kasperbauer, I practice at National Jewish Health and I've also served as a speaker an advisor with Insmed.
MR. WINTHROP: Kevin Winthrop from Oregon Health Science University in Portland, Oregon. I'm a -- I have potential conflicts including funding from FDA, NIH, Macquarie (ph). I've received research funding and consultant honorarium from several of the companies here that I can remember, Insmed, Spero, ParaTech, I think those three companies.
MR. DALEY: My name is Chuck Daley. I head the Division of Mycobacterial and Respiratory Infections at National Jewish. I have the same conflicts that he has. I think he left out a couple maybe, but also Spero Horizon (ph), ParaTech (ph) Johnson & Johnson and Insmed advisory boards and Phase 2 site investigator for Aircase (ph) trial.
MS. O'DONNELL: Anne O'Donnell from Georgetown University here in D.C. And my conflicts kind of harmonize with the prior one, Insmed, Aradigm, Parion (ph), the COPD Foundation and Electro-Med.

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MR. CHALMERS: My name is James Chalmers. I'm a chest physician from the University of Dundee in the U.K. And my conflicts of interest are, I'm chair of the European Bronchiectasis Registry, which receives funding from a number of companies including Insmed. And I've served as an advisor to Insmed, Savara and a number of other companies.
MS. NAMBIAR: Good morning. I'm Sumathi Nambiar, Director, Division of Anti-Infective Products CDER, FDA.
MR. FLUME: I'm Patrick Flume, for the Medical University of South Carolina. I have similar relationships designing and conduct of clinical trials with multiple industry partners.
MR. COX: And another thing folks in the audience motioning, do try and get close to the microphone. The pickup is best when you're very close, so thank you.
MS. HIGGINS: Hi, I'm Karen Higgins with the FDA. I'm a statistics team leader, supporting the Division of Anti-Infective Products.
MR. OLIVIER: I'm Ken Olivier. I'm the chief

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of the Pulmonary Branch at the National Heart, Lung, and Blood Institute that has corporate research and development agreements with AIT Therapeutics, Matinas Biopharma. I'm also on an external advisory committee for the CF Foundation for the research and development program focused on NTM at National Jewish University of Colorado.
MR. KIM: Good morning. My name is Peter Kim. A medical team leader, Division of Anti-Infective Products, FDA.
MR. AKSAMIT: Tim Aksamit, Mayo Clinic, Rochester, Minnesota. I participate in a number of clinical trials. All those monies go to my employer, Mayo Clinic Foundation for Education and Research. I don't receive anything personally, and currently chair of the U.S. Bronchiectasis and NTM Registry.
MS. LEITMAN: Amy Leitman for NTM Info and Research. Our organization receives corporate support from several sources. I do not have any personal funding coming to me.
MS. HIRUY: Hiwot Hiruy, clinical reviewer, FDA.

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MR. CHEN: Wen-Hung Chen, team leader, Clinical Outcome Assessment staff in Office of New Drug, under CDER, FDA.

MS. SLAGLE: Good morning. I'm Ashley Slagle, a scientific and regulatory consultant. I am focused on patients that are at end points and clinical outcome assessments. I consult to a number of pharmaceutical companies, and I was formally with the FDA.

MS. EREMENCO: Good morning. I'm Sonya Eremenco, Associate Director of the Patient Reported Outcome Consortium at the Critical Path Institute. And I'm a full time employee of C-Path.

MR. TRAPNELL: Good morning. I'm Bruce Trapnell. I'm a pulmonologist from Cincinnati, and I have a grant funding from the NIH and commercial sources as well involved in clinical trials, although not in NTM.

MR. LIM: Hi, my name is Bob Lim. I'm the clinical team leader in the Division of Pulmonary Allergy and Rheumatology Products, FDA.

MR. COX: Great. Thank you all. And over

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the course of the day too, we'll continue to try and do our best to get as close to these microphones. They really do have a limited pickup. But folks in the audience don't hesitate to remind us because you're a good cue for us for all the folks who maybe listening via the web, of the importance of using the microphone so that all can hear.

And at this point I'd like to turn it over to Sumathi. Sumathi Nambiar and James Chalmers, who will guide us through the next session. Thank you very much.

MS. NAMBIAR: Thanks, Ed. Maybe Dr. Kalfus, I think we missed you during the introductions.

DR. KALFUS: Hi, good morning. I'm Dr. Ira Kalfus. I'm with RedHill Biopharma, medical director in charge of their NTM program.

SESSION 1: GENERAL CONSIDERATIONS FOR NTM DISEASE

MS. NAMBIAR: Thank you. I hope you can hear me. This is the closest I can get. It's kind of limited in -- all right. So along with Dr. Chalmers who is the co-chair for the first two sessions. I want to welcome you to today's workshop. So first

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session is on discussion on the general considerations for NTM disease. We have three presentations. The schedule is a little tight. So what we'll try to do is at the end of each presenter's talk, maybe 1 or 2 minutes if there are clarifying questions, if the questions are more general maybe you can hold them until the final discussion. That'll help us keep to time.

So our first speaker today is Dr. O'Donnell, who is the chief, Division of Pulmonary Critical Care and Sleep Medicine at Georgetown University Hospital. And as you've heard during the introduction, she has been a principal investigator in some of the recent trials. Dr. O'Donnell?

DIAGNOSIS AND TREATMENT OF NTM: CURRENT STATE AND FUTURE CONSIDERATIONS

MS. O'DONNELL: Yes, good morning. Good morning to everyone and thank you very much for the invitation to speak and thanks to the FDA for convening this meeting. My job is kind of lay the groundwork I think for understanding this disease in terms of how we diagnose it and what we are currently

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doing in terms of treatment. So I'll advance the slide. Sorry, a little technical difficulty. Okay, okay. Sorry. So these are my disclosures. You already heard -- this already when we went around the room.

So as I said, we're going to talk about how we diagnose this disease, how the disease manifest itself clinically, what the radiographic findings and laboratory confirmation. That's sort of the triad of having -- confirm the diagnoses of NTM lung disease. We review the standard treatment, some salvage options that are currently in use and discuss a little bit about pipeline therapies and we're going to hear more about that later.

First off, you know, this disease although quiet uncommon is certainly more common than mycobacterial tuberculosis. In 2010, thanks to our friends at the NIH, the estimate was about 86,000 cases in the U.S. This has tripled over the next four years. This is a disease of older adults primarily, although you can see it across the whole spectrum of age. It's a female predominant disease, about 60:40

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female to male. We see similar reports from other parts of the world and there's definitely increasing mortality and this disproportionately is affecting older Caucasian women.

Again, from Jen Adjemian at the NIH, this was a look at where NTM lung disease is occurring in the U.S. And those dark areas are the ones with the highest prevalence. So you can see, it's kind of a coastal disease. And we know that the water content or the humidity content in the environment may have something to do with this. Actually, the highest prevalence, as you can see, is in Hawaii.

It's especially important infection in patients who have cystic fibrosis. So when -- at least from the U.S. database, from the U.S. CF Foundation, about 14 percent of CF patients have at least a culture positivity for NTM. There is some spatial clustering along the lines of what we just saw. It's low in Europe. And the European CF patient registry for reasons that are not entirely clear. In the CF world, there is also some concern about patient-to-patient transmission. But this is limited

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right now to mycobacterial abscesses not to MAC.

Okay, so when we see the patient, how do we confirm the diagnosis? And like I said, it's a triad, you need the symptoms, you need the radiographic findings and you need culture positivity to confirm the presence of the disease. So the patients often present with nonspecific pulmonary symptoms like chronic cough, some low-grade sputum production, occasionally they have hemoptysis, sometimes chest pain. The other big thing with these patients is they often have subtle systemic symptoms like weight loss, night sweats, low-grade fever, and you know something less -- even less specific fatigue and malaise. So often it's a diagnosis that's not thought of, and it obviously it will take some thinking on the part of the clinician to come to the realization the patient may have this.

So what kind of underlying diseases? I already mentioned CF, but there is a group of these patients that we clearly recognize who appear to have no underlying obvious pulmonary disease and yet get this infection. And these patients are particularly

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noteworthy because they often have a specific body type, Ken Olivier did a lot of this work that showed that abnormal morphology thin, tall, older Caucasian women, some of them have scalable disorders like pectus excavatum and scoliosis, some of these patients have other muscular skeletal issues. And so this body type in women, seems to predispose to getting this infection.

Clearly, those patients with underlying lung disease, pre-existing lung disease who get NTM infections, and primarily this is bronchiectasis, also COPD emphysema, patients with underlying preexisting fibrotic lung disease, stuff like cystic fibrosis, patients who had tuberculosis in the past and were scarred, their lungs were scarred because of the TB, are at risk for getting NTM infections and then genetic disorders like cystic fibrosis and alpha-1 antitrypsin deficiency, put the patient at risk.

There are a bunch of identifiable immune disorders that can predispose to these infections. Now the ones I've listed, the rare genetic ones on top here, are actually more likely to cause systemic

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disease, not so much pulmonary disease. And the acquired ones like untreated HIV disease, certainly is associated with NTM. But things like chemotherapeutic agents that reduce the patient's immune system functioning, antirheumatic agents, Kevin Winthrop is expert on this issue. The drugs that we use for rheumatoid arthritis and related diseases definitely put the patient at risk for getting NTM lung disease.

Transplant immunosuppressive therapies, and these therapies sort of overlap with other chronic lung diseases that we've -- use these drugs. And another important one and probably very underrecognized is the patient inhaled corticosteroids. There's now three studies that have looked at this issue. And you know, ICS therapy is very, very common in people with airways disease. And yet, this does seem to pose a risk for developing NTM infection. So there are these underlying conditions.

Some other ones are chronic reflux or aspiration, low-grade aspiration. I already mentioned the rheumatologic drugs, but the rheumatologic diseases like Sjogren's and RA, put the patient at

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risk for getting this type of infection and also inflammatory bowel disease. But the big question is, you know, why me? Why now? You know, this is what patients ask us, like, "Hey, I have this underlying disorder or I don't. But why all of a sudden do I have NTM lung infection." And we really believe it's kind of a two-hit hypothesis that the patient is predisposed for reasons like I just mentioned and then they're exposed because these organisms are in the environment, in the soil and in the water. So in the right side are scenarios where the patient has a predisposition and the exposures there, the person gets actual infection with the bacteria.

So those are the patients at risk. And then, you know, they come to us sometimes with imaging studies, sometimes without. But we really need a CT scan to confirm the diagnosis of pulmonary NTM. Although the findings are not totally specific, there are some hints in these CT images that suggest that the patient may have NTM infection. And I'll show you some representative images. There's fibronodular changes in the lungs, what the radiologists often

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refers to as tree-in-bud nodularity or bronchiolitis that suggest NTM patients with fibrocavitary disease. One of the features of the radiographic imaging is that there is often a waxing and waning, because this disease is characterized by mucus plugging, and difficulty clearing the airways.

So on the left hand panel is an example of what we would characterize as a fibronodular disorder. You can see sort of that diffused nodularity, I wish I can point it out, but I'm sure you can see that there's mucus plugging in those areas and on the right side of the -- right up below -- I am sorry the right middle lobe, right lower lobe. Whereas the size of CT on the right shows a patient who has that kind of finding but also has a cavity. You can see that in -- on the left lower lobe, there. So these are the typical radiographic findings, this is -- I know people struggle with this concept of tree-in-bud nodularity, but this is what a tree-in-bud looks like. If we go outside, we see some more. And you can see on the CT scan, why the radiologist has adopted that term. There's mucus probably in the small airways

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associated with the bronchiectasis.

The thing about this though is that this is not diagnostic of NTM. Other infections can cause this type of a radiographic abnormality. But it is at least a suggested finding and should lead to laboratory testing. And that's the third part of the triad of diagnosing this disease, so you have the patient's clinical symptoms, you have the imaging, and then you the lab. And, you know, these two types of mycobacterial now the biggest ones in the U.S. about 80 percent of our patients have mycobacterium avium complex, MAC, and a smaller number 10 or so percent, mycobacterium abscessus complex. You can see within that there's subspecies. One of the problems that we have is that the clinical labs are not totally attentive to providing every last detail on these culture results.

Another important message is that these patients, many of these patients don't just have NTM infection, and this complicates obviously how we treat them. This is data from our U.S. bronchiectasis registry that showed a significant number, 23 to 52

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percent of the patients who've had NTM infection with bronchiectasis, also had another organism like pseudomonas. Some of these patients are co-infected with staph aureus, some with H. flu, stenotrophomonas, so this is one of the difficulties of designing clinical trials into NTM, because many of these patients have other organisms there. It can be difficult to tell really kind of what's driving their symptoms.

You know, a key thing is to get respiratory symptoms, and you know this is easier said than done in many circumstances. There's sort of been a downplaying of sputum cultures in the world of pulmonary medicine, the adult pulmonary medicine, but we need these in order to make the diagnosis. And some patients like the CT scan on top, you know, we have kind of just nodular disease are not very productive where patients with the more extensive and cystic and cavitary disease, it's often fairly easy to get them to cough up a nice sputum specimen.

We have some tricks but they're not -- in the clinical treatment of this disease is that, you know,

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collecting sputum is sort of a lost art and not many places have a isolation booth to collect sputum so that others in the suite or in the lab are not affected. Sometimes we use a saline nebulization, what we call, sputum induction to try to get these specimens. And sometimes we have to resort to bronchoscopy.

So in order to confirm the diagnosis of NTM lung infection, as I'm harping on, the idea is that they have symptoms, they have radiographic findings consistent with the disease and then we confirm it with the culture. The clinical symptoms can be nonspecific. I already said the radiographic findings are also not totally specific, and then we need those cultures.

And some of the challenges, you know, just clinically taking care of these patients is how many cultures do we need? You know, how do the patients collect these cultures, and some of the limitations of the laboratory. So right now we have the U.S. ID assay and ATS guidelines that were published in 2007, that say you see -- you need two positive sputum

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cultures or run positive culture from a bronchoscopy to confirm the presence of NTM infection.

Some of the challenges, and again, we'll get into this. I think we're going to talk mainly about MAC, when it comes to treatment. But some of the issues is the labs. The labs that we use here in the U.S. are not really, shall we say, vibrantly involved in mycobacterial disease anymore. So we get the result from the lab that the culture is MAC, but subspeciation is not routinely done in most clinical labs. And the other problem is that the lab will send, if the clinician requests, they'll send a susceptibility panel. And that can be difficult for people to interpret. It may not be totally relevant to the actual clinical outcome with certain antibiotics. And there's a lot of challenges when it comes to interpreting the results of the lab, and this complicates treatment on the database as well.

I just put this in here, there's a lot of fine print when it comes to the lab results that we get and you really have to look at -- this is a plea to the FDA to clean this up too, if you could.

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Because it's really -- you know, for the average ID physician or a pulmonary physician, who doesn't deal with this infection all the time; again, there's a lot of fine print in the lab reports that you may have to specifically request and may not be forthcoming.

Likewise, the susceptibility reports sometimes are difficult to understand. So that leads us to, you know, we have the answer, the patient has the disease, we know what the culture showed, we have some sense of these susceptibility reports, then what we do to treat this infection in 2019? So the first step is, if there's an underlying cause, an underlying abnormality in the patient, we'd like to try to address that particularly if, you know, that's a treatable thing. So obviously if there's an immune deficiency that we can mitigate, we think about doing that. If the disease is because the patient is chronically refluxing, we'll treat the patient for that. We focus a lot on nutrition and sort of general good healthcare.

Many of these patients lose a significant amount of weight and they are already thin to begin

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with. So sort of general care of these patients is very important step too, if you will. After that is to think about doing airway clearance modalities, I'll show you that in a second, and then antibiotics and for an occasional patient surgery.

So these are some of the devices that we like to prescribe for patients. These are so-called airway clearance things. They include these flutter devices, up on the top there, left. Some patients are prescribed a vest, a chest wall oscillating vest, to help them mobilize secretions. And one of the important treatments that we like the patients to do, although what they usually don't do, what this patient does is to exercise or to enroll in pulmonary rehabilitation so that the general condition of the patient is improved.

Okay. So what's the current antibiotic regimen for these patients? So again, this is a -- the primary reference for this is the 2007 guidelines, which are currently in revision. There are also are British guidelines that were published in 2017 by Charlie Haworth that are listed there. So for nodular

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bronchiectatic disease, their recommendation is the three oral drugs. Usually in a de novo, you know, the first go around the treatment, they'll give those drugs three times a week. And what's the result of that? In general we talk about 70 percent or so of those patients clear their sputum culture i.e. convert to negative by their own treatment, but unfortunately many patients either relapse or they get infected with a new strain of mycobacterium avium complex. So about a year or so out maybe about 50 percent of the patients are again positive by culture.

You know, it's very difficult to define what a cure is in this disease. Because again, you're dealing with a microbiologic infection superimposed usually on some chronic lung damage. And so again, the notion of -- this is not a urinary tract infection that, you know, have a positive culture and three days of antibiotics makes it negative. It's just not that. Generally again, from the guidelines, the recommendation is to treat with antibiotics for 12 months after the sputum converts to negative. So the idea is that we're collecting sputum while the patient

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is in antibiotic therapy. And usually this turns into 18 -- 15 to 18 months of antibiotic therapy when you're dealing with sort of straightforward MAC.

If the patient has cavities, if the lung damage is more significant, then the recommendation from the guidelines is daily therapy. And usually with the addition of aminoglycoside, for many patients that means an intravenous aminoglycoside like amikacin. We also used inhaled formulations (ph), we'll hear more about that.

One of the really big problems, I mean, just think of yourself trying to take this regimen for as long as we're trying to prescribe it. It's difficult for patients to take these treatments, number one; and number two, there's not great enthusiasm in the world of pulmonary and ID physicians to prescribe these things. So there's a couple of studies by a gentleman in (inaudible 0:30:36.2) that show that clinicians generally don't adhere to this guidelines for the treatment regimen.

We have ones liposomal amikacin that was approved late last year. This is a add-on drug for

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patients who have had 6 months of standard oral therapy and are still culture positive. This drug has about a 30 percent success rate and then converting the patient to negative. So you know, for MAC, we just -- you know, we have drugs, we have drugs that the patient can tolerate but the regimen is complicated and the add-on therapy that we have right now amikacin inhaled, has some success but obviously not 100 percent.

When we think about mycobacterium abscessus, it's even more complex because the regimen requires IV therapy generally upfront. So this means patients receiving home IV antibiotics, the length of time for these treatments is not entirely clear. It's often like as long as the patient can tolerate having the PICC line and getting the antibiotics. And we know that it's very, very difficult, even more difficult than this MAC to clear these infections, even with this complex regimen that I've put up here on the slide.

We also know that treating these patients does make them feel better, so even if we can't

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convert their sputum to negative, they still benefit in terms of quality of life improvement. You know, quickly the toxicities of the standard therapies are legion. We think of macrolides as a fairly benign treatment. But when you have to take it for 18 months, patients wind up sometimes with GI symptoms. There's cardiac rhythm issues, QT interval drug and drug/drug interactions, loss of hearing. We know with Ethambutol, there's a risk of developing problems with vision that have to do with optic neuritis. It was about a 10 percent discontinuation rate because of that. Rifampin causes GI hepatic and hematologic abnormalities; and aminoglycosides, auditory, vestibular, renal issues.

So some of the challenges that we have and hopefully some of the things that we're going to get out of this conference is, you know, what to do if the patient can't tolerate three or more drugs, are two drugs sufficient? What if the patient doesn't want to take the 18 to 24 month therapy, could we come up with a shorter regimen? That's one of the big questions I think that patients have. If the patient has a

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resistance, if they have MAC that's resistant to macrolide, you know what are our options there? And Dave Griffith has published data that show that mortality with macrolide resistant MAC is similar to mortality from MDR T).

There's cost issues about patients accessing these drugs we're constantly, you know, calling the insurance benefits managers to try to justify prescribing these drugs and expertise is somewhat limited. So we need new drugs, with new treatment regimens, new paradigms, it's a growing patient population, patients are older maybe sicker, it's clearly a priority to find something new and better. We have a paucity of effective and well tolerated drugs, we're recycling old drugs for new purposes here and trying to come up with combinations that the patients can tolerate.

So some of the old drugs for this bug, for both MAC and abscessus, I've listed here. Linezolid, tedizolid, tigecycline, possibly some of the new tetracycline drugs. Clofazimine, again there's limited data. Clofazimine is not actually on the

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market but it can be obtained. And the one thing we think is not effective is the Fluoroquinolones.

So what's in the pipeline? We're going to hear more today I think, but these are some of the drugs that have had some case hearings or some limited enthusiasm for using like the bedaquiline, inhaled nitric oxide, there's a dry powder form of nitric oxide, B-lactams and other antibiotics that are modified to improve the outcomes.

Surgery is sometimes a consideration for patients with localized disease. But this is a very small number of patients. I think one thing I wanted to read, you know, with the FDA there's been a lot of coverage this week in the local newspapers about stem cell treatments. I mean, patients are asking about this all the time in bronchiectasis and in NTM. So this is a hazard, that some of these things that are being advertised for patients really. They're totally unproven and makes me sad when patients, you know, are willing to spend huge amounts of money for this kind of stuff like stem cells, like this other conditioning regimens promise of a cure for bronchiectasis, this is

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bad stuff that we want to make sure patients are aware they shouldn't do.

So I'm just going to conclude by showing this very nice table that was published late last year by Wu (ph) that shows where we are with drug discovery and we'll be hearing more about this. This is clear, you know, discovery phase up to Phase IV and I just would say that our patients and this was published in the animals -- are asking, you know, for preventive the environmental issues, better diagnostics, the priority for patients is quality of life. So they want to improve treatment regimens and they want to know what their outcomes are going to be.

So I'll just conclude by saying this is a difficult disease because it's very heterogeneous and there are patients that, you know, we culture the bug from but they actually don't have progressive disease. And then there are some patients who really progress and go on to one failure and it can be difficult to prognosticate. So I look forward to hearing more about what we're going to do next. So thank you very much and I guess a minute for questions for sure.

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MS. NAMBIAR: Thank you, Dr. O'Donnell. It was very, very extensive. Thank you. Are there any questions, clarifying questions for doctor -- yes, Erica.

MS. BRITTAIN: That was a really great talk. You mentioned how during -- when patients are treated, sometimes patients with symptoms will get a lot better but the culture is still positive.

MS. O'DONNELL: Yes.

MS. BRITTAIN: Can you give -- I'm trying to understand what that means. What do you think when that happens?

MS. O'DONNELL: I mean clearly, sometimes patients just feel better even if we don't give antibodies, we give them airway clearance and exercise even though they're still culture positive. So that's one of the real challenges, because the culture may stay positive, the CT scan may get better, the patient feels better and, you know, how often does that happen? You know, it varies. Even if you see only the sickest patients it doesn't happen, but in patients with kind of mild disease, it's not uncommon.

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A lot of patients do feel better, you know, when they initiate antibiotics too, as long as they tolerate them. And then it's, you know, it's a struggle to get patients to continue on those therapies.

UNIDENTIFIED SPEAKER: I have a question related to our discussion this afternoon. What -- in your experience, what fraction of patients are positive on the sputum culture versus requiring either a biopsy or BAL (ph)?

MS. O'DONNELL: So the question is -- can you get this -- from sputum? I mean see, it really depends on how hard you try. So in the average pulmonologist hand, there's still a lot of patients are getting diagnosed by BAL, because they're not really inducing sputum's in the office. But like, in my hands, I rarely do a bronchoscopy because we do our best to get the sputum. So it's hard to give you an exact number, but it really depends on your practice setting I would say.

UNIDENTIFIED SPEAKER: I just want to make a brief comment though about the sputum culture positivity and the symptom improvement. Getting back

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to your point about the complexity of understanding what positive cultures mean in patients who are on therapy where we may see multiple organisms, multiple different species and not necessarily the species that was -- that was originally present when we started therapy. And unfortunately, as you also pointed out, laboratories in the United States don't help us do that. There are only a couple places where we can tease all of that out.

UNIDENTIFIED SPEAKER: And then we just for completeness also just emphasize that I think it's our clinical experience that in most instances, to answer your question, we do see a concordance between microbiological response and symptom response in most instances. And the microbiological response is something I think we'll address as the day goes on, quantitatively how many positive, that sort of thing. But I just want to leave and make sure that we start from a position that in most instances symptoms and microbiological response go hand-in-hand, not always.

UNIDENTIFIED SPEAKER: Great talk, Anne. Can I quickly ask you a question? You mentioned the

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waxing and waning of the CT. Can you just make a brief comment about the use of CT for monitoring response to therapy? Because I guess that might come up later when we talk about endpoints.

MS. O'DONNELL: Right, that's a good question. I mean, how do we monitor these patients either when they're on therapy or not. And because obviously, we don't want to overdo imaging, there's no standard approach I would say to how often we image patients in follow-up. Neither is there really a standard approach to how often do we culture them, you know, either during or after therapy. I think, you know, people want to limit the exposure to the radiation. But unfortunately the CT is the best way to tell. I mean we can sometimes -- if the disease is significant enough use a plain chest X-ray. So I would say the answer to that question is, you know, maybe a 6-month CT therapy and then maybe yearly or 2 years after that, really patient specific. Great question though.

UNIDENTIFIED SPEAKER: And maybe just to follow that up. Much like the microbiological

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response, the radiograph does not often clear even with successful treatments? So someone feels better, their sputum clears, they do well, they complete 18, 24 months whatever that is, but they will not have normal chest X-rays or CT scans at that point. They very often will have some residual abnormalities. So I think the expectation that we're going to clear a X-ray or clear a chest CT scan is a misnomer with or without therapy.

UNIDENTIFIED SPEAKER: I've got an answer too. I would only just clarify too, it depends what kind of patient is. We all seem to be talking about, bronchiectatic patients that don't have cavities. But if patients have cavitary disease whether they have bronchiectasis or not, you're going to try image at different intervals and you may be able to just use an x-ray if it's a cavity you are following. But really those are the people you're much more worried about progressing and you might radiologically be more interested in following them more closely.

MS. NAMBIAR: Thank you, Dr. O'Donnell. So we go to the next presentation from Dr. Kim, on the

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regulatory perspective on development of antibacterial drugs for NTM. Dr. Kim is a medical team leader in the division and leads a team whose portfolio includes drugs and development for NTM disease. Peter?

DEVELOPMENT OF ANTIBACTERIAL DRUGS FOR NTM: A REGULATORY PERSPECTIVE

MR. KIM: Good morning. My name is Peter Kim, and I'll be discussing development of antibacterial drugs for NTM from a regulatory perspective. So there is interest in developing inhaled and oral therapies for the treatment of NTM lung infections. Approved products include inhaled liposomal amikacin, as well as clarithromycin and azithromycin. Regarding inhaled amikacin or arikayce, received accelerated approval based on sputum culture conversion. There were limited clinical safety and effectiveness data, and the indication for use is currently in a limited population of patients with refractory MAC lung disease with limited or no treatment options.

Clinical benefit has not yet been established. There is a post marketing requirement to

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conduct a randomized double-blind placebo controlled clinical trial to assess and describe the clinical benefit of arikayce in patients with MAC lung disease. Some of the lessons -- we learned a lot from this application. And some of these lessons include an uncertainty as to the relation of a surrogate endpoints, sputum culture conversion to clinical benefit in patients with MAC lung disease. We noted inconsistent results in clinical outcomes between the Phase 2 and Phase 3 trials. In Phase 2, there was improvement in the 6-minute walk test distance seen in the inhaled amikacin arm.

However, in Phase 3, we did not see a clinical benefit on the measured outcomes such as the 6-minute walk test or in the patient reported outcomes. There was one error in the printed slides. The quality of life assessment tool was not the QOL-B but a different quality of life questionnaire. Additionally, comparison between study arms on long-term endpoint was difficult because a large fraction of patients were allowed to cross over to the treatment arm. For inhaled therapies, inclusion of

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inhaled placebo or vehicle control may help in the attribution of adverse events for the purposes of blinding trials.

Regarding the surrogate endpoint, as discussed at the advisory committee meeting on August 7, 2018; key findings from our review of the literature to support the correlation between the surrogate endpoint and clinical benefit included. There were retrospective, nonrandomized studies, which suggests a higher mortality rate in patients with MAC lung disease, who remain culture positive despite treatment compared to those who convert to culture negative. Some studies are from single centers or specific subtypes of MAC lung disease, which limits generalized ability to the overall population.

The main limitation that we noted is that it is possible that converters are inherently different from nonconverters in certain disease or patient characteristics. And hence it is difficult to assess if sputum conversion is a surrogate for a clinical outcome.

Some considerations for future development.

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So at this point, we have more questions than answers. But these are some of the issues that we're thinking about. As Dr. O'Donnell noted, there's a lot of heterogeneity in the patient population. Which types of patients should be enrolled? We have questions regarding trial design, superiority versus noninferiority, how best to monitor patients during the study. Questions on clinical endpoints and also how long to tree-in for -- how long should follow up occur in these clinical trials.

Regarding patient population heterogeneity, patients maybe different based on treatment experience. There are treatment naïve patients and also those with refractory disease. The disease manifests differently, nodular bronchiectatic disease versus fibrocavitary versus mixed picture. The etiologic organism varies, a patient can have MAC or a non-MAC NTM. Patients may have underlying comorbid conditions such as cystic fibrosis or COPD. And it's possible that response to stay (ph) drugs may vary based on any or all of the above.

Regarding trial design: so superiority trials

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are scientifically sound and readily interpretable. An evidence based noninferiority margin needs to be established based on the clinical outcome to have an interpretable noninferiority trial. So currently demonstrating superiority to standard of care maybe accomplished by adding a new drug to standard of care versus standard of care plus placebo or assessment of a new combination regimen versus standard of care or placebo. And we'll need to address the contribution of each component in such a new combination regimen.

How do we monitor patients to determine clinical benefit? As previously noted, there are limitations to microbiological results as an outcome measure. During the discussion of the cases later today, we'll be considering the feasibility and acceptability of bonding investigators and patients to culture conversions status during the trials. Patients could withdraw for clinical reasons, such as, increased fatigue, or worsening respiratory symptoms. But not solely because of failure to convert sputum culture to negative. This could allow for an unbiased assessment of whether culture conversion is

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unacceptable or surrogate for clinical benefit.

In addition, we'd like to hear your thoughts on avoiding crossover between treatment arms during trials. Clinical endpoints: so more work needs to be done to define clinically meaningful endpoints and assessments in NTM patients. Currently, microbiologic outcomes are not linked to how patients feel, function or survive. One option would be a patient reported outcome. But then the question is, is the PRO fit for purpose? And this would be assessed based on the reliability, validity, sensitivity to detect change and thresholds the meaningful change to the patient.

Beyond PROs, what other clinical outcome assessments, such as clinician reported, observer reported, or performance outcomes be more feasible and/or acceptable. And once again, with any of these clinical outcome assessment tools, we'll need to define a clinically meaningful change in NTM patients.

In addition, we'll talk more about these clinical outcome assessment tools later today. Assuming that the primary endpoint is designed to assess direct clinical benefit, how patients feel,

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function or survive; when should such an endpoint be assessed? More questions, should the endpoint be assessed on therapy versus off therapy; at 6 months, 12 months, 24 months after initiating therapy? Does the timing depend on the type of patient? Based on treatment experience, disease type or underlying comorbid conditions, should the assessment be based on a fixed time point or on a summary of clinical outcome assessment scores over time?

If based on a summary of scores, how frequently should assessments be made; daily, weekly, monthly, every 6 months? Regarding duration of treatment and follow-up, what is the evidence to support an optimal duration of treatment? Is it based on clinical benefit? In trials, we note that early treatment discontinuations may complicate assessments of long-term follow-up. How long is it acceptable for patients to be on placebo in the control arm? Does this depend on the study population?

We hope to cover these concepts in further detail during the course of our discussions today. And thank you for your attention. Are there any

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clarifying questions? Thank you.

MS. NAMBIAR: Thanks, Peter. So we move on to the third presentation from Amy Leitman, who is the director of policy and advocacy at the NTM Info and Research, a nonprofit advocacy group for patients with pulmonary NTM mycobacterial disease. Thank you.

PATIENT PERSPECTIVE FOR TREATMENT OF NTM DISEASE

MS. LEITMAN: Thank you. Good morning. I'd like to thank the FDA for convening this workshop. Hang on, what did I press? Here we go. These are my disclosures. NTM patients experience a variety of symptoms, side effects and impacts from both. These include, long delays to diagnosis, often 2 years or more; lengthy and burdensome treatments. Side effects, some of them quite severe, and some of them leaving permanent damage, including hearing or vision loss, vestibular dysfunction, or renal or hepatic dysfunction. A few of the more notable symptoms include severe cough, often producing mucus, extremely debilitating fatigue and shortness of breath.

At an FDA led, patient focused, drug

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development meeting in October 2015, the word "fatigue" was mentioned 49 times. 30 of those mentioned were from patients. The word "cough" was mentioned 98 times, 64 of those were from patients. At this same meeting, several patients noted coughing so severe that they have fractured ribs or vertebrae. Patients have noted that the disease is unpredictable and how they feel and function can vary widely from day-to-day. They've also noted social isolation and stigma that comes with a chronic illness and symptoms such as coughing and sputum production. Saying that friends tend to withdraw and for many it places a strain on their families as well.

These things can often lead to anxiety, depression and loneliness for the patient at a time when they most need a support system. In advance of this workshop, NTM Info and Research undertook a survey of patients to learn more about their preferences for treatments, outcomes and clinical trials. We worked jointly with the head of medical affairs, at Spero pharmaceuticals to develop questions that would try to elicit useful information from the

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patients.

The survey had 57 questions in total, asking for both quantitative and qualitative responses, and used branched logic to follow patients dependent on their previous answers. The survey was reviewed internally by NTM IR staff by several research staff at the COPD Foundation. A researcher at OHSU (ph), and a panel of five NTM patients. Once it was finalized, we distributed the survey through the internet, social media and online patient forms at NTMinfo.org and our Social360 platform which is developed jointly as part of Bronchiectasis and NTM Initiative.

The direct reach was approximately 400 -- excuse me, 4,500 patients. The survey was opened for just under 3 weeks and we had a total of 465 responses. Because of the short time frame from the close of the survey, we analyzed some data that we thought would best inform today's discussions. And now I report on these findings.

Respondents ranged in the age from 18 to 94 years, averaging 65.9 years old. 92 percent of the

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respondents were female, 8 percent male. Already more than 70 percent currently have an NTM lung infection. For the other nearly 29 percent, some had previously had an NTM lung infection. Those who have never had an NTM lung infection were exited from the survey after that question. About 60 percent were diagnosed more than 3 years ago and one quarter of them are diagnosed 1 to 3 years ago. The vast majority of respondents, 90 percent had MAC; about 18 percent had abscesses. There were a number of respondents that had coinfecting streams. We did not have a chance to fully analyze those data and we will be looking at that in the next wave of analysis.

Looking at other infections; just over 1/3 have another type of infection along with their NTM. More than half of those with coinfections had pseudomonas and one quarter had aspergillus. And again, some of them had more than one and we will be looking at that information again more closely.

Looking at comorbidities, more than 80 percent of the respondents had bronchiectasis, which we did not find at all surprising. Some respondents

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likely selected bronchiectasis, plus one of the other comorbidities listed. 84 percent of the respondents have at some point been treated with antibiotics for their NTM infections specifically. 42 percent of respondents are currently on antibiotic treatment for their NTM infection.

We use patients to tell us what symptoms they've experienced. We gave them an extensive list to select from, plus an other option that they could fill in. Here we have the top 10 symptoms that were selected, and this is where we start to pick up on some familiar themes that we're going to see throughout. The top three are fatigue, coughing up sputum and dyspnea, which in the survey was worded as shortness of breath with the word dyspnea in brackets. Throughout the survey we worded things in terms that patients would be more likely to understand with the more technically correct medical term in brackets.

So those were the symptoms patients experienced. We asked then what were the most bothersome symptoms? And again, there's a familiar pattern. The most bothersome ranked: fatigue, cough,

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shortness of breath. We didn't ask patients to tell us why they selected their number one most bothersome symptoms as the most bothersome. So this is a small sampling of the feedback we got, and it suggests that the fatigue is from a variety of factors including infection, treatment and symptoms, and the coughing seems to contribute quite a bit to the fatigue. This actually echoes a lot of what we heard at the PFDD meeting.

We then asked about the impact of their most bothersome symptom, and this is a sampling of the qualitative feedback we got. Again, it highlights the impact of fatigue as well as the social isolation. And some patients noted that unpredictable nature of their disease and how it adversely affects their day-to-day life. Here we see responses to the question "What do you hope that treating an NTM lung infection would do to improve your life?" The top response indicated a focus more on quality of life overall. And further along in the survey, we asked questions to sort of drill down into what they thought that might mean.

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This slide shows responses to questions about the side effects of the antibiotics. In this slide, we show the percentage of respondents who selected a particular side effect of antibiotic treatment as one they have experienced versus the one they found most bothersome. The light blue bars are a percentage of patients who selected the side effect as one they experienced. The dark blue bars are percentage of patients who selected the side effect as most bothersome. Fatigue remains the one that patients have experienced the most, and we know from their feedback it can be a combination of various things including symptoms and side effects.

Overall with side effects ranked most bothersome, we're still seeing fatigue respiratory symptoms and gastric symptoms. This is a sample of some of the feedback from patients on, how to these side effects have impacted their lives. In a permanent -- in addition to permanent side effects like hearing loss, when we looked at the qualitative data here, we once again saw a lot of emphasis on the fatigue and cough, which both might present as

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symptoms compounded with the side effects. It raises the question of whether we should further explore adjunct therapies to help alleviate these symptoms and side effects? And whether doing so would also help to any degree with the dyspnea?

We asked them about culture conversion, approximately half of respondents indicated that their treatment achieved this. We asked patients how long after they stopped treatment did the side effects subside. Noting a nearly 40 percent who responded that they haven't gone away, when we looked at the qualitative data for this response said, we saw that many of the side effects they referred to were more permanent ones, such as vision hearing, vestibular and neuropathy, knowing that these are possibilities, it would again be useful to have therapies developed that act as protectants against these side effects.

