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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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12	AMY LEITMAN	12	SONYA EREMENCO
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<p>1 PROCEEDINGS</p> <p>2 INTRODUCTORY REMARKS AND PANEL INTRODUCTION</p> <p>3 MR. COX: Good morning, everybody. We're at</p> <p>4 8:30, so we thought we'd go ahead and get started.</p> <p>5 And first of all, I'd just like to welcome everybody</p> <p>6 to today's Workshop on the Development of</p> <p>7 Antibacterial Drugs for Treatment of Nontuberculous</p> <p>8 Mycobacterial Disease. I'm Ed Cox. I'm the Director</p> <p>9 of the Office of Antimicrobial Products.</p> <p>10 And we greatly appreciate everybody joining</p> <p>11 us here today. We've got a diverse group of</p> <p>12 stakeholders and we think that's really important.</p> <p>13 We're grateful for all the academics, the clinical</p> <p>14 investigators, the practitioners, folks who are</p> <p>15 representing patients, patient groups, regulatory</p> <p>16 colleagues, folks involved in research in this area,</p> <p>17 and all of you for joining us here today, both here in</p> <p>18 person and also on the web. Now there's a number of</p> <p>19 folks that are watching via the webcast too.</p> <p>20 In general, we do workshops and we face</p> <p>21 particularly challenging issues with regards to drug</p> <p>22 development clinical trial design and development of</p>	<p>1 patients benefit from the improved care that the</p> <p>2 knowledge generated leads to.</p> <p>3 Understanding the disease, what works, how</p> <p>4 much it works, what it does, what it doesn't do, can</p> <p>5 help us to understand a disease and lead to the</p> <p>6 identification of interventions or a combination of</p> <p>7 interventions that are best able to benefit patients.</p> <p>8 So we've got a fairly full day. You've</p> <p>9 noticed we've divvied it up into essentially three</p> <p>10 main sections, where we talk about NTM disease. And</p> <p>11 we'll hear some -- from what we've learned from our</p> <p>12 experiences to date with clinical trials that have</p> <p>13 been reformed so far. And then we'll have an</p> <p>14 opportunity to go through some case studies.</p> <p>15 And the case studies are meant to be</p> <p>16 essentially hypothetical situations to try and help us</p> <p>17 to identify some of what we know, some of what we</p> <p>18 could benefit from, from additional learnings and, you</p> <p>19 know, how we can essentially move forward in the</p> <p>20 field.</p> <p>21 I would encourage people to keep in mind a</p> <p>22 few thoughts as we work through the discussions over</p>
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<p>1 drugs for treatment of patients with nontuberculous</p> <p>2 mycobacterial disease is certainly a challenging area.</p> <p>3 The workshops -- current knowledge and how we might</p> <p>4 address the evidence gaps that we face in order to</p> <p>5 improve what we do in the future. And really the</p> <p>6 ultimate goal here is to improve the care of patients</p> <p>7 affected with the NTM disease.</p> <p>8 The workshops bring the community together</p> <p>9 and they help us to both prioritize and focus our</p> <p>10 efforts. There's always a large number of different</p> <p>11 possible exercises or activities that can be</p> <p>12 undertaken to try and address some of the gaps in a</p> <p>13 particular area. The question is always, which are</p> <p>14 the ones that are most important for us to address</p> <p>15 right off the bat in order to move things forward most</p> <p>16 quickly. Generating quality evidence can be</p> <p>17 challenging, but it really is essential to the care of</p> <p>18 patients. Physicians can use it to guide the care of</p> <p>19 their patients; clinician investigators can use it,</p> <p>20 that is quality evidence, to evaluate products to</p> <p>21 identify appropriate endpoints for clinical trials and</p> <p>22 when to measure such endpoints. And ultimately,</p>	<p>1 the course of the day. You might, as you're thinking</p> <p>2 about this, frame things in the following way: What do</p> <p>3 we understand that's supported by evidence? What are</p> <p>4 the gaps in our understanding? How can we address</p> <p>5 these gaps? Are the designs that are durable despite</p> <p>6 these knowledge gaps? In essence, ideas and what</p> <p>7 could be done today to help us understand what</p> <p>8 interventions help patients?</p> <p>9 So I want to thank you for your attention to</p> <p>10 my brief remarks here. And we look forward to a</p> <p>11 productive day. And I think what we'll do now is</p> <p>12 we'll also go around the table and have folks</p> <p>13 introduce themselves. And if you'll state your name,</p> <p>14 your affiliation and any conflicts of interests that</p> <p>15 you'd like to bring to the attention of the group.</p> <p>16 And typically, our conflicts of interests are also</p> <p>17 available on the written materials.</p> <p>18 And I'll turn to Erica Brittain, on the far</p> <p>19 side, to start us out. Erica?</p> <p>20 MS. BRITTAİN: Erica Brittain, National --</p> <p>21 I'm a statistician at National Institute of Allergy</p> <p>22 and Infectious Diseases, NIH.</p>