Looking at the side effects that patients indicated went away during treatment versus those that did not, we again see fatigue and respiratory symptoms, where we also note a large imbalance in vision change symptoms and hearing change and pain.

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We asked patients how long after you began treatment did you begin to feel better? Nearly one quarter of them felt a change within 1 month and stretching out up to 3 months, it's nearly one third, nearly 35 percent did not feel better. Considering the lung damage that we know they experienced from this disease, it's likely impacting how they feel after treatment as well.

Here we see the top 10 symptoms that patients reported as improved due to treatment. Again, we see that fatigue and the respiratory symptoms at the top of the list. We asked for some qualitative feedback, what bothers you most about your disease? And this is some of the qualitative feedback we got. And we see some common themes here again, the respiratory symptoms, the impact on their lives, and the treatment options or lack thereof.

We asked them if your treatment could change one thing about your NTM lung disease, what would you want that one thing to be? The overwhelming majority of those who responded to this question indicated culture conversion as their top preference.

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Regardless of their other preferences, it remains a priority for them. Given that they associate some of their symptoms with both the illness and the treatment, they might view this outcome as a way to eventually alleviate both by getting rid of the infection and getting off treatment.

Right under culture conversion, we see a pattern that is probably very familiar by now, fatigue and respiratory symptoms. Here we presented one of three hypothetical clinical trials scenario to respondents, if they had never been treated for their NTM lung disease and have the opportunity to enroll in clinical trial, where they would receive either the investigational new drug or a placebo, what length of time did they think would be reasonable to take a placebo? More than 50 percent felt that it was 6 months or less, that number increases to about 65 percent when going up to 9 months. Only 6 percent said they felt comfortable with anything over 12 months. And only 12 percent said they would feel comfortable with a 10 to 12 month placebo arm.

In the second hypothetical scenario, the

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respondent was asked if they'd already been on treatment? If they had already been on treatment? And would receive either the investigational therapy or placebo, in addition to standard of care, how long did they think was reasonable to be on placebo? At this point, the number of patients willing to go up to 6 months drops to about 45 percent. The number of people who'd be willing to go past 12 months is roughly the same as is the number of people who choose not to participate in this kind of clinical trial.

The third hypothetical asks if the respondent was already on treatment, and will receive either the investigational therapy or a placebo instead of standard of care, what would be an acceptable length of time for placebo? Roughly 50 percent selected up to 6 months, but nearly 30 percent selected they would not participate in such a trial, which is nearly double that of the other two hypotheticals.

Based on the results on all three scenarios and given that we've already seen previously how challenging it can be to enroll for NTM trials, placebo beyond 6 months presents both practical and

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ethical challenges in terms of being able to enroll.

The next series of questions pertaining to respondents who participated in clinical trials had much smaller sample sizes. More than one third of those respondents who participated in clinical trials indicated that it took at least 2 months, and as long as 12 months, to feel a benefit while taking an investigational therapy. This may make the development of a validated PRO tool more challenging as we would need to determine how far out we will need to measure with the tool in order to accurately assess the benefit of the therapy. And that time frame may vary depending on what the tool is measuring.

We asked patients what they noticed after they started an investigational therapy in a clinical trial? And this chart summarizes the analysis of their responses. Again, we see this familiar pattern of response with fatigue and respiratory symptoms. This is a sample of feedback from patients who were in clinical trials when we asked them what improvements they noticed once they began taking the investigational therapy? These same patients were

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asked, what improvements they noticed first? This chart summarizes the analysis of responses with their answers tracking strongly to the preferences that have been expressed by patients in earlier questions and to the symptoms that they experience. This is a sampling of their feedback from those patients who were in clinical trials when asked to report on the first improvement or benefit that they noticed.

So I guess, we can conclude this with a brief summary of fatigue, cough, dyspnea, sputum. The results of this sends some strong messages, fatigue is overwhelmingly a problem for these patients, and fatigue itself is not currently measured as a standalone item. There are validated fatigue assessments available but none have been validated for NTM specifically. But this may present an opportunity to look at these PRO tools to determine whether one of them can be repurposed as a validated tool for NTM.

Finally, I'd like to thank some people, most important of all the reason we're here today, the MTM patients, those who reviewed the survey and those who took the survey, for taking their time out of a very

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busy day filled with treatments in airway clearance, to give us information that we hope will be useful in drug development.

Stephanie Unis (ph) at NTMIR, who assisted with data analysis and the data presentation; Kate Selham (ph) at Spero with whom I partnered on the survey construction and data analysis; and Emily Hink (ph) at OHSU, who also served as a reviewer for the survey before it was finalized; and to the COPD Foundation, who also reviewed the survey and helped distribute it to patients, and with whom we partnered on with so many successful initiatives. Thank you.

MS. NAMBIAR: For questions. Amy thank you very much for sharing the results, and many thanks on our behalf as well to the NTM patients who participated in the survey, I think, very useful information.

We have a couple of minutes, so I want to make sure if any members of the audience that might have questions for any of the three speakers from this morning, no?

UNIDENTIFIED SPEAKER: Amy? It looked liked

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the numbers on the patients that responded to questions related to clinical trials is relatively small. Do you know what the total number was like in those?

MS. LEITMAN: I think it was either 16 or 18, it was a very small sample size, which we would like to actually conduct a separate survey that's targeted only to clinical trials patients. We -- one of the things we're trying to figure out is how do we target those patients specifically. So that's something we're going to be working on. Because we think it's important to get a bigger sample size for those.

UNIDENTIFIED SPEAKER: Hi, Mary Antego (ph) with Cistern (ph). I was always impressed how little C.diff we saw on these patients with diarrhea despite very broad spectrum antibiotics. Amy, did you drill down into the causes of diarrhea? Was this simply related to the antimicrobial or was there C.diff also?

MS. LEITMAN: We don't see a lot of mention of C.diffs specifically but we did see a lot of mention of diarrhea. I don't know how much how much the patients are being tested for C. diff, but it's

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certainly an important symptom, the gastric symptoms were certainly an important concern for patients, we did see quite a bit of that reporting. So it would not surprise me to find that a number of them had developed C. diff.

UNIDENTIFIED SPEAKER: I'll comment on that. I haven't been doing this as long as Dave, he's a lot older than me, but I've -- what have you got? I've been doing this 15 or 16 years, I've created one C.diff case in my entire career. And maybe that's because I don't use Forcolons (ph). Dave is wild about Forcolons. I don't know what everyone else's experience is, but it's just not something we see.

UNIDENTIFIED SPEAKER: Right it's a frequent side effect, of course, of erythromycin which -- and I'm like you, I don't know that I've had a documented C.diff case in 25 years.

UNIDENTIFIED SPEAKER: The other comment I made Amy and great public -- great survey, and of course we partnered on a lot of surveys like this. I will just say in terms of the acceptability of placebo, it really depends on -- it's a hard question

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to ask someone on a survey. And having, you know, placebo controlled trials on going where a lot of the patients are cite to be on placebo and they actually want to be on placebo for as long as possible. So it really depends on who you're enrolling and what kind of disease they have of course, and what they're interested in. So it's a hard question, I think, to survey people without giving them some scenarios about, you know, how they might feel or what kind of disease type they have. So I just offer that as a -- something to consider.

UNIDENTIFIED SPEAKER: It didn't seem to be -- the survey is not a scientific survey, right? So I guess I was wondering how representative you thought it was for the whole population. It would seem like it was 92 percent female, which where I think we heard it was like 60 percent female in the broader group. So I was wondering what you thought about that? And not just about that but just how representative it is?

MS. LEITMAN: Sure I -- you know obviously we would like to get more representativeness, but given the short time frame what we were really trying to

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elicit was information on what do these patients want to see in terms of outcomes? You know, what are their experiences and as much as it's not a scientific survey, the results were not at all surprising. It's something we've been hearing for -- from October 2015 now, so 4 years almost. We've been hearing the same things. Now we just have a nice little data chunk that tells us that yes, these patients that this is what they're saying. And we have a, you know, sort of a combination of qualitative and quantitative responses, that are telling us exactly that. And they -- we asked the questions in several different ways to see how much difference we got. There really wasn't a lot of difference, the responses were consistent.

So I'm not sure how much different it would be with a larger sample size or slightly more diverse sample size, I think the experience is going to be very similar. But yeah, we would certainly love to be able to, you know, to broaden this. There certainly -- we'd certainly love to explore the idea of reopening the survey and administering it to more patients.

UNIDENTIFIED SPEAKER: And Amy, you've

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thought about this for some time now, in several years, were there any particular aspects of this survey that were surprising or unexpected?

MS. LEITMAN: No.

UNIDENTIFIED SPEAKER: And that's just the point I think it's very consistent what our experience is and what we hear from patients on a day in day out basis.

MS. LEITMAN: Thank you.

UNIDENTIFIED SPEAKER: My name is Lee Young (ph), thanks for your presentation. I just want to know in this TB or NTB -- NTM tests conducted simultaneously and whether there are some unnecessary test and treatments, especially racial profiling maybe forced by -- racial profiling by police or there is something some unjust treatment just like a -- they try to find something as excuses. You get what I mean? Whether this test and --

MR. COX: Yeah, we appreciate your question. I think it's a complicated question you're asking, maybe you all can talk at the break and get a little more detail.

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UNIDENTIFIED SPEAKER: Thank you.

MR. COX: Okay. Thank you.

MS. NAMBIAR: Maybe we will take a comment from Dr. Proschan and then break.

MR. PROSCHAN: Yes, I was a little bit surprised that, you know, patients ranked so high the outcome of culture conversion, and I wonder what do you think the explanation for that is, because that's something they wouldn't necessarily even feel, right?

MS. LEITMAN: Sorry, are you asking for an explanation of how they reported culture conversion?

MR. PROSCHAN: No, why the patients felt that, that was so important to?

MS. LEITMAN: Sure, well, so the symptoms make them feel really lousy, the treatments make them feel really lousy, I think a lot of them view getting rid of the infection means they alleviate treatment and they can alleviate some of the symptoms, I think that's their hope. Certainly their -- if they culture convert, they're not taking the antibiotics, and the antibiotics have some really brutal side effects. So, I mean, I think that's one of the main reasons why

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they view it as so important. And you know, I think like anybody else who's dealing with the serious chronic illness, they're probably -- they're facing their own mortality and a lot of them are very frightened. And they would like to see something that's going to clear the infection and, you know, for -- and we did see some qualitative feedback that said, you know, I would like to know that I'm going to live a normal lifespan or that I'm not going to die young. So I think all of those things factor in.

MR. COX: Yeah, I'll just --

MR. PROSCHAN: Did you ask them that? I didn't see that question up there about fear of death?

MS. LEITMAN: We do not ask them that specific question.

MR. COX: I'll just add a comment too, I mean turning your cultures negative is your road towards someday stopping therapy, which is what you're saying. And you know, without that it's very hard to stop anyone's therapy for very long. So I think patients -- and we've done these same service with Amy and we've got this patient center outcome workgroup and panel

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for a long time for years, patients understand that their, you know, best shot at getting off the antibiotics is to turn their cultures negative, and have them negative for a long time, so that they can stop. So that's the path, it's progress, and it's a path towards treatment, completion, or stopping.

UNIDENTIFIED SPEAKER: It might actually be more simple than that, and that's they believe that is the cause of all of the problems that they have. So if you get rid of that, it will -- but I will also tell you that patients are not the only ones that perseverate on what's in the micro cultures, I know this discussion is not about antimicrobial resistance, but in the world of inhaled antibiotics, we hear repeatedly great fear about any bugs that might appear in a culture because the assumption is always that it's bad.

UNIDENTIFIED SPEAKER: I'll just add a comment to that. If you do any survey in any disease, usually the top answer from patients will be cure. And I think a lot of patients will equate getting rid of the bugs, with cure. And the second aspect will

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be, I think if you asked a lot of my patients, they would put culture conversion very high, because I asked them about to submit cultures at every visit. And I talk to them about their culture results at every visit. And so it gets very much ingrained in their heads that this is very important.

UNIDENTIFIED SPEAKER: I will say that in some of the qualitative responses with that as well, we also -- that, you know, our patients are -- they educate themselves very well about their disease. And we did see several patients responding, you know, if it can't get rid of the bug at least reduce the amount of bacteria. So they understand the difference between, you know, reduction of bacterial load and culture conversion.

UNIDENTIFIED SPEAKER: And I might just also make a comment and or a plea that I think we need to think more broadly about this culture conversion. And I think standard culture conversion by microbiological responses Dr. O'Donnell said, sometimes we can get a sputum. So I think we need to think more broadly. Are there other technical aspects, PCR, some other

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sampling, some other way to make an assessment about microbiological response other than conventional old sputum culture data? I think that's going to be dated with the new platforms that are available. And I think we collectively should begin to explore, are there better more sensitive and more specific measures of microbiological assessment and response than what we have right now because right now it's terrible.

UNIDENTIFIED SPEAKER: Yeah. Just with respect to the timing of a potential clinical endpoint the survey suggests that among patients who are going to have a symptomatic response, you see it within about 6 months, does that coincide with the experience of the clinicians on the panel?

UNIDENTIFIED SPEAKER: Yes, 3 months. I agree with you all, 3 to 6. 3 is the minimum, I think, in my mind.

MS. NAMBIAR: Okay. So I think with that we'll take a break. We're running a few minutes late so maybe if we can reconvene in about 10 or 15 minutes, and we should get started with the second session. Thank you.

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BREAK

SESSION 2: TRIAL DESIGN CONSIDERATIONS AND CHALLENGES FOR NTM DISEASE

LESSONS LEARNED FROM COMPLETED NTM TRIALS AND IMPLICATIONS FOR FUTURE TRIALS

MR. SULLIVAN: Here are some of the learnings that Insmed has gained based on the clinical trials that we've conducted in patients with NTM lung disease. I'll begin with a brief overview of the clinical trials that we've conducted, then address these four specific topics.

We observed that culture conversion, as defined in our pivotal trial, did in fact seem to predict durable microbiologic response. That is the maintenance of sputum culture negativity throughout the remaining course of treatment and out to 3 months after having stopped all NTM therapy.

We observed that the study population was very heterogeneous despite the fact that these studies were conducted in a subset of MAC patients who are considered to be refractory to available therapy. And we believe that this heterogeneity introduces noise,

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which can make it more difficult to detect the treatment effect of an investigational drug. We found that the 6-minute walk test was not a reliable clinic trial endpoint for various reasons.

And finally, we believe that drug tolerability issues may confound the assessment of clinical benefit during the course of treatment.

So first, a brief description of the NTM trials. There were three trials conducted with Amikacin Liposome Inhalation Suspension or ALIS in patients with NTM. Today I will discuss the first two listed here which were the randomized trials. And much of the data that I will present will be from the pivotal Phase III study, Study 212. This was the largest study and it included only patients with MAC. Whereas the Phase II study included both MAC and abscessus patients.

So first a brief overview of the designs of the trials. The Phase II study, Study 112, was a randomized, double-blind, placebo-controlled trial of ALIS in patients with NTM lung disease who are persistently culture positive on treatment. In

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contrast to the subsequent pivotal study, this study enrolled both patients with MAC and patients with M. abscessus.

Another significant difference is that this study enrolled both patients with and patients without underlying cystic fibrosis. The overall objective was to evaluate the safety, efficacy and tolerability of ALIS versus placebo when added to a background multidrug regimen.

The randomized, double-blind treatment period was 84 days in duration. After the double-blind phase, patients entered into an open-label phase where they received ALIS plus their background multidrug regimen for another 40 to 84 days. Patients were then followed for an additional 12 months off of ALIS. This study failed to demonstrate statistical significance on its primary endpoint, which was a semiquantitative measure of micro bacterial burden in the sputum at day 84. However, other study findings prompted Insmed to continue development. And I will share some of the data from this study in a few moments.

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The pivotal study, Study 212, was a randomized open-label multicenter study in adult patients with MAC lung disease who are persistently culture positive for at least 6 months while on a guideline based multidrug treatment regimen. Patients were randomized two to one to either ALIS 590 milligrams once daily, plus their multidrug regimen or to their multidrug regimen alone.

The primary endpoint was sputum culture conversion by month 6. In this study sputum culture conversion was rigorously defined. Each month two to three samples were obtained. In order to achieve culture conversion, all samples had to be negative for 3 consecutive months. This primary endpoint was considered to be a surrogate endpoint for the purposes of marketing approval in the United States under the Accelerated Approval regulations.

Once the month 6 sputum cultures results were available for the last patient enrolled, the database was locked and the primary and key secondary endpoints were analyzed. Patients in either arm who achieved the primary endpoint and remained culture negative

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through month 6 continued in the study to complete their course of treatment, which was 12 months following their conversion date.

Patients who did not achieve culture conversion through month 6 were enrolled in Study 312. Following completion of 12 months of treatment, after having achieved culture conversion patients in Study 212 stopped all MAC therapy. These patients were then assessed at 3 months and through 12 months off all antibiotic therapy.

Study 212 met the primary endpoint with a higher proportion of patients treated with ALIS achieving culture conversion by month 6. The absolute difference between the treatment groups was 20.1 percent. And this finding was highly statistically significant. This study demonstrated the treatment with ALIS converted significantly more patients than a multidrug regimen alone within 6 months.

Here you see the most common adverse events in Study 212. Respiratory adverse events were the most commonly reported category, and these included dystonia, cough, bronchospasm and hemoptysis. All of

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the adverse events listed here were more frequently reported in ALIS-treated patients than in the control group.

The first observation from Study 212 was that sputum culture conversion by month 6 seemed to predict a durable microbiologic response. Once again, here's the design the 212 study. The results that I just showed you were for the primary endpoint of 6 months. Patients who met the primary endpoint continued on their assigned treatment for a complete course. What we found was that patients who converted by month 6 using the rigorous definition of culture conversion deployed in the study tended to maintain their negative sputum cultures throughout the course of treatment and even 3 months after stopping treatment.

These are the interim data which were discussed at the FDA Advisory Committee meeting held last August. As of a cutoff date of April 2018, durability results were available for 48 of the 65 patients on ALIS who achieve culture conversion by month 6, and for 7 of the 10 patients who achieved culture conversion on the multidrug regimen alone.

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As you can see 81.3 percent of patients who achieved culture conversion on ALIS had remained culture negative throughout their course of treatment and through 3 months after having stopped all MAC treatment. In contrast, none of the patients who achieved culture conversion on their Multidrug regimen alone had remained culture negative at this time point.

More complete study data which will be described at the upcoming American Thoracic Society meeting are consistent with these data, suggesting that culture conversion by month 6 predicts durable culture conversion. The implication of these data for future studies is that early microbiological assessments may be informative in regard to longer-term microbiologic outcomes.

The next observation I would like to share with you relates to the nature of the study population. What we found was that despite the fact that we focused our Phase III study on a specific subset of NTM patients. Only those with MAC and who were refractory to guideline-based treatment. The

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study population was very heterogeneous.

Although balance between treatment groups, there was significant variability in the baseline characteristics of the overall population. For instance, in regard to the number of drugs in the background regimen some patients were on two and some are on four or more. Likewise, approximately one-third of the patients were on a drug other than a ethambutol, macrolide or rifamycin.

There was also wide variability in the specific multidrug regimens that were used. In this slide E stands for ethambutol, M for macrolide, R for rifamycin and O for any other medication deemed to be a component of the background regimen by the investigator. Fifty-five percent of patients were on the classic combination of macrolide, rifamycin and ethambutol. But the remainder were on various other combinations.

Similarly, the duration of the diagnosis of MAC was quite diverse. The inclusion criteria required patients to have failed to obtain negative sputum cultures after a minimum of 6 months. But

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there were patients who had had their MAC lung disease for 20 to 30 years. What I've shown you so far is the diversity of various descriptive baseline characteristics in our study population.

There was also significant baseline variability in regard to metrics that might serve as potential outcome variables. For instance, here we see great diversity in the baseline scores on the St George's Respiratory Questionnaire in Study 212. Both a total score and the symptom score domain. Both of these have a range of 0 to 100. What you can see is that the four cortiles on these scores span almost the entire range of possible scores. Some patients are severely impaired and some have little room for improvement from baseline.

In the Phase II study we didn't use the SGRQ, but you can see the same phenomenon on the QOL-B which was the patient-reported outcome instrument we used in that study. The data are shown here for the entire study population on the left, and only for the MAC patients on the right. Again, some patients were severely impaired at baseline and some have very

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little room for improvement.
I'll say a bit more about the 6-minute walk test in a moment. But here I just like to point out the significant diversity in our study population in terms of their baseline 6-minute walk test distance. Some patients showed severe impairment and others had values seen in healthy subjects. The point here is that even among the subset of MAC patients who are refractory to guideline-based treatment, there is significant heterogeneity in the clinical phenotype.
In general, decreasing heterogeneity in a study population will increase study power and assay sensitivity, the ability of a clinical trial to demonstrate a treatment effect if one is present. So the implication of these observations for future clinical studies is that effort should be made to limit relevant heterogeneity in the study population.
Now, I would like to say a little more about the 6-minute walk test. Because early on we were intrigued with the possibility that this might be a means to demonstrate a direct clinical benefit early in the course of treatment. This notion was driven by

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the findings in our Phase II study in which the 6-minute walk test had been included as an exploratory endpoint.
So what we saw in the Phase II study was the treatment with ALIS was associated with an apparent benefit on 6-minute walk distance. Even as early as day 84. Shown here are the 6-minute walk test results from that study. The mean difference between treatment groups in the change from baseline to day 84 was 47 meters. Although the nominal P value had to be interpreted with caution, since this was just an exploratory endpoint, the results were intriguing enough that we decided to include the 6-minute walk test as a secondary endpoint in the subsequent pivotal trial.
Unfortunately, in the pivotal trial there was no apparent effect of treatment with ALIS on the 6-minute walk test distance at month 6. So what happened? Why did the signal on 6-minute walk test looks so different between the two studies? We think there are a number of challenges to the use of 6-minute walk test as an endpoint in NTM trials.

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I already showed you the data on the left side of this slide demonstrating the wide variability in terms of the baseline 6-minute walk test distance in the study population. There were patients who had very poor 6-minute walk test distances as well as patients who had performed so well at baseline that there was little room for improvement.
The right side of this slide shows the variability in terms of the treatment response during the first 6 months of the study. The change from baseline to month 6, which you can see is that there were patients who had dramatic declines as well as patients who had dramatic improvements in this measure.
This degree of variability both at baseline and during the course of treatment make it challenging to demonstrate a treatment effect in a clinical trial. There are other challenges in regard to the use of 6-minute walk test as an important clinical endpoint in NTM trials. First of all, the 6-minute walk test is not a test that is typically performed clinically to assess NTM patients nor is it something that is

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typically used in the clinical practices of many of the physicians who care for these patients.
Therefore, study sites may not have ready access to a satisfactory test course and site personnel may have limited experience with its conduct. Another factor to consider is the presence of underlying structural lung disease. The underlying lung disease in these patients, often bronchiectasis and COPD may be an important factor in their performance, A factor which would remain even after the infection is cleared, thus putting a ceiling on the potential benefit of even successful anti-microbial therapies.
In addition, the clinical course of COPD and bronchiectasis often varies with episodic worsening. This variability unrelated to the NTM disease activity may introduce further noise on the endpoint. It's also possible that the benefit of treatment maybe most profound among patients who achieve microbiologic success. If the study population is one in which microbiologic success is less common, for instance in already treatment refractory population, the observed

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effect size maybe blunted.

Finally, significant physiologic benefit may not occur early in the course of treatment. If durable microbiologic cure is necessary before significant physiologic benefit can be achieved, the current very lengthy -- treatment courses for this disease introduce challenges in regard to complete follow up in clinical trials and the impact of missing data.

Lastly, I'll introduce the topic of drug tolerability and how it may impact the assessment of clinical benefit in the trial. We know that the assortment of existing drugs used to treat NTM have certain safety and tolerability issues which can be quite challenging for patients. Nonetheless, we use these drugs because we think that the goal of ultimately curing the infection is worth the cost. And that once treatment is complete, if the infection can be eradicated, the patient will feel better off.

So what does this mean for clinical trials? We have some evidence from our trials that suggests that the burden of the multidrug regimen itself in

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addition to the burden of the disease may be captured in patient reported outcome measures.

Here we show the St. George's Respiratory Questionnaire data from Study 212. Although not validated for use in NTM, the generally accepted threshold for a minimally important difference in other respiratory diseases is four units on this instrument. Shown here are the percentages of patients who achieved this threshold when assessed at their end of treatment visit, and when assessed 3 months off all treatment. For both the SGRQ symptom score and the total score we observed that more patients achieved a change equal to or greater than the MID once they had been off treatment for 3 months.

Similarly, in Study 112 with a PRL instrument was the QoL-B we saw some evidence of improvement in the scores 1 month after cessation of drugs. Similar to the existing investigational drugs -- similar to the existing drugs, investigational drugs may be associate with certain tolerability issues. And tolerability issues may impact patient reported outcome scores during treatment.

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It's certainly important for a trial to collect data to inform and understanding of the safety and tolerability of an investigational drug during the course of treatment. But if the primary goal of the PRO assessment is to characterize the ultimate clinical benefit that a patient will derive following a course of treatment, a PRO assessment following completion of treatment may be a more relevant index.

So I'll end with this list of four learnings that we derived from our clinical trials in patients with NTM lung disease. The implications for future trials are early microbiologic findings may predict for later microbiologic outcomes. Attempt should be made to limit study population heterogeneity. The 6-minute walk test may not be a useful endpoint in NTM lung disease trials. And attention should be paid to the most appropriate timing of clinical outcome assessments. Thank you.

MR. CHALMERS: Thank you very much. So we're going to have a full discussion of all these presentations during the panel discussion between 11:00 and 12:00. But we have time for a couple of

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clarifying questions, if anyone has any, please.

UNIDENTIFIED SPEAKER: So I guess slide 11 seemed like a really important slide. And I'm not sure I understood everything that was going on in that slide. Could you just walk us through that?

MR. SULLIVAN: Back button is not working. Is there anyone who can help me get back to the slide presentation? I'm hitting back. Oh now I got it, yeah. Play. Okay. So 11. Okay.

So this is data that we had shown at the advisory committee meeting. And this is looking at of the patients who at that time we had data who had achieved the primary endpoint culture conversion by month 6. And we had data out to this time point, 3 months after stopping.

So for instance, in the ALIS column there were 65 patients who -- we had -- who had converted at month 6 and 48 of them had already gone all the way to that 3-month time point. And of those 48, 81 percent maintain their negativity through the course of treatment and then having been off all drugs for 3 months.

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UNIDENTIFIED SPEAKER: But I guess I'm more interested in the others --
MR. SULLIVAN: Yes.
UNIDENTIFIED SPEAKER: The other side. So I'm trying to understand. So 10 -- what's the 7, what's the 10 or what's the zero?
MR. SULLIVAN: So the other side are patients who -- there were 10 patients in the trial, initial randomization who achieved culture conversion on the multidrug regimen, on their background Regimen. But if you follow those, we -- when we got data on seven of those who had made it all the way so far to the 3 months off, and none of them maintained it. So I think a comment had been made of the adviser to be that it certainly looks predictive on an effective drug, but how do we explain the fact that zero of seven. And so it may be that even despite the rigor of our definition of culture conversion, meaning we thought when we called you culture converted, you really were because there were several specimens for many months. But despite that rigor, if they were out -- if these were refractory patients who are only

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treated with MDR, it didn't hold.
UNIDENTIFIED SPEAKER: All right. So your title is it that month 6 result predicts, is that not necessary -- you're saying maybe that's not true in the other group?
MR. SULLIVAN: Well, the numbers are with 7, I think if you combine them you would still say of the 58, the percentage would still be pretty high if you said irrespective of their treatment.
UNIDENTIFIED SPEAKER: Please.
UNIDENTIFIED SPEAKER: Yeah, but I bet you would see a statistically significant difference between those two --
MR. SULLIVAN: Yeah.
UNIDENTIFIED SPEAKER: -- durable. So I mean what you want with a surrogate endpoint is you want to be able to predict what the difference between arms would be on the real endpoint of interest. And so if there's a different relationship between the surrogate and the ultimate endpoint of interest in the two arms, that's a problem for being a good surrogate.
MR. SULLIVAN: I think that -- I understand

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your point. I think that if anything this would underestimate the ultimate benefit. Now we'll talk later about what this is a surrogate for. This -- in this study, the 6 months was a surrogate for 3 months off. But given what we've seen here, you might be fooled. You would look at the 29 percent versus 9 percent who achieved culture conversion at month 6 and say that's going to predict the magnitude of benefit. But if the patients on the control group have sort of false positive, in other words, it's only going to underestimate the treatment effect, the long-term treatment effect.
MR. CHALMERS: I suspect we're going to have a long discussion about culture conversion and what it means during the panel discussion. So in the interest of time I'm going to -- so the next presentation is going to be by Kevin Winthrop, who you've already met, from Oregon Health and Science University on trial design considerations and examples. Kevin's background, he's a professor of public health and infectious diseases at Oregon Health and Science University and very heavily involved in multicenter

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NTM trials. Thanks Kevin.
TRIAL DESIGN CONSIDERATIONS AND EXAMPLES
DR. WINTHROP: Good. Thanks. Thanks James. So I want to thank doctors Nambiar and Cox for holding this. And I thank you for coming to our symposium meeting in November in Oregon. It was a long to go for you and for following it up with this is exactly what we need to be doing so. So thank you for bringing us together.
I was asked to just give some general and maybe some specific ideas around what's been done. And of course Dr. Sullivan just outlined what's been done in the Insmed development program. So I won't go into too much detail around their program, but I think some of this is largely theoretical. I showed Dave my talk, he said it was provocative, it was funny, but it was only half true.
So I will do my best to point out the parts that are half true. And then, you know, some of the things are there really just to make people think and hopefully stimulate discussion in the next hour. So my disclosures, I already disclosed. Although I

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had forgot a few and so they're all up there for you now.

So we're at the stalemate and this is why we need to all come together. We have companies looking for advice and physicians giving advice and FDA looking for advice and trying to give advice. And whose move is it next? So I think, you know, I don't know who's going to make the first move after this conference, but I think we'll all be better informed and someone's going to move and we'll get out of the stalemate. So currently approved therapies are really, there's just two. And if you look in their label, Azithromycin is labeled for disseminated MAC in patients with HIV, it's very specific and also very specific it says in combination with ethambutol.

For Clarithromycin it also mentions disseminated MAC in patients with HIV, but there's no mention of companion drugs. So these of course -- there's quite a bit of data in the Clarithromycin label outlining how it was evaluated in the context of disseminated MAC in HIV decades ago. So this is all we have approved for NTM. And of course the approval

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here is very specific to the setting that we're not even talking about today. This is disseminated MAC in HIV and this is not pulmonary MAC which essentially is not in HIV related disease almost at all. I mean there's a few HIV patients that get this, but it's 99.9 percent non-HIV and it's limited to pulmonary NTM.

See what did I do there? Current NTM -- these are the current RCTs. And this was already highlighted. And I think Anne showed a nice slide. This is just if you go to clinical trials.gov, this is what's registered. I'll make some comments about some of these trials that are ongoing use them as examples but suffice to say there looks like there's kind of a lot going on, at least compared to say 5 years ago this slide was pretty much blank, that's encouraging.

So considerations and examples. So I want to talk a bit about patient selection and disease state, follow-up some of Dr. Sullivan's comments about when to measure things. The treatment exposure groups who really need to think hard about, I'll just tell you I think we need placebo control trials and I'll give you

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some ideas why I think that's true. Our outcome measures of course we're going to probably spend 10 hours debating our outcome measures, but some ideas of what's been done and maybe things we can consider in the future. And then trial lengths. And I think we all want shorter trials and patients want shorter trials.

So in terms of patients in the disease state. So some simple ideas here. One problem we've had particularly in bronchiectasis trials, which is a related area is that we enroll patients maybe that aren't at the greatest capacity change. So for RCTs what we really -- if we want to study therapy, we want to enroll people who are going to change with the therapy, so we can measure difference with therapy.

Another general idea is when you're studying the safety and efficacy of a drug it's a lot easier to understand it if it's being used in monotherapy. If it's being layered on to a study with four other drugs in one arm and three other drugs in the other arm, so it's just totally different. I mean all you're figuring out is the safety and efficacy of that drug

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in the context of the other drugs.

Then there is -- this is a big issue. It's, you know, you say this, you learn this in med school. If someone walks in the ER, they're sick or they're not sick, figure it out in a second. And if they're sick, they go down a different pathway than if they're not sick. When we enrolled patients in clinical trials, mostly what we're talking about here is we're talking about people who aren't that sick. Yes, they have all the symptoms Amy just described but they're not dying, they're not people with cavitary disease or have "consumption" and need to start therapy right away. It's a different -- that's a different type of person. And those types of people are probably not suitable for clinical trials, because they're too sick.

So what is the standard of care. Anne outlined this in her talk. And, you know, Chuck and I stand up and talk about this a lot. Most of our patients who come in even if they're symptomatic, but they're not cavitary patients and about 20 percent of patients have cavities, the other 80 percent don't.

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They have symptoms but you take some time to sort them out. You do not start them on antibiotic therapy right away. There's a lot of reasons for that.

Most patients need to work on other things like clearance and bronchial hygiene. They need to develop an exercise routine. They need to eat better, they need to try to gain weight, there's a lot of things to work on before you start layering on three or four antibiotics many of which have adverse events. Many of which cause people not to want to eat or they get diarrhea like Amy mentioned, it makes weight gain difficult, et cetera. So you need to educate the patient about the drugs, what to expect and how to manage the side-effects. All those things take 3 to 6 months. So you have a window of time if you're planning a trial where you can enroll patients who have symptomatic, pulmonary MAC, noncavitary disease to work on some of these things and randomize people to a drug in active arm and a placebo arm. And again, the exception is those that are sick.

So what is the natural history of pulmonary MAC. And we -- the first part is actually fully true.

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It's not half true. And this comes from our studies, it comes from Ted Marisa's (ph) studies, Becky Trevor's (ph) studies. And we've looked population-wide in various places in the U.S. and Canada and it's, we see the same phenomenon. About 50 percent of people who meet disease criteria start therapy in the next 3 to 5 years. And the other 50 percent never do.

And there's various reasons why they don't. They might die, they might have other severe diseases that just preclude consideration of treatment of this, i.e. lung cancer is a good example. And then you can see the other reasons. Ten or 15 percent of patients actually convert to negative spontaneously, probably just with better bronchial hygiene and exercise. And then another about quarter patients remain stable for years.

How many years is years? Well I tell my patients, you know, some day you will progress, but it could be in 10 years, it could be in 5 years. And so the data where they followed people out 3 to 5 years after diagnosis. About 20 to 25 percent of people will stay stable. And factors associated with staying

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stable are certainly are listed there. I have a question mark around clearance and bronchial hygiene, it's just simply because we don't have a lot of data or prospective data looking at that, but an observational cohort certainly having cavitary disease being too skinny make these ideas of stability less likely.

So if you're fit, if you're a good weight, you have noncavitary disease, you're much more likely to remain stable for some time period. So let's talk about -- so really we talk about two groups of people for these trials, refractory disease. So the intimate program focused on refractory disease. So these are my thoughts about refractory disease.

This is an arbitrary definition. We kind of came up with it as a group because we looked at the data. And again this is observational study data from largely institutions. But around 10 or 20 percent of people depending on which series you look at don't convert by 12 months into therapy. So we've decided to call these people refractory. They're refractory to guideline-based therapy or whatever we're giving

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them, which is usually the drugs that were already outlined by Anne and by Eugene.

So we came up with that definition and then we kind of debated 6 months to 12 months, and in fact there's a publication that I cite in here on a subsequent slide where we just decided 6 months was long enough before we felt like we would want to try something else.

So the benefit of studying refractory patients is that you can actually power studies with patients who are taking background multidrug therapy. Meaning you could have a comparator arm that actually people aren't actually real antibiotics that should be active because the placebo group in this group is unlikely to change. They've already been on therapy for 6 to 12 months, having converted their sputum and still don't feel good. They're probably not going to change a whole lot. So if you add a drug and causes a little bit of change, you're hopefully going to find that statistically. So you can actually power that study.

The con of this is that measurable change in

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both the placebo group and the new therapy group could be quite minimal. And I just wrote M. abscessus an example. I treat a lot of M. abscessus and pretty much all those people, and this is subspecies abscessus. Pretty much all those people were refractory. And I put new drugs on all the time, and I don't see any change, they're still refractory.

So if I were doing a study and I had some abscessus patients on three drugs and they're refractory and I just chose some other drug to study, if I added it, I don't think I'd see any change at all. That's the risk of studying that group of people, refractory disease. So I won't go through this. Dr. Sullivan already went through their design. And they did show some benefit. And you can see there was some benefit. Again it was very small in the placebo group as expected as people probably aren't going to change much.

So what about treatment naive patients? So my bias is this is where we should be focusing. This is the group that has the greatest capacity to change. It's easier to measure change, you can measure change

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more quickly and sooner. The trial doesn't have to be as long. You can actually power these studies against placebo, that's the benefit.

The con is that it's difficult to power the study with an active comparator. If you take two groups of people and you put them both on effective therapy and 85 percent of people convert their sputums and get better in each arm, you got to have a huge study to show a difference.

So here's one example. This is the FDA R1 sponsored Clofazimine trial that many of us in this room are participating in. It's a Phase II RCT, its placebo-controlled. It's clofazimine monotherapy versus sugar pill. You have to be a non-cavitary patient, you're supposed to be "stable" which is a hard thing to define. But we all know when we see it. There have symptoms but they're not that sick, and they're not that excited about taking antibiotics to be honest.

Outcome measures or culture conversion at 24 weeks, which I'll make some comments about. We're also looking at a semi-quantitative culture. You can

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see with the power assumptions below, if we assume 35 percent of conversion in the clofazimine and 10 percent spontaneous conversion of placebo arm. You only need 102 people to do this study, 51 in each arm. So there's no active comparator. This is a placebo comparator.

If you do a multidrug active comparator trial, you can see this at the bottom with a circle, N equals 500. It's a totally different story from a investment standpoint for patients, resources and time and statistical power. So this is a multi-drug active comparative trial that we've been funded through Precorian (ph), it's a large study that involves our consortium and our trials network up to 35 sites. And we're comparing two drugs versus three drugs, azithromycin and ethambutol verses azithromycin, ethambutol or rifampin. It's a simple question. Are these regimens equivalent?

So this is actually noninferiority design which helped us a little bit on power but not much, and culture conversion and tolerability at 12 months outcome measures. And again, we're assuming about 85

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percent of conversion in each group because we think both these regimens are active. And we think based on observational data that's probably what we're going to see. So again, you need a very large study to do this.

Okay. Let's switch to outcome measures. Efficacy, we were talking about the microbiologic outcome. We'll be talking more about it. We have some thoughts. I have some thoughts on QOL or quality of life. And I'll mention some of the other things here as well. So one question I have for the group was actually a big please. Can we define culture conversion with two consecutive sputums and not three? This was the results of our voting. This is our NTM that consensus statement part of the European -- joint European-Japanese-U.S. guideline effort. And we came up with some definitions about "cure" and different aspects of therapy. And one was culture conversion. You can see the voting there.

So choice number two -- I don't know if I have a thing -- yeah, I do have a thing. But choice number two you can see is the question was finding of

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at least two consecutive negative cultures collected at least four weeks apart. They got six votes. And then number four is finding of at least three consecutive negative cultures at least 1 month apart. So that got six votes also. So they tied, six versus six. And when we did a tiebreaker and in the tiebreaker you can see that the one down below, which was seven before (ph) got nine. And that was if, you know, three consecutive cultures over, it's really over 2 months that would be considered culture conversion.

Here's an example of the Bedaquiline program, in fact I'm not going to say much about TB because I don't think we should even think about TB when we think about these trials, but their culture conversion definition was two. This is a registration trial and led to approval and they used two over a month time period. In fact, there's a number of TB trials that have used two consecutive negative cultures over a month time period.

So one question is do two consecutive negatives predict three? I think the Insmed data

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probably says yes to that. And I think there's other data that probably says yes to that. Concept of sustainability while on treatment, this is important. If you put someone on an antibiotic and they convert, you'd like to know that they stay converted. We all know that that's not always true, even with our current regimens that aren't improved, certain people pop up passes time here time again, but in general we'd like to know that there's some sustainable effect what's being used. This idea of durability of treatment. I think I'm not sure what the clinical relevance of this is. The infection rate from the environment or the re-infection rate is so high, it's 50 percent in 3 years. I'm not sure that is where the patient came from. Did they come from a placebo group and they were negative or they came from a active drug group in negative.

We learned 3 years ago half of them are going to be positive again. So I'm not a big fan of this durability measure and I don't think it tells us a whole lot. I think the durability studies could be done and the main utility is defining the optimal

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treatment duration for a particular regiment. What is the minimum time I need to give this to someone, is it 12 months? Or I guess how long do I stick negative after 12 months versus how long we going to stay negative after 18 months, and it may be just the same.

Lastly semi-quantitative cultures, we've done them. Dave's published a nice analysis showing it predicts conversion. I think it does. There's also a idea of time to conversion and we could talk about that as a potential micro outcome measure.

Okay. Quality of life. We can just march right through this. So we just submitted a response to the FDA R1 and I know others in the room did as well, looking at developing or further honing quality of life questionnaires in bronchiectasis but also the NTM component of bronchiectasis.

We've worked a lot with RSS or the respiratory questionnaire the QoL-B for years. It's undergone quite a bit of refinement and study. Dr. Chalmers, I mean Patrick, lots of us in this room have been using this in various studies on our own or together and show good internal consistency, test-

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retest reliability, convergence and some responsibility in bronchiectasis but still need some refinement, which we hope to do, particularly with regards to defining the minimal important difference.

And the big question is, is it useful in NTM bronchiectasis? There's very little study in MTM bronchiectasis with this tool. The questions of one to measure are huge, and I think Eugene was getting at that. And I'm going to show you some more thoughts on that in a second.

And lastly, the NTM module. This is a module that was developed years ago with help from NTM IOR and others and patient panels, in terms of defining the symptoms that are important to these patients. And they're all the same symptoms that Amy just mentioned today. This module takes into account fatigue, along with a number of other things. It certainly needs to be refined and needs to be tested. I'd say it's something that that looks promising but needs longitudinal evaluation.

The QoL-B and NTM, again has received very little study. We are presenting this at ATS. This

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comes out of our biobank, and it's a small -- it's a preliminary analysis in terms of the number of people. But we looked at people who start therapy. And then 12 months later we looked at them again. And the people who started therapy, their quality of life improved.

And it seemed to correlate with culture conversion. But, you know, when you look at the people who improved, it's really the people who had the ability to improve, the people who felt like crap to begin with. The people who felt pretty good at start don't improve. So that speaks to the point I think Dr. Sullivan was trying to make, measure people who have the capacity to change.

In the last bullet there you'll see the people who'd already started therapy more than 3 months ago, they didn't change at all. In fact, their change had already occurred and it had occurred before we started measuring them. So there is this 3 to 6 month window, I believe as Chuck and I were saying where there is a change to be anticipated and it's measurable.

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So I was on the plane. And I was very squeezed in. I mean, the guy next to me was a lot bigger than me. And the lady next to him had an emotional support dog, with a little jersey on that said, "Number 9 Emotional Support Dog," with a round thing on it. Anyway, I'm allergic to dogs. You can tell I'm a little stuffed up today. So thanks, Delta. Actually, I was in Alaska.

But anyway, here's what I think. The top line is -- so this is bronchiectasis. This is our problem. When you look back at all the bronchiectasis trials, it's amazing to me that lots of them have measured quality of life and people who shouldn't have a change in quality of life. Because we measure them at baseline. We enroll them at baseline, their quality of life kind of just stays the same. When they exacerbate they feel worse. And then they go back to baseline.

And so if our trial is 3-month long or 6 months or whatever, it will never exacerbate. You kind of just stay on this plateau. Maybe there's a little up and down here and there. But by and large,

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you're not really seeing much change because people are at baseline.

Now I have thoughts about that. I mean, not everyone's the same. There's heterogeneity just like Eugene said, people who are heavily colonized with pseudomonas, you know, they may be more susceptible to whatever therapy you're giving them as compared to someone who's not colonized with pseudomonas. And James is doing some great work looking at this. And we hope to work with him further looking at basilar burden, et cetera.

I think those same concepts are true in NTM. So in NTM, it's different. You don't have this baseline exacerbate, baseline exacerbate thing. What you have is this kind of gradual long slide down. And at some point that gradual long slide down you decide to treat someone.

So let's say you start your treatment there. And they tend to stabilize this first 3 months. They may even improve. But you can see the delta here as if you haven't treated them, it's very small. So in 3 months the question is how much change can you really

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measure? And if you imagine the dotted line below, this is someone we've -- actually this is someone we haven't treated. So the solid line keeps going down. There's very little change or drop in the 3-month window. Someone you have treated here, they may stabilize and then just gradually improve over months or years. And they'll probably get back to about their baseline but maybe not quite.

So it really depends on your time window and when you choose to measure these patients. And not to mention there's the issue that was also just mentioned about your therapies. Giving a respiratory therapy may cause respiratory symptoms. And so if you're measuring respiratory symptoms, it may not be the best time to do it while they're actually taking therapy. So the last three columns about this, pulmonary function test generally show no change during therapy, they're mostly fixed due to the underlying lung damage of bronchiectasis or emphysema. The 6-minute walk test took me 1 minute to walk to the bathroom. I would bathe and it took me like 6 minutes to walk back. So that just tells you what I think of it.

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It's very operator dependent. There's a lot of heterogeneity. There's problems that were already outlined by Dr. Sullivan. I think exercise capacity, one thing we just put into our grant submission is we're going to give everyone Fitbits. I think you can probably measure overall activity and steps and functionality based on something like that, some real-world daily measurement. And I talk about that with my patients. We don't usually give them Fitbits in clinic but we do talk about the overall daily energy output in terms of what they're doing from an exercise standpoint.

So my last point I'll talk is just to emphasize this. NTM is not TB. TB is curable. Culture conversion has a definition and it's a surrogate for cure. Cure has a definition and it's contagious, you have to treat it. You can't let people with TB go untreated. So placebo-controlled studies are out of the question.

NTM is an infectious disease but it's not contagious. It behaves more like a chronic inflammatory disease like an autoimmune disease. I

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like to use rheumatoid arthritis as my analogy. Treatment is really guided by disease activity and by patients, patient input. It's generally not curable, although it's usually suppressible.

My experience with therapy is almost everyone feels better with therapy or at least stabilizes. They don't continue to go downhill except for maybe 10 or 15 percent of people that are refractory. And then relapse/re-infection is common after therapy, particularly in the nodular bronchiectatic patients it's around 50 percent from Dave's data and similar from other experiences elsewhere.

Lastly, culture conversion is only part of the story. And I hear lots of comments about culture conversion. It doesn't always correlate with how patient feels or functions, but I think it generally does and does not always correlate with radiographic change. A lot of our patients' radiographs improve and they get worse and then they improve again and then they get worse. And it's because a lot of times we're seeing things that aren't necessarily MAC on the radiograph. They get treatment buds (ph) from the H

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flu (ph) or from their pseudomonas. And we think, well maybe I'm actually a little better or worse, 3 months later the treatment bud's gone. So it's hard to understand how that correlates with culture sometimes.

And then clinical meaningfulness. I think every question here is going to say yes, culture conversion has meaning, it means you're on the road to being able to stop someone's treatment. So lastly, I think we need better outcomes measures. I gave this plea in Oregon, and I'm going to give it again really quick here as my time runs out. But I think we should think about disease activity. We need some sort of index that incorporates subjective science, subjective feelings, patients and physician input, and something that's meaningful to the patient and the physician. So the analogy I -- what I've looked towards is rheumatology, literature. They've done this with chronic inflammatory drug disease. We're dealing with chronic inflammatory airway disease. They have a composite measure that requires 20 percent improvement in both physician and patient global assessments, a

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functional measure, a pain scale and an inflammatory objective measure, inflammatory measure.

We've submitted a grant that we hope to do this with everybody in this room, that, you know, we have a provision of disease activity score. And we're using kind of all the things we're talking about. Inflammatory markers, cultural results, symptom scores from NTM module, the respiratory scores, and the QoL-B, CT scan results, and then physician visual analog scale and patient VAS scores. So how do you feel on a zero to 10 today? These are the kinds of things that all the other chronic inflammatory diseases use. And I think that might be applicable here.

It drives with our patient-centered panel and a patient-centered research priority that was published that I think Amy mentioned. And this was as part of a precory (ph) funded initiatives, a developing composite measure of disease activity severity that actually reflects how patients feel and function is the top priority for patients.

So in summary, NTM trials. Placebo controlled trials, you can power, they're ethical if

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you don't involve people with cavities. You can look at drugs as monotherapy or as multi-drug therapy combinations. And I think you can show efficacy in as little as 3 to 4 months with a number of the outcome measures that were just mentioned. And I do think disease activity should be something we consider and work together to formulate a case definition for. So my last slide, the quote, "Figure out a drug safety/efficacy first, approve it, and then figure out how best to use it." You can see the citation that was me.

Last shown, Alaska Air, Seat 10F, and that was after I had a discussion with emotional support dog. But we often mess up the ideas of registrational studies with strategy trials. And once that idea is approved, we can do the strategy trial to figure out how best to use it. And I think those are separate concepts, and we should try to keep them separate.

Phase III trials, I agree generally should reflect how you think a drug should be used post-approval, and this will have impact as well as the idea of drug resistance.

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Now given a drug where there's no known issue of resistance, maybe you can give that drug in monotherapy. Giving a drug where you're worried about acquired resistance, monotherapy is probably not a good idea. And then the strategy trials I just mentioned, you can figure out how to use things later. Here's a simple study design. Rheumatology is full of dozens and dozens of these examples. You have someone with high disease activity, you give them placebo, or you give him one of your two doses of your compound. This is a JAK inhibitor called baricitnib. And you follow them out for a certain time period you have rescue available for people who aren't responding. This is very simple design.

There's my very simple design. This was also from a different plane flight. But I think you can do the same thing, randomize people to drug or drugs versus placebo. You can have your primary outcome measure at 24 weeks if you're talking about 6 months culture conversion. But I think we can look to see who's converting sooner than 6 months, and I think some of the other outcome measures we can measure

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somewhere at 12 to 16 weeks. So I think this is doable with shorter trials.

And if you switch people over, I'm not sure why there's resistance to this idea, you do in all the other diseases, but you can certainly take people on placebo and after your primary outcome measures you can switch them to an active drug and see what happens to them. And I'll tell you what's going to happen to them. This is what's going to happen to them. You got placebo up top, you've got active drug down below, disease activity has fallen, you switch the placebo group at month 3 to active drug, and within a month they look exactly like the treatment group. And that's what you're going to see if you do this with NTM. And it's nice to see, it's reassuring, and it allows you to collect more safety data.

Last slide, a small trial to prove efficacy with focused patient populations and vested clinicians who are experts and a good drug, you can always do a larger trial later to prove safety that's cheaper and easier. This is one thought particular as an orphan disease, we don't -- I don't think we need to do two

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Phase III trials that show the same thing. I think it's impossible. I think we need one Phase III trial that's doable and short. It shows efficacy and safety. And then we can refine some of ideas about how to use the drug later, and we can do larger safety studies later.

That was it. Thank you to everyone here who I work with. Cheers.

UNIDENTIFIED SPEAKER: Thank you very much, Kevin. We're running a little bit behind. But we've got time for one clarifying question if there's any questions. Looks like your talk was perfectly clear. Thank you, Kevin. So the final presentation is from Dr. Chen. The title is, Use of Patient-Reported Outcome Measures in NTM Trials.

USE OF PATIENT-REPORTED OUTCOME MEASURES IN NTM TRIALS

MR. CHEN: Good morning. So actually with the wonderful presentation from Dr. Sullivan, Dr. Winthrop and Dr. Leitman, I don't think I need to be here. Actually it's just that it's been -- actually it's shown that that we all have thinking the same

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thing we all are thinking important things in, I mean other than just the cultural conversion but what's the outcomes and that's my job. So I'm only here to just emphasize that FDA are thinking about the same thing.

Usually, that's what we do. So I just want to mention that the brief introduction about COA staff. We are in the office on new drug in CDER. Our mission is to promote and develop and implement of patient-focus endpoint measure in medical product development to describe clinical benefit in labeling. This is an overview of my presentations.

But we have seen many discussion this morning about how outcomes majors in this NTM space and I think it's very clear. So actually I will just jump over a lot of my slides. I don't need to be repeat the same information. Now given this great presentation this morning. Maybe just a few thing that I just like to point out. So from FDA's perspectives how we measuring clinical benefit.

We focus on, you know, (inaudible 0:56:04.6) internal pump, patient feel, function or survived. Now we know that biologic endpoint doesn't really tell

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us how a patient feel, function or survive. So we have the need of outcome, other outcome measure, what we call the clinical outcome assessment. And we have seen discussion this morning quality of life, symptoms, functions and even the not very good 6-minute walk test. Those are one of the outcome assessments.

And so speaking of which, here are the four major type of clinical outcome assessment. We actually for the NTM probably the most relevant and important one will be the PRO Patient-Reported Outcomes studies, the symptom or function reported by the patient themselves. (Inaudible 0:56:57.0) clinician reported outcome that may be also useful as maybe including like say, for example, is the activities that Dr. Winthrop just proposed. There's also performance outcomes and that's the infamous 6-walk test is performance outcome. And also so the report the outcome is used when the patient can now report the outcomes by themselves within the pediatric patients.

This one new model of outcomes that also that

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Dr. Winthrop just mentioned, I will repeat that we have been able to qualify to classify into one of these four is the one in the pattern now with this actual risk state, digital house technology tool. These other new type of outcomes that you wear. It's like wearable like Fitbit like (inaudible 0:57:48.9). This may be able to use your monitoring your daily activities, your sleep, your physical functions.

So these are the type of the COAs and these could be -- in NTM space this could be any one of them. We can consider all of them or just one. But I think it is the framework that we will be discussing today which will be the better outcomes. Now as I mentioned, the patient-reported outcome is probably the most relevant and important one because the patient are able to report about their own symptoms with their functions, their daily activities. For example cough, shortness of breath, fatigue as Amy mentioned this morning.

Fit-for-purpose that we need instruments that is fit-for-purpose and the definition of fit-for-purpose is that fit-for-purpose instruments is a

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conclusion that the level of validation associated with the tool is sufficient to support this conduct we use. Pretty general and here's the more expanded definitions of fit-for-purpose COA as is probably for its intended including the study design patient populations is valid and reliable, is measuring a concept that are clinical relevant, important to the patients and from the FDA's perspective also can be communicated in the level, in a way that is accurate, interpretable and not misleading.

And in 2009 FDA had published a patient-reported outcome guidance, laid out the general principle in develop a fit-for-purpose clinical outcome assessments. What about NTM space? Actually we've been hearing a lot, I'm just -- I don't need to repeat all these symptoms that we heard from 2005 Patient Focus Drug Development Meeting and also what Amy presented this morning.

There is a roadmap that regarding how you develop a fit-for-purpose instruments. The first step is understanding the disease of the condition. I think we pretty much have a lot of information about

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knowledge to that. They are too -- this slide is too small to read, they are in FDA's website. But I want to point out what is the most important one is at the bottom of this roadmap engage FDA early and through our medical develop -- product development. And that is the point I want to emphasize by showing this slide.

We are willing to collaborate, to work with you to develop a fit-for-purpose outcome assessment. Now, the system we worked at has been mentioned a couple of times. They are all patient reported outcome instruments and ensuring the result not maybe (inaudible 1:01:02.1). And actually my first reaction is actually maybe the choice is not sensitive enough. So this is something that we also we want to discuss in the panel and in this afternoon. How can we develop a more sensitive instrument for the patient who seems not able to improve but actually that because we don't have a good tool.

So considering for developing the PRO in NTM understanding the natural history -- we have seen a lot presented this morning. I think we have good

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understandings. Symptom PRO, we know Function PRO, we know (inaudible 1:01:44.0) function of PRO that we can use or we can developed while doing my patient functions, I mean patient functioning in daily life.

As Amy mentioned, actually it is also social, psychological. They feel depressed, they feel isolated. This may be, you know, something that is also relevant and important to the patients. So not just physical functions. So what do the patient say? These are all we can take into considerations. These considerations, I would just skip over them. These are the way that you can engage us in terms of the COA, the patient-reported outcome that you individually can go through the IND/NDA/BLA Pathway that we've been talking a lot about this morning.

However, there's another two pathway that you can engage FDA in terms of developing appropriate fit-for-purpose PRO or COAs. There's DDT, the Drug Development Tool, COA qualification pathway, you can submit your proposal for qualifications. There's another pathway is nonbinding nonformal discussion between FDA and you is what we call the CP, critical

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path innovation meeting pathway that you have a great idea.

For example like Dr. Winthrop's is the activity for NMT, that would be a great -- the CPE meeting will be a great way to communicate to talk about this disease activities and then we can go from there. So I just want to present the way to talk to us that we will love to work with them about this COAs.

The conclusions, we encourage the development and implementation of patient-reported outcomes assessment in clinical trial especially in NTM space. Patient input is the critical importance and understand what we are able to measure. And then keep in mind is that we do want to improve the symptoms. We want to withhold, we want to improve the function or we want to improve both or cure what have you. Early communication with FDA is important. In this website link now you can go find for more information, including the qualification program and the CPIMs. Thank you.

MR. CHALMERS: So I think we now move on to

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the panel discussion part of the morning. And I think we're going to get some questions. So these are the questions that FDA would like the panel to focus on over the next hour of discussion. So it's organized into three real overarching questions. What patient population should be prioritized for clinical trials, what the clinical symptoms, signs or measures should be incorporated into outcome assessments and clinical trials. And then assuming that the primary endpoint is designed to assess direct clinical benefits, when should it be assessed. So without further ado, open the floor to questions.

PANEL DISCUSSION

UNIDENTIFIED SPEAKER: James, is it possible, I might make a comment about Kevin's presentation?

MR. CHALMERS: About the percentage of truthfulness.

UNIDENTIFIED SPEAKER: No, it's a superb presentation, very thought-provoking and I think excellent. But I disagree in a fundamental way with Kevin about curability. And I would use our own data that we have generated to discuss that. It is true

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that in our data with nodular bronchiectatic patients, within 3 to 4 years, about half have a microbiologic occurrence, but two things. Half don't.

So to dwell on the half that have reoccurred is misleading. But the other important thing is that of the 50 percent who have their microbiological occurrence, 75 percent are new genotypes. And so in a sense, this is -- these people require we think isolate. So another perspective is that for the genotype that the patient was treated for initially, there is, if you will, cure and that the patient then because of the underlying structural lung disease reacquires another infection.

I think -- I don't want that to get lost. I believe it is an infectious disease. And I would be -- I would certainly welcome other comments that is treatable and in a real way curable. I don't want -- I don't want to -- I think it's easy to become nihilistic because we have all of these complicating factors. We have underlying bronchiectasis, we have multiple organisms, and we -- all of these, there's an interplay of so many factors. But we are able to

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produce cure for some patients, many patients.

MR. WINTHROP: Dave, I agree with everything you just said. But that's all a joke. No, I do. I actually agree. But I think in terms of, I would just rephrase -- I guess I would shoot back that in terms of trial design and development, this the issue of cure is less of what we should be talking about. Because cure takes a long time to effectuate and your data, as you just said, a lot of people who are cured get reinfected. And it's pretty high percent, and it's within a pretty short time period.

So in terms of trial design and studies, you know, if we focus on cures and outcome, we're never going to make any headway at all. So, yeah, but well, I guess that was my point.

UNIDENTIFIED SPEAKER: So I also just want to clarify that of these 25 to 50 percent of people that we're talking about that do have another infection and we say that most of those are reinfection, it does not equate to pathogenic infection in all those patients. So we start over.

And again, maybe 50 percent of those will

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need to be treated similar to our original group. But just because we say they have a new organism does not mean that they have a pathogenic organism like they had initially.

UNIDENTIFIED SPEAKER: Well, I disagree with both David and Kevin. No, what I hear though, there's tension in that we're discussing, which is, is this an infectious disease or not? So if it's an infectious disease, we think about curing infections. And if it's a chronic inflammatory disease, we think about improving how the patient feels. I mean -- but see, it turns out as both. And I think that's why we're struggling a little bit, because we need to address both of those issues. And I think if we could show better to everyone that there was a correlation, then the discussion would be over.

So I think somehow we need to think about how we better document correlation with the micro biologic response to how patients feel and function.

UNIDENTIFIED SPEAKER: I agree with that. I'd add to it, I mean, just use a clinician, when you enter into treating these people, I mean, you don't

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tell them you're going to cure them. I mean, I never tell them that. Like, I think that's -- I mean, I tell them we might cure it, we might get rid of it, but we're going to make you feel better number one. And we're going to suppress -- we're going to get rid of as much of it as we can. And that's what I say.

And then if we do get rid of it, you might get it back. So I mean, you have to understand that as a patient going into treatment that this is more like your RA man. I can put it in remission and I can stop your treatment. You may stay in remission forever, or it may bounce back on you.

UNIDENTIFIED SPEAKER: You think you spend too much time with rheumatologist. But I disagree, I just think it's important to know that there's more than one -- more than one -- what am I trying to say -- approach to this. Tim, help me out here.

UNIDENTIFIED SPEAKER: Just if I could, I wonder if there are different patients in whom when they come in the clinic, you think my goal here is I think I can cure this, but others you just know --

UNIDENTIFIED SPEAKER: That's a great point.

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There's heterogeneity which you were talking about in the talk, and I was mentioning absolutely, yeah. And there are people that you think you probably could cure and you may go for that and you tell them that, but then there's other people that you're not.

UNIDENTIFIED SPEAKER: So could do you think you could design a trial, you know, with inclusion criteria for the appropriate endpoint? So for this type of phenotype, my endpoint is going to be, I'm aiming for cure. For this…

UNIDENTIFIED SPEAKER: Yes, so I mean I'll just tell you what I think, I know this from our population-based data in Oregon. We've seen it. We followed people out for 9 years. And people with bronchiectasis get it back, people with COP and emphysema only, not bronchiectasis, you can actually cure them. And they don't get it back. And their rate of getting it back is super miniscule compared to some of the bronchiectasis.

Does it happen? Sure, if they have an existing cavity, they can get re-infected. But if you can close your cavity or if you can treat them, cure

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them, you're much more likely to cure that person. The caveat being you got to get them early. If you get them late and they've got too much involvement, it's impossible.

UNIDENTIFIED SPEAKER: Well, I know this is, you know, we're mincing words here. But again, they reacquire organisms. And as Shannon said, that isn't treatment failure and they are successfully treated for a specific episode. I don't know what you want to call that.

UNIDENTIFIED SPEAKER: But I think we have to be unsatisfied with the current treatment regimen because, right, I mean it's 50 percent at best. And so I think in answer to some of these questions, you know, treatment naïve is probably where we need to start, but we need to blow up the treatment paradigm I think. And we need to maybe, you know, decide who we're going to treat and then treat them super aggressive for 3 months or something. You know, add another jug, add something.

And the standard therapy is not working then I think with regards to this reinfection, we probably

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need to come up with some sort of maintenance strategy.

UNIDENTIFIED SPEAKER: What you're speaking to is the broader goals of what are the objectives of therapy? And, you know, this is a perfect point to highlight the fact that it may be different for different stages of disease. What you define as cure and a treatment inexperienced population is a completely different thing than what your expectation and definition of cure might be in a treatment experienced patient. So I think that in terms of the broader goals for both populations we need to step back and as a group consider what are the objectives of therapy and are they different in Phase II, Phase III, different populations.

UNIDENTIFIED SPEAKER: Yeah, I totally agree, and I would just say, look, I agree with what Dave said. But I don't think the word cure enters into a discussion around clinical trial design for phase two and three. And I -- it's a concept we can debate and we can define, but it shouldn't enter into this because to affect cure takes way too long. And we

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cannot do studies of new drugs that take that long to go cure someone and then have them get infected anyway later. So I, you know --

UNIDENTIFIED SPEAKER: (Cross talk).

UNIDENTIFIED SPEAKER: I know. You wanted to make the point that this is infectious, we can care, which I agree with. We can't --

UNIDENTIFIED SPEAKER: And I think -- I mean we really need to clarify that we're really talking about microbiological response, not a cure. That is, we don't do bronchoscopy, we don't do biopsies, we don't do an aggressive evaluation to know is that organism cleared. I think when we have culture conversion by standard sputum analysis, does that mean that I can find any MAC at that point if I look really hard by bronchoscopy or biopsy or something. And the answer is probably not. So I think we just need to also be very clear about the terminology and then where that patient is.

And I would feel much better about a microbiological assessment rather than or culture conversion is even better than cure. Cure implies a

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whole different -- so but treatment is in most instances again in parallel. So you're saying that there may be instances where we don't have a microbiological response and yet patients feel a lot better. I don't know that that happens a lot. And I'd like to -- I mean I would as part of the clinical study try to determine what that means microbiological response discordant with what their clinical symptoms are.

I think that that's a pivotal part especially for the naïve patients. And we understand for nodular bronchiectatic disease as was mentioned, I mean 85, 90 percent clearance rates for sure I think are easily as established with thrice weekly therapy.

MR. CHALMERS: Erica?

MS. BRITTAIN: Yeah, I keep thinking about it as that the outcome shouldn't separate the micro and the clinical. You could say the best outcome is someone who's successful on both. The worst outcome is someone who is not successful on either and where -- how you want to call the discordant ones, I'm not sure which is worse, which is better being -- I would

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think being -- having a good result on clinical and not a good result on culture is better than having a good result on culture and nothing on clinical. But it seems like one way to approach this is not to divorce them but to put them together into one outcome.

MR. CHALMERS: Okay. Ed.

MR. COX: Yes. So when I think about surrogate endpoints and, you know, their development and how we usually get to them. Usually what you have is a trial where you actually show a clinical benefit. So you've established clinical benefit and in that same trial you also have collected the data for the surrogate and you look to be able to show that that surrogate, you know, appears to be associated with the clinical outcome. You know, there's also an understanding that it's on the causal pathway that's important.

And ideally you've got that repeated across a few different trials. And that allows you to come to a firm conclusion that the surrogates you're seeing is actually associated with clinical benefit. You know,

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we think ultimately what we're trying to do here for patients, we're trying to improve the patient's overall condition, trying to make them feel better, we're trying to make them live longer, we're trying to have a more functional.

And so I think, I mean, you know, I agree with you. We have to be very thoughtful as we're talking about microbiologic response versus clinical response. But I think a key thing here is to try and think about how we understand what's going on clinically with the patient. Is the patient better off, and if so, how?

MR. CHALMERS: Bruce?

MR. TRAPNELL: Yeah, I think the discussion around cure is really centered on two different things. Cure the infection, what David's comments and cure the patient in terms of the risk of reinfection, propensity for disinfection. So have to pick which thing we're talking about and focus on that, you know, from a trial standpoint, well, you have to have something specific that you can measure. And there are future -- the patient's future risk of reinfection

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may be linked to that underlying disease in a way that allows you to cure an infection as David is saying. But the patient is not cured in the sense of their risk of reinfection or reemergence.

UNIDENTIFIED SPEAKER: But I would just argue, this isn't any microbial discussion. And so really the infection is the primary focus. I think it's a lot to expect of an antibiotic to have an effect on their underlying susceptibility for reinfection unless we're talking about suppressive therapy or secondary prophylaxis.

MR. TRAPNELL: I couldn't agree more. I think there's two different ways the word cure is being used, with reference to the patient and the risk for whatever's going to happen in the future and specifically about a particular infection at any given time. So we just have to be cleared which thing we're talking about as we go forward so not confused.

UNIDENTIFIED SPEAKER: I agree those thoughts. And I think Tim said it on the -- hit it on the head. I think we should A) just stop talking about cure, because I don't even know what we're

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talking about. I mean we don't even know who's cured.
And Tim's right. Unless you took someone's lungs out, ground them up and culture them, you don't know who's got and who doesn't. And there's a lot of people that have negative cultures and I'm sure they still have MAC laying in biofilm or within a macrophage or something like that. So I don't know that we even need to talk about it anymore now.
UNIDENTIFIED SPEAKER: So I need to bring in the CF analogy then. So our current model in NTM is the micro doesn't define who needs to be treated, it just tells you what you're going to treat. And our decision to treat is based upon symptoms in radiology. If you go back to the history of dealing with Pseudomonas in CF, it all began with an approach of chronic suppressive therapy. You know, the evidence that Pseudomonas was associated with symptoms and progression of disease exacerbations.
But our treatment approach evolved to an eradication strategy. And so now we are driven by micro, we are treating patients at first identification of Pseudomonas. We don't call it cure,

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we say they're culture negative. Some people use the term eradication. And we fully expect that they're going to have it again. And the median time to recurrence is about 2 years. And then we hit them again.
I'm not suggesting that we're at a point where we should talk about eradication strategies for positive cultures in these patients, but that's the focus in terms of what -- how we start thinking about these definitions in terms of true use. So, you know, cure them of their cystic fibrosis.
UNIDENTIFIED SPEAKER: Can we go back to Kevin's point? I want to see if we can, you know, the idea that within 3 months patients who are successfully being treated should feel better. And Kevin, you're talking about a treatment-naïve patient population there, because what we're -- again I'm trying to push this towards the idea of clinical benefit.
MR. WINTHROP: Yeah, absolutely, yeah, treatment naïve.
UNIDENTIFIED SPEAKER: So treat the naïve

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patients, you expect to see a benefit within 3 month.
MR. WINTHROP: I expect to see the start of that benefit around 3 months. I mean, because I think some people actually get worse the first 2 weeks you start a treatment because they start killing bugs, they have more inflammation, maybe their cough gets worse. And then they tend to level out and they can start feeling better. But I would pick 3 months as kind of my minimum. I don't know what my colleagues think, but.
UNIDENTIFIED SPEAKER: Okay. I would just show -- point out that David actually has data in that regard from the study that was in the blue journal in 2015 and a treatment-naïve patient population where they looked at predictors of ultimate microbiologic effect at 12 months. And so reduction in colony counts predicted that, but also a reduction in symptoms predominantly cough at 3 months was predictive of what we're seeing at 12 months. So I do think within that 3-month period that you're seeing culture conversion in the majority of treatment-naïve

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patients, you're also seeing improvement in the symptom of cough, which was what was focused on…
UNIDENTIFIED SPEAKER: Yeah. And that paper is seminal because I mean this -- the idea that you're decreasing basilar burden and it correlates with improvements overall ultimately in microbiology but also in how patients are doing is really what we're all talking about here, you know, what is culture conversion or decreasing basilar burden meaning to the patient.
UNIDENTIFIED SPEAKER: And if you believe the data in that cohort, that's a discriminator to sort out who's going to respond for a treatment success and who's not. And that does discriminate fairly well in as durable than throughout that rest of that period of time.
UNIDENTIFIED SPEAKER: I was only going to point out though that the correlation gets much stronger at 6 months.
UNIDENTIFIED SPEAKER: So I guess the question to go back to these panel questions would be could you design a study in treatment-naïve patients

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where the endpoint was symptoms at 6 months and you'd be confident that that's sufficiently predictive that long-term outcome would be affected?

UNIDENTIFIED SPEAKER: Well, I have a question about that specifically regarding 1H (ph), treatment-naïve versus treatment refractory because now we're talking about predicting that seeing an improvement in symptoms at 3 months with the treatment-naïve population is somewhat predictive of culture conversion. So if we're going to look at a clinical trial that treats treatment-naïve patients and I think that might be beneficial because they might end up with less lung damage. But then when we get to the end of the clinical trial, we're talking about labeling and, you know, indications for that drug. What's the label look like?

I mean or is it also going to be approved for refractory patients and then conversely, you know, what happens when you're studying a drug for refractory patients, can you then say it can be used to treat treatment-naïve patients if we know that treating a patient whose treatment-naïve might be able

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to help them get a better result?

UNIDENTIFIED SPEAKER: And that's a valuable question for translation from an early efficacy read that one might be looking for in Phase II study in order to, you know, figure out if you have a drug worth pursuing, worth extending into a long study that could potentially run as long as 8 years. And then moving into Phase III and a different population, a treatment refractory population. So, you know, one of the questions for this group is how does that translate an early efficacy look in one patient population to Phase III or to your point if we study only in treatment-naïve because it's the cleanest, how does that translate to treatment refractory patients and labeling?

UNIDENTIFIED SPEAKER: So in terms of your question regarding labeling, I mean in general the label reflects the population that was studied in the clinical trials.

So I think this question is more to do with, you know, that there is an unmet need right now and then we're looking at feasibility, how should we

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prioritize clinical trials going forward, So I think it's not that whether we -- one population is preferred over the other. I think given where our knowledge is right now and what would be the, you know, in terms of prioritizing do -- should we focus on treatment-naïve.

I mean we heard from Kevin that there are some advantages and maybe focusing on treatment naïve population at this point. But does that necessarily translate into treatment effect on in a refractory population. I think is very hard to answer. Again, the endpoints you choose -- the timing of the endpoints all of that would really be dictated by the patient population that you plan to study.

UNIDENTIFIED SPEAKER: I don't know that those two populations need to be one or the other. I think their advantages are both. It depends on the drug. I think it depends on whether or not we've got adequate preclinical data to show effect, which I'm not sure we really have animal models that give you a definitive answer of that.

And I think it depends a lot on how much

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money you have to spend on your first in target disease trial. So I think if you've got somewhat shaky animal data to invest a lot of money into a large study and treatment-naïve patient population, we really don't have an effect -- an idea of what this is going to do in human disease, may not be a preferable way to go for a given drug. It may be for another drug where you have some experience already in other diseases showing effect or showing safety.

UNIDENTIFIED SPEAKER: So I'm not sure if there's a requirement to lump them or separate them, but I think we've heard that there's enough differences between these patient populations such as the endpoint, the timing might be different so then there are difficulties in combining them into one patient study.

UNIDENTIFIED SPEAKER: So I have something that's really important as you're designing this and considering, if you're going to have a placebo arm, a true placebo arm, I would not study that in a treatment refractory group.

UNIDENTIFIED SPEAKER: We haven't heard any

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comments yet on whether to put CF and non-CF patients in the same trials, which is question number three.

UNIDENTIFIED SPEAKER: No.

UNIDENTIFIED SPEAKER: No.

UNIDENTIFIED SPEAKER: I have my own bias.

UNIDENTIFIED SPEAKER: No.

UNIDENTIFIED SPEAKER: So answers is no, because they're so different.

UNIDENTIFIED SPEAKER: No.

UNIDENTIFIED SPEAKER: Does anyone disagree with that?

UNIDENTIFIED SPEAKER: No.

UNIDENTIFIED SPEAKER: I'm going to take that one on that. So there's -- well, first I just want to make one comment about treatment refractory and what worries me about studies in this population that they've already proven they're not, well, microbiologically responsive to the therapy. One question is are you actually getting drug to the bug? And if you're not, adding another drug isn't going to expect to improve upon that. It's particularly a case of cavitary disease.

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So in the CF versus non-CF, you know, James made it clear why they sort of targeted a specific population in the Phase III study with Liposomal Amikacin. There was a small subset of CF patients in there. And they didn't seem to have the same robust response. And that's a decision moving forward, but you still have to come forward as explaining why that population is different and would not be responsive to a therapeutic treatment.