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

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1 companies who are represented here.  
 2 MS. KASPERBAUER: Shannon Kasperbauer, I  
 3 practice at National Jewish Health and I've also  
 4 served as a speaker an advisor with Insmmed.  
 5 MR. WINTHROP: Kevin Winthrop from Oregon  
 6 Health Science University in Portland, Oregon. I'm a  
 7 -- I have potential conflicts including funding from  
 8 FDA, NIH, Macquarie (ph). I've received research  
 9 funding and consultant honorarium from several of the  
 10 companies here that I can remember, Insmmed, Spero,  
 11 ParaTech, I think those three companies.  
 12 MR. DALEY: My name is Chuck Daley. I head  
 13 the Division of Mycobacterial and Respiratory  
 14 Infections at National Jewish. I have the same  
 15 conflicts that he has. I think he left out a couple  
 16 maybe, but also Spero Horizon (ph), ParaTech (ph)  
 17 Johnson & Johnson and Insmmed advisory boards and Phase  
 18 2 site investigator for Aircase (ph) trial.  
 19 MS. O'DONNELL: Anne O'Donnell from  
 20 Georgetown University here in D.C. And my conflicts  
 21 kind of harmonize with the prior one, Insmmed, Aradigm,  
 22 Parion (ph), the COPD Foundation and Electro-Med.

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

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

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1 MR. CHEN: Wen-Hung Chen, team leader,  
 2 Clinical Outcome Assessment staff in Office of New  
 3 Drug, under CDER, FDA.  
 4 MS. SLAGLE: Good morning. I'm Ashley  
 5 Slagle, a scientific and regulatory consultant. I am  
 6 focused on patients that are at end points and  
 7 clinical outcome assessments. I consult to a number  
 8 of pharmaceutical companies, and I was formally with  
 9 the FDA.  
 10 MS. EREMENCO: Good morning. I'm Sonya  
 11 Eremenco, Associate Director of the Patient Reported  
 12 Outcome Consortium at the Critical Path Institute.  
 13 And I'm a full time employee of C-Path.  
 14 MR. TRAPNELL: Good morning. I'm Bruce  
 15 Trapnell. I'm a pulmonologist from Cincinnati, and I  
 16 have a grant funding from the NIH and commercial  
 17 sources as well involved in clinical trials, although  
 18 not in NTM.  
 19 MR. LIM: Hi, my name is Bob Lim. I'm the  
 20 clinical team leader in the Division of Pulmonary  
 21 Allergy and Rheumatology Products, FDA.  
 22 MR. COX: Great. Thank you all. And over

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1 the course of the day too, we'll continue to try and  
 2 do our best to get as close to these microphones.  
 3 They really do have a limited pickup. But folks in  
 4 the audience don't hesitate to remind us because  
 5 you're a good cue for us for all the folks who maybe  
 6 listening via the web, of the importance of using the  
 7 microphone so that all can hear.  
 8 And at this point I'd like to turn it over to  
 9 Sumathi. Sumathi Nambiar and James Chalmers, who will  
 10 guide us through the next session. Thank you very  
 11 much.  
 12 MS. NAMBIAR: Thanks, Ed. Maybe Dr. Kalfus,  
 13 I think we missed you during the introductions.  
 14 DR. KALFUS: Hi, good morning. I'm Dr. Ira  
 15 Kalfus. I'm with RedHill Biopharma, medical director  
 16 in charge of their NTM program.  
 17 SESSION 1: GENERAL CONSIDERATIONS FOR NTM DISEASE  
 18 MS. NAMBIAR: Thank you. I hope you can hear  
 19 me. This is the closest I can get. It's kind of  
 20 limited in -- all right. So along with Dr. Chalmers  
 21 who is the co-chair for the first two sessions. I  
 22 want to welcome you to today's workshop. So first

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1 session is on discussion on the general considerations  
 2 for NTM disease. We have three presentations. The  
 3 schedule is a little tight. So what we'll try to do  
 4 is at the end of each presenter's talk, maybe 1 or 2  
 5 minutes if there are clarifying questions, if the  
 6 questions are more general maybe you can hold them  
 7 until the final discussion. That'll help us keep to  
 8 time.  
 9 So our first speaker today is Dr. O'Donnell,  
 10 who is the chief, Division of Pulmonary Critical Care  
 11 and Sleep Medicine at Georgetown University Hospital.  
 12 And as you've heard during the introduction, she has  
 13 been a principal investigator in some of the recent  
 14 trials. Dr. O'Donnell?  
 15 DIAGNOSIS AND TREATMENT OF NTM: CURRENT STATE AND  
 16 FUTURE CONSIDERATIONS  
 17 MS. O'DONNELL: Yes, good morning. Good  
 18 morning to everyone and thank you very much for the  
 19 invitation to speak and thanks to the FDA for  
 20 convening this meeting. My job is kind of lay the  
 21 groundwork I think for understanding this disease in  
 22 terms of how we diagnose it and what we are currently