I can tell you that when we've done the numbers, looking at CF studies only, you got a feasibility problem in terms of how many patients you could actually study. So the CF Foundation is actually investing a large sum of money into the investigation of NTM, obviously their interest is in the CF population, but fully committed to if there are therapies that are beneficial to those that don't have CF, that's okay with them. So in our discussions we actually are contemplating whether to include non-CF patients in our therapeutic trials. But I haven't heard anybody throw up a reason why they couldn't be enrolled in a study.

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UNIDENTIFIED SPEAKER: My concern is power. How do you power that kind of study if the CF -- if the CF population is already having trouble enrolling studies? And we've already seen how difficult it is to enroll in a non-CF population. Once you get, you know, done with a study, you have to start stratifying the data out and looking at the two different populations. And once you stratify the data, you start losing power. So you really have to overpower at the study. What does that look like? How do you power that study? I'm concerned about that.

UNIDENTIFIED SPEAKER: You would have them all in one big group as part of your primary analysis that would do an analysis afterwards.

UNIDENTIFIED SPEAKER: You can't stay with primary analysis.

UNIDENTIFIED SPEAKER: The issue isn't so much that there's a reason why they wouldn't respond, but that they might respond differently or the assessment of their response might be different, you know, the instrument might…

UNIDENTIFIED SPEAKER: And I think --

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heterogeneity into already a very heterogeneous group, the NCF and non-NCF, we've even burned enough times with the bronchiectasis experiences. So I would be inclined as far as NTM goes to try to keep that sorted out at least initially because if for no other reason heterogeneity. The other aspect of this, we have to also be clear about say treatment-naïve. It's not just about even culture conversion microbiological response, but time, shorten that interval. Why should we have 12 months, 18 months, 24 months of therapy.

So having a new strategy to shorten therapy and then look at durability would be a sufficient endpoint in itself. So it may be that the culture conversion rate is the same but I can do what I do now and say 12 or 18 or 24 months in 3 or 6 or 9 months. And that would be a tremendous benefit for patients in cost.

UNIDENTIFIED SPEAKER: Just to repeat, the variability that is what we're all concerned about with all the heterogeneity. And as you introduce different patient populations you increase the variability of the response in a small patient

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population, which just gets larger and larger, requires stratification, harder to stratify, more sites around the country. It's best to be get an answer and then study whatever we want to study and what's appropriate to study in the right population.

UNIDENTIFIED SPEAKER: Yeah. And I agree, I mean I think you'd be -- you could incorporate them, you could deal with it, you could, you know, randomize, equaling each groups and minimize -- there's ways to deal with for trial sample. But I disagree with Patrick, I think you can totally power the studies in CF if you do placebo controlled trial. So you have to enroll the right patients that you think is ethical to enroll placebo weighing. But I do think those patients are out there and you could power study with, you know, 50 to 75 CF kids.

And it depends on your outcome measures too, but I think you, you know, if you look at bacillary outcomes, particular through the quantitative and you look at your patient-reported outcomes, CFQR, things like that, I think you can do it but --

UNIDENTIFIED SPEAKER: If you can get it down

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to 50 to 70, I would agree with you.

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: The worry is that it is exceeding that. I just want to make a comment that the issue with bronchiectasis was that the temptation was there is CF and there is non-CF bronchiectasis. And I think a big failure of our trials is the assumption that non-CF bronchiectatic patients will respond similar to bronchiectasis patients. But now is for learning is that there's multiple endotypes and multiple phenotypes and trying to hash out which of those patients are most likely to respond.

And so to just start thinking nodular bronchiectasis is going to be the model is going to fit that, I'm not so sure that that's right. I think Kevin has a point that you're looking for the population that is likely to demonstrate ability to change is what you're after.

UNIDENTIFIED SPEAKER: Yeah. I'd like to add to that because that's my area, I mean in terms of CF versus non-CF, even for the treatment-naïve versus the refectories NTM, are we still talking about the same

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outcomes that, for example, maybe for the treatment-naïve the main primary outcome should be cultural conversion but for the refectory we should looking at how patient feel, function, these outcomes. So if we -- if different outcomes is more appropriate for different subpopulation should we then actually combine them into the same study? So that's my question for you.

UNIDENTIFIED SPEAKER: Goes back to the objectives of therapy, you can -- I think you can think of these as three different subsets of patients. Because the -- what the patient is most interested in if they're a CF patients or if they're a treatment refractory patient with macro or treatment-naive patient may be completely different priorities. And, you know, defining those outcome specific to that patient population at which you're going to see a response may be a cure associated with some clinical improvement in less fatigue in the treatment-naive population. In the treatment-experienced population, they are looking for a clinical response on treatment period that makes their quality of life improved. So,

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you know, I think it goes to the same extent to the CF patients as well. But these needs to be separately defined.

UNIDENTIFIED SPEAKER: And I think this begins to raise the question of is it statistically or methodologically possible to use one, two, three or four different outcomes as any one of those four as a positive study. So if you say that I'm going to pick a PRO or a sputum or FEB1 or something else and you'll take any of those four then -- and the question I guess I would go to the maybe FDA and the stance folks from a methodological problem is that is that legal essentially.

UNIDENTIFIED SPEAKER: Yeah, I'll start and then Erica is going to fill in. So, you know, in a field where you're still trying to figure out what's the best endpoint, what's changing, I mean that sounds like where you want to do sort of a Phase II study. And you want to see if you can figure things out. Now Phase II is hard sometimes because the numbers are small. So unless the change is dramatic you may not see too much. But, you know, ideally you want to try

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and figure out what it is that you're measuring before you get into a Phase III trial.

And then as Erica will tell us in just a minute, you know, if you do start to go in with multiple different endpoints, then, you know, there's multiple different ways that you can win then there are certain additional sort of statistical, you know, you have to divide your alfa across the multiple different ways you can win because as you have more different ways you can win that the likelihood of winning by chance alone is greater, but Erica is going to help us with that okay.

MS. BRITTAIN: Okay. We already said it but, no, I mean it is legal if it -- I think that was a question, was it is legal. Yes, it's legal but you have to do it in a very -- in a conservative way so that you're not cheating. I guess the potential downside is it end up interpretable depending on how you do it.

UNIDENTIFIED SPEAKER: So I guess just a quick comment…

UNIDENTIFIED SPEAKER: It may increase your

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sample size too considerably, so if you can…

MS. BRITTAIN: They could, right.

UNIDENTIFIED SPEAKER: If you can pick a best way before you get into Phase III, your sample size, you know, won't balloon incredibly because you're going to win, you're going to win many different ways.

UNIDENTIFIED SPEAKER: So the way I heard Tim's question was not to have four primary outcomes but was to have a kind of composite of multiple outcomes where one is response. And if you think about it, most PROs are a composite. They take cough and breathlessness and sputum and they give you a final score. And I think what I picked up was Tim was saying, well you could have an improvement in 6-minute walk or an improvement in call for, and they make one outcome and that would be…

MS. BRITTAIN: Right. So that's similar to what I was trying to say before, that you don't necessarily have to have separate outcomes and then do a multiple comparisons which is the penalty that Ed was referring to. But you could set it up so that your outcome is just inherently multifactorial. That

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does lead to interpretation issues but it's something to consider.

UNIDENTIFIED SPEAKER: But I think what we heard this morning was that some patients have coughs, some patients don't, so if your primary outcome is cough, you lose a significant chunk of your patients who could not improve. The same with exercise capacity. So in some ways it makes complete sense to measure multifactorial outcomes.

UNIDENTIFIED SPEAKER: I think I'd like to make a plug for a recent FDA guidance, the multiple endpoints guidance is very instructive in this regard and walk-through all the different ways you can handle, well to whether it's a composite and so forth, and it's actually really good read if you're interested.

UNIDENTIFIED SPEAKER: Yeah, I mean, that's why I make this pitch for a combined outcome measure for all these reasons. And you know look at the ACR 20, and the ACR 50, and the ACR -- so ACR 20 is 20 percent improvement across those five measures. So you don't have to improve in each of them. In fact

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you might have even got worse in one of them. But overall you've had this overall improvement. And that -- and then statistically you don't have these multiple comparison issues. And of course this doesn't help we don't have a combined outcome measure. Now I have this provisional I wrote on a plan, but, you know, I think we should commit ourselves to developing it, that's what I think we should do.

UNIDENTIFIED SPEAKER: Right so we're talking about 2 very different things. I mean you can have a composite end point. And it is correct that oftentimes, you know, PRO instruments look at multiple different domains in multiple different, you know, things that they're assessing. And that's all fine. So I think we need to be really clear about what we're talking about because we're talking about composite endpoints or PRO instrument that's measuring a variety of different things. It's then coming out to a single score. Yeah, that's, you know, quite common, so -- and it's very different in the multiple endpoint issue.

UNIDENTIFIED SPEAKER: So, you know, I think

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the more you make things tailored to the specific patient the better from the standpoint that you're measuring whether that patient improved and the worse in terms of figuring out what the effect of the drug, you know, is. So, you know, for particular patient that -- for them, you know, the fact that they used to be active might be the most important thing.

So for them a change in their physical activity, you know, would be huge. And so conceivably you could say, okay, at baseline what's the most important thing to you, what would, you know, if you change in this area what would be the most important one.

And you could actually say, you know, okay, for this patient it's a change in this. And if you did that at baseline you'd have a valid test. But then at the end of the day, you know, it'd be kind of difficult. You'd say, okay, this drug help patients improve in what was most important to them. But the fact is it was different for different patients. So that becomes hard to, you know.

But could I just -- you know, you guys

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actually needed statistical help before and didn't realize it with the stratification and then the CF. You know, what's really important is whether there is a treatment difference in CF and non-CF. So the fact that it's adding variability is not a problem at all. If you're going to do a stratified analysis, which doesn't mean what I think many people at this table thank it means.

Stratified analysis means you're going to compute the treatment effects separately in these different groups but then you will combine them, you know, and so you will not necessarily lose power if the effective treatment is the same in CF and in non-CF. That's really the important question is, is the effective treatment the same in those two groups?

UNIDENTIFIED SPEAKER: Can I ask a question? Okay. And so we have we have all kinds of questions about the population and when to study and what to study. But like if we had to design a trial tomorrow, and I'm getting the sense it might be in a bronchiectatic nodular group in general, I'm getting that sense possibly.

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And if that's the case, what would be the set of symptoms or signs that we'd be interested in? Is there a PRO that we can use today? And then if so, if we were to measure it at 3 months or 6 months, and we saw a clinical benefit 3 months or 6 months, how long will we anticipate that clinical benefit would continue beyond that 3 to 6 months for anyone?

UNIDENTIFIED SPEAKER: Well, so there's a lot of questions there, but I'll just -- I'll take the first one and that I -- and I said in my talk, I would enroll noncavitary patients. And that's how I would write it in your inclusion criteria. Because if you said nodular bronchiectatic, it means they have to have nodules in bronchiectasis.

And not everyone has bronchiectasis. So I think this is this about whether you can use a placebo. And I don't think you can use a placebo when people have cavitary disease, so I would exclude those individuals.

MR. DALEY: But just to take that thought maybe one step further, so if you are using a microbiologic outcome, then using your argument

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earlier you want to get people who can have change. So the people who have the greatest chance of change are those with the highest bacterial load, right?

UNIDENTIFIED SPEAKER: Yeah.

MR. DALEY: So because not nodular bronchiectatic disease has a lower bacterial load. So now we've already set the curve maybe against us a little bit on the microbiologic outcome.

UNIDENTIFIED SPEAKER: Yeah, I agree with Chuck completely. So I think you're going to do cavitary patients, which I'm all for, you just can't have a placebo -- you can have placebo-controlled trial but you've got have two active arms, like you can't have just placebo. That's -- I mean ethically I don't think we could do that.

UNIDENTIFIED SPEAKER: And what about if -- I mean you mentioned if you are looking at micro, I mean I get the point about the high micro count, but how about if you wanted to look at clinical as your primary endpoint, so that's a clinical outcome and let's say it's a PRO?

UNIDENTIFIED SPEAKER: Chuck is right, those

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people get better. I mean we're talking about cure. And I already said I don't think we should ever say that word again today. But you can cure those people.

UNIDENTIFIED SPEAKER: You said it.

UNIDENTIFIED SPEAKER: They have fevers, they have night sweats, they're weight losing, they're being -- they have consumption basically, so you can measure improvements in all those…

UNIDENTIFIED SPEAKER: So the clinical change should be present also?

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: Kevin, you showed data with the QoL-B that the only patients in your observational cohort who got better had a score less than 70, so would you advocate enrolling patients with a minimum symptoms score?

MR. WINTHROP: Yeah, it's a really good idea. I mean if that's going to be your primary outcome measure, a part of it, then I think you got to enroll the people who might change. So having some exclusionary criteria around that or at least a priority statistical analysis plan that takes into

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account would be key, I think.

UNIDENTIFIED SPEAKER: Or you might be able to stratify depending on multiple endpoints and just stratify for patient enrollment, whether it's by symptoms score and even which one of the domains versus culture conversion in the context of a nodular bronchiectatic patient versus otherwise. Because if you have a large bacterial burden or bacillary burden and someone fibrocavitary disease, and you use a drug that's not going to at all get to that cavity, it doesn't really matter at all. You're not going to be any further along and having any positive impact there. And that's predictable. So even though you got the right population for that particular drug whatever that example would be would be a poor choice.

UNIDENTIFIED SPEAKER: So I guess a more broader question are -- do we still need to do more Phase II or are we ready for Phase III, because if we're ready for Phase III we need a clinical endpoint.

UNIDENTIFIED SPEAKER: And I think the easy answer is, yes, I think it's both. It depends on circumstance and what you want to start with and what

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the goal of therapy I think, Angela as you had pointed out, I think as long as you're a priority clear about that, what you're trying to do for a specific population I think some things we'll need to go back to Phase II and some things we'll be ready to go right at Phase III.

UNIDENTIFIED SPEAKER: And I think just because it's Phase II doesn't mean that we don't want to use the clinical endpoint for that early efficacy read.

UNIDENTIFIED SPEAKER: Could you imagine abandoning the micro endpoint and just be on clinical and do 3 months of therapy and be satisfied and let us figure out how long to treat them in the long run? And where I'm going with that is if I ask the docs in the room, if it's 6 months, your patient says I feel great, their x-ray was better, and they still were positive, would you change your therapy? And then when I look at the treatment refractory patients and they're on drug for 6 years on average, if it wasn't working doing something, why didn't the docs just stop it out completely?

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UNIDENTIFIED SPEAKER: There is an issue though with coinfection with these patients, because we're talking about antibiotics. So in a bronchiectasis patient who I put on multiple broad spectrum antibiotics, if they feel a lot better but they still contrapositive it may be something else that I'm treating, it may be the pseudomonas or something else.

UNIDENTIFIED SPEAKER: And I mean we do that all the time in the NTM world. I mean, patients don't have a micro biological improvement yet they feel much better and we're inclined to continue therapy. And I think we'd be inclined not to stop therapy in that particular group we just extended. And we do that all the time day in day out.

UNIDENTIFIED SPEAKER: So how long have you extended the -- what's the determining factor?

UNIDENTIFIED SPEAKER: Well, it depends on how -- and that's something we should -- that would be based on symptoms and sometimes it goes on for years.

UNIDENTIFIED SPEAKER: Sometimes forever. I mean, think of your abscessus patients, I mean, they

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don't change -- your goal is stability, I mean, that's the goal, it's not to make them better. The goal is to keep them from getting worse. And that's true for some of the MAC patients too, it depends on how severe a disease is. But that's a win. And you don't need to make them better, include a sterum (ph) your way. If you can do that, that's fantastic. Your win is to keep them from getting worse.

UNIDENTIFIED SPEAKER: Understood. And I mean I -- yeah, we want patients to feel better. But for designing the clinical trial, it can't go on forever, right? We have to have like defined endpoints either 3 months 6 months or what not. And then we need to know what that means a little bit longer term for that patient as well when they're off therapy perhaps.

UNIDENTIFIED SPEAKER: Borrowing from other fields perhaps. As Kevin's alluded to with the rheumatology study, as you know from the oncology world we look at endpoints that are progression-free survival, right. And so extending that to this population for every treatment refractory and looking

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at delay and disease progression, period, as opposed to a different goal for therapy with the treatment-naive population I think is where we're trying to get to in the treatment refractory.

UNIDENTIFIED SPEAKER: Patrick, so would you suggest palliative therapy? It's -- you say we take microbiology out as an endpoint. I can make people feel better without antibiotics. Is -- I'm curious what -- are you completely dissociating this as an infectious disease?

MR. FLUME: No, but I'm saying you're making them feel better with antibiotics.

UNIDENTIFIED SPEAKER: But your endpoint was making feel better, which is of course is paramount. But I can make them feel better without giving them antibiotics.

UNIDENTIFIED SPEAKER: Yeah, you can also make them feel worse giving them antibiotics, seriously. It's hard to…

UNIDENTIFIED SPEAKER: Gene actually showed a slide that showed the thing that made them feel the best was stopping the drugs altogether.

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UNIDENTIFIED SPEAKER: That's right.

UNIDENTIFIED SPEAKER: Well, covering the benefit perhaps (cross talk).

MR. WINTHROP: So then it gets to -- when to measure and what not. But again we're now back to talking about refractory patients. So I think refractory patients is a very separate group. And to me I try to say in my talk, there is -- the reasons to choose whether you're going to study treatment refractory or naive have to do with what your -- how active you drug is, what your competitor is and what type of patient you're putting -- you know, when you're going to measure your success. And those are the reasons to choose one or the other.

UNIDENTIFIED SPEAKER: So how would you respond to Peter's question, Kevin?

MR. WINTHROP: My question, what I would say is that we should spend the rest of today talk about how to treat treatment-naïve people, that's what I think. Because I think if you show benefit to treatment-naive, you have -- what you want to show is you have an active drug that works and is safe. So,

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you know, focus on people that have the capacity to change, show that there's benefit. Then you can do studies later and salvage therapy and, you know, treatment refractory patients to figure out how best to treat them in combination with other drugs that's already failing.

UNIDENTIFIED SPEAKER: So I tend to agree with you that it's going to be very hard to show symptom benefits in people with refractory disease. But I think we've heard from a number of people including Amy and the patients earlier. The big advantage of a salvage regimen is to be able to allow you to stop it earlier. So is the end stop therapy earlier? And then patients may feel better than the comparator who are still on drugs. Is there a way we can design timing of PROs to compare or to capture the benefit of a microbiological response in that we can stop drugs and patients feel better once the drugs have stopped rather than assessing the endpoint at 12 months when they're both still on drugs and you will not show a difference?

UNIDENTIFIED SPEAKER: This is key, I mean

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you're measuring respiratory symptoms and you give them something that makes the respiratory symptoms worse. You got to think of that.

UNIDENTIFIED SPEAKER: And I think if you have a platform that you're doing this in real time rather than intermittently every month, every other month, every 3 months, something like that, I mean with new platforms and the data analysis that's available, you know, every day or every other day and do continuous development, I think that that's probably where the opportunity lies to get a little bit better representation, whether I'm really having a positive impact on symptom control. So we -- I think those platforms are close to being available.

UNIDENTIFIED SPEAKER: And just -- hearing the discussion to about, you know, can you, you know, use the PRO to measure some of the adverse effects of the antibiotics, I mean there's always two sides of the equation, there is a benefit side and a risk side. And so, you know, I hear the part about wanting to stop the antibiotic sooner because of the, you know, adverse effects that they're causing, and that makes

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total sense. But, you know, it's still somehow we have to figure out what's going on in the benefit side of the equation too, you know, are, you know, are we providing clinical benefit to the patient?

UNIDENTIFIED SPEAKER: I guess the point is the benefit might be the microbiological benefit that you can stop drugs earlier in patients over the course of 24 months will feel better because they got off drugs earlier.

MR. COX: Well, yeah, no, I get that. I think the part that we're missing here is that changing their microbiology, changing their culture is actually providing them with clinical benefit, that's what we need. And if in fact you're treating them with antimicrobial and making their cultures go negative helps them, you know, it slows disease progression, you know, physiologically they can function better, they feel better, they have less fatigue, they have less cough, whatever that may be. It seems that we really need to understand what that clinical benefit is because obviously, you know, these therapies do have adverse effects and we're trying to

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balance the equation here on benefit and risk.

UNIDENTIFIED SPEAKER: No, I agree Dr. Cox. I just think it plays into when you measure. So I think if you have a 6-month trial and you're stopping 6 months, sure you measured 6 months, but you should also measure a month later no matter what drug you're studying. And because that benefit, the clinical benefit of the drug may be much more apparent a month later than it is the day you're stopping drug due to those antibiotics associated adverse effect.

UNIDENTIFIED SPEAKER: So we may see clinical benefit 1 month after stopping the drugs, but then how long does that clinical benefit typically last in your clinical experiences?

UNIDENTIFIED SPEAKER: 10 days.

UNIDENTIFIED SPEAKER: Well no, that goes back to the paper that that we talked -- that our paper from 2015. Now, it wasn't -- it didn't involve an inhaled antibiotic, but patients who -- patients were better at 6 months and that predicted microbiologic outcome, that predicted both clinical and microbiologic outcome. So I recognize that we --

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you tossed in a complicating factor which is in an irritating substance that people are inhaling. But I do think at 6 months -- but, you know, when you're talking about the kind of outcomes though you're way beyond a 3-month and 6-month trial. And what I think about as multi drug resistant TB, again not to -- we don't want to talk about TB, people are miserable the entire time they take much medicines for MDRTB, and then they're better. I don't know exactly (cross talk).

UNIDENTIFIED SPEAKER: And I think maybe the answer to your question, Peter, my experience is that if patients do respond and we finish our course of therapy that that response is sustained for at least 3, 6, 12 months minimum before they get re-infected or re-symptomatic. And then we address that question that Shannon brought up about do they need to be re-treated again.

Usually that's not within the first year. And then there are always exceptions and that sort of thing. But for the most part if somebody's really had a favorable response, completes a full course of

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therapy, it's generally sustained for at least a few months, 3, 6, 12 months before they started having symptoms, sometimes even longer periods than that.

UNIDENTIFIED SPEAKER: I mean one thing we haven't discussed is the co-infection issue, and, you know, should we really be studying a totally clean MAC population with no identifiable co-infection because, you know, a lot of the drugs we looked at -- and that's why CF complicates it too, because we know they have pseudo moments, right?

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: So we haven't really figured that question out either. And maybe we'd be better off with a very pure NTM-only population.

UNIDENTIFIED SPEAKER: One thing you just said, I'm sorry, you were just talking about when a patient gets, completes a course of therapy and then they could be clean for the next 6 months, 9 months, 2 years. You know, we're hearing conversations about a 6-month course of therapy. And you just said, you know, when a patient completes a course of therapy, I imagine your course of therapy is not 6 months.

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UNIDENTIFIED SPEAKER: Right now, I mean we would use guideline-based 12 months sputum negativity as a full course, whatever that is. Sometimes that takes, you know, 15 months, 18 months something like that. But 12 months of sputum negativity is what the current standard is based on the guideline.

MR. CHALMERS: So Bruce has been waiting a while to make a point.

MR. TRAPNELL: I just wanted to clarify our target of the discussion is, are we -- is the outcome measure discussion-centered on treating an infection or the risk of the patient getting re-infection in the future?

UNIDENTIFIED SPEAKER: That's treating an infection.

MR. TRAPNELL: Because that might help our discussion, specific outcome measures if we're really clear about that distinction.

UNIDENTIFIED SPEAKER: So I mean we want to make the patient feel better, function better and survive longer.

MR. TRAPNELL: Of course, but if you're going

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to do a trial, it may be very helpful to be quite specific about exactly what it is you're trying to --

UNIDENTIFIED SPEAKER: We're trying to make the patient feel better, function better and survive better.

MR. TRAPNELL: And want -- and have them live long and be (cross talk)

UNIDENTIFIED SPEAKER: Yeah, yeah, and -- but remember here that the hypothesis is that the bacteria that's in their lungs is what's causing them troubles, and that's what's making, you know, the patient have difficulties. And so treating that should result in the patient feeling better, function better or surviving longer. You would hope to see a correlation between the patient having a clinical benefit and the change in those cultures from that trial.

MR. TRAPNELL: So it sounds to me like you're talking about treating the infection that they have at the time they enter the trial?

UNIDENTIFIED SPEAKER: Yeah.

MR. CHALMERS: Is there question from the floor.

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MS. COHEN: Hi, yeah, thanks very much. It's Kera Cohen (ph) from Johns Hopkins. Just -- I'm not sure why there's such doubt about the microbiologic outcomes for patients who are treatment naive with their first episode of MAC. We all take care of these patients and they tend to -- once you put them on treatment, if they're going to respond you see a response within 3 to 6 months for symptoms, but you generally tend to see that with their culture data as well, that they're -- they may not go from culture positive to culture negative which is a dichotomous end point.

But we definitely see their time to positivity of their culture decreased, their bacterial burden. They may go from AFP smear positive to smear negative. And there's other data that are telling us that killing these bacteria and decreasing their bacterial burden is helping improve their symptoms.

UNIDENTIFIED SPEAKER: And that wouldn't be a problem.

UNIDENTIFIED SPEAKER: We agree. We agree. Yeah, I mean if in fact the trial can show, you know,

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the reduction in microbiology, you know, microbiological counts, microbiological cultures and that correlates well with the clinical improvement then that shouldn't be an issue, the clinical improvement will be there.

UNIDENTIFIED SPEAKER: Chuck made the point about concern that we would enroll patients with too low a bacillary burden to really be able to demonstrate that benefit, how do we get around that?

UNIDENTIFIED SPEAKER: Well, yeah, but I had pushed because I wanted to not lose track of something. And said -- and that's about co morbid or co-pathogens. I mean if we start getting a really tight definition of what treatment naive is and then we say that 30 to 50 percent of the people who we know are going to be co-infected can't be enrolled in the study, we get into really a nonviable situation.

So I would say -- and we know the people enrolled in studies become infected during the course of the study with copathogens like Pseudomonas. So I would say that it would be nice to have that clean. But I think in practicality it'd be very difficult to

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require no co-pathogens at the beginning of therapy. And because it will change during the course of therapy.

In terms of the -- well, you know, I come from TB where something is very clear to me that's different between TB patients and NTM is TB patients have a very consistent microbial load. If they're smear positive in three specimens, at least two or three will be.

In NTM it's all over the place. The variability from sputum to sputum is significantly different than TB patient. So in TB patients we know that it's just -- if they come on the first 3 specimens, it's very consistent bacterial load no matter how many times you check it, but with NTM it's not. So when we start getting these less sick patients, with less extensive disease, we recognize that bacterial load will be lower. I mean that's just I think that's a fact. You agree?

UNIDENTIFIED SPEAKER: I agree. Yeah, I agree.

UNIDENTIFIED SPEAKER: I mean two other

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considerations. I understand the appeal of the treatment-naive patient population with being able to do placebo controlled studies with a single drug. But the issue is that, especially, as you get patients enrolling with higher bacillary burdens, those monotherapy trials have been done before and issues of resistance developing a relatively early on is an issue.

If you set a 3-month endpoint for the trial or a 6-month endpoint for the trial and you plan to stop your single drug then you've got the issue of dormancy and potential for true relapse for recurring not reinfection. So it's a bit more complicated than that.

You know, if you're going to try to get around resistance, you're talking about putting multiple drugs on, you've got interacting affects of that. One of the appeals of the treatment refractory population is that they are already on those multiple drugs. But I understand that there are differences. I just want to make sure that those other factors are taken into account if we're moving the day's

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conversation toward a treatment-naive patient population.

UNIDENTIFIED SPEAKER: Yeah, no, I think those are right on, and I tried to touch on it. I think you could do a monotherapy placebo-controlled trial, but you could do also multidrug combination. It's just the -- it's a lot harder to do, right? You have to justify the combination, you have to produce preclinical data that says this makes sense. So it's just a bit longer of a pathway. But if you're really worried about resistance of your particular drug. I mean it seems like that's what you want to do. And if it extreme, you want your drug used -- to be used with, you know, drug A, B, C then that's probably what you're going to do because it's going to be in your label.

I mean, maybe the best way to do it is the three-arm study where you have placebo, you have a mono-therapy wing for some time period anyway to learn about the drug and you have another exposure group that's multidrug exposure group that you think your best regimen is. I mean you could think of lots of

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permutations of this, but.
MR. CHALMERS: We're running into lunch, so our colleagues have been standing here for a while waiting to ask questions.
MR. NOLE: Jeff Nole (ph) with Cupex (ph). So rather than a dichotomous variable, could you look at a categorical analysis of the combination? So the best outcome would be eradication and improvement in symptoms. And at the other end of that spectrum would obviously be worsening of symptoms which might be due to the disease or the drugs and then eradication. So that would allow -- and then you'd look for a shift to the right of those categories as the case may be. Could that be acceptable as a potential analysis?
UNIDENTIFIED SPEAKER: So that was what I suggest previously as something to consider. And I would consider an ordinal outcome where the best outcome is improvement on both. On the -- and the worst outcome is failure on both. And then you'd have to decide how you order the discordant ones. So those are the four possibilities.
If you did that though I think you would

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really have to also look at individual -- the clinical outcome by itself and micro outcome but itself. But if we really think the right way to do this is the clinical outcome, I don't know if that's the way to go.
MR. CHALMERS: So final point before lunch.
UNIDENTIFIED SPEAKER: Yes. So I have a comment and a question. So I think in treating any infection, I just want to agree with David, in treating any infection you have to treat the infection you have, right, whether it's a catheter infection. We don't usually say, oh -- but they will get another catheter infection in a year.
So I think, you know, microbiologically, you follow this and you can tell whether it's a new infection a re-infection. So I just want -- but I actually wanted to ask, it seems like people are considering additional one drug to -- what would it look like? What would these clinical trials look like if you had a completely new regimen that you want to compare in naive patients with what's there?
MR. CHALMERS: Does anyone want to take that?

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UNIDENTIFIED SPEAKER: Well, I mean there's the issue of demonstrating the effect of each individual drug in the combination, if it's problematic to treat a drug with any individual drug because of resistance concerns. And you may not be able to establish it clinically. I think the question is, could there be -- given it is an infectious disease, could there be a constellation of in-vitro and in-vivo animal models studies that could be done to demonstrate that each of the elements of the combination actually do contribute in the petri dish in the animal models and so forth that that would give you enough confidence that each drug is actually contributing to the clinical fact in the clinical trial because you're unable to do it in the clinical setting.
MS. NAMBIAR: And I think some of these questions will come up during the case study this afternoon, so I'm hoping after lunch we can clarify that. Thank you.
MR. CHALMERS: Okay. Well thank you to all of the panelists for a lively discussion, enjoy your

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lunch. But back at 1:00 for the public comments and other case studies.
LUNCH
FORMAL PUBLIC COMMENTS
UNIDENTIFIED SPEAKER: Should we do it?
UNIDENTIFIED SPEAKER: Sure.
UNIDENTIFIED SPEAKER: Okay. Welcome everybody back from lunch. And we'll start out the afternoon session with the opportunity for public comments.
UNIDENTIFIED SPEAKER: One of the presenter's -- the one who is talking.
UNIDENTIFIED SPEAKER: Okay. Do we -- do we have our --
UNIDENTIFIED SPEAKER: I have the names.
UNIDENTIFIED SPEAKER: Yeah. And do we have --
UNIDENTIFIED SPEAKER: We have slides.
UNIDENTIFIED SPEAKER: -- some degree of organization here?
UNIDENTIFIED SPEAKER: Yeah, we have.
UNIDENTIFIED SPEAKER: Okay. So I think our

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first public commenter, is it -- and you'll help me with the pronunciation when you get to the podium, but I'll try. So Gyanu Lamichhane --

MR. LAMICHHANE: 100 percent correct.

UNIDENTIFIED SPEAKER: -- from Johns Hopkins University. And please reintroduce yourself so we learn the correct pronunciation please.

MR. LAMICHHANE: Hi. I'm Gyanu Lamichhane.

UNIDENTIFIED SPEAKER: Okay.

MR. LAMICHHANE: I am a basic scientist at Johns Hopkins University in the Division of Infectious Diseases in the Department of Medicine. And our lab has been working on NTMs for the last 6-plus years, and among NTMs, we focus on abscessus primarily and we've also done a little bit of work on the -- on mycobacterium avium. And between these two NTMs, we focus on the molecular vulnerabilities in the synthesis of the cell wall: if you can destroy the cell wall, these bugs die.

So our work has been around that. And we do from very basic work, but with the focus on translation, so from the bed to the bench back to the

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bed kind of work. And you will hear about this in the next set of slides what we have done so far. And Liz will present that, Liz Story-Roller. She's a fellow in our division and in our lab and she's done this translational work, but based on very basic science.

And before I leave, I would like to thank the organizers for putting this thing together and allocating time to share so that we could share our findings.

MS. STORY-ROLLER: So I just want to say thank you for letting me share some of the research that I've done over the past 2 years with you guys. And so what we're going to be focusing on is using Dual beta-lactam combinations for treatment of M. abscessus specifically.

And so there's been a lot of press towards trying to repurpose currently available antibiotics, as you guys know, in order to see if maybe we could more quickly and rapidly get combinations that are actually therapeutics against M. abscessus, especially in the setting of drug resistance.

So I just wanted to talk very quickly about

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the in vitro work that we've done initially and then we also have some vivo data to share with you as well. So what we did was we took a total of 206 combinations of beta-lactams with a couple of rifamycins and beta-lactam inhibiters and tested them initially in vitro against ATCC 19977, which is the Mab reference strain, in a checkerboard assay, which is kind of the standard method for determining whether or not there's synergy that exists between two drugs.

So we preferentially chose cephalosporins that were oral bioavailable, but didn't require more than twice daily dosing just to kind of ease administration in patients, and then several of the carbapenems that were available not necessarily in this country, but in other places in the world they have been used since those seem to be more efficacies against Mab in general among the beta-lactams.

We also looked at the rifamycins because rifabutin has been shown to have some activity. And just a couple of others as well, but they hadn't been tested in synergy -- synergies as well. And then a couple of the beta-lactams inhibitors.

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So this is actually in a table form of the synergistic combinations that I just showed you on the checkerboard assay. So we find 24 total combinations that did exhibit synergy based on the Fractional Inhibitory Concentration Index, which is kind of a mathematical version of how you would determine how -- the degree to which combination is able to be synergistic against a bacteria.

And so we have the drugs that are listed on the left hand side. The table on the left are -- you know, we're looking at MIC of the single drugs by themselves and then the MICs that are extrapolated based on if they're in combination together using the FICI to mathematically determine those.

And on the left, those are the drugs that hypothetically bring the MICs within a therapeutic range. Unfortunately, the CLSI breakpoints for abscessus really are only available for cefpodoxime and imipenem. So we just used those as surrogates and extrapolated the rest of the breakpoints based on those for the (inaudible 0:05:26) respectively.

The table on the right were combinations that

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didn't quite bring the MICs down to the -- within the therapeutic range. But as you see, a lot of them had very high MICs to begin with. And so even though there was, you know, several log decrease in MIC for a lot of them, it just was not enough to kind of bring them within that range that we'd like to see.

However, it's possible that the addition of additional agents either non beta-lactams as we usually use, you know, multidrug therapy against abscessus might potentially bring those within a range that we'd be able to have therapeutic effect.

The other thing to note is that there are a couple of agents that are not currently FDA approved for use in the U.S. Biapenem actually showed to have -- seemed to have a good amount of efficacy against Mab in vitro and then also in preliminary in vivo studies that I'll talk about.

And in addition to faropenem and tebipenem -- and tebi actually is a recently started Phase III trials for us UTI. So that's exciting and those are both orally bioavailable.

So that's a -- and I'll go on to this one.

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Just very briefly, we wanted to look at drug resistance frequency in regards to the frequency of development of spontaneous drug resistance mutants in each individual drug plus when they're using combination, because it will be something that will be important when we're thinking about new therapies to try to increase the longevity abuse in the clinical setting. We like to decrease, you know the occurrence of resistance.

And so, as you see, there's a definite decrease in the rate of resistance with all of the combinations. Some did better than others, especially among the cephalosporins. They seem to have a pretty good decrease in the amount of resistance that we're seeing, which is, you know, promising.

And so the last slide. I just want to talk a little bit about -- because kind of already mentioned as the discussion has been had, you know, about we really do need, you know, a mouse model or at least some of kind of animal model for these pre-clinical studies. And this is very, very preliminary data. We've only done a couple of studies so far. But it

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seems like a potentially viable system that we could potentially use for additional studies down the road.

And so our lab -- and Emily Maggioncalda in our lab has kind of headed this, where we're using an aerosolized Mab pulmonary infection in a immunocompromised mouse. It's immunocompetent C3HeB/FeJ mouse that's immunocompromised with dexamethasone or cortisone. And that seems to work the best, where we're able to, you know, immunocompromise them enough to have a sustained pulmonary infection. And then they do develop these caseating granulomas after cessation of -- immunocessation in the expressive therapy and then kind of reconstitution of the immune system.

So it's not perfect. It's, you know -- especially, in the CF population and people with bronchiectasis, it's -- the lung physiology is much more robust and potentially more difficult to treat those infections. However, it's something that we could potentially use, you know, as an initial model to go forward with this.

And so I can't show you the data because it's

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so unfortunately under review currently, but we took five of our in vitro synergistic combinations and tested them in this system. And we did show that -- we did find that they seem to be very effective against Mab, at least the ATCC we're referencing. And so that's quite promising in terms of potential future studies as well.

And so it seemed like maybe we might be able to get complete eradication of the infection within, you know, 5 to 7 weeks using these combinations. And so there's a lot more work to be done, but it's something that we could potentially use, you know, for future studies as well. So that's it. Thank you and happy to answer any questions.

UNIDENTIFIED SPEAKER: Thank you.

UNIDENTIFIED SPEAKER: Can I ask why you choose -- which of the rifamycins? Did you use some rifabutins, some rifapentine and some rifampin with your combinations?

MS. STORY-ROLLER: So we tested all of the -- all three of them against all of the other beta-lactams. Rifabutin seemed to have the greatest

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activity against M. abscessus, but we use kind of TB as the stepping out point. So we have seen some activity with rifapentine and rifampin.

However, they had not been tested in a dual beta-lactam setting against Mab, and so we just wanted to see if there was potentially any synergy that might exist among, you know, those other agents plus -- and we did see, you know, in especially the earlier generation of cephalosporins that there was some degree of synergy, but maybe not enough to bring it within that therapeutic range with the MIC there.

UNIDENTIFIED SPEAKER: Great. Thanks. And now our next speaker. Ho Namkoong, welcome to the podium.

MR. NAMKOONG: Okay. Thanks for giving me chance to talk today. I am Ho Namkoong at the -- a postdoc at NIH right now. And I am doing research on the host genetics (ph) on primary NTM infection and bronchiectasis. And I am primarily physician background in Japan and I came to the United States one year ago. And yes -- oh, yes, last few weeks ago very casually I applied for this public comment

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session, but so surprised to see this session, so. Yeah.

Anyway, I would like to address today two major comments. And some comments are very public, but some, yes, comments are very personal request to clinicians and the researchers and patient support group and the drug company, yes, attending this conference.

And before I'll commence, I'd like to introduce Japanese NTM clinical situations and also research situation in Japan. In Japan, the incidence and the mortality of NTM is increasing, as you know. And we -- yes, a few years ago, we performed a biological study -- study and which reported that incidence rate of NTM was 14.7 per 100,000 person years and suggesting that -- so Japan is one of the highest incident countries. And the MAC lung disease is the most common form of NTM pulmonary infection in Japan. So generally causes slowly in Japan and in the immunocompetent host and that compromised 90 percent of NTM. And also the mortality of MAC already increases that of the tuberculosis in Japan.

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And based on these situations, in my university in Japan, Keio University Hospital, we plan a prospective observation study that has been conducted from June of 2012. And the study includes adult patients with diagnosed or suspected with NTM lung diseases and are registered according to the ATS/IDSA 2007 statements. And we collected clinical data and the pulmonary function test, CAT scan and 6-minute walk, SF-36 and SGRQ and the patient's DNA samples and the plasma.

And also in addition to one, yes, prospective cohort, we studied to -- we studied a collaborative register in Japan, so NTM B registry in Japan. So based on the INBOX (ph) study and also NTM and B registry in United States, so we studied collaborative study with, yes, these -- about 15 institutions and now registered 800 patients.

And based on these situations, my first comment is about international joint clinical research and trials. So as I introduced here -- so many Japanese clinicians and researchers are making efforts to be ready for the international clinical research.

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And as you know, when coming to the, yes, clinical research, the sample size is very important. So, yes. So when you think about the clinical trials or clinical studies think about, yes, joint program with Asian countries such as Japan and Korea.

And my second comment is about this platform. I'm very surprised to see that -- or to see that clinicians and the researchers and the patient group and the drug companies sit at the same table and that this situation very, very unbelievable for the Asian countries. So if you have a chance just -- I'd like to introduce this platform, but if you guys have a chance to, yes, collaborate with other countries as a global leader so I'd like you to introduce this platform. Thank you.

UNIDENTIFIED SPEAKER: Okay. Thanks for your comments.

MR. NAMKOONG: Any questions?

MR. LAMICHHANE: Any quick questions? All right. Thank you very much. And Khalid Dousa if you are here, if you'll find your way to the podium. Seeing nobody moving, I'm thinking Khalid is not here.

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All right. Well, that closes our public comment period and I will now turn the microphone over to the Karen and Patrick. Thank you.

SESSION 3: CASE STUDIES

MS. HIGGINS: Hi. Good afternoon. So I'm Karen Higgins and I'll chair this session with Patrick Flume. So in this session, session 3, FDA will present two case studies to help frame this afternoon's discussion. Please note that these are hypothetical cases. The intent is to bring about a robust panel discussion around the clinical development challenges such as the control used in the trial; the endpoints, including the use of clinical outcome assessments; the timing of the endpoint assessments and the durations of therapy.

When Dr. Hiruy, a FDA medical officer, is describing these cases, think about what additional information is needed in order to design and conduct this type of study and what aspects are more or less feasible.

So Dr. Hiruy will present each case study, and after each case, it will be followed by an

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academic and industry perspective. Dr. Hiruy.

PRESENTATION OF HYPOTHETICAL CASE STUDY #1: DEVELOPMENT OF A NOVEL DRUG AS AN ADD-ON TO A BACKGROUND REGIMEN FOR TREATMENT OF PULMONARY MAC DISEASE

DR. HIRUY: Good afternoon. We will be presenting two case studies as you heard. We want to emphasize once again that the study -- the case studies are hypothetical and are not intended to cover every developmental stage and requirement for specific drug program.

There should not be a head to head comparison of the two cases either. Our intent is to discuss two patient populations in the pulmonary MAC disease spectrum. Although non-clinical work is an integral part of a drug development program, for the purposes of these case discussions, we will primarily focus on the clinical programs with the assumption that the necessary non-clinical work has been successfully completed and the development program has transitioned to the clinical space.

Similarly, safety assessment is a critical

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part of drug development. However, for the purposes of today's discussion, we will mainly focus on assessment of efficacy of these hypothetical drugs with the assumption that the drugs mentioned in the cases have acceptable safety profile.

The case studies present broad topics and ideas, and this was done purposely to spur discussion on key topics such as clinically-oriented primary endpoint and time of assessment of such endpoints.

As part of the discussion around clinically-oriented primary endpoints, the case will refer to clinical outcome assessment tools such as patient-reported outcomes. Today's case study discussions will not focus on the process of validation of these tools. As you heard from my colleague, Dr. Chen, earlier, the FDA has a dedicated team to help with the development and validation of such tools.

In the case studies, our main focus for the discussion will be the contents of such assessment tools. We will assume that the clinical assessment tools mentioned are fit-for-purpose, meaning they have been studied and validated for patients with pulmonary

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MAC disease.

With that, we will move on to our first case discussion of Drug X: Novel Drug Developed as Add-on to a Background Regimen for Treatment of Refractory Pulmonary MAC Disease. The background regimen will be referred to as BR in the subsequent slides.

So Drug X is an oral formulation of a new molecular entity with a novel mechanism of action. It has shown potent in vitro activity against M. avium, intracellulare and abscessus. Pre-clinical prove of concept murine models demonstrated bacterial load reduction with the addition of Drug X to the background regimen compared to background regimen alone.

Several Phase I studies were completed in healthy volunteers, including first-in-human, randomized, double-blind, placebo-controlled study to assess safety, tolerability, PK of single and multiple ascending doses.

Drug X was also noted to get into the lung tissue with quantification of Drug X in the epithelial lining fluid. Potential drug-drug interaction with

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anti-infectives used for treatment of MAC disease such as clarithromycin and rifampin were also evaluated. Main adverse event noted during these studies was gastrointestinal, nausea, abdominal discomfort, which were mild to moderate in severity.

A dose ranging Phase II trial was done comparing three dose of -- three doses of Drug X as an add-on to background regimen versus background regimen plus placebo in patients with refractory pulmonary MAC disease. Refractory pulmonary MAC disease was defined as failing to achieve three consecutive negative monthly sputum cultures after 6 months of ATS/IDSA guideline based multidrug regimen. The primary endpoint for the Phase II was a proportion of patients with culture conversion at month 6.

Secondary endpoints encompassed a new PRO and an existing PRO, Quality of Life Bronchiectasis respiratory module modified for patients with NTM. Microbiological assessment of sputum culture conversion, functional assessment with 6-minute walk test and treatment emergent adverse events and serious adverse events.

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Overall, the result of the trial showed the 20 milligram dose was the -- had optimal efficacy and safety profile, and hence, that dose was chosen for the Phase III trial.

Moving forward to the Phase III trial, the trial also focused on the same patient population as the Phase III, namely patient with refractory MAC disease. The Phase III was a multicenter, double-blind, randomized trial comparing Drug X plus background regimen to background regimen plus placebo was at 2:1 randomization scheme. The background regimen adhered to ATS/IDSA guideline, but varied based on investigator's discretion and patient's characteristics such as prior therapy and concomitant medication.

Study duration was 16 months on treatment and 8 months off treatment follow-up period. Monthly clinical and microbiological assessments were carried out for the 16 months while on treatment, followed by every 3 months assessment from months 16 to 24. No study arm cross-over was permitted.

Of note, investigators and patients remained

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blinded to treatment assignment and culture conversion as long as patients remained clinically stable and rescue therapy was not deemed necessary.

The primary endpoint was a PRO at month 16. The secondary endpoints included culture conversion at the end of treatment as well as off treatment to assess durability of culture conversion, sustainability of improvement in PRO during the off treatment and follow up at month 19 and 24, changes from baseline 6-minute walk distance at end of treatment and end of study. Assume the sample size of the trial was adequate to show clinical meaningful difference in the PRO between the two arms with a 90 percent power.

The results showed Drug X plus background regimen met the pre-specified primary endpoint of meaningful improvement in PRO compared to background regimen plus placebo. However, there was no significant difference in culture conversion at month 16. There was no -- there was also no significant difference in reported treatment-emergent adverse events, serious adverse events and mortality between

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the two arms.

We have three main questions for the panel. The first one is asking about the knowledge gap in our understanding of the patient population, including the definition of refractory pulmonary MAC disease. In the literature currently refractory population is defined as those that failed culture conversion after 6 months of multidrug regimen.

Is it clinically appropriate to include all types of pulmonary MAC patients who failed to convert after 6 months of treatment or do we still need to think about the disease subtypes?

How about the knowledge gap regarding primary endpoints to assess direct clinical benefit for this patient population? For example, development of a new symptom-based or functioning-based PRO. Or is there an existing PRO that can be modified and used in this population? And what about the idea of timing of assessment of such clinically-oriented endpoints and length of trial?

We also want a discussion around the feasibility of making clinical decisions based solely

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on patient's clinical status without sputum culture results. How about limiting cross-over from the control arm to test arm? And the feasibility of standardizing the background regimen is also another discussion point we would like to have.

For all the existing knowledge gaps, how can we address them? And finally, despite these knowledge gaps, what can be done to move forward to design scientifically sound clinical trials for patients with pulmonary MAC disease? This concludes the first case study presentation.

MS. HIGGINS: Thank you, Dr. Hiruy. So Dr. Chalmers from the University of Dundee will give a academic perspective.

ACADEMIC AND INDUSTRY PERSPECTIVES ON CASE STUDY #1

MR. CHALMERS: Thank you very much. So the questions we were asked to address in the case study are very similar to the questions that we were asked to address in the panel study before lunch. So I think we have to accept that if 30 of the world's leading experts didn't come to a consensus before

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lunch, it's unlikely I'm going to give you the secret to this disease in the next 5 minutes. So I'm going to very briefly make a few comments, then open for the rest of the panel.

I'm going to focus quite a bit on the contents of the potential assessment tool because I know that was -- you mentioned in the introduction that's the key thing you want to focus on. We obviously have existing tools like the QOL-B and the QOL-B NTM module and the SGRQ. The concern I have with all of the existing tools and the reason I think we probably need to develop a new tool is not that they don't incorporate all of the things that we need in an NTM tool.

So we heard from Amy earlier, I think we could all name the dominant symptoms in pulmonary NTM. They are cough, sputum, breathlessness, fatigue. It's -- the really key issue is how they are weighted in these particular PROs, how much relative importance is given to each one. And in those tools that have been developed for different disease, they generally give weights to different symptom.

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There's a really great example of this, which is in bronchiectasis in the RESPIRE trials, which were trials of inhaled ciprofloxacin. They did two PROs, the SGRQ and the Quality of Life Bronchiectasis questionnaire.

In the same trial, the SGRQ improved and QOL-B did not despite the fact they measure virtually the same thing. And it's all determined by the relative weight you give to chronic bronchitis symptom versus breathlessness, for example.

So I think we run the risk if we use tools that were developed for other disease like the SGRQ that we're measuring the right symptoms, but we're weighing them in a way that means that they won't detect response to NTM therapy. So I think that's the first sort of key point.

The other issue is about the recall period. So a lot of these tools recall symptoms over, for example, a week. But you heard from Amy that the -- one of the things the patient says is their symptoms go up and down very frequently. So if you have a PRO that detects symptoms over a week in a disease that

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people are taking treatment for 24 months, we're going to lose an awful lot of information. So that's another thing we need to take into account in developing a PRO.

The other -- another issue is when we analyze the primary outcome. So in a lot of trials, we pick a defined time point, 12 months or 16 months or 24 months, and say that's when we're going to measure the quality of life change from baseline.

We have experience again in the bronchiectasis field that that's not the best approach. So in the ORBIT trials of liposomal ciprofloxacin, the outcome was changed at the end of the final cycle of treatment in a 12-month study, which ignores all of the information of how the patients felt during that year while they were on treatment.

And so in this disease where symptoms wax and wane, where drug toxicity waxes and wanes depending on what we do, I think you have to capture all of the information that happens in between. So we need to use more sophisticated analyses like repeated measures

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analyses to look at changes over time. And in fact when you do that in the Orbit studies post hoc, you see differences that are not evident by picking individual time points.

I want to pick up again on the point that Tim made earlier about the potential to use a composite endpoint rather than potentially a PRO, although, as I said earlier, PROs are composite endpoints. If we know that some patients feel better in terms of cough, some patients feel better in terms of breathlessness, some patients feel better in terms of fatigue, wouldn't it make sense to develop an endpoint that captures those things using existing questionnaires?

So we have, as Amy said, existing questionnaires for fatigue. We have the 6-minute walk test, which is validated. It doesn't work as an endpoint because not everybody has an impaired 6-minute walk test at baseline. But if you took a clinically meaningful improvement in one of those three domains to be a clinical response, you would have an endpoint that would detect different responses, but each of them with equal weights, which

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is what regulatory guidance for development of composite endpoints takes into account.

One of the other points that was raised was the blinding of sputum cultures during therapy. I can see people having different views on this. I would really struggle I think over a 24-month study to not know what my patient's culture results were.

I think you would inevitably in that trail design have a window, an escape valve that the clinicians could say, "But they're clinically unstable. Therefore, I can look at the culture results." And my concern is that lots of clinicians like me would press that escape valve pretty early and allow ourselves to look at the culture results.

I'm not sure you get that much benefit by blinding the cultural results, because we don't know for sure even if they change from culture positive to culture negative that they're on active drug, because some patients on placebo in previous trials have converted. But I do think you'll get problems with patients dropping out or clinicians pulling the patients out because they want to know the

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microbiological information.

So I do have concerns about that, and I'm not sure it would give you that much benefit. I think that's enough probably from me in terms of feedback.

MS. HIGGINS: Okay, thank you. Okay. So now we'll have the industry perspective. Dr. Angela Talley is Vice President of Clinical Development at Spero Therapeutics.

MS. TALLEY: I guess I'll deliver mine from up here because I made slides. So hi. I'm Angela Talley and Vice President of Clinical Development at Spero Therapeutics in Cambridge. Thank you for the opportunity to offer the industry perspective on the drug development path for NTM.

As mentioned -- oh, wait -- let see. Yup, I got it. As mentioned at the start of the session, I'm a full-time employee of Spero. So as I think we've heard earlier today, there's an increasing urgency to determine the utility of new or existing agents and new regimens in the treatment of NTM disease. And from an industry perspective, the opportunity today to outline a feasible and efficient development path for

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evaluating novel anti-NTM drug candidates is critical in bringing new, effective agents and treatment regimens to patients.

So what does this mean? From the -- for perspective, we'll offer this broad development timeline overview for candidate agents such as Drug X. Drug X was presented in the case study and noted to have demonstrated in vitro activity versus clinically relevant NTM pathogens both in vitro and alone and in combination with other agents in vivo in mouse MAC models.

And one key issue here is that for Drug X and other agents is that in general there's poor translation of preclinical data from animal models to efficacy in human. So although the goal today may be defining clinical endpoints in clinical trial design, I'll just note that elucidation of translational data indicative of clinical efficacy in humans is still important to the discussion.

And on that note, we and others are exploring the utility of hollow-fiber models for this purpose in order to better define activity of new agents for NTM

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and model human exposures, resistance potential and to identify potential partner agents for use in combination regimens.

So in general, it takes about 3 years to generate these non-clinical safety and efficacy data before you go into a Phase I study in humans evaluating a single and multiple dose to outline the safety in the human PK of your agent, or in this case, Drug X. As noted for the drug -- typically, additional Phase I studies in healthy volunteers are required to evaluate potential drug-drug interactions and to generate additional PK data in certain special populations, as well as to support ongoing dose selection for use in patients.

The case for Drug X also outlines a Phase I ELF study, although unlike the bacterial pneumonias, the utility of this data is unclear for NTM and TB and not typically included in TB development programs and it may not be required for NTM agents. Perhaps that's a question for this panel as well.

From an industry and regulatory perspective, the non-clinical safety and efficacy and Phase I data

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collectively constitute a proof of principle for moving a new agent into the clinic. So for Drug X, the data leading up to Phase II likely represents 5 to 6 years of development before we finally get to evaluate this promising new agent in the clinic. From this point, the approach to demonstration of efficacy in patients is unclear and is the focus of the workshop today.

Based on the case outlined for Drug X and the timeline for similar trials, it would likely take 2 to 3 years to get an early efficacy read for Drug X supporting further evaluation in Phase III. And similarly, based on the number of factors and prior experience delivery of a 200 to 300 patient trial, Phase III study is likely to extend delivery of this drug to patients by an additional 5 to 8 years.

So in terms of the assessment of efficacy and the appropriate development path, I think we have more questions than answers, we can all agree on that. And we know from the earlier presentations that this is generally representative of the current status of our understanding of development in this field.

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So we've been thinking about this a lot, and the next few slides sort of outline the major questions that we've struggled with. And the one -- one of them I brought up a couple of times today already and that is: what is the objective of treatment for pulmonary NTM? Is it cure? Is cure possible? Is it stage specific? Is -- durable micro response up to 24 months, is that a reasonable objective of therapy? Or shall we focus on symptomatic improvement and which symptoms? How to measure them?

Is improvement a delay of disease progression, as I alluded to earlier, a more appropriate endpoint in terms of progression free survival? And again, is it patient specific? What's the appropriate timing for assessment of the response? Is there a possibility to define an earlier definitive primary endpoint in 6-months or less?

So these questions have all been discussed earlier, but I'll just highlight that they are key questions to develop the development path in terms of who do we study, are there different populations

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appropriate for Phase II or pivotal trials, which endpoints are appropriate to assess benefit.

In this study -- a case study of Drug X, we're adding on Drug X to standard of care in a treatment refractory population. It's unclear if that's the most appropriate population to get an early efficacy read.

Likewise, the endpoint for Drug X is sputum conversion at 6 months, but there's a 24-month follow up. And it's unclear whether a durable response for phase is relevant -- for a Phase II study, which tends to be focused on the dose ranging, early efficacy read and PK.

So the timing feasibility I think is the big question. What is the minimum treatment duration for a specific micro clinical endpoint in which we might detect a meaningful difference? Is it possible that we can deliver these trials earlier by defining an endpoint under 6-months so that we can move on to identifying a drug that's a promising candidate and move it into a Phase III pivotal trial design?

In terms of the comparators, we struggle with

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thinking about how to standardize the background regimen in a treatment refractory population, particularly for an early efficacy assessment and looking for a readout in clinical efficacy at 6-months. Is it appropriate to add a single agent on to a potentially failing regimen? And in terms of the monotherapy versus placebo, I think there's similar ethical questions about the utility or length of duration of a placebo.

So given all of these feasibility and recruitment challenges, is it possible to take a different approach to study design in terms of a platform trial collaboration? And what other lessons can we draw from other fields? We've heard some examples from the rheumatology field today, but I think there may be others.

So again, as we started out this session, we have more questions than answers. But what is clear is that this is a very heterogeneous disease that progresses through a variety of inflammatory states, and depending on where you come in as a patient into this process, the trial designs and endpoints for

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evaluating a new therapy may differ considerably. So I think that we need to consider at each stage if we're starting treatment of naive patients, that the endpoints' timing and follow up may differ considerably versus a treatment refractory population in terms of this, particularly based on the goals of therapy.

So bottom line from an industry perspective and I think for the field in general, there are a number of needs and challenges, obstacles to getting drugs to patients faster. We need a better understanding of the pathophysiology, a better translation of the...

MR. FLUME: All right. So we're going to open up to the floor.

MODERATED PANEL DISCUSSION

(CASE STUDY #1)

UNIDENTIFIED SPEAKER: Can I just -- I'll start. So I know you want direct comments on this case study, so I'll try to limit to that. I was going to just pitch back to James, so -- I mean, I don't know that we need to develop new tools from scratch

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and I don't know that -- I don't know that that's what you really think. But -- I mean, I -- we have tools, like the NT module was developed, you know, using the standard way of developing these with NTM patients at NTM treatment centers with the help of a patient FAQ. I mean, it's done all that. What's lacking is, you know, perspective evaluation refinement. And I wouldn't -- I wouldn't, you know, ditch it to try to do something new here.

And on the bronch side -- I mean, obviously we just spent a grant together. We're working to do this together. I mean, I think there's components of the QOL-B that likely will prove to be very worthwhile and it may be different for different types of patients. And the only way we're going to find that out is with perspective assessments.

So I don't know that -- I don't know that I would just start over. I do think there are tools that have been developed in the right disease settings. We just haven't had the chance to look at them prospectively and figure out the minimum important difference and things like that.

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MR. CHALMERS: No. I think there are two ways of developing a tool: you make something from scratch or you modify something that already exists. And most PROs are modifications in some form or another of something that already exists.

I think what we have struggled with with PROs has been the responsiveness aspect of the validation. So we often -- we get all these symptoms together and then you measure them in a population with any disease, and sure people with more breathlessness and more cough are sicker and you get what's convergent validity.

UNIDENTIFIED SPEAKER: Right.

MR. CHALMERS: But it's understanding what changes. That's really important.

UNIDENTIFIED SPEAKER: Yeah.

MR. CHALMERS: Because then you have a -- in a lot of questionnaires, you have a lot of fixed variables that don't change with treatment, which makes it hard to then show a response. The most useful piece of data we can probably get would be the individual patient response data from some of the

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completed trials --
UNIDENTIFIED SPEAKER: Exactly.
MR. CHALMERS: -- to say what symptom is it that actually changes when you treat refractory MAC --
UNIDENTIFIED SPEAKER: Yeah.
MR. CHALMERS: -- and then weight your questionnaire accordingly --
UNIDENTIFIED SPEAKER: Yeah. And --
MR. CHALMERS: -- so that it is possible to show a difference.
UNIDENTIFIED SPEAKER: Exactly. And that's the data we've been lacking, right, even outside of MAC and just regular old " bronchiectasis" has been a challenge, so. So I do think Phase II is a place to potentially sort some of that out. And I think this morning's discussion, we just -- I don't know, we weren't really -- Ken and I were talking. We weren't really talking about Phase II and Phase III or Phase I. So such type of case study kind of goes through that. But I do think that you can potentially address some of these issues in your Phase II programs or Phase II programs.

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The other thing I would just say is that I don't think we should even talk about this. I think we should talk about treatment naive studies. That's my thing.
UNIDENTIFIED SPEAKER: So I wanted to talk about the results of the Phase III study because I thought that was interesting that you got -- that the results were significant with the PRO and not for the bacterial -- I mean, the microbiological endpoint.
So that -- I had all sorts of thoughts related to that. One was maybe the power -- maybe the PRO was continuous and the microbiological endpoint was binary and doesn't have the same power. So just because they're discordant at that level, just crossing 05 or not isn't necessarily that meaningful. Maybe it was -- maybe the culture endpoint was close.
But also I think it would be -- if that happened, that would give you an opportunity to look at the data and really dig deep and see: Who are the discordant patients? What happened to those patients over time? Did those patients who were discordant -- I mean, who were looking good on clinical and not

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looking good on the culture endpoint, did those patients, you know, have relapses in terms of their symptoms after they were off drug? It gives an opportunity to understand what that discordance means.
And one other final question -- one -- this is -- you mentioned about the rescue therapy. That I assume only works if you're using a binary endpoint. I mean, I don't know how you would do -- how you would handle those patients otherwise. At least it would work much more easily with a binary endpoint. But again, I -- my main point is that I think the results may not be as discordant as it sound and it's an opportunity to understand the discordance.
UNIDENTIFIED SPEAKER: I think you should ask the panel. I mean, how many people at this table would approve a drug with those Phase III findings? I mean, would anyone here vote yes for that? I mean -- that's a question to everyone. You have a drug that helps your PRO over 18 months, but it doesn't improve your vascular burden, at least just measured by binary outcome and -- I mean, you're right, maybe it does and we just aren't seeing it because of the way it was

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measured.
UNIDENTIFIED SPEAKER: Maybe the P value (ph) is 0.06. We don't know. I mean, again I think there's --
MR. CHALMERS: It's difficult...
MS. TALLY: -- (cross talk) subtly there.
MR. CHALMERS: If it was hypertonic saline, you would vote yes. But it's an antibiotic --
UNIDENTIFIED SPEAKER: Yeah, you're right, you're right.
MR. CHALMERS: -- so it gives you concern, yeah.
UNIDENTIFIED SPEAKER: Ken?
MR. OLIVIER: I'd like to back up to the Phase II for a bit if we could. So the Phase II chose a primary microbiological outcome, which I would like to vote in favor of: if your drug doesn't kill the bug, it's a showstopper. So I agree with all the other discussion about the need for clinical outcomes, but I think in the Phase II setting that that has to be your primary bar to achieve.
I would like to make an argument for not

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having a 24-month long Phase II study. This is an expensive process to get through and we're dealing with a limited number of patients. I think the 6-month mark may be a good place to pick that and I think that gives you time to get a feel for your clinical outcome measures, which will be secondary in this case to see how responsive they are and how good you set that. And then you've got to go with what you've got in putting your Phase III trial together.

I understand all the benefits of continuing to follow these patients longer in a Phase II setting, but if that's going to delay your ability to analyze data from that and get it into a Phase III trial, I think that's difficult to do.

UNIDENTIFIED SPEAKER: So how long would be the ideal follow up?

MR. OLIVIER: I would suggest 6 months and then if you need a, you know, additional month, the safety follow up after that. I think that would be reasonable.

UNIDENTIFIED SPEAKER: I would -- those are exactly what I wanted to say. I mean, for a Phase II

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trial to go 24 months, I mean, I think that just shuts down drug development right there. So -- and I do believe also in a microbiologic outcome in that Phase II trial. Even following people this long starts getting to be a problem I think because of just standard of care, what starts to happen in terms of airway clearance, stopping and starting, antibiotics given for other reason. Just the longer you go, the more difficult I think it will be to understand the activity of the drug. So I would vote for a 6-month microbiologic.

UNIDENTIFIED SPEAKER: Yeah, I agree completely.

UNIDENTIFIED SPEAKER: And I would just add to the microbiological part of that. It doesn't necessarily mean that there would be sputum conversion, but either stabilization or improvement microbiologically like there would be in clinical symptoms. So the notion of preventing progression. So that if you had some microbiological response, however that is defined, and that the clinical symptoms improved, albeit not resolve, that that would

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be a positive effect.

And again, just as was expressed earlier as far as part of routine clinical practice, when we have patients that are feeling better with a particular regimen, we're going to continue that independent of their microbiological response. We like to see a favorable response for sure and think that that's an important element. But if somebody went from smear positive to smear negative or quantitatively went from 4 plus to 1 or 2 plus and they had a positive clinical response, I think that would justify a positive response rather than set the bar so high that we need to have sputum conversion and to have a positive impact on MIDs and PRO from baseline as opposed to the -- and this is for the refractory individuals who are presumably symptomatic and continuing to progress over that 6-month period.

So I -- again, my point is that I think we should also look at stabilization and a lack of progression as much as improvement from our baseline.

UNIDENTIFIED SPEAKER: I too am going to agree with Ken's comment about the Phase II. This is

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typical of the aerosolized antibiotic studies, where your primary is demonstrating the micro effect and your key secondary is really testing what you're going to take as your primary in the Phase III.

But I'm going to ask about having a short study in Phase III. First, feasibility. It would be hard to recruit patients to do 16 months and never have access to the drug, if that's why they entered the study in the first place. That would be a recruitment nightmare.

But since this goal was to try to find a clinical outcome, could you achieve that in 6 months and it doesn't depend upon the micro endpoint. And perhaps you had -- if I could test with all the clinicians up here that in general if you're making a change in regimen, at 6 months you want to make a decision about whether to pivot. And that decision of pivoting to some other therapy is probably based on symptoms and radiographic features, not so much on micro.

Which means you could shorten that study duration considerably. And I -- if I misquote Kevin,

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I apologize. But then figure out the regimen later. You don't need to have a 5-year or a 6-year study to try to get that done.

UNIDENTIFIED SPEAKER: I agree.

UNIDENTIFIED SPEAKER: So we were just looking at the day. I mean, your Phase III study should be 6 months, and that's it. Your primary outcome should be at 3 or 4 months in. Your Phase III study should be for 6 months. You cannot study these drugs for 24 months. You'll never -- we'll never have new drugs ever, and there's no reason to.

I don't understand -- there is this odd -- I think it's the elephant in the room. Why do you guys care about durability response after you stop therapy? This is not something that we need to care about. I mean, it's not something you should enter into trial design and development and running these. And I think we need to talk about that, because the rate of reinfection so high.

And, you know, if your question is: if you're on Drug X and you're on placebo and then you see after everyone stops how -- what percentage stays converted

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in each group? Like, I mean, "da," like of course it's going to be higher in the people that were on the drug. And so what if it was for 2 months? So what if it was for 6 months? Like these aren't -- these are not questions that need to enter into the trial design.

So we need a 6-month study with primary outcome measures at 3 to 4 months. And you should be able to swap people over to your active drug arm. You don't need to keep people on placebo from 1 to 6 months. That's my opinion and I'd love to hear my colleagues opinion. But I think that's really important. Otherwise I don't think we're going to get new drugs.

UNIDENTIFIED SPEAKER: I tend to agree with you, especially in the treatment refractory population. You know, this is a chronic disease state for most of the patients. So expecting them to have a durability response off therapy I think is completely unreasonable in this setting.

UNIDENTIFIED SPEAKER: Let me just ask the FDA to comment, because I'm sort of seeing two

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different versions of durability of response. So why don't I agree with both of you that after stopping therapy, remaining culture negative, especially when we've already heard that they get reinfected.

But this is one of the things we talk with aerosolized antibiotics studies that you wanted to see multiple cycles or prolonged course for drugs that are likely to be used for a very long time, so that you don't just see a benefit at 2 weeks, you see a benefit over 6 months of therapy. And that's a different measure of durability of response.

UNIDENTIFIED SPEAKER: Yeah. So -- I mean, if you can show a clinical benefit and that happens during that first 6 month time period, I mean, you've got something, right? It hasn't answered the question of how durable that effect will be down the road. That's a separate question that could be answered. But if those trials are not, you know, something that could ever be done, we'll then -- we'll never know.

But, yeah -- I mean, I think where we are, is we're struggling to show or to find, you know, the clinical benefit. And we had some discussion over the

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lunch period about, you know, what time period might you expect to see clinical benefit. And it may not occur until some later point in time with at least some of what was discussed as a possibility in the refractory patient population. But perhaps in the treatment naive population, maybe you would see something earlier.

So you would at least -- you know, even though these two patient populations appear to be behaving somewhat differently probably because of the nature of their disease and the chronicity -- I mean, if you could show a clinical benefit early on in a particular patient population like the treatment naive patient population, I mean, that would seem to be a reasonable thing and you've got, you know, a clinic benefit at that early time point. So...

UNIDENTIFIED SPEAKER: I'm not sure that...

UNIDENTIFIED SPEAKER: I think one thing we struggle with is like defining disease progression, because that's really -- we need like some combination of culture, symptoms and radiographic findings and we don't have that. I think that would be the best

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endpoint. Just like you said, in cancer, you know, success or failure is based on disease progression. That's what we really need to figure out.

UNIDENTIFIED SPEAKER: I mean, clinically you do that, right, with individual patients?

UNIDENTIFIED SPEAKER: But we don't have a way to do it in a child.

UNIDENTIFIED SPEAKER: Yeah. And so -- and we were talking about to the extent you could use clinician judgment at the individual level.

MR. CHALMERS: I mean, that was why I asked you the question in the first session about CT because I find when I'm wondering "is this patient progressing," I put a lot of weight on the CT.

UNIDENTIFIED SPEAKER: I mean, it's a question...

MR. CHALMERS: And it's a missed opportunity that in this -- for example, we didn't do CT in the Phase II in this trial to see is there something you can see that you could use for progression free survival, which again is a really attractive --

MR. AKSAMIT: (cross talk) just a little

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bit...

MR. CHALMERS: -- is an attractive concept.

MR. AKSAMIT: And I think that we will know within 6 months. I mean, in the clinical experiences, you have a pretty good idea within the first few months whether somebody is going to respond. There's a rare individual that gets placed on treatment and gets better at 9 or 12 months and had no improvement in the first 6 months. I've not seen that. I would defer to my other colleagues.

But if people are going to get better, as was said earlier, they're going to get better in -- you'll know within the first 3 months. And if you wanted to extend that to 6 months to be, you know, conservative about it, that will be all right too.

But you'll know relatively quickly whether this is going to be a successful regimen clinically. They'll either feel better or not. You don't have to wait more than 6 months, 9 months or 12 months.

MR. CHALMERS: But is the issue, Tim, not that in the refractory population the trials have not shown major symptomatic benefits, but there are

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microbiological? And so the question is can we show lack of progression without necessarily showing a big symptomatic benefit?

MR. AKSAMIT: Well -- and this is where the composite endpoint comes in with the lack of progression and that's exactly what then the definition is from a radiographic. What do you say is a lack of progression quantitatively so that you could use that for clinical trials for the PRO issues and then microbiological lack of progression, or a slight improvement or a delta, if you will.

UNIDENTIFIED SPEAKER: Yes. So we think too about, you know, surrogate endpoints or nonclinical endpoints. So you're thinking about, you know, radiographs. You're thinking about microbiology. I mean, the reason that they tell you something important is because you know that they correlate with a clinical effect. And the way that you get that is from a trial that looks at clinical outcomes and then starts to look to see what else seems to be going along with it and that there's a passive physiologic basis for expecting that that is causally related.

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And so -- I mean, the way to get there is to do the study to look at the clinical outcome and then see what else is going along with it. And if you've done that, you know -- I mean, once would be great. You know, twice starts to firm up those relationships more. And three and four times, it really starts to firm them up.

That's what's happened in other fields. I mean, if we talk about learning from other fields, that's one of the learnings from other fields and certainly could translate here. That's challenging, I get that. But I think that's what we need to think about, you know, how do we get to understand the clinical effects on patients and how can we use these surrogate markers as correlates -- or as, you know, surrogates I should say of the clinical outcome and the data that we need to establish the clinical outcome and then look to see what, you know, is causally associated with that.

UNIDENTIFIED SPEAKER: All right. Kevin -- if you all could introduce yourself when you...

MR. FENNELLY: Okay. Kevin Fennelly, NIH,

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NHLBI. Now, unless I've had a postprandial lapse, I'm not remembering what patient group this hypothetical patient would fall in. And I don't think that we've defined today or answered question number one. We've talked a lot about heterogeneity.

But I'd like to comment on a patient group that I think has been neglected a bit in our -- relatively neglected in our discussions, and that are the COPD patients who have NTM disease. They -- the other Kevin and I had the good fortune to work with some folks in the VA, the Veterans Administration, and we published a study last year, which we had I think over 6,000 NTM cases in the U.S. VA population. Of course over two-thirds of them had underlying COPD.

And the remarkable thing is that in the first 6 months after diagnosis, there was a 40 percent risk of death. So we haven't talked about mortality as an endpoint, but it exists. It will fall within the 6-month period that you're asking for, or you could even extend it out 12 months.

But, you know, it's fairly unambiguous except maybe in Game of Thrones or a few other circumstances.

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And it's of great importance to the patients and their families of course. So I would just urge for us to consider the COPD patients.

When I was in Florida, I took care of a lot of these folks. There seemed to be a lot more smoking down there and they usually come in really sick. And you can make them better, they feel much better, and you can prevent progression with treatment.

UNIDENTIFIED SPEAKER: Thanks.

UNIDENTIFIED SPEAKER: Yeah, so I'm Tohand Ugumbu (ph) from Bela (ph). Two issues. So the first one is the microbiological endpoint. And I think somebody mentioned a very important point. We tend to think of it as either/or, right? But there are tools that are used in the clinic now where you can have a quantitative -- use it as a quantitative measure so that, you know, it's not either/or, right? You know, you can tell if there is a decrease in bacterial data.

I know there is a lot of noise in sputum samples. But it doesn't have to be either/or, right, in terms of microbiological outcome. And that might improve the power and reduce sample sizes.

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The second issue is -- it's interesting I think -- I asked earlier -- so we -- and I'm not saying -- so when we're looking at the stage where we are with all the new drugs coming -- and this was mentioned in case 2 with all the drugs coming. Should we concentrate on adding drugs one by one to what we have, which, if you did iteratively given how long it takes, you're going to take a couple of decades, right, to switch in, get in? Or should we start thinking "by whatever means"?

And Tim from Hopkins presented, you know, ways of trying to combine this. And there are different ways. But shouldn't we be thinking of in MAC and certainly in M. abscessus where standard therapy is, you know? No good, right?

So shouldn't we be thinking of building new regimens and taking those now to Phase II and Phase III clinical trials faster? Otherwise it's going to take us decades to just change the MAC regimen, right? So that's my question.

UNIDENTIFIED SPEAKER: Well, I'm not really sure how to fully respond to that, but the -- there's

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developing drugs, there's developing regimens, which are really two different pathways. And if you're talking about combinations, getting into the combination role to find out how these drugs not only interact with each other, but also which one is adding anything to the regimen itself. So...

UNIDENTIFIED SPEAKER: Hi. Thanks. It's Kira Kahn (ph) from Johns Hopkins again. And just to the point earlier that James Chalmers raised about the feasibility of blinding clinicians and PIs to cultural results. In my opinion, that's a terrible idea. Patients deserve to know and I as a treating physician deserve to know in particular what the drug's susceptibility pattern is of the background regimen.

So if you're blinding us to the culture results to know whose culture positive after several months of treatment in a trial, you're also blinding us to know whose culture positive and who may have developed macrolide resistance, for example.

And it's a very different treatment decision for patients whether they are macrolide susceptible or resistant. And I think that patients deserve to have

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the best available information about what their chances are of achieving a good outcome. And that means that we need to have that information at that time.

UNIDENTIFIED SPEAKER: So my experience is that doctors aren't getting that many cultures. I'd like to hear from people when they are treating, how many are getting monthly cultures on their patients or how many are getting them every 3 months or every 6 months.

UNIDENTIFIED SPEAKER: There's like here (inaudible 1:05:20) they get them every like 3 or 4 days.

UNIDENTIFIED SPEAKER: I got them about every 2 months for -- to throw it out there.

UNIDENTIFIED SPEAKER: Yeah, my sense is -- you know, taking a lot of patients from out of state, we see that the practice will -- our practice is monthly or every other month. But it's hugely variable on the community. Sometimes it's never, you know: "We're going to treat you for 12 months and see how you do." So -- not that that's the right thing to

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do.

UNIDENTIFIED SPEAKER: And my guess is that there are only a handful of people who are actually getting susceptibility testing, period, but certainly with any regularity.

MR. AKSAMIT: Yeah. Yeah, I think that even though we would do this monthly, we wouldn't necessarily repeat susceptibility testing on a regular basis unless there was an indication somebody was failing therapy.

I don't know that that's part of standard practice, at least that's not mine. But I think to collect every month. And looking not only for treatment response with respect to the microbiological endpoint, but also is their new a pathogen present. Because that's not an infrequent occurrence. They have another second NTM show up during primary therapy.

MR. FLUME: But if Kira was speaking to this particular case, that would be 24 months of not knowing the culture results. So I think most of us at 6 months would -- if they're still positive and we

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knew that, would probably be obtaining susceptibility studies at that point.

MR. CHALMERS: Yeah. And I think Patrick is talking about the general NTM population. And this is refractory patients, so you're changing therapy on -- and I think we all would recommend that you should be doing more frequent cultures than your normal practice. And I think most physicians would end up break the blind.

UNIDENTIFIED SPEAKER: And even if they don't do it in their clinical practice, in the setting of a clinical trial if there's a macrolide resistance that has developed or abscesses (ph) is now growing, I think there's some ethical issues about not knowing about it.

MR. CHALMERS: And you'd also have to explain it to the patient when you enroll them that for the next 24 months we're not going to be able to look at anything that goes on in your lungs. Even if your normal practice is not to do it very frequently, that's going to be a real disincentive to the patient.

UNIDENTIFIED SPEAKER: But I...

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UNIDENTIFIED SPEAKER: Yeah, I actually wanted to make a quick comment about that. Because again, we have not had a chance to analyze all of the qualitative data from the survey, but I can tell you that there was a lot of feedback from patients who were not necessarily being treated by one of the more expert physicians, so most of the people in this room.

But their feedback generally is that the physicians out in the general community need to be better educated about the disease, about how to treat it, how to diagnose it.

So now if you take a potential clinical trial patient and say to them, "Well, your physician is not going to know what your cultures look like for 2 years," your enrollment probability -- you're going to have like maybe -- maybe a quarter of the patients are going to be willing to enroll. I don't see that as being ethical and I don't see it as being feasible to enroll.

UNIDENTIFIED SPEAKER: Okay. I'm going to just assume that everyone agrees that we're not going to be blinded for 16 months, so that we're all into a

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6-month treatment regimen.
MR. CHALMERS: Yeah.
UNIDENTIFIED SPEAKER: But I want to ask Chuck to just qualify what do you do then if you have a patient who is clinically better on your regimen during the MAC and now the culture grows abscesses?
UNIDENTIFIED SPEAKER: I turn on my clinician hat and I make a decision: "Do I think this is harming the patient?" Usually, what that would mean is collection of additional sputum, because it may have been a onetime culture. I'll get a CT scan if we haven't already gotten one, assess the patient's symptom-wise and just do a clinical assessment. And if I think that is hurting them, I will treat them for it.
UNIDENTIFIED SPEAKER: So if you're in a clinical trial where -- I realize you can't see what I've drawn here -- that they're 6 months in treatment and you're given that opportunity to make a change in therapy at 6 months or in that open period afterwards based upon radiographic findings or clinical findings, you have that opportunity to do that.

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UNIDENTIFIED SPEAKER: At 6 months, yes.
UNIDENTIFIED SPEAKER: And that clinical hat thing you described is going to take about 3 months to sort out, right? You're going to get -- you're going to get repeated cultures, you're going to get a scan, and you're going to see how the patient does. This can take 3 months to deal with that, so.
UNIDENTIFIED SPEAKER: Yeah.
UNIDENTIFIED SPEAKER: Can I just make a quick comment? I've heard a couple of people advocating to go back to using the semi-quantitative scale as a sensitive tool. And I'd love to hear Ken's opinion on this too, but my feeling from practice is that it's not the right tool to use in these patients. There is too much noise and it's variable on the quality of the specimen obtained.
UNIDENTIFIED SPEAKER: Since David is out of the room, we can talk about it freely.
UNIDENTIFIED SPEAKER: Now, that I said was seminal.
UNIDENTIFIED SPEAKER: Yeah. So, you know...
UNIDENTIFIED SPEAKER: It was terrible

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actually.
UNIDENTIFIED SPEAKER: And in David's defense, because I think he's comfortable with a lab that he has a lot of confidence. And so you raise a really important point that for Dave and those that practice at Tyler, they're used to that. It's a hammer they've gotten a lot of mileage out of and feel very comfortable with. But is that the same hammer that we all or that community ID and pulmonary physicians have? And the answer is no. So if you're...
UNIDENTIFIED SPEAKER: But I think (cross talk) use their lab and that tool failed.
UNIDENTIFIED SPEAKER: Right. But let me just point out that it didn't fail. But that was in a treatment refractory population, where presumably the variability would be higher. And so I don't discount or doubt the results that they got in a treatment naive population. I think it probably is helpful there in the data or the data.
But, you know, there can be a lot of variability, especially if there are penalties

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assigned in how that scale is constructed and you have a lot of people dropping out, which I think is one of the main problems that that showed.
UNIDENTIFIED SPEAKER: Can I bring the conversation to the first point, which is the patient population to be studied? And since this case was about a refractory case, that's not what I'm getting at.
But if the point is to find patients who are likely to change, if you're -- you've got your clinical endpoint, can that now be an inclusion criteria which defines this? And I'll use as my example that in the CF trials were FEV1 can change, recruitment patients in those trials has an FEV1 between X and Y, because those are patients who are likely to change.
So your inclusion criteria not just nodular bronchiectasis. Or it could be NTM lung disease excluding cavitary disease. But then they also might need to have something that -- a cough score of X or your PRO score less than Y. So that you increase -- you enrich your population for effect. That was

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intended to be a conversation...
MR. CHALMERS: So since nobody -- since nobody is willing to contradict you, I'll play devil's advocate and say, I mean, we have talked a lot about not reducing the pool of patients because of the need to have generalizable data. And I guess if you say we need a QOL-B score less than 60 based on Dr. Sullivan's graphs, she'd exclude maybe a third of the patients. So the study becomes more difficult to enroll.
So I think that's the argument against it, is if you -- again, coming back to this idea of a composite, if you said they have to have cough or breathlessness or fatigue because your endpoint encompasses all of them, then you don't have -- you have more generalized ability and you find it easier to enroll. Having said that, I think if I were designing a study tomorrow, I'd go for A QOL-B less than 70.
UNIDENTIFIED SPEAKER: Yeah, I think that was a very important presentation and I think that that's a really important lesson from your trials, this idea

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that if you're going to measure something over time, they've got to start with it. And if they don't have it, then it's not going to work. It's -- it's...
UNIDENTIFIED SPEAKER: (off mic)
UNIDENTIFIED SPEAKER: Yeah, it's going to always fail. But I would also point out from your data that we still haven't defined refractory yet, because even though we know what your inclusion criteria were at least 6 months, you showed the people had been on it for years, had been treated for years.
Now, I don't think clinically a patient who has been on a treatment for 10 years is the same as someone who hasn't converted in 6 months.
UNIDENTIFIED SPEAKER: I agree.
UNIDENTIFIED SPEAKER: And so I will say -- and the definition of refractory, we really need to tighten that up also.
UNIDENTIFIED SPEAKER: Yet given that 30 percent of those patients did convert...
UNIDENTIFIED SPEAKER: Yeah, it was the hardest group you can imagine clinically. And so for clinicians, I think we were very impressed by that

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number. But not everyone was.
UNIDENTIFIED SPEAKER: Erica, did you want to say something?
MS. BRITTAIN: I think somebody else has already said it.
UNIDENTIFIED SPEAKER: Hi. May I? Hi. Christian Campbell (ph) with Johnson & Johnson. So on that question of refractoriness, Dr. Daley, what do you think would be a reasonable time period to make that cut of what constitutes refractoriness that belongs in the clinical trial?
MR. DALEY: Well, I think the trial showed us that, I mean, in 6 months. Because if you -- beyond 6 months if you don't do something, they stay the same. I mean, I think it was very powerful from both Phase II, Phase III that you have to do something. And if you don't, they just stay the same.
So it could be -- but it's really 4 months. We know by really the culture that was taken at 4 months in the Phase III trial, because that's how you -- it was 29 percent at 4 months, because it was by 6 months. But it had to be obtained at 4 months.

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So I think we know that it's 6 months beyond we need to do something. And it may be that it's earlier than that, 3 months or 4 months, which we need to understand because that would again just tighten up shortened durations.
UNIDENTIFIED SPEAKER: But are you advocating putting a length of refractoriness limit on that?
MR. DALEY: Yes.
UNIDENTIFIED SPEAKER: It's probably not a new term. They're probably still refractory. They're just like super refractory. And for the purposes of a trial, maybe those are the ones you don't want to (cross talk)...
UNIDENTIFIED SPEAKER: But you just argued that if they don't do anything at 6 months, they're not going to change?
UNIDENTIFIED SPEAKER: Well -- so that's (cross talk) population. It's -- and I think this will be an interesting analysis that maybe you've done and haven't presented it: What is the difference in the outcome between those who were -- would need like 6 months versus 3 years? I mean, try to dichotomize

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or develop it into periods post or years of treatment and then see what the outcomes. So how much does that change?

UNIDENTIFIED SPEAKER: Right. I don't have that data, but Kevin seems to. But I think the point is really to -- that you want to pick a population that's going to be sensitive to the treatment effect, if there is one. And it may be that those people who have had the disease for 30 years are not going to even be sensitive to a treatment effect.

UNIDENTIFIED SPEAKER: And what Angela said - that then determines probably what you want to see change. I mean, if you're -- if you've had fibrocavitary disease for 15 years, you know, I'd -- some of those symptoms are not going to change. It may be cough, for example.

UNIDENTIFIED SPEAKER: No, I agree with Chuck. If we're going to really do this type of study, which I've already said I'd recommend against, you'd have to define refractory disease. Because there were -- I mean, your case definition was -- there's two different types of people in that study.

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And there's people who have been on therapy for 6 months and still culture positive. And there's people who had a history of that basically and now they're culture positive again. They didn't have to be on therapy at that time. They just had to be on therapy only for the last 12 months or something.

So there is kind of two different groups of people in there. And, yeah, they're all like kind of the same people and their balance between arms and I don't think there's any difference between them. But it just -- it serves to Chuck's point that there's really -- this is not something we've fully defined in...

UNIDENTIFIED SPEAKER: And, Eugene, can you clarify on the data that you presented? There was duration of NTM diagnosis -- not necessarily therapy, but diagnosis. And my question is, how much therapy did they get? Was that close to the duration of diagnosis or was that completely separate and unassociated type of relationship?

MR. SULLIVAN: I think the easiest thing to quantify was self-reported how long -- when were you

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diagnosed. And that's what I reported. Because so many patients come on and off and then they had sort of a holiday for a while. So the data on actual how many years were you on how many drugs is a little less firm.

UNIDENTIFIED SPEAKER: And you have colleagues here, but in the manuscript that was published it described a median of like 3 years of treatment.

UNIDENTIFIED SPEAKER: Yes, treatment direction.

UNIDENTIFIED SPEAKER: Total treatment.

MR. SULLIVAN: That was captured, but what I showed was duration.

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: And while we're doing math, there was another suggestion about changing the definition of culture conversion to even just to how much would that have changed the study results for 212 and 312?

UNIDENTIFIED SPEAKER: You know, this is not published data, but I think it's been looked at by

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some of the folks that were involved, and it looked like if you have two, you're likely to have three.

UNIDENTIFIED SPEAKER: I mean, that's what your graph -- you know (cross talk)...

UNIDENTIFIED SPEAKER: It doesn't give...

UNIDENTIFIED SPEAKER: Well, your data shows that if you have three, you're likely to stay negative. So I would think if you had two, that that would be (cross talk).

UNIDENTIFIED SPEAKER: Yeah. So it could conceivably be an adequate diagnose of culture of conversation too. We always emphasized how rigorous we were requiring three. It turned out that three -- the third one didn't add all that much.

UNIDENTIFIED SPEAKER: Path of your primary outcome, you can back of an envelope and do it, right? You can tell that, so.

UNIDENTIFIED SPEAKER: No, because they -- that's -- only those that had met the definition of three consecutives -- so earliest they could do it would be month 1. But in -- if we're saying 2, you could get it positive and it will be negative in 5 and

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6 and have met the criteria and that would not be in that graph.

UNIDENTIFIED SPEAKER: Well -- but most of people that met that -- I mean, what was the positive at 3 months? I mean, you could see it 3 months or 2 months. You could see the majority of those people that were converters were already identified as converters at that time, which would imply that if they have two consecutive, they're going to get a third, most of them.

UNIDENTIFIED SPEAKER: And just to put this in perspective. I think just if we look at the data - - Eugene, as you're here -- we talked about -- so you've got refractory people that have been on and off therapy for at least 3 years, for lack of argument. More than 3 years of therapy on and off in the refractory disease. They get put on therapy, and within 3 months, they got signal. I mean, that answers his question about what's that timeframe...

UNIDENTIFIED SPEAKER: A signal on the micro --

UNIDENTIFIED SPEAKER: Correct.

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UNIDENTIFIED SPEAKER: -- not necessarily a signal...

UNIDENTIFIED SPEAKER: Correct. Exactly.

UNIDENTIFIED SPEAKER: So I just want to just add to still look -- so Dr. Kevin Minch (ph) (inaudible 1:20:51) and holds stock in the company. So a couple of points. So everyone that had three consecutive negative cultures had two consecutive negative cultures, right? There's that perfect correlation, right? You know, so that's the math, Patrick, you were saying.

So you have a higher proportion that would have met success if you only required two. So -- and when you had your first negative culture, it occurred really around 2 months, right, for the first time. So you did see some people that had their first negative culture, but you had some other people that had their first negative culture a bit later as well too, as well as in the trial.

So there is that heterogeneity a bit that, again, in a difficult to treat refractory population median time of NTM duration of 4 years and a median

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exposure to drug somewhere around 3 years. So again, it's in that population.

So two seemed to be reasonable and predicted three perfectly because three required two. So I'll just add that color to that. So hopefully that answers a few more questions.

UNIDENTIFIED SPEAKER: Yeah. No, my question was just does it go from 30 percent to 35 percent?

UNIDENTIFIED SPEAKER: So --

UNIDENTIFIED SPEAKER: It had to be more.

UNIDENTIFIED SPEAKER: -- it will add about 10 percent to 15 percent more patients.

UNIDENTIFIED SPEAKER: That's not trivial?

UNIDENTIFIED SPEAKER: It's not trivial.

UNIDENTIFIED SPEAKER: And also I think too it will be much more likely -- I mean, I'm -- I pitched the two idea. And I think in a treatment naive group it's probably much more potentially meaningful than in a refractory population. I mean, that would be my guess. But...

UNIDENTIFIED SPEAKER: And I'm wondering, you're saying it raises it about 10 percent. Is that

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in both arms?

UNIDENTIFIED SPEAKER: I can go back --

UNIDENTIFIED SPEAKER: I mean, it's probably to some degree...

UNIDENTIFIED SPEAKER: -- (cross talk) double check that.

UNIDENTIFIED SPEAKER: Okay.

UNIDENTIFIED SPEAKER: It's a fair question and I want to go back and just double check the accuracy. So for the investigational arm at that time, for sure. But I just want to double check that and come back to you on that please.

UNIDENTIFIED SPEAKER: Thank you.

UNIDENTIFIED SPEAKER: So if I could ask you a question before you leave. So in trying to define the refractory population, is there anything that we can glean from that? So if the mean or the median is around 3 years, does that help us? And what's the variability around that and does that help us any in defining who's more likely to respond?

UNIDENTIFIED SPEAKER: I think Dr. Sullivan showed the slide that showed the range of that -

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again, NTM duration of 4 years was a medium, but you had people that had that diagnosis for 30 years.

UNIDENTIFIED SPEAKER: No, not the diagnosis, but --

UNIDENTIFIED SPEAKER: Yeah, the treatment, right.

UNIDENTIFIED SPEAKER: -- how long that they were on treatment?

UNIDENTIFIED SPEAKER: Again, 40 percent of patients had, you know, 3 or 4 years. We'd have to go back and look at that upper range to give you a sense of how wide it was, but it was pretty significant. And we did see a bit in some of the modeling that we've done that those who tended to be shorter in duration tended to have a higher probability of culture conversion.

Again, we're talking, again, the numbers in the study, but it was still very significant. And you saw that treatment effect when you added Alice (ph) on top of the background regimen. You did not see that effect in the control arm, because they were already resistant to treatment, right? As you said, they've

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been treated for a very long time, they remain culture negative.

But when you added Alice on top of that background regimen, if they were in the lower half of the median -- just choosing the median as an arbitrary binary -- they tend to do culture convert a bit more than those who had been, you know, higher than a median duration.

UNIDENTIFIED SPEAKER: I want to next take the question to the limiting cross-over since we've now said we're not going to do a 16-month trial for decision making, and because that was an issue during the advisory panel for Alice. Is that a problem if your endpoint is within 6 months that those patients who were randomized to control would be allowed to rollover into open label extension?

UNIDENTIFIED SPEAKER: So obviously, if the primary endpoint is before when the crossover happens, you're okay for the primary endpoint. But it could -- it could complicate assessment of safety and other longer term endpoints that you would want to know about. So it's not a total free lunch.

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UNIDENTIFIED SPEAKER: So then we're back to a longer study, which I had thought we had talked about trying to shorten down. So either we're stopping it at 6 months or we're continuing for 24 months in assessing safety and whatever else you need to assess in the long term in the same study.

UNIDENTIFIED SPEAKER: So it's tradeoffs, right? So, you know, it, you know, depends on whether you feel you could get a better study by doing 6 months in the cross-over. I mean, you'd have to see how the tradeoffs played out.

UNIDENTIFIED SPEAKER: And for the shorter study, I mean, it seems like there's maybe some uncertainty or some differences of opinion about the clinical events that would happen during that shorter time period? That's on the efficacy side.

UNIDENTIFIED SPEAKER: So I guess something else that we're thinking about is, if the guideline say treat for 12 months from the time of culture negativity, then it would seem that patients would be on therapy roughly 16 months. And so we'd want information with this drug for that 16 months ideally

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if that's how long its use would be in the clinical practice.

I understand people may come off a drug and then get reinfect and go on a drug again, but ideally we want to capture some sense of safety and efficacy over the expected duration of practice, ideally, understanding the -- it sounds like -- in general the people -- everyone here on the panel is saying 6 months is what patients would likely tolerate. So then that raises a question for us: How do we get that additional experience beyond 6 months given that guidelines may --

UNIDENTIFIED SPEAKER: Right.

UNIDENTIFIED SPEAKER: -- recommend longer therapy?

UNIDENTIFIED SPEAKER: Could you imagine a study where patients are randomized to the active versus the control arm for 6 months? At 6 months, the clinician has an opportunity to pivot and say, "I don't know what they're on, but it ain't working and I'm going to change their regimen." So they now are on that arm. And if the patients were doing well,

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they could remain in the arm that they were in.
And at some point, you'll break the blind on the cultures, because if you're going to adhere to 12 months of treatment, then you could do that. So your treatment arm could continue for 12-plus months, which is now based on a micro aspect, but you've already hit your primary at 6 months.
UNIDENTIFIED SPEAKER: And that's essentially what 212 was designed going in the 312, is that correct?
UNIDENTIFIED SPEAKER: But it had -- micro is the primary...
UNIDENTIFIED SPEAKER: Yeah, that's -- not quite. But I think -- and why do you say fixed at 6 months? What about if you randomized to active or control blinded and the outcome variable is the physician and patient deciding, "It's not working. We need to get you on a guideline base there." So it's a time to event analysis.
UNIDENTIFIED SPEAKER: It's a treatment failure...
UNIDENTIFIED SPEAKER: Where the event is

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treatment failure and such that the physician and patient say, "Whatever it is you're on, I don't know. You could be on active or you could be on placebo."
UNIDENTIFIED SPEAKER: I do have that. But at 6 months, you've given yourself that opportunity -- I mean, sure a person could get worse in that 6 months and you have to figure out, "Well, why are they worse?" But after that 6 months, if your patients on your control arm are doing well --
UNIDENTIFIED SPEAKER: They would stay.
UNIDENTIFIED SPEAKER: -- you would continue with that. If they're on your treatment arm and they're doing well, you would continue that. But you have that opportunity to pivot from that.
UNIDENTIFIED SPEAKER: Yeah.
UNIDENTIFIED SPEAKER: And the only difference I'm saying is -- so then your analysis would be: at 6 months how many patients of each group bailed out? And the only difference with what I'm saying is it's not at six months, it's a time to event. So it allows that to happen at any point.
UNIDENTIFIED SPEAKER: Yes. So I think the

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answer is -- you know, what the guidelines are going to say, we don't know. They're going to be out in another 3 or 4 years. Is there right? I'm checking back on -- but that's why you should just cross people over, whether you do it the way Patrick just said or the way Eugene said, crossing them over. Like you don't need placebo information or control information past 6 months, for example, if you have a short term trial and your primary outcome measures are in that time period.
So you cross them over and you treat everyone. Everyone gets 16 months of active drug. So you get the information you want and people are treated in accordance with the guidelines.
UNIDENTIFIED SPEAKER: So I guess then the question is, why do they need that full 12 months of therapy other than a group of people decided that they need 12 months of therapy from culture negativity?
UNIDENTIFIED SPEAKER: You know, we don't think they do.
UNIDENTIFIED SPEAKER: Okay. I'm just going by what's published in the guidelines.

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UNIDENTIFIED SPEAKER: So I was going to come in from the guidelines perspective that I don't think you need to stick too hard to the guidelines because those guidelines are based on no evidence or very, very -- and I'll tell you, very low certainty of effects.
So we don't have data on what's the optimum treatment. And until we do, we can't really change that recommendation based on guideline development. So we're stuck until someone does a trial that shows us that we don't need to do what we recommended in 2007.
UNIDENTIFIED SPEAKER: And we'd love that trial. We'd love to see that trial.
UNIDENTIFIED SPEAKER: Well -- I mean, you cross over and over and half the people will stop at 12 months and half of the people go for 18 months.
UNIDENTIFIED SPEAKER: The challenges, though, I think we have to be careful, because primarily we're trying to design the trial to demonstrate that the drug works. And if we also try to solve another question in the same trial, it gets

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really complicated and could ruin both.
UNIDENTIFIED SPEAKER: So Dr. Cox asked what would be the criteria for bailing out?
UNIDENTIFIED SPEAKER: I think as a clinician you'd want to know clinical, how do they feel, function or survive. And if those are -- you know, if they're failing clinically, you'd bail. And I -- you know, we use CT imaging. So I think you couldn't do this without having imaging. They're just tied too closely together.
UNIDENTIFIED SPEAKER: Yeah, I agree. I mean, I'll just give an example. We are CLO-FaST (ph) monotherapy trials, a few people and nothing. We have people on monotherapy CLO-FaST, which might also be nothing, we don't know. We're going to find out.
But I had a patient 3 months in and she's had no improvement. She actually felt like she was coughing more. She was more tired. I scanned her. Her scan looked a lot worse. And I pulled her out of the trial. That was -- those were my criteria for bailing on the...
UNIDENTIFIED SPEAKER: So could you do it

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without a surrogate? Because I think what the agency is concerned about is if the surrogate -- which in this case will be a CAT scan -- if that's driving your decision, that's not all that heartening to them. It doesn't really reflect a clinical. So could you have a bailing criteria that didn't involve some sort of surrogate, be it radiologic or microbiological?
UNIDENTIFIED SPEAKER: Yeah. Well, I think what Shannon was saying, what I was trying to backup, it was a constellation of -- you know, it's putting your clinical hat on. It was a constellation of findings that this person is not doing well.
And you're right. Let's say her scan was stable. I probably would have pulled her anyway, because she felt terrible and it didn't seem like whatever we were doing was helping her.
So I don't know. I guess you could -- you know, you could debate the nuances. But I think those -- and you know what? I didn't even look at her cultures because I'm blinded. So I didn't really care. I just figured she's still culture positive. So...

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UNIDENTIFIED SPEAKER: So I guess Dr. Winthrop, is there a way to quantify your clinical intuition into some sort of a clinical outcome assessment tool?
MR. WINTHROP: Yeah.
UNIDENTIFIED SPEAKER: Yeah.
UNIDENTIFIED SPEAKER: It's what I was trying to do with that thing, that napkin thing I drew on his point. I mean, yeah, I look at their sputum. I look at their radiograph. I look at their symptoms. I look at them and say, "God, they look great, they look bad, they look okay." And they tell me they look bad, they look great, they look okay.
And, I mean -- so, you know, you got to collect that data prospectively and, you know, see how it plays out and how responsive it is to treatment. But we don't -- we haven't done that yet, you know, with a lot of these things. So I realize we're not solving any problems today...
UNIDENTIFIED SPEAKER: I also think it's easier, although it's really quite difficult, as we all know, to look at something as to positive clinical

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outcome, to quantify a negative clinical outcome in a rescue. You know, there's no Hy's law with liver function test for NTM, you know, to say, "Oh my God, you know, my LFT has gone up three to five times I repeated it." That that doesn't really exist.
So I think we're trying to do a lot of things. So I think what the -- the focus area of the clinical outcome is, you know, looking at the measures that we have now and trying to figure out how we can tailor those to marry "we live better, live longer, live fuller," you know, dictum that we are all trying to achieve here.
UNIDENTIFIED SPEAKER: Yeah. So for a design like this, blinding would seem to be particularly important, blinding the treatment assignment. Yeah. I see heads nodding.
UNIDENTIFIED SPEAKER: Is our next case the abscesses case?
UNIDENTIFIED SPEAKER: It's a new regimen.
UNIDENTIFIED SPEAKER: So treatment naive?
UNIDENTIFIED SPEAKER: Yeah.
UNIDENTIFIED SPEAKER: All right. I think

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we've kind of addressed most of these questions for you all, but we haven't talked about abscesses.

UNIDENTIFIED SPEAKER: One thing, Patrick, good about this issue of standardizing the background regimen, because I think we saw a gene slide that showed, you know, how diverse the background regimens were. And to me, you know, that raises red flags if people were on terrible background regimen and you added a new drug that helped them, it was just the new drug.

UNIDENTIFIED SPEAKER: Yeah. I mean, yeah, I chose the efficacy of the new drug whether or not it was on a wise background. It's hard to do. These are patients that have been on drugs for many years and you couldn't change them all over to a standard. I mean...

UNIDENTIFIED SPEAKER: I mean, it was agnostic (ph). But, you know, it is a question. You know, to design a new trial, how are we going to do this?

UNIDENTIFIED SPEAKER: So I think as long as your bad background regimen is equally distributed and

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you're looking to see that your drug is working, I'm not sure that makes a whole bit of difference.

UNIDENTIFIED SPEAKER: This is not quite the same thing, but we faced it with our STOP trial, which is choosing antibiotics for treatment of pulmonary exacerbations, CF. And we knew we couldn't be rigorous about the choices, because there's different bugs that people are treating and there's allergies or intolerances. But we did make them adhere to an approach, where, if there's pseudomonas in the culture, you have to pick two drugs from this table; and if you have MRSA, you pick from this. So you could try to at least find some minimum two drug regimen of what would be acceptable and ideally if it's MAC, it's got a macrolide as part of the regimen.

MR. CHALMERS: So the counter argument to that was I think Anne showed this slide in her talk of the Vaningan (ph) paper, where less than a quarter of patients worldwide were on the recommended background therapy for MAC. So again, you run into the feasibility problem if that data is generalizable. Most patients are not going to be eligible for a trial

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that mandates appropriate guideline based therapy.

UNIDENTIFIED SPEAKER: That's just because the new guidelines haven't come out. Anyone wants to talk about abscesses?

UNIDENTIFIED SPEAKER: I do.

UNIDENTIFIED SPEAKER: I mean, we clear -- it's clearly an unmet need.

UNIDENTIFIED SPEAKER: No, just a quick question. Is there a timeline for those guidelines, by the way?

UNIDENTIFIED SPEAKER: We heard 3 to 4 years.

UNIDENTIFIED SPEAKER: Three to four years. No. The guidelines have been under review for 2 months at each of the four societies that are sponsoring them, and they are supposed to be back, all the reviews. Three societies were able to get it done a little faster than the last society, but they won't send the reviews until all are in.

So hopefully, perhaps this week they will all be in. I hope certainly by next week. Then they must be -- those comments must be addressed, re-reviewed by the writing committee to see if they agree, then go

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back to the societies for a faster review. So a few months, not years.

UNIDENTIFIED SPEAKER: All right. 15 minutes on abscesses.

UNIDENTIFIED SPEAKER: What do you want to talk about?

UNIDENTIFIED SPEAKER: Is it the same conversation or is there something unique about abscesses that would be different for this study design?

UNIDENTIFIED SPEAKER: I think it's different in a number of ways. One, if you thought you had trouble with a background regimen with MAC, you're going to really have trouble with abscesses. And I think it's much more difficult to think about monotherapy trials with abscesses.

And the whole issue of what symptoms are important may be different, particularly if you're talking about abscesses and cystic fibrosis, where there tends to be a lot of fever and very acute type presentations as it progresses and worsens. I think it's -- in general it's going to be a more difficult

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trial design conversation.
UNIDENTIFIED SPEAKER: So, yeah, what Ken said. But abscesses is one of the most difficult strains to treat. So if it takes X number of months to see a, you know, microbiological response with MAC, it's going to take -- I would think it would take longer with abscesses.
I would think that the trial design will change based on how long you have to measure out not only in a surrogate endpoint, but possibly also in clinical endpoints.
UNIDENTIFIED SPEAKER: Yeah, I agree with those thoughts and I think Ken is absolutely right. And I should also just restate that I'm not against studying refractory people. I think we need to do those studies. But for registrational studies, I think they're much more difficult and treatment naive will be much easier.
So that being said about abscesses, I would also recommend treatment naive patients, but it brings up a host of things that Ken just mentioned in terms of, you know, you have to be really careful about who

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you enroll and, you know, what kind of control arm that you'd allow them to be on.
I think if you're going to do a refractory of such trial, the regimen -- background regimen issues, as Ken said, makes it very difficult. I think you go for a treatment naive trial.
I think CF and non-CF are different, just like Ken said. I think, however -- this will be my thought -- that there's a lot of abscesses patients out there that behave like MAC patients and they just cook along and they cook along with really minimal disease progression over months and years, and then something happens and they go down the tubes.
And I think there is a group of patients out there that you can enroll and you can enroll them into a multidrug regimen versus placebo. And you could do the same type of study we were talking about for MAC. That will be my -- that will be the way I'd do it.
UNIDENTIFIED SPEAKER: I wonder if we could put our registries and whatnot together now to just gather some observational data on our -- on how we're treating abscesses and outcome -- you know, something

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that we could do within our registries, because it's all over the places, as you say, and people just have opinions on. And that could possibly inform a real term.
UNIDENTIFIED SPEAKER: I think we have that data, but I think it's going to be just as you say, it's going to be all over the (cross talk).
UNIDENTIFIED SPEAKER: We have to do it more organized than --
UNIDENTIFIED SPEAKER: Right.
UNIDENTIFIED SPEAKER: -- we have now.
UNIDENTIFIED SPEAKER: Right.
UNIDENTIFIED SPEAKER: But I think too about -- going back to refractory disease, I mean, that point of my talk. I feel like my refractory abscesses patients they're refractory to everything. Like I don't know that any new drug on the planet is going to change the refractoriness. So I -- again, I would try to enroll patients that you think has a propensity to respond to a therapy.
MR. CHALMERS: That's how I think as well. I mean, there's plenty of data now on abscesses biofilms

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and CF and bronchiectasis and I start to think about it like pseudomonas infection, that you'll never eradicate your more suppressive therapy.
UNIDENTIFIED SPEAKER: And you mentioned registry data. How granular is the registry data? Could it start to be interrogated in a way that might help to inform the development of a clinical outcome assessment?
UNIDENTIFIED SPEAKER: I think sort of. But we could certainly put a push on to do a better job in a relatively short fashion to get more data.
UNIDENTIFIED SPEAKER: Because if you get an understanding of what's changing when, you know, for a relevant patient population -- and what I mean by that is it's the patient population that would be enrolled in the trial. That may be really important to trying to figure out what will change in 6 months and what would be, you know, a reasonable endpoint to have in a 6 months trial.
UNIDENTIFIED SPEAKER: Yeah. I mean, I think the U.S. Bronchiectasis Registry -- our registry is not granular enough to answer those questions.

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UNIDENTIFIED SPEAKER: Right. And that's what I would say...
UNIDENTIFIED SPEAKER: We'd have to do something prospective.
UNIDENTIFIED SPEAKER: Yeah, yeah.
UNIDENTIFIED SPEAKER: We'd have to change what we're doing.
UNIDENTIFIED SPEAKER: There is an example of that in the CF run out of National Jewish, Colorado, is the predict in-patient study. And we predict our CF patients who have newly identified NTM. And they're just in an observational arm. It's not rigorous like with routine study visits. It's tied to their routine clinic visits.
And then if they now get to a position where the clinician feels they need to treat them, they go into the patient's arm, which is following an algorithmic approach for treating for both abscesses and for MAC. Again, this is entirely CF patients. I think there's 9 or 10 centers now involved and likely expansion to more.
UNIDENTIFIED SPEAKER: But what kind of

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outcome assessments are they doing regularly? In other words, sometimes you have this historical data and you're trying to look for what changes when. But if you haven't captured the particular instruments, it's not that helpful, you know.
UNIDENTIFIED SPEAKER: Well, I know they're getting micro and some laboratory assessments, certainly lung function, but I think they're probably CFQR.
UNIDENTIFIED SPEAKER: Okay.
UNIDENTIFIED SPEAKER: So it's the -- it's just clinical data as would be captured during routine care, but it doesn't queue the CFQR, which is a respiratory questionnaire for CF symptoms every 3 months. But beyond the CFQR every 3 months, it's just clinical data as it would be captured usually in the CF registry.
UNIDENTIFIED SPEAKER: So if that's not a validated instrument for NTM or for the abscesses part of it, then it's something.
UNIDENTIFIED SPEAKER: Yeah. It might not get you all the way there, but it might help to sort

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of inform, you know, where you'd focus in on on subsequent development. So, yeah, no. But agree completely your comments, yeah.
MR. CHALMERS: And just to fill in the discussion on registry. So in Europe, there's about 16,000 patients now in the bronchiectasis and NTM registry, but only about a thousand of them have NTM. But they have annual quality of life bronchiectasis questionnaire data. So that could be used to look at some aspects of treatment response.
UNIDENTIFIED SPEAKER: And I would just say from the CF registry standpoint, since 2010, there's been NTM data in that we've learned a tremendous amount about. If the CF Foundation could go one step further and put in NTM treatment data in there, I think it could be an even more useful tool on a greater number of patients that could help address some of these time to response and drug differential type of questions that we're having.
UNIDENTIFIED SPEAKER: And how often CFQRs? Over 3 months? Is that...
UNIDENTIFIED SPEAKER: It's not routinely

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captured, yeah.
UNIDENTIFIED SPEAKER: Oh, it's not routinely captured.
UNIDENTIFIED SPEAKER: Well, it just so happens we have our registry committee meeting on Wednesday and Thursday. So I'll bring that up for you.
UNIDENTIFIED SPEAKER: You know anybody that's going to that?
UNIDENTIFIED SPEAKER: Yes, I'll be there.
BREAK
PRESENTATION OF HYPOTHETICAL CASE STUDY #2:REGIMEN Y: A NEW DRUG REGIMEN FOR TREATMENT OF NEWLY DIAGNOSED BRONCHIECTATIC NODULAR PULMONARY MAC DISEASE
MS. HIWOT: Drug regimen for treatment of newly diagnosed bronchiectatic nodular pulmonary mac disease. Regimen Y is a combination of two antimycobacterial drugs. Clinical microbiology studies were conducted to rule out antagonistic effects in the combination and resistance development to the combination. The contribution of each drug was demonstrated by hollow-fiber models and animal model

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studies. Phase 1 studies to assess the safety tolerability PK of a single and multiple semi-doses were also completed.

The Phase 2 trial was a randomized double blind placebo-controlled trial in patients newly diagnosed with bronchiectatic nodular pulmonary MAC infection that fulfilled the ATS/IDSA criteria for pulmonary disease. The study duration was 18 months. Primary endpoint was culture conversion at month 6, which was defined as three consecutive negative monthly sputum cultures without reversion.

Secondary endpoints include changing the new clinical outcome assessment tool at month 6, 12 and 18; microbiological assessment of sputum culture conversion at months 12 and 18. Functional assessment was a 6-minute walk test and quality of life bronchiectatic respiratory module modified for NTM patients.

The results showed 45 percent more patients treated with Regimen Y achieved culture conversion at month 6 compared to placebo-treated patients. It was also noted that there were more treatment emergent

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adverse events reported in patients with Regimen Y compared to placebo. However, the serious adverse events and mortality were comparable between the two arms. Based on the Phase 2 data, the program went on to the Phase 3 trial, which was a multi-center, randomized, double blind placebo-controlled trial which included similar patient population to the Phase 2 trial, mainly adults with bronchiectatic nodular pulmonary MAC infection, who met the ATS/IDSA criteria for pulmonary disease and were treatment naive.

Study duration was 24 months, 12 months on therapy and 12 months of treatment. Unblinding and rescue therapy was allowed only in clinical deteriorating patients. The primary endpoint was clinical outcome assessment at months 12.

Secondary endpoints include change in COA at a later time points, microbiological endpoint of culture conversion at end of treatment, and 6 months and 12 months of treatment. And functional assessment was 6-minute walk at the end of treatment and of treatment. Sample size for the trial was adequate to show meaningful difference in the clinical outcome

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assessment tool between the two arms was a 90 percent power.

The result of the study showed that Regimen Y met the prespecified clinical meaningful improvement in the COA compared to placebo. Secondary influence of culture conversion also showed 40 percent more patients treated with Regimen Y achieved culture conversion compared to placebo at months 12 and sustained conversion at months 24, was 20 percent higher in patients treated with Regimen Y versus placebo.

There was a higher incidence of GI and dermatologic treatment emergent adverse events reported with Regimen Y compared to placebo that no significant difference and serious adverse events and mortality.

Similar to case study 1, we have the three main questions. The first one is regarding our knowledge gap in our understanding of acceptability of duration of placebo, using the control arm for the patient -- this patient population. What the preferred primary endpoint may be to assess a direct

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clinical benefit for this patient population, symptom-based, functioning-based PRO be suitable or with functional assessment such as 6-minute walk or a PFT (ph) be appropriate in this treatment naïve population compared to the previous treatment experience population. And when should the clinically oriented primary endpoint be assessed and how long should the patients be followed?

For the above mentioned points, how can we address any existing gap? And finally, despite all of the knowledge gaps, what can be done now for these patient population to design a scientifically sound clinical trial? That's the conclusion of the second case.

MS. HIGGINS: Thank you, Hiwot. So we will have Charles Daley give the academic perspective and Dr. Daley's a pulmonologist at National Jewish Health.

ACADEMIC AND INDUSTRY PERSPECTIVES ON CASE STUDY #2

DR. DALEY: Thank you. And like my colleague Dr. Chalmers, I do not have slides. The academicians amazingly came without slides. So let me just

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highlight something about this case as we began which is different than the previous case. One is this is a regimen, not a drug, that we're studying, includes two drugs, and it's first placebo versus placebo in both the Phase 2 and Phase 3 trial. It's newly diagnosed. I guess that's the same as treatment naive. But again, I would even argue we haven't really made clear what we mean by treatment naive, more on that in a moment. And it's nodular bronchiectasis, so that's who we're studying here.

So in this regimen study, we have some data presented, both preclinical, Phase 1. The preclinical includes in vitro information; the hollow fiber models; animal models. As we're going to be combining drugs, this is very important data because we're going to have to use this preclinical information to figure out which drugs should or shouldn't go together. And so I think this is even more important than the data from in the first case, that no extra cellular lining fluid is mentioned here. It wasn't the first one, but I don't think you need it. So I'm glad that it's not presented.

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The Phase 2 was placebo control, again, two drugs versus placebo. And I think this is the same discussion we had before. The duration here is 18 months in our Phase 2 trial. I just don't understand why we would need to do an 18-month treatment regimen. With culture conversion, it's 6 months. So to me, it's 6 months instead of 18 months. They also add the clinical assessment tool and it goes all the way out to 18 months, but it doesn't start till 6 months. And I think we all feel that this actually begins to show a difference earlier than that, like at 3 months. So I'm not sure why we wait to the end to start making that assessment.

45 percent improved culture conversion was noted. So as compared to placebo, so maybe we'll hear from the panel what they think about that. Two drugs -- two new drugs, because what we think would happen with our standard regimen, but we're not comparing to our standard regimen. So is this good? It's better than placebo. But as mentioned earlier, saline is better probably than placebo. So we need to think about kind of what expectations we would have.

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The Phase 3 trial also randomized, double blind, placebo control, same patient population, here I think this issue came up earlier also, and this is the idea of blinding to culture status. And here we're going to be doing this for 24 months because there's 12 months of treatment. So not 12 months be on speed of culture conversion, which we talked about before, but this is a fixed time treatment, which personally I prefer over everyone getting a slightly different treatment duration. And the 12 months of follow up. And I think that's a reasonable time for follow up in Phase 3 trial.

But as we've heard, we're going to be blinded now for quite a while to culture status. We are going to be gathering clinical information along that way. And I think that's a long time to treat people without some information or are they progressing, are they failing or not. But at the same time, I think this has to be fairly clearly defined what the rules are of pulling out of a trial, and not just let docs make that decision. Because that will be -- really it's not a randomized process the way doctors think. So I

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would want to have clear criteria if we're going to have some way to pull out. Otherwise, I don't feel comfortable going a year of treatment being blinded.

And then the other thing that has come up relates to this clinical assessment tool. And I think it became very clear to me hearing the discussion today that, if you're going to start off with a tool that lists let's say symptoms, then you've got to enroll the right patients, or you're just not going to be able to determine whether people are improving. So that's I think is a very important thing is to consider the enrollment criteria. The other thing I would say is that this is going to take forever. So I kind of think this is unacceptable approach. And we should be starting to borrow, I think when we get to the stage of regimen testing, thinking about adaptive designs, other ways to be able to get more information over shorter periods of time because this process I think is going to be very long. And we've learned this already in MDR TB. This is how we started. And we've evolved now to some other more interesting designs.

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Ultimately, I think one of the questions that we were asked is about coprimary. And I actually, through the discussions today, I almost don't see any other way around it. And you know, you don't get a home run in these patients. They don't all feel better. They don't all have radiographic improvement and they don't all convert. But they often improve in one of those domains. And clinically is that important for the patient? So I do think we should rethink how we measure outcomes. And I think this idea of using multiple domains is probably the way to go. That's it for me.

MS. HIGGINS: Okay. Thank you Dr. Daley. For the industry perspective, we'll have Ira Kalfus. He's the medical director of RedHill Biopharma where he oversees the NTM program.

DR. KALFUS: I want to thank the panel for inviting us. I think it's really been a wonderful day. I know I'm the last guy with slides. I won't say last but not least, we're an Israeli company. The Israeli phrases are (foreign language). "The last is the most cherished." It's what I tell my youngest

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kid. I'm not sure if that's really the right attitude for today. But that's what I'm going with. Screen right.

So I go with just about everything that's been said today. I mean, we know that we have issues with heterogeneity in populations. We know that we have issues with what a clinical outcome analysis is -- - a clinical outcome assessment is going to be. We also all know that a positive sputum culture that turns into a negative sputum culture is beneficial. It's beneficial in pneumonia, it's beneficial in meningitis, it's beneficial in multiple disease states.

And it's what our KOLs have told us that when they are taking care of these patients, it's beneficial for their patients. I think this particular case illustrates something different from what we've been discussing and these two antibiotics, as I understood the case, are known antibiotics, known -- drugs with known experience in treating this particular patient population treating NTM, although in a different -- I apologize, a different patient

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population. If it's a macrolite (ph), we saw the slides about macrolites are approved. If it's erythromycin or verbutin (ph) compound, we know that this has been approved in the HIV population.

So these are drugs that actually there's a fair amount of experience. So I think there's a little bit difference in how we can approach the drug development. And hopefully, we can actually make this go a little bit faster because what I've heard all morning is that we need to do this better and faster for our patients. There are clinical guidelines out there, there are new clinical guidelines that are coming. Clinical guidelines or our clinical guidelines are not FDA-approved products and what we have to do as clinicians is we have to marry our clinical experience with the regulatory environment so that we can get drugs out for our patients.

The defined patient population in this study, a naive patient population or a newly diagnosed patient population that does not have cavitary disease has no currently approved therapy. There is no universally prescribed therapy. We saw today the

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patients were getting, you know, whatever a doctor happens to be prescribing. He may have looked at the guidelines years ago, he may have looked at the guidelines that morning. Patient I was discussing with somebody earlier today, one of the breaks, that a patient comes in, isn't feeling that well, so they'll change the prescription to an off-guideline therapeutic because they think the patient is having an adverse events.

So right now, even as they're on therapy, there is no standard of care that's currently being used. And this is a patient population that's an orphan disease. There's a significant unmet need and we as clinicians have to do something for this particular patient population. The clinical outcomes assessment is yet as undefined, is invalidated and not for the purpose of this talk were to assume that it is. We've heard about the top three symptoms, cough, dysphonia and fatigue. Everybody agrees that these are clinically relevant. And if we can get our patients to improve in these symptoms, we will win.

But as Chuck (ph) just said, not every

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patient is going to win on all three of these. And you have to prospectively, if we're going to have a clinical outcome assessment, we have to figure out a way to prospectively to include those patients that have an outcome that can improve because if they don't have an outcome that can improve, then we're wasting a lot of time and effort doing this study.

It may take a long time to demonstrate this statistical significance. It may take 6 months -- for sputum culture it may take 6 months for some of the outcomes we've looked at. We've had discussion as to how long do we treat people afterwards. I would love a 6-month study to a primary outcome of sputum with a clinical outcome. So -- but we know that the guidelines now talk about an additional 9 months. Actually, it adds up to 15 months in my math, not 16. But it's the fourth month is when that first one comes in plus an additional basically, you know, if you need 12 months total of therapy, it's 12 plus 3, it's actually 15 month therapeutic. But then we have to think about whether it's a follow-on and I agree, I think a 24 months study in this particular patient

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population that really needs an approved product is probably too long.

What I was suggesting a population who is being studied with drugs that are currently approved and other disease indications and may even be improved in various indications that are related to this NTM is I would look at a accelerated subpart H approval. And I would look at 3 to 6 months. We've heard about 3 months you can start seeing symptomatic improvement. Certainly 6 months you need for 3 sputums in a row. I would look at safety and tolerability and I would look up, you know, because we would have to follow for the durability of the sputum conversion. We need to discuss how long we should be treating placebo patients, but if placebo patients are doing well, I see no reason why we can't really keep maintaining patients on placebo if we have to.

We have to consider re-randomization of responders based upon what data risk committee and further discussion comes up with this, what would be necessary to get an approval. And I think we do the clinical outcome assessment. And I think we need to

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have that based upon discussions with all the stakeholders. It's the patients who are in the room, the patients who aren't in the room. It's the key opinion leaders and obviously it's the FDA.

And I think that if we took the patient population that is treated with drugs that are already approved and on the market, and have safety and efficacy demonstrated by in previous and different indications and have a 6-month study that shows that there's efficacious and they're safety and there's tolerability, I would argue that that should be a pivotal study. It should allow for approval. And if a post-approval commitment is necessary, then that post-approval commitment for full approval will be designed based upon the clinical outcomes that come out of that Phase 2 study because we don't know for sure which ones are the ones that are going to work, which ones are going to best measure. And the best way of doing that is actually like we said earlier today, we've got to do the work to figure out how to best define what we're going to be doing next. Thank you.

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(Applause)

UNIDENTIFIED SPEAKER: All right. We'll open the floor to questions or comment.

MODERATED PANEL DISCUSSION

(CASE STUDY #2)

UNIDENTIFIED SPEAKER: I'm just going to make one quick comment because I have to go. I want to thank everyone for this. It was excellent. And I basically disagreed with pretty much everything Chuck said that the one comment, the caveat would be that I think we should just study non-cavitary disease. I don't know that we need to specify that they have bronchiectasis because that will eliminate a big pool of patients who have COPD or other underlying lung diseases that have this. So I'd just be careful of that. Thanks.

UNIDENTIFIED SPEAKER: I had a question. We've had talked about the duration of these studies, and it's challenging that they be long. And one particular issue I'm concerned about is missing data. If the endpoint is a change in a COA from baseline to month 12 in this case, what's your sense of how many

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patients in the control group might have dropped out because of worsening and so have missing data? And then how best to handle that maybe from the statisticians?

MS. BRITTAIN: Well, I guess one compromise is, is if the primary endpoint is relatively early.

UNIDENTIFIED SPEAKER: Erica, can you get closer? Thank you.

MS. BRITTAIN: Sorry. One possible compromise is if the primary endpoint is relatively early, like 6 months, but that, you know, you're still going to evaluate longer term endpoints with, you know, recognizing that you're going to have more missing data.

UNIDENTIFIED SPEAKER: I might also add, I'm just not sure about the premise of this particular study, knowing that standard of care has relatively high conversion rates over short periods of time. I mean, I think most of us would quote minimum 80 percent, maybe 90 percent conversion rates, given standard treatment. And so I think compare this to a placebo control, unless there's some other reason to

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do this to shorten this up, I can't envision if the decision was this patient needs treatment to put this person on placebo or and they have expected 45 percent better rate, it seems we're not in alignment with what our current clinical practice is.

And I mean, again, I would defer to my colleagues. So, you know, if you had -- rather than placebo, you had standard of care in a non-inferiority and you were looking to shorten the regimen, that would be a whole different set of questions that I would be interested in. If you say, well, I'm going to do this in 2 or 3 months, rather than 6 or 9 months to get to a singular endpoint, then I would -- I'd buy into that. So I think this design would need to be changed substantially for me to buy in.

UNIDENTIFIED SPEAKER: Yeah, so just -- I mean a couple of things to think about. I mean, one might be, you know, could you -- would it be ethical and adequately safe to think about a treatment delay strategy, you know? And it might, you know, if you were debating treatment for some period of time, and it was started this month, started a month down the

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road, or 2 months down the road, and it's something else to think about and if you do start to think about non-inferiority margins, then we need to have a treatment effect, you know, to get to the non-inferiority margin. So we'd have to be able to sort of sort through that and have an evidence base to define the treatment.

UNIDENTIFIED SPEAKER: And I would ask what's the goal of a delayed treatment strategy as long as that was defined a priority, I think that that would be possibly, it would have to spelled out up front.

UNIDENTIFIED SPEAKER: Yeah. And a delay treatment approach might be to allow you to show superiority over a shorter time period. And then for the patients who didn't get treatment initially, you know, then they would get treatment thereafter. So it'd have to be a delay that people were comfortable with and that would not cause, you know, the patient harm or consequences.

UNIDENTIFIED SPEAKER: So these would be symptomatic patients who are candidates for observation, right?

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UNIDENTIFIED SPEAKER: I think what you're seeing, Tim, is that this is -- these studies are designed to demonstrate that the drugs -- these regimen works, not designed to compare how it works in comparison to existing guideline base, which are like two different questions. But the regulatory purpose would be to demonstrate efficacy.

DR. AKSAMIT: Yeah. And so I mean, again, ethically, you'd be said -- I really wanted -- I think we need to treat this person. You're going to say, I don't know if this treatment works or not, I'm going to give you a placebo. I don't know about that --

UNIDENTIFIED SPEAKER: You have to have (cross talk), yeah.

UNIDENTIFIED SPEAKER: And it sort of brings us back to the, you know, the basis for the, you know, the clinical desire to treat the patient. I mean, is there evidence that shows that, in fact, if you delay treatment, you didn't treat that patient immediately that, you know, there would be consequences to the patient? And if so, what are they and that sort of thing?

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MS. HIGGINS: Mike, you want to say something?

MR. PROSCHAN: So I'm a big believer in avoiding non-inferiority trials whenever possible. It's almost always better if it's ethical to do a placebo-controlled trial. And you know, all the things that should hurt you in a clinical trial actually can help you in a non-inferiority trial, like people crossing over to the other, you know, treatment. And so, you know, I think if you can avoid that, and it's ethical, I think you want to. Also if you're talking about, you know, 90 percent with the standard regimen, then a non-inferiority margin, a realistic non-inferiority margin, I don't think 10 percent to me is non-inferior. If it's 90 versus 80, that's a pretty big difference. And the smaller your non-inferiority margin, of course, the higher your sample size. So I think, you know, avoid them whenever possible, non-inferiority.

MS. BRITTAIN: Right. Also, with the non-inferiority, given how much is sort of unknown about the clinical outcome, you really cannot do, at least

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at this point, I don't see how you could do the clinical outcome with non-inferiority.

UNIDENTIFIED SPEAKER: Yeah, I guess I don't know what you would do with these two drugs when you've got done.

UNIDENTIFIED SPEAKER: So maybe I'll just try and fill in a couple of lines here. So, you know, I think this is in part sort of an idea that's come from the TB world. And in the TB world, if you have patient populations where the available therapies are not very good, you know, there is the possibility to show something dramatic like, you can treat MDR and XDR TB like you can treat drug-sensitive TB. And in that setting, you'd go in not with one drug, but you would go in with a combination. And you know, the idea is, is that you'd show the value of each of the components with other pieces of data, and you wouldn't necessarily do like a full factorial design. So the idea with going in with a regimen is to essentially achieve a big advance. You know, all of a sudden, you can treat patients and you can have a dramatic improvement. And you know, it's so dramatic that you

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wouldn't, you know, you wouldn't go back and do the individual drugs in a clinical trial. So that's sort of the idea.

UNIDENTIFIED SPEAKER: But in TB, you wouldn't have a placebo comparison to it. I mean, that's -- it's a little confusing. When you get done with this design, where do you position these two drugs?

UNIDENTIFIED SPEAKER: So in TB, you're right, you would show a dramatic effect over what would be current standard of care. And the issue is standard of care is already very effective, then it's hard to show a dramatic effect over standard of care. So then you're faced with the question of is it ethical to either delay treatment, or to have a placebo group for some period of time? And that I think was what we were sort of coming back to.

UNIDENTIFIED SPEAKER: Or is it better than standard of care, better in the sense of medicines that were better well-tolerated, or could do it for over a much shorter period of time rather? And that would be a big deal and the patients would buy into

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that. And I think we would advance the field if we could make what arguably is a 15 or 18-month regimen now 6 months and still have similar outcomes. That's a big deal.

UNIDENTIFIED SPEAKER: You also…

UNIDENTIFIED SPEAKER: But that's not this design. So you would then be using historical controls compared to what you're studying here.

UNIDENTIFIED SPEAKER: But you also could have better -- theoretically, you could have better compliance and better adherence with a prescribed approved product as opposed to currently what is being used in the community. If it's a combination product that was a single capsule that had a combination of both products, where you actually couldn't make an alteration to what the product was.

UNIDENTIFIED SPEAKER: I think…

UNIDENTIFIED SPEAKER: So I mean, this would be the first step. It would show that this regimen is effective the first time we've shown that. And then you could do a subsequent trial would say, well, let's do one head-to-head and try to see how different it

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is. But this would be the cleanest way to say this regimen is better than placebo. And the second question is, but how's it compared to some other regimen?

UNIDENTIFIED SPEAKER: I mean, the only patients you put in a placebo-controlled trial, I don't think you're going to see a big bang, you know, because these are on sick patients that, you know, we would feel comfortable watching. So I'm with Tim and Ken over there. I think what we need is a shorter duration of therapy and you know, a good upfront response.

UNIDENTIFIED SPEAKER: So it sounds like the group is leaning towards the active controlled trial. And then the question is could you show superiority or a significant treatment shortening? And then when the other thing too is, we'd still want to see the clinical benefit here to tell us that we're actually doing something somewhere in this mix.

UNIDENTIFIED SPEAKER: Yeah, and that -- I think you're then shifting the non-inferiority to -- because the end of your sentence was could we do

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shorter treatment and have similar outcomes? So we'd have to have some way of saying, yes, you've got similar outcomes which is non-inferiority, which is the same problem. I think we can't solve two things at once. We can't change the duration of the regimen and add drugs and try to make a clean trial.

UNIDENTIFIED SPEAKER: It may be an approach that just doesn't fit too well here. I mean, we were trying to think of other ideas and things that we could drive from other areas. But this may be one -- you know, sometimes we learn from other areas why something doesn't necessarily work too well in a different area. There may be regions, you know, the disease is different, the biology is different, you know, there may be other factors. But that's the value of the discussion.

UNIDENTIFIED SPEAKER: So there were several pieces to that. One is the feasibility about a placebo-controlled trial and then the regimen versus drug analysis. But I will go on record as saying I don't believe there's an 85 percent culture conversion rate. My review of the literature, generally

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speaking, patients are dropped out of the analysis. And so when you see high reports of treatment success, you ask why did 50 percent of the patients get excluded from the analysis? And I'll bet my nickel that the actual culture conversion rate is probably closer to 50 percent.

UNIDENTIFIED SPEAKER: Can I just sort of stir the pot here a little bit? Right? Nobody throw chairs at me. Okay. So we talked a little bit about the refractory patient population, and part of the discussion there was is that it was going to take, you know, a long period of time in order to see a clinical effect. So there was some, you know, at least among some folks, and then there was, you know, some people thought that within, you know, the first 3 to 6 months, we could actually show a clinical effect in the refractory patient population with the correct clinical outcome assessment. So that's sort of one piece. Here, too, if we think about the naive population, I thought one of the ideas was, you know, that in the naive population, we would in fact be able to see a treatment effect earlier on.

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Now, if we can't get to non-inferiority because we haven't been able to define the treatment effect in the treatment naive population, maybe that's possible, but it's eluded us so far. Then the question is, is what is the design here? And if it's superiority, it could be challenging if standard of care is highly effective already to show superiority over something that's highly effective. And here I saw you raise your hand, is there something else I'm missing here? Whatever, help me correct or fill in the gaps. But so where does that leave us?

UNIDENTIFIED SPEAKER: I wouldn't want to be accused of not wanting to throw chairs.

UNIDENTIFIED SPEAKER: But I agree with you.

UNIDENTIFIED SPEAKER: I'm sure I agree with him. I like that. I mean, it's because I do think standard of care is at least modestly, at worst, you know, effective. So I think we have a pretty good regimen. We just -- it's too long and there are too many side effects of what we're using at the moment.

UNIDENTIFIED SPEAKER: But I'm not -- I haven't heard that we can define a treatment effect

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for the treatment naïve population.
UNIDENTIFIED SPEAKER: Well, I think here we might use or weigh more heavily on a microbiological response in addition to these clinical response, so we're looking at a different clinical…
UNIDENTIFIED SPEAKER: But that's sort of getting back toward the start of our problem though, right?
UNIDENTIFIED SPEAKER: Exactly.
UNIDENTIFIED SPEAKER: Because we haven't shown the clinical benefit linking to the microbiological effect.
UNIDENTIFIED SPEAKER: Correct.
UNIDENTIFIED SPEAKER: Now it's time for the chair, right?
UNIDENTIFIED SPEAKER: No, I…
MS. HIGGINS: Thanks. I know that -- you know, I don't want to be accused of not wanting new drugs because I desperately think we need new drugs for this disease. But it sounds like one of the things that we need is a trial of our current standard triple drug therapy for MAC thrice weekly, with

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treatment duration as the primary thing that we're looking at. So a trial that shows beyond culture conversion, do we need people to go 3 months beyond culture conversion on that regimen, 6 months beyond culture conversion, 9 months, 12 months to see whether -- and the outcome there would be relapse, meaning that you have the same bacteria that we were treating from time zero that we later identified, meaning that we didn't fully eradicate that in that person. Not re-infection meaning another species identified at a later time point.
UNIDENTIFIED SPEAKER: Yeah, that could be an informative trial because if you had longer duration being associated with improved clinical outcomes, you know, you've answered a very important question, in essence, the longer duration being superior to the shorter duration. So, yeah. And I mean, it is challenging in a field where, you know, you don't have all the evidence that you want for what has already been adopted a standard of care because it makes follow-on studies that much more difficult because you haven't really defined exactly what the standard of

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care does. So it can actually impede the subsequent development of additional therapies that could benefit patients. So a very fair point and the trial design you talk about could be helpful.
MS. HIGGINS: Thank you. Can we go back to the question of the enrolling patients who are symptomatic, but candidates for observation in this sort of study design? And Tim, I hear you having some objections to that. But that is essentially I guess the more conservative, protecting against resistance manner of the monotherapy versus placebo control, as is going on right now for the Clofazimine study.
MR. AKSAMIT: So I think, again, the starting position is a little bit different. If we have a cohort of individuals, let's say they're not so sick, we can either observe them or give them monotherapy Clofazimine, for example, but they're not so sick. That's a different group then that group that comes in and we say, there's no doubt what the diagnosis is, there's no doubt that they're symptomatic enough, we need to do some treatment, in which case then we're going to commit them to a placebo as opposed to the

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first group which aren't so sick. You say, "Okay, yeah, we can watch them versus the monotherapy." That's a different group and I don't have any hesitation about that.
UNIDENTIFIED SPEAKER: Can I push just a little bit on that? Would it be possible to take those patients, I mean obviously there's a spectrum here. So you've got the ones that you'd be comfortable waiting on, and those that you'd not be, and then you've got, you know, a gray area where you're still putting the category of not being comfortable, but, you know, maybe there's a little bit more gray there. Could you monitor patients in a way that would allow you to be comfortable holding off for a little bit in this sort of gray area of where you might want to treat to keep patients out of trouble?
DR. O'DONNELL: I mean, that is basically what we do in practice, right? We see the patient, they're not super-sick, but then we usually do something like airway clearance. And that we would have to sort of standardize that, I think, which is super difficult.

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UNIDENTIFIED SPEAKER: And I think that that's the key Anne brings up is as long as for the clinical trial means different than clinical practice, where we get started and look at the patient, take the holistic kind of approach and say, okay, we're ready to pull the trigger and treat or not treat. For clinical trial design, we really need to have objective criteria that guide us, yes, treat, don't treat. And so we're comparing similar groups I think.

UNIDENTIFIED SPEAKER: And I'm going to agree with you it'd be better to have the standard approaches. But if you -- I mean if -- as long as it was not antimicrobial, and you destilted (ph) it in both arms and you were blinded and it was a superiority design, I see Erica saying yes, I'm thinking that maybe you'd still have something that would be informative.

MS. BRITTAIN: But if you have a binary, if your endpoint is going to be binary, and you have a -- this decision that someone does need treatment is made in a blinded fashion, it seems like that would be the solution to the ethical dilemma.

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UNIDENTIFIED SPEAKER: Yes, I think Tim's issue was entirely the ethics of withholding therapy from a patient for a while, but you've got some patients who come in and they're asymptomatic and you're really not putting them on therapy, you're going to just observe those. You may have some patients who come in that you want to treat day 1, but that usually is because they've got cavitary disease on radiographs. And so you've got the people in between and as Anne has suggested, we don't start with antibiotics, we start with the other things, treating the underlying condition, treating their bronchiectasis.

And so you could be randomizing those patients then to be getting that approach plus placebo versus that approach plus your active drug. And I think at that point, 6 months doesn't seem too long.

UNIDENTIFIED SPEAKER: We heard 3 to 6 months earlier this morning as well. So could you define a period or an efficacy endpoint, clinical outcome at 3 months that was more definitive, at which point you could reassess and potentially work in (cross talk).

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UNIDENTIFIED SPEAKER: The missing piece in here, so getting back to Dr. Cox's repeated request that we need a clinical outcome to measure is, it's one thing to say this is what you get when you use the antibiotics, but also what do you get when you do airway clearance? In terms of how much that will change, and then with the addition of antibiotics?

UNIDENTIFIED SPEAKER: Well, and in that case that you raise an interesting point because that then becomes standard of care for that population, right? If you're -- have a population that are candidates for observation, and they don't want to go on treatment right away, then in the absence of a trial, that would be their standard of care.

DR. MELNICK: Yeah, David Melnick from Spero. You guys sort of stole my points here, you know, if the goal here is to come up with a superiority design to demonstrate that a new agent has activity against the drug, is the concern about a placebo-controlled trial the ethical concern of withholding treatment because I think we're in the situation that you pointed out, where, you know, patients are symptomatic

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candidates for therapy. You know, they've been observed, you're going to -- you know, and then randomize them in both arms, either to receiving a placebo or the drug. I mean, is the concern, the ethical concern about maintaining those patients on placebo for 6 months because the conversation seemed (cross talk).

UNIDENTIFIED SPEAKER: Kind of a clinical issue more. You know, it's kind of like you're facing the patient one-on-one. And it's very difficult for a patient to -- for us, I think, to say 6 -- we're going to wait 6 months, when, you know, it looks like they really need the antibiotic. This is just not very black and white, these patients.

UNIDENTIFIED SPEAKER: So that would be upon us to define a clinical endpoint at 3 months, or sooner than 6 months, that 4 to 6 months, that could allow that assessment to be sooner and definitive.

UNIDENTIFIED SPEAKER: Well, I think that the thing that's slowing us down the most right now is we don't have a clinical outcome assessment.

UNIDENTIFIED SPEAKER: Correct.

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UNIDENTIFIED SPEAKER: Exactly.
UNIDENTIFIED SPEAKER: And to do it right from the start is going to take a while. So how could we design -- to your question earlier, how -- if we had to design tomorrow, what would we do? And I'm wondering though, could we take this destilted (ph) assessment and use that as the -- so rather than a clinical outcome assessment, but the doctors decision that you're here, I don't -- wouldn't normally treat you right now, I would watch you and I'm going to watch you as part of this trial, I'm going to see you every hour. Don't worry, when I think you need to get treated, I will initiate treatment, but you'll be randomized to during that time.
UNIDENTIFIED SPEAKER: And…
UNIDENTIFIED SPEAKER: I think it would help us because we have this Clofaz (ph) versus placebo trial starting --
UNIDENTIFIED SPEAKER: Yeah.
UNIDENTIFIED SPEAKER: -- to know what -- how that goes before we take on another placebo-controlled trial.

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UNIDENTIFIED SPEAKER: So if we did the superiority study, though, with that front end, and somebody that wasn't really sick, if I had somebody that I knew needed to be treated and I needed to give them best care, it would be -- I'd be hard pressed now to at least give them an arm of placebo. It just wouldn't be the thing to do.
UNIDENTIFIED SPEAKER: Right.
UNIDENTIFIED SPEAKER: Right.
UNIDENTIFIED SPEAKER: On the other hand, if you said -- and this patient comes in, I don't know if you're going to need to be, you know, on treatment or in this gray zone, if you will, and say we could justify treatment or a placebo in addition to standard of care with just chest physio, airway clearance, all that sort of thing and do that for 6 months, and knowing that I'm not going to lose macrolite, I'm not going to create macrolite resistance, or put that patient in a difficult spot as far as not responding to standard of care should that need arise at a later date, I'd be okay with that. And that would clearly be something that for a 6 month period would -- I

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would find that very acceptable. And frankly understanding that this may in fact based on the Phase 2 studies, or in the pre-studies to understand that if after 6 months, they may not need any treatment at all. And that would be enough justification to say, okay, let's proceed with placebo controlled study with standard of care airway clearance and see what happens at that 6-month period knowing I'm not going to put that person in a position to not receive what I would consider best care of macrolite-based regimen at that point.
And if you're following them regularly, then at any moment, you could say you've gotten worse now, you need to come off randomized treatment and go on real treatment. And you could consider -- conceivably do that for a long time. And the endpoint the time too I think that's better to me, I know it's statistically more powerful than at 6 months, how many have gone on versus how many haven't, I would probably prefer a time to event.
UNIDENTIFIED SPEAKER: But the…
UNIDENTIFIED SPEAKER: If you're going to

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borrow from other fields for a moment, the rheumatology, early HIV days, you know, it's not that we think you should go on therapy and we're not doing it, it's that we don't know actually when the right point is to start therapy. It could be that patients would benefit from earlier intervention all around and that this current practice of monitoring patients with pulmonary hygiene and that sort of thing is not sufficient and we're actually doing harm to patients by not starting therapy sooner. Therefore, when you're sitting in front of a patient, and you're not presenting it like I'm withholding a therapy from you, but actually, we're doing a study because we don't know we need to further elucidate the pathophysiology of this disease. It could be of great benefit to stop the inflammation in your airways that may be occurring at this stage in your disease.
UNIDENTIFIED SPEAKER: But the risk of this study is we're testing two hypotheses. So one is the efficacy of the drug, the other one is the effect of early intervention in relatively mild MAC disease. So it's positive. It's no problem. We know the drug

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works. If it's negative, we don't know whether that's because the drug combination lacks activity or because the patients didn't require treatment. And Tim was cautious in only putting in the patients that didn't really need treatment.

MR. AKSAMIT: I think you have to define right now what you mean by positive or negative, or working and not working. If it's a microbiological sputum conversion, there's no positive or -- I mean, you'll know whether the antibiotic combination worked. If it's a combination of a clinical outcome assessment, and we're giving pulmonary toilet and we're giving respiratory care, it's very hard to define a priority without first doing that study what will define a positive endpoint for that -- from that perspective.

UNIDENTIFIED SPEAKER: I mean the tension here is you want to prove some new drug or new drug combination works, right? Microbiologically, presumably, versus what we face in the clinic, which is (audio gap) and we can't tell on day 1 which patient is going to progress and which patient

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doesn't. That's what we really need. I think what Karen said was real important, I mean why do we really want to know right now, we want to know who to treat, right, number 1, with antibiotics. And number 2, we want a shorter regimen, or that's what the patients want, like a built-up shorter regimen.

UNIDENTIFIED SPEAKER: If I could just respond to James, I think that's a real concern that there, you know, we might -- it might not be a sensitive assay because these patients never go on. That's sort of why I would favor not a 6-month time point. (Audio gap).

UNIDENTIFIED SPEAKER: By clearing exercises in one arm, and then the other arm, you did airway clearing, and then you gave an antibiotic. And there was no difference in the clinical outcome. But the patients who got the antibiotic had more clearing of, you know, their microbiological culture, you know, but you had no effect on the clinical outcome. I'm not sure what you're doing there. I mean, you're altering the culture. We know antibiotics can change people's, you know, cultures. You'd really want to show a

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clinical benefit here. I mean, ultimately. Now, maybe you're not measuring the right thing, maybe you're not measuring it at the right time, maybe it's going to take longer. But if all you've done is alter the culture, and there's no demonstrable clinical advantage to the patient, I'm not sure that it's worth doing that.

UNIDENTIFIED SPEAKER: So I just want to go back a little bit further to how we're defining the population for the study. Are we defining the, you know, in this theoretical situation, are we defining the population as just a positive MAC culture, or are we defining the population as positive MAC culture and meets criteria -- ATS/IDSA criteria for beginning treatment?

UNIDENTIFIED SPEAKER: You know, I think we would have to start with the position that they would fulfill criteria, but even fulfilling ATS criteria at the moment, doesn't in itself warrant treatment in all those cases.

UNIDENTIFIED SPEAKER: So at that aquapoised (ph), then would it be okay if you had a population

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who met ATS/IDSA criteria for starting treatment, is there aquapoise to randomize them to treatment versus placebo?

UNIDENTIFIED SPEAKER: In a gray zone group, my position would be yes. And I think it comes down to I think if we had a better clinical assessment tool, something that would be very sensitive, not necessarily even specific, but sensitive enough to pick up signal for treatment that is we're making the chronic fatigue and dyspnea better, or one of those three better, in addition to microbiological response, then I'm onboard. That's…

UNIDENTIFIED SPEAKER: And then I have another question. So in clinical experience in these -- this particular patient population, when you clear their culture, are they symptomatically better?

UNIDENTIFIED SPEAKER: Generally, yes. Not always, but generally. And you want to -- I mean…

UNIDENTIFIED SPEAKER: I just had a clarification comment. There's -- in the ATS criteria, that's a criteria for diagnosis. There are no clear criteria for when to start treatment.

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UNIDENTIFIED SPEAKER: I just don't think this is the unmet need that we -- I mean, that sort of philosophically, there's the unmet needs that we've heard about, I don't think this type of study addresses that.

UNIDENTIFIED SPEAKER: And that's in contrast to the unmet need of a shorter, better regimen. That's a big unmet need for the current standard of care.

UNIDENTIFIED SPEAKER: And the other unmet need in this population is less toxic therapy.

UNIDENTIFIED SPEAKER: That's exactly -- because, you know, there's a reason, one of the reasons that we don't treat everybody is because we recognize that the morbidity of the drugs that we use. And some of that is benign sort of nausea, diarrhea stuff, but you know, we've all seen visual toxicity, hearing issues, the -- these meds are hard to take. And that's why, you know, you think about it, we're using drugs to treat MAC that are really basically would use to TB, nobody treating TB is talking about the toxicity of their drugs. Maybe you guys are, but

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in general, you're pulling the trigger pretty quick, but we have a lot of angst about it in our NTM patients, because, you know, you're going to put a 80-year-old woman on this therapy. So you want to be as certain as you can be that it's actually going to provide benefit. So I think there is a clear need for something better in this patient population and shorter as well.

UNIDENTIFIED SPEAKER: And part of what I think I'm hearing is, is that we don't really have the benefit well characterized here. I mean, compared to TB, I mean in TB, the benefit is well characterized. And then there's also the issue of, you know, the contagiousness of the disease to others. But it feels like here part of the issue is not just the toxicity, the multiple meds, but also, you know, not really having a really strong handle on the benefit side.

UNIDENTIFIED SPEAKER: And I want to resist going back to the TB analogies, but I'm going to go back there in LTBI, so, you know, 4 months of rifampin versus 9 months of isoniazid or the 3HP now regimen, I mean those are regimens that from an efficacy

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standpoint for the most part they're relatively similar. But would you rather take something 4 months or 9 months?

UNIDENTIFIED SPEAKER: In the background there too is we've got a pretty good idea of the effective treatment for latent TB and sort of preventing, you know, recurrence of TB, which helps us. That's our foothold.

MR. FENNELLY: Kevin Fennelly, NIH. So since you guys brought up TB, so I've spent a fair amount of my career studying cough and TB. And one of the things that we observe in treating TB patients is that -- it's if -- if we're using a good regimen, their cough often goes down pretty quickly. And so I have a question for the panel and for the FDA, and that is we've talked about the heterogeneity a lot. So why don't we get real narrow and pick something that we can measure both subjectively and objectively? So, in 2019, there are two devices out there that will measure cough frequency, we can measure the urge to cough by doing inhaled capsaicin studies, and it would be fairly clean. Patients who are wracked with cough

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usually want treatment, they're really uncomfortable. So would a trial where the patient population were patients with severe cough from their NTM disease, would that be acceptable?

UNIDENTIFIED SPEAKER: So, I mean, it sounds like what you're trying to do is put a construct together where cough is at the clinical endpoint. So I mean, a couple of things; I mean, we've also heard in the discussion the heterogeneity of the disease, and that some patients have cough, some people have, you know, cough with sputum production. Some people have shortness of breath, other people have fatigue. So, I mean, you're proposing to use just the cough population, and look for reduction in cough.

UNIDENTIFIED SPEAKER: We want a clinical outcome. So a clinical outcome is cough, and study those patients.

UNIDENTIFIED SPEAKER: So theoretically that sounds possible. It sounds like you're focusing in on a small portion of the population and one particular manifestation of the disease.

UNIDENTIFIED SPEAKER: Yeah, I don't think

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it's so small.
UNIDENTIFIED SPEAKER: Okay.
UNIDENTIFIED SPEAKER: Well, it's…
UNIDENTIFIED SPEAKER: I think it's 80 percent of patients cough. So I think it's the same issue with a clinical instrument, which is, if you're going to measure cough, they need to have cough. And how would you measure cough though? I think this is the most difficult part of this is cough is so prevalent, and particularly with inhaled agent. So how would you measure cough again?
UNIDENTIFIED SPEAKER: There are two instruments available now that are devices that will, you know, attach to the body, kind of like a Holter monitor with for cardiology, and you measure 24-hour cough frequency. And you could do that periodically, you know.
UNIDENTIFIED SPEAKER: And what if the patient still said I have a terrible cough, and this isn't helping my cough?
UNIDENTIFIED SPEAKER: You could -- there are subjective tools that, you know, you can use analog

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scale or the Liester (ph) cough questionnaire, Leicester Cough Questionnaire.
UNIDENTIFIED SPEAKER: They've been used successfully in Phase 2 studies of cough-suppressing medication. So they are sort of validated.
UNIDENTIFIED SPEAKER: But it hasn't been successful…
UNIDENTIFIED SPEAKER: Yeah, and these devices are being used in FDA-approved studies. So it's not like it's something new.
UNIDENTIFIED SPEAKER: But it had -- you brought up TB, you know, it hasn't been successful in TB trials. So looking at clinical symptoms…
UNIDENTIFIED SPEAKER: No, there's -- well, a different -- there's two different groups that have used ambulatory cough monitors and TB.
UNIDENTIFIED SPEAKER: No, I mean cough assessment, the cough scales.
UNIDENTIFIED SPEAKER: Oh, yeah, but I mean, I'm just talking about getting a 24-hour cough frequency. It's just an idea, just trying to…
UNIDENTIFIED SPEAKER: No, but to your point

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there are certain cardinal symptoms associated with the disease that if you can find the top two, you know, according to Amy's presentation, that was fatigue and cough, and it -- and find a way to work that into an outcome assessment, an early outcome assessment, in the absence of a PRO -- a validated PRO, or a PRO that most focuses on those two.
UNIDENTIFIED SPEAKER: And what I meant by the small population was if you were going for patients that exclusively only had cough because I'm guessing that they also have, you know, fatigue and dyspnea and I think that'd be really tough.
UNIDENTIFIED SPEAKER: Measure the content…
UNIDENTIFIED SPEAKER: Missing anything? I do want to come back to the -- that we've picked out the PRO, but it needs to be one that also not just to find something that can be measured, and they'd have to find the population that would be responsive. And so is there a need perhaps for just an observational study of these patients with an existing PRO?
UNIDENTIFIED SPEAKER: You guys want to talk about the -- how we develop outcome assessment tools,

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sort of the various steps along the way?
UNIDENTIFIED SPEAKER: So the observational study, the PRO, will be able to tell us whether the PRO, the council evaluating this in the PRO is important, relevant to the patients. Unless the patients get worse or get better, we are -- we won't have the data to know whether they -- the instrument is sensitive to that change. You know, because if they -- I heard that it being -- it will be stable for quite a while, maybe they will get worse. But we know -- we don't know if the score -- if they get better, the score will be, you know, going up as showing that.
So that power will probably still to (inaudible 0:55:16.7) to see a PRO still need to have a clinical trial. Now, we can observe in that patient that have not improved. I do have the question about -- about the PRO because I heard many times that the patient not have different symptom, shortness of breath, fatigue and cough. For example, we have a instrument which requests three questions and there's a -- they talk about heterogeneity and we need to evaluate patient depending on what symptom they have.

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So my question for the panelists that is there no concerned -- or should we be concerned that, for example, patient at the baseline have very severe cough. So we say, okay, for this patient, we will evaluate a cough. At the end of the trial, the coughs get better, but their shortness of breath or their fatigue got worse, do we need to worry about that? So if we need to worry about that, then we probably need to evaluate all important symptoms, not just based on what the symptom they have at the baseline. That's one question.

The second question I heard about, I also heard that the patient need to be symptomatic at the baseline so that we can see improvement at the end. That's one scenario. But also I heard that the one of the treatment goal is that the patient not getting worse, that they remain stable. So if they are remaining stable, then they don't need to be symptomatic at the baseline, and they just don't have a symptom in that again they don't have a symptom, so there's these two different patient populations. One final comment, I heard about this study design, vision

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for vision, I think about that. But I also hear that we don't have endpoints. You know, so it's very difficult for me to think about all these studies done without an endpoints. So that's all my questions.

MS. HIGGINS: So to the question about whether we need observational study to evaluate clinical outcome assessments, I guess I would want to ask first, the existing instruments that have been used previously have scores that are based on combining a bunch of different symptom items and impact items and tolerability items into a single scale score, and they're not working well. But some of these items are very specific to cough and shortness of breath and things that probably will work well. Is there existing -- are there existing data that will allow us to look at the item level changes on the very narrow specific cough, shortness of breath, outside of these scale scores that are not very good in this context for looking at clinical benefit?

And so in early studies, if you've used the QLLB (ph) respiratory domain, looking at those

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individual items, and maybe it's a matter of rescoring some of the instruments that are available to a very small subset of items that actually work because I'm not that familiar with this condition, but I've been looking at the scales that are available. And just on their face, some of them have items that are clearly not going to move with treatment and so I don't know that we need to develop something new, it may be a matter of using the data, we have to try to combine something into a better score that we can use.

UNIDENTIFIED SPEAKER: So I'll just -- I'll briefly comment on that because I made a similar point during my short presentation. There's no question that there are data sets already with item level data. So in this med (ph) clearly will have item level data. And we've done some item level analyses of some of the unsuccessful bronchiectasis trials. And I alluded to it a little bit in my discussion that you see in some of these studies that the cough domains get better and the breathlessness get worse. And so the average score is the patient looks as if they've not improved. But on the subjective question in the database of

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would the patient like to remain on treatment, and the answer is yes which suggests that the patient valued the improvement in cough more than they didn't like the change that they've reported in some of the other domains. And so we need to adjust the weighting I think of some of these to more match what's important to patients.

MS. HIGGINS: Right. And I think the survey that was done helps with the (audio gap). Based on James' comment, wouldn't a joint decision by the patient and the physician in terms of the need for an alternate therapy be a reasonable clinical endpoint and in terms of the time to failure in that setting? What is that joint decision based on?

UNIDENTIFIED SPEAKER: It's, I mean, obviously it would be multi-factorial, but for some -- one patient, it could be like my cough isn't there anymore, or I or my cough has come back. I, you know, I don't care that the sputum is positive, I'm achieving benefit. I don't want to change, whereas the clinician is uncertain something.

UNIDENTIFIED SPEAKER: Yeah, the clinical

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endpoint becomes the patient walking in and saying, I feel lousy, I want off this therapy, take me out of the trial. And that becomes the time to event analysis. And it's I think perhaps a reasonable reflection of the way the patient feels.

UNIDENTIFIED SPEAKER: So the challenge…

UNIDENTIFIED SPEAKER: And it brings in the physician's assessment, we've talked about this --

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: -- historic (ph) assessment of my patients doing well or not.

UNIDENTIFIED SPEAKER: Right. The one challenge I see with that is that it at a data level score level, we won't know if those decisions are made because of tolerability issues or lack of efficacy. But -- and so I think we need to be able to clearly define how those decisions to change treatment are made or to treat and be able to measure those. These global assessments are really difficult to interpret at the end of the day. We don't know if the decision to change treatment or to treat was based on the culture alone in those cases and that doesn't get us

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to having any information on the clinical benefit.

UNIDENTIFIED SPEAKER: And I would caution just a little bit to that's overweighed the specific domains. And let's take cough as a example, and as it was just shared, so we have a patient that's on some therapy comes in, says my cough is terrible, I want to get off this therapy, well, it turns out that they've now got pseudomonas or they've got a sinus infection, or they've got some other reason they have coughs. It's not that their cough isn't worse, it's not that they don't feel badly, but it's two true and unrelated type of issues. So we have to be a little bit cautious not to overweight cough and attribute with a great deal of specificity that symptom of cough. And in fact our experience clinically is just as was shared about this heterogeneity, and that holds true for the symptoms as well, that we if we overweight that then that's going to be a problem. So we have to just be a little cautious going into this and assigning too much weight to give us spurious results essentially.

UNIDENTIFIED SPEAKER: You say it's

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unrelated, but I mean, if treatment gets rid of some of those other things, that is making the patient feel better, and that's, you know, improving their quality of life.

UNIDENTIFIED SPEAKER: Yeah. So, you know, in this -- in that example, again, I'll just over-generalize, so that per same person comes in, has cough, and now they've got pseudomonas, they get treated for their pseudomonas. And 10 days later, after they get treated for their pseudomonas, they come back and say, hey, I feel great again. And they're still on their same treatment for the MAC, say, that's been there all along, just that we treated the secondary issue that caused cough. And again, it was completely removed from the therapeutic for the primary therapy of the MAC.

UNIDENTIFIED SPEAKER: But I'm saying that how do you know that the treatment for the MAC isn't going to have an effect on those other things as well?

UNIDENTIFIED SPEAKER: And it's possible. So again, in this example, where somebody stated been on MAC therapy for a month or 2 or 3 or 6 months, and

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comes in analysis, I feel crummy because my cough is worse. And that person has the impression I think my MAC is back and so I just want to come off therapy, and then you -- we make our assessment and lo and behold, well, it's not because they have a bacterial exacerbation or they have a sinus infection, which can be taken care of very easily. And the symptoms they have 3 months or 6 months that they attributed to their MAC coming back wasn't in fact the MAC at all and something else. We treated in a very simple and easy way. Those symptoms go away and they'll say, "Okay, I'll stay on the MAC treatment now."

UNIDENTIFIED SPEAKER: Right. So I mean, it sounds like, you know, that's one of the issues with having the patient have a big say in the outcome. And I think, you know, what I would worry about is this conflict between, you know, you give them the results of the culture, there's -- it was expressed earlier they have to give them the results of the culture. I'm worried that that can have a big effect on their PRO. You know, maybe they felt great until you told them that that they're, you know -- you know, I would

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like to get those PROs before giving them the information about the culture.

MS. HIGGINS: Okay. Can I address…

UNIDENTIFIED SPEAKER: I just want to weigh in on that. I was thinking about that earlier, when we were talking about the blinding and I completely agree. I would say you don't want to give the PRO, have them administer it before any of the other assessments, before the 6-minute walk if you're going to do that, because you don't want anything to bias their -- how they feel -- how they think they feel, and I agree that giving them their results of their culture could actually have an impact. We're worried earlier that it can be the other thing, that if the sputum results were -- it's a conversion that happened, then we might artificially think they're better --

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: -- because of that result.

UNIDENTIFIED SPEAKER: And just for the record, so with the PRO and the culture, so if

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somebody comes in for say a study clinic visit, they collect the sputum and do their 6-minute walk test, that sputum will be available up to 2 months later. So it would not be in real time for sure.

UNIDENTIFIED SPEAKER: But still it could be -- they might be affected by the one from before. But it seems like it might be okay. Some of the designs people didn't like the MD not knowing the sputum result. So maybe there could be, you know, the MD could have the -- the health professional could have the sputum result in a patient not for a possibility.

UNIDENTIFIED SPEAKER: (Off mic). Six month (off mic).

UNIDENTIFIED SPEAKER: I think in the scenario we were talking about where these are sort of mild patients might not -- you could conceivably --

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: -- keep everyone blinded. I think you bring up this point of the non-specificity of the symptoms and we're always going to face that there may be underlying COPD that gets a little worse that, you know -- or a flare of the

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bronchiolectasis. And I think that's going to be some noise in the system that is unavoidable.

UNIDENTIFIED SPEAKER: I also think when you start measuring multiple outcomes like fatigue and cough, I think we're going to have to remember -- and maybe the best thing is to measure those things together, but we're always going to face the fact that the cough contributes to the fatigue. And that's something we saw -- I was reading our PFDD transcript recently and the patients described the cough as exhausting. And if you think about -- if you're talking about a cough that causes them to fracture bones, and that's what it does sometimes, that is the nature of the cough they're experiencing, it is exhausting for them. And they do it constantly and sometimes it's, you know, sometimes -- a lot of times they just cough, and sometimes they have to do it on purpose to clear their lungs. So it's they really almost have no choice. Those things are going to confound measurements, no matter what, I'm not sure how to get around that. That's not my area of expertise. That's why a lot of you are here. But I

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think no matter how sensitive the tool is, we're always going to have that confounding factor.

UNIDENTIFIED SPEAKER: I have a question for the clinicians. In this less sick population, where you have less lung damage, is there any other functional assessment that can be done to follow these patients in addition to PRO or on its own?

UNIDENTIFIED SPEAKER: When we pulmonary function tests, you know, there are things we do, but the PFTs are not very sensitive at all. So…

UNIDENTIFIED SPEAKER: Yeah. To make it short, the answer would be no.

UNIDENTIFIED SPEAKER: Yeah.

UNIDENTIFIED SPEAKER: (Cross talk).

UNIDENTIFIED SPEAKER: It -- really the PROs would be the main thing if -- I mean we -- obviously in clinical practice, it's not a formalized PRO, it's like how you're doing kind of thing, right?

UNIDENTIFIED SPEAKER: Yeah.

MR. CHEN: So instead of the pulmonary function, the symptoms that we know this, we have difficulty evaluating the symptoms that they are all

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inter correlated, and we didn't know how to weight that and I don't think it will -- I also think it will be difficult to weight by the degree of bother because the degree of bother is different for different patients, some patient more bothered by shortening of breath, some people -- some patient more bothered by fatigue. So the weightings is used -- I think usually we will see, you know, based -- the instrument should be based on what is most relevant and important to the patient. But instead of symptoms, that because of the cough, because of the shortening of breath, can we measure their activity to their daily functions, that, you know, rather than a 6-minute walk test at one time point, but how about ask them to say, you know, are you able to run a mile, walk up 10 flight of stairs, what is useful to ask them to do, physical function PROs, daily activity PRO?

UNIDENTIFIED SPEAKER: I think the PRO that asks them those kinds of questions about daily functions would be more useful. But again, looking at patient feedback, and again -- (audio gap) and stop and rest. It takes them several days to do a couple

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of loads of laundry. Those kinds of things that we would walk into the house and think nothing of doing, they have to plan and sometimes they have to plan days in advance. And if they're having a bad day with their lungs, they are not going to be able to do it. If the weather is not good, they might not be able to do it. So if they see improvements over time in just their basic daily functioning tasks, that also might be a measurement. We may not consider those things important like, oh, great, I did a load of laundry today. For us, that's not a big deal. For someone who's unable to do that, for someone who's unable to walk across one room, for someone who's unable to walk up one flight of stairs, a change in that measurement for them might be very significant. And I don't think we can tell them if it's not significant, if it is important to them.

UNIDENTIFIED SPEAKER: But I think -- I mean you -- it's a little bit of a skewed population you're talking the more severe patients, we're also discussing real mild patients that we might want to intervene on. And they're not having those issues.

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UNIDENTIFIED SPEAKER: They're not, but we have to consider developing tools that are going to work across a broader spectrum.

UNIDENTIFIED SPEAKER: Right. I understand that. But I think, you know, when we're talking about enrolling patients, milder patients, our tools are different.

UNIDENTIFIED SPEAKER: Not different, but different results.

UNIDENTIFIED SPEAKER: You mean -- I think your survey probably represents a somewhat skewed population.

UNIDENTIFIED SPEAKER: Probably does. But again, we're going to end up dealing with refractory patients at some point in clinical trials.

UNIDENTIFIED SPEAKER: Right. Now…

UNIDENTIFIED SPEAKER: And if the tool isn't going to measure, you know, across multiple patient populations, then, you know, then we're looking at developing multiple tools for multiple patient populations, it becomes an even more complex issue.

UNIDENTIFIED SPEAKER: But it does seem to be

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advantageous to measure something, you know, daily, rather than have it, you know, they had the 6-minute walk test on a bad day for them, you know…

UNIDENTIFIED SPEAKER: I mean, that's why the Fitbit idea?

UNIDENTIFIED SPEAKER: Yeah. Yeah.

UNIDENTIFIED SPEAKER: Something along those lines, some activity monitor (cross talk).

UNIDENTIFIED SPEAKER: Right.

UNIDENTIFIED SPEAKER: Yeah, just a comment on the Fitbit, though. I had 893 steps today. So it's a bad day.

(Laughter)

UNIDENTIFIED SPEAKER: I just wanted to make one comment to your original question, because the -- yes, the NTM therapy can have other benefits and I'll just pick the MAC providers as an example. It's a common therapy in bronchiectasis. So they could get additional benefits from a drug like that that's unrelated to the effect on the MAC.

MS. YANG: Thank you. My name is Lee Yang (ph). I heard you the whole day and I think we are

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going to the -- (audio gap). There's nothing to do with TB or NTM. So I would like you to be -- pay attention. You are going to provide a health care. You are not going to (inaudible 1:13:55.4) something misleading cost and consequences related to the disease or health prevention. Instead you were to focus on the healthcare. So something is misleading, you have to get rid of it, for instance the fatigue. Now if you go to some people, which are providing some to people to (inaudible 1:14:19) and they already have, so there are more instance.

DR. FLUME: All right, let me interrupt you for a moment, because if -- I'm not understanding the question completely and we can talk about this afterwards, but we are talking about -- (audio gap).

MS. YANG: -- to pay attention to healthcare. So instead of the healthcare, you are talking about something else. They allow them to make the excuses.

DR. FLUME: Okay. Thank you.

MS. YANG: So now, I still have the other point that you just mentioned now, I want you to redirect your attention. So instead of like false

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constant consequences, now you got to view the right decision, this is healthcare. This is not something for you to mislead, you go to wrong direction.

DR. FLUME: Okay. Thank you. You may…

MS. YANG: So let me point something you just mentioned not too long ago, so you have fresh memory. So I would like you to say that this is like (inaudible 1:15:23.2) or how much you want to know decision and I would like to tell you a lot of veterans, a lot of (inaudible 1:15:25), they are sent to mental hospital or rehab center by the month, or 6 months or even longer. And they transfer --

DR. FLUME: Okay.

MS. YANG: -- to the different institution.

DR. FLUME: Let me interrupt you there because I think we're getting off track, we're talking about (cross talk).

MS. YANG: Yes. I said you are getting off-track.

DR. FLUME: NTM therapy -- I'd be happy to talk to you after the session.

MS. YANG: No. I would like you to my

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correction. This is the word you are talking about. I mean not us too long ago -- (audio gap). This is that we are talking about system problem. And then you just learn the system direct to where you should go. I would like you to -- and I respect you as a medical health professional, what I try to say is that this is not on a medical direction problem. They also offer socialist workers --

DR. FLUME: Ma'am?

MS. YANG: -- and provide or nobody have any health -- any kind of credentials.

DR. FLUME: Ma'am, I'll stop by and talk a little bit later with you, okay? We appreciate you…

MS. YANG: (Cross talk).

DR. FLUME: Excuse me, ma'am. Ma'am, we appreciate your comments.

MS. YANG: (Cross talk). I was from your -- that information. So you had (cross talk).

DR. FLUME: Please do.

MS. YANG: Yeah. That would be good. If you can just give me a bit in a thought.

DR. FLUME: I will stop by in a moment and

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talk with you, okay? But…

MS. YANG: I'm ready to go and I'm not going to spend anymore.

DR. FLUME: Then I will come and talk with you right now.

MS. YANG: And I even mentioned, I hope you sent to the FDA director, okay?

DR. FLUME: All right. Dr. Cox and thank you. Have we addressed all of the questions for the panel? I just want to make sure that -- because we are going to come to time where we need to wrap it up.

MS. HIGGINS: I think there were some questions in case 1 that perhaps in the treatment -- in the refractory case were potentially more applicable to here. But we also have that follow-on overall questions for both cases. So I don't know if that's -- you're moving on to that or wanted to go back and…

DR. FLUME: I don't recall that we had other questions to follow on. I have one question that came in from the webcast I do want to get to before we close. But do we have other questions that we had to

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follow on? These are the questions to you.
UNIDENTIFIED SPEAKER: Yes.
UNIDENTIFIED SPEAKER: These are the same question.
UNIDENTIFIED SPEAKER: (Off mic).
DR. FLUME: From the first case.
UNIDENTIFIED SPEAKER: We're asking couple of bulleted items from the previous…
MS. HIGGINS: Right, yeah. So I don't think we got through all of the questions from the last case.
DR. FLUME: Which one did we not get to?
MS. HIGGINS: In terms of the feasibility of standardizing the background regimen, some of these things…
UNIDENTIFIED SPEAKER: Is it possible bring up slide 12, questions for panel from the prior case? Is there anyone from AV here? Thank you. For case study 1.
MS. HIGGINS: So while we're waiting for that, I have a question that I'm -- in going back and forth between these two cases, what we heard in the

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first case was that for -- in the case of a Phase 2 study, where you're looking for an early efficacy readout, that a placebo-controlled study design would be potentially feasible in a treatment naive population. And in -- if you're saying that it's more difficult in the Phase 3 study design in a treatment naive population versus placebo, what about in the treatment refractory Phase 3?
And the question that I'm wondering about is the translation of data for -- from a Phase 2 in a treatment naive population to efficacy in a Phase 3 in a treatment refractory population? Do we think that there are particular difficulties in translating data from the early Phase 2 efficacy read in a treatment naive population to an ultimate pivotal study in a treatment refractory population?
UNIDENTIFIED SPEAKER: Yeah. So short answer I think would be yes. I mean, they're completely two separate questions clinically.
MS. HIGGINS: Yeah.
UNIDENTIFIED SPEAKER: And I am -- as a clinician, I'm not sure that I would extrapolate an

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automatic -- there would be no grounds to know for sure that those two separate different situations have any connection. They may and there may be benefit in both.
MS. HIGGINS: Yeah, I guess, I should have asked it in a slightly different way, which would be how would one potentially translate that data as informative from a treatment naive population into a treatment refractory population. And I guess the same would extend to an approval in one of those populations in use of the -- (audio gap).
UNIDENTIFIED SPEAKER: Right.
UNIDENTIFIED SPEAKER: For what we've heard, it does seem like they have two very different patient populations.
UNIDENTIFIED SPEAKER: Yeah.
UNIDENTIFIED SPEAKER: So it would be very hard for you to extrapolate what you've seen in the Phase 2 to design your Phase 3 trial for a totally different patient population. And I think the same would hold for, you know, approval. I mean the approval really will depend on what population you

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study.
MS. HIGGINS: Right.
UNIDENTIFIED SPEAKER: And Angela, would you be looking for a clinical practice or an expanded indication from the FDA for that -- and to answer your question --
DR. TALLEY: Well…
UNIDENTIFIED SPEAKER: -- because in practice, it's done all the time.
DR. TALLEY: I think it gets…
UNIDENTIFIED SPEAKER: And we do a lot of things that are applied to situations where the efficacy has been shown in a completely separate issue, and then we clinically still use it, just because there's no data there.
DR. TALLEY: Yeah.
UNIDENTIFIED SPEAKER: But you're looking for a broader indication that that then isn't embraced by the FDA, and that's what I think would be the sticking point.
DR. TALLEY: Yeah, I mean, either questions are relevant. I think ultimately it comes down to a

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question of what data does a clinician need to be convinced in terms of the utility of a new agent or of a standard of care.

UNIDENTIFIED SPEAKER: Another study?

UNIDENTIFIED SPEAKER: So I do have a sort of follow up comment. And we heard a lot of discussion about why the Phase 2 trial shouldn't be long and I think we get that because it's not feasible. But if there is so much uncertainty around what is an appropriate outcome assessment, and we're cutting short the Phase 2 trials. We're really not going up to the point where we think we're going to see the benefit on the clinical outcome, then I think we are taking a big risk in moving into Phase 3 trials and I sort of wanted the committee to opine on that because I -- that's been bothering me. I mean, everyone seems to think we need a clinical outcome assessment. We don't exactly what it is. We think it might be 3 months, it might be 6, it might be longer. We're going to cut short our Phase 2 at 6 because beyond that is not feasible. And then we're going to design our Phase 3 trial based on very limited information

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that we've collected in Phase 2. So just wondering how we can tie all that together.

UNIDENTIFIED SPEAKER: I mean, I think this is where we've been burned in the bronchiectasis trials that we have killed bug in Phase 2. But no clinical benefit, you know, and then they flame out in Phase 3. So, you know, I think we take a risk if we don't have more information. I'm looking at Ken because we -- you know, this issue of like, kill the bug -- and that's the proof-of-concept, but it's failed now in multiple Phase 3 trials for…

DR. OLIVIER: I didn't mean to imply that that is all you need.

UNIDENTIFIED SPEAKER: No, I'm not (cross talk).

DR. OLIVIER: But if it doesn't do that, then I don't see the point of going forward is all I was trying to say. I think the Phase 2, you've got to collect some information that will give you a hint about what's important to move on to measure in Phase 3, that's going to relate to clinical outcomes. And maybe 6 months isn't long enough to do that.

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UNIDENTIFIED SPEAKER: So I guess that's the question is what lessons have we learned from these other trials, right, that we could apply here?

UNIDENTIFIED SPEAKER: I think the key lesson is that you have your clinical endpoint and a population that will respond to it. So if for example, in the bronchiectasis trials, if you're going after exacerbations and your placebo group has an exacerbation rate half of what you dreamed it would be, it's not a surprise that it didn't result in a win for the study. So a key here is it's not just what the end point is, is you got to have a population that will be changed by it.

UNIDENTIFIED SPEAKER: In the Phase 2, we really haven't gone out long enough because right now I think there's a lot of uncertainty because we -- in the first place, we haven't defined what the clinical outcome assessment tool is, right?

UNIDENTIFIED SPEAKER: Right.

UNIDENTIFIED SPEAKER: I think we have a general feel that maybe months 3, we have some ideas, some people think it might be month 6. But what if

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you are stopping the trial -- the Phase 2 trial earlier, you haven't gone long enough where you actually have the potential to see this clinical benefit, then how can you appropriately design your Phase 3 trial? I think that's the question.

UNIDENTIFIED SPEAKER: I think what I'm hearing or what I'm thinking is that 6 months seems to be the magic timeframe which we would make a decision about whether we need to change our approach to treating the patient. So if -- I'll think two different patient populations; one is whom they're symptomatic, and you're trying -- your goal is to improve their symptoms. And the other is to try and prevent worsening. So those are two different populations, you're looking at two different approaches to what that clinical endpoint would be. But I think, and I hear repeatedly, 6 months is that sweet spot, that if you don't have it by 6 months, you've got to do something different. And if you see it before 6 months, well, terrific. So if you're doing a micro endpoint at 6 months, you'll collect your clinical data in the interim there.

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UNIDENTIFIED SPEAKER: I guess one of the things we talked about was the trade off of -- so I think you're implying that the Phase 2 study is for 6 months. But the primary endpoint of a pivotal trial is going to be at 18 months, you don't really have that data. And I guess earlier I had voiced I am concerned about having the primary endpoint being at 18 months because of so much missing data and then there was the possibility of entertaining a trade off where okay, we would we would have the primary endpoint at 6 months for purposes of having robust data set. And then…

UNIDENTIFIED SPEAKER: I mean, I don't even know to say that 18 months is the correct timing. I mean, that's also based on no data. So are we better served because there's so much uncertainty here in doing more work in Phase 2, so that we then don't, you know, like, I think the point Dr. O'Donnell made, we've seen in bronchiectasis trials that selection of the endpoint might have been the problem. So I -- really I cannot tell you that 18 months is the right endpoint because I have no more information than

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anybody else has. So --

UNIDENTIFIED SPEAKER: That's pointed out.

UNIDENTIFIED SPEAKER: -- how can we make a more learned effort to get to a right endpoint, be it the definition of the endpoint or the timing of the endpoint? Or even if it's time to enrich, which I know is your preferred approach, how do we define that event? What exactly are the components of that event?

UNIDENTIFIED SPEAKER: That's the challenge.

UNIDENTIFIED SPEAKER: I think that's the issue.

UNIDENTIFIED SPEAKER: It's called patient -- or physician-inpatient global assessment kind of a thing.

UNIDENTIFIED SPEAKER: Right.

UNIDENTIFIED SPEAKER: So that -- that thing is perfect. I just put that out there because in the absence of a current validated instrument that might be the most facile way to at least proceed.

UNIDENTIFIED SPEAKER: Sure.

UNIDENTIFIED SPEAKER: But I think, you know, Ed made the point, when you have a standard of care

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that's based upon expert judgment, but not a lot of data and we're always going to wonder is this 12 months of culture negativity necessary and why are we even doing that and -- but I really worry if we try to answer that question and whether a drug works in the same trial, it's going to make it really messy.

MR. CHEN: I have a related question, I think I heard earlier. So suppose that we can refine QOL-B to make it more sensitive in term of a score or adding different items, maybe the changes, I heard that the patient actually starting feeling better minimum at 3 months and then they probably -- most of them will feel better at 6 months. So in a Phase 2 trial, 6 months Phase 2 trial, is that sufficient time to validate that refined PRO endpoints?

UNIDENTIFIED SPEAKER: I think we might be underselling how valuable 6 months would be. I mean, I take the analogy of the bronchiectasis studies, but there the Phase 2 is at 28 days out of a treatment that you'll get for 20 years, whereas this is 6 months out of a treatment you'll get for 18 months. So to my mind, it's not that bad. And most of the treatment

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response you'll see at least in the treatment naive patients is within the first 3 to 6 months. So you would expect that if you're not seeing a symptomatic improvement after 6 months, then some patients will feel better after that, but you should get a large chunk of the response within that period of time. So I don't think this is quite the same as the bronchiectasis…

MR. CHEN: Right. So a 6 month Phase 2 trial is sufficient for us to evaluate the PRO outcomes that we're trying to use for Phase 3 trials. So the only question would be if a Phase 3 trial is a longer, saying not 18 months, but by 12 months, at the PRO, you see evaluated at 6 months in Phase 2 trial and do we expect the -- how the patient feel the clinical outcomes will be last more than 6 months that -- so in the 12 months Phase 3 trial, we still see the sustained improvement after 6 months using that PRO?

UNIDENTIFIED SPEAKER: Maybe improvement, then stabilization rather than continuing…

MR. CHEN: Right. So okay. Yeah, for example, we see improvement starting at 3 months and

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then month six, but then it probably won't go higher up, but that improvement would stay, you won't go getting worse, go back down?

UNIDENTIFIED SPEAKER: Probably.

MR. CHEN: Probably.

UNIDENTIFIED SPEAKER: It makes sense according to the biology just now and once you get sputum culture conversion, the antibiotic then can't keep improving your quality of life because it's dealt with the issue that -- it was there to deal with. But it shouldn't go down.

UNIDENTIFIED SPEAKER: I think what we really need that we don't have is some kind of progression of disease composite, yeah, scorecard or something for the longer trials, particularly the refractory patients.

DR. FLUME: To make sure that we finish on time here, there was one question that came in over the web with respect to abscesses. We need a combination regimen to advance to clinical trial. So the question is do we have such a promising regimen to move forward? And if so please share the drugs and

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combinations.

(Laughter)

UNIDENTIFIED SPEAKER: I thought that this was going to be covered at the next meeting.

UNIDENTIFIED SPEAKER: That's what Kevin said.

UNIDENTIFIED SPEAKER: What?

UNIDENTIFIED SPEAKER: I'm not sure how to answer that. We all have that regimen. It's just a different one. I mean, we -- this is -- I mean abscesses is another whole day. I mean, it's just such a complex discussion, you know, but I was looking -- (audio gap) the SGRQ in abscesses patients from -- (audio gap) -- but I think our patients get better as Tim said earlier. I mean, so I would proceed. So one of the action items should be -- (audio gap).

DR. COX: Do you want to tackle the summary?

UNIDENTIFIED SPEAKER: So Ed gave me the toughest job like a few minutes ago, so I'm going to try.

(Laughter)

UNIDENTIFIED SPEAKER: So I'm going to try to

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summarize this very complicated and interesting discussion. I may not necessarily have them in the right order of research. I just wrote them up as all of you were talking. So I think one important message that at least I heard during this discussion this morning and during the case studies is that there is certainly a recognition that we need a clinical outcome assessments tool. We don't have one readily available, one that's perfect. Whether it's only going to be a patient-reported outcome or there could be some component of a clinician-reported outcome. I think we need to have further discussion around it.

UNIDENTIFIED SPEAKER: And we talked some, I'll throw in a little bit here, too. We talked some too about the survey that showed the cough fatigue and shortness of breath and that seems to be what we're hearing from everybody is sort of the key things that we're seeing as clinical symptoms that patients are reporting.

UNIDENTIFIED SPEAKER: Yeah. And then -- yeah, and there was discussion around whether we need to start from scratch with new tools, or I think

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there's a preference to maybe use or modify existing tools because I think there are some existing tools, but probably they need some more work. There was discussion around what would be the appropriate timing of the endpoint, whether we choose an endpoint in a fixed time-point or whether we -- the preferred approach would be a time-to-event analysis. I think there was some degree of agreement that an earlier time-point for a clinical outcome assessment would be optimal, whether it's 3 months or 6 months, I think still needs further discussion. And even for a time-to-event analysis, one would need to define the components of what exactly constitutes the event. Yeah. Sorry?

UNIDENTIFIED SPEAKER: So we talked some too -- we were sort of just trading this back and forth, but we talked some too about enrolling the patient population that, you know, has manifestations of disease so you can actually see a response. You know, Dr. Sullivan showed us some interesting slides about the variability of various different characteristics of the patients in the trial that they enrolled.

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UNIDENTIFIED SPEAKER: Then regarding the patient population where the one would study a treatment naive population or a refractory population, I think there was a preference that one would start with the treatment naive population. But there was a fair bit of discussion around the feasibility of doing placebo-controlled trials in this patient population. But I think where we ended up was it might be possible for us to define a patient population in whom it should be ethical and to conduct a placebo-controlled trial.

There was discussion around the potential need for outcome assessment tools that might be different depending on the specific patient population because treatment naive patient population is definitely different from that of a refractory treatment population. I think we heard clearly that NI trials are not the preferred options, superiority trials are the preferred options for this clinical condition. We have -- we will -- we think identifying an evidence-based treatment effect would be very difficult for this disease, which then makes the NI

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trials very difficult to justify.

There was discussion about potential use of registry data or data from existing clinical trials to better understand what improvements and symptoms might be seen with treatment in these patients. And then there was also I think a very clear message that in our hypothetical examples, the duration of the Phase 2 trials was too long and certainly would not be feasible in terms of development programs. So Phase 2 trials would certainly have to be shorter. But -- and that the clinical outcomes, it might be possible to measure them in these trials as well because somewhere by month 3 to 6 we should see fair degree of clinical improvement in these patients. Did I capture them all, Ed?

DR. COX: Medication tolerability.

UNIDENTIFIED SPEAKER: Yeah, I think there was --

DR. COX: Events.

UNIDENTIFIED SPEAKER: Yeah, I think there was some discussion around adverse events tolerability, how one might include that in the

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endpoint. We -- I think we didn't go into a lot of discussion around it, but I think certainly other disease areas, we've had this discussion, and one has to be very careful in combining efficacy and safety endpoints. But again, something that we have to work on. So I think there's a very interesting and robust discussion. I think the main message is we as a group have a lot of work to do. I don't think we have answers to all the problems. But this is a good place to start and I think there's enough momentum here and interest that I think if we as a community work together, we should be able to find ways to design these trials and get patients the medications they need.

DR. COX: Agree very much. And I want to, you know, thank everybody for really rolling up their sleeves, all the work that's been done so far. And you know, the continued interest and commitment to continue to develop therapies for patient with NTM and I think it's really important. And you know, like many areas in infectious diseases, there's some significant challenges here. But from those

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challenges can certainly come rewards as far as improving the care of patients. So we're very grateful. Thank everybody.

UNIDENTIFIED SPEAKER: Yeah.

DR. COX: Wish them well for the travel and all.

SUMMARY AND CLOSING REMARKS

UNIDENTIFIED SPEAKER: Right. So thank you, everybody. Thank you for everybody -- every member of the audience that was here to listen and for those of you that participated. Many thanks to all members of the panel for your keen interest, and I think it's really contributed a lot to the discussions today. So we thank you all for that.

Amy, we do thank you for bringing the voice of the patient forward to this meeting. I think that's really appreciated. And many thanks to Sunita for having coordinated and put this workshop together. We really appreciate that as well. Wish you all safe travels and I'm sure you'd hear from us soon. So thank you.

(Applause)

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