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1 doing in terms of treatment. So I'll advance the  
 2 slide. Sorry, a little technical difficulty. Okay,  
 3 okay. Sorry. So these are my disclosures. You  
 4 already heard -- this already when we went around the  
 5 room.  
 6 So as I said, we're going to talk about how  
 7 we diagnose this disease, how the disease manifest  
 8 itself clinically, what the radiographic findings and  
 9 laboratory confirmation. That's sort of the triad of  
 10 having -- confirm the diagnoses of NTM lung disease.  
 11 We review the standard treatment, some salvage options  
 12 that are currently in use and discuss a little bit  
 13 about pipeline therapies and we're going to hear more  
 14 about that later.  
 15 First off, you know, this disease although  
 16 quiet uncommon is certainly more common than  
 17 mycobacterial tuberculosis. In 2010, thanks to our  
 18 friends at the NIH, the estimate was about 86,000  
 19 cases in the U.S. This has tripled over the next four  
 20 years. This is a disease of older adults primarily,  
 21 although you can see it across the whole spectrum of  
 22 age. It's a female predominant disease, about 60:40

<p style="text-align: right;">Page 22</p> <p>1 female to male. We see similar reports from other                  2 parts of the world and there's definitely increasing                  3 mortality and this disproportionately is affecting                  4 older Caucasian women.</p> <p>5       Again, from Jen Adjemian at the NIH, this was                  6 a look at where NTM lung disease is occurring in the                  7 U.S. And those dark areas are the ones with the                  8 highest prevalence. So you can see, it's kind of a                  9 coastal disease. And we know that the water content                  10 or the humidity content in the environment may have                  11 something to do with this. Actually, the highest                  12 prevalence, as you can see, is in Hawaii.</p> <p>13       It's especially important infection in                  14 patients who have cystic fibrosis. So when -- at                  15 least from the U.S. database, from the U.S. CF                  16 Foundation, about 14 percent of CF patients have at                  17 least a culture positivity for NTM. There is some                  18 spatial clustering along the lines of what we just                  19 saw. It's low in Europe. And the European CF patient                  20 registry for reasons that are not entirely clear. In                  21 the CF world, there is also some concern about                  22 patient-to-patient transmission. But this is limited</p>	<p style="text-align: right;">Page 24</p> <p>1 noteworthy because they often have a specific body                  2 type, Ken Olivier did a lot of this work that showed                  3 that abnormal morphology thin, tall, older Caucasian                  4 women, some of them have scalable disorders like                  5 pectus excavatum and scoliosis, some of these patients                  6 have other muscular skeletal issues. And so this body                  7 type in women, seems to predispose to getting this                  8 infection.</p> <p>9       Clearly, those patients with underlying lung                  10 disease, pre-existing lung disease who get NTM                  11 infections, and primarily this is bronchiectasis, also                  12 COPD emphysema, patients with underlying preexisting                  13 fibrotic lung disease, stuff like cystic fibrosis,                  14 patients who had tuberculosis in the past and were                  15 scarred, their lungs were scarred because of the TB,                  16 are at risk for getting NTM infections and then                  17 genetic disorders like cystic fibrosis and alpha-1                  18 antitrypsin deficiency, put the patient at risk.</p> <p>19       There are a bunch of identifiable immune                  20 disorders that can predispose to these infections.                  21 Now the ones I've listed, the rare genetic ones on top                  22 here, are actually more likely to cause systemic</p>
<p style="text-align: right;">Page 23</p> <p>1 right now to mycobacterial abscesses not to MAC.</p> <p>2       Okay, so when we see the patient, how do we                  3 confirm the diagnosis? And like I said, it's a triad,                  4 you need the symptoms, you need the radiographic                  5 findings and you need culture positivity to confirm                  6 the presence of the disease. So the patients often                  7 present with nonspecific pulmonary symptoms like                  8 chronic cough, some low-grade sputum production,                  9 occasionally they have hemoptysis, sometimes chest                  10 pain. The other big thing with these patients is they                  11 often have subtle systemic symptoms like weight loss,                  12 night sweats, low-grade fever, and you know something                  13 less -- even less specific fatigue and malaise. So                  14 often it's a diagnosis that's not thought of, and it                  15 obviously it will take some thinking on the part of                  16 the clinician to come to the realization the patient                  17 may have this.</p> <p>18       So what kind of underlying diseases? I                  19 already mentioned CF, but there is a group of these                  20 patients that we clearly recognize who appear to have                  21 no underlying obvious pulmonary disease and yet get                  22 this infection. And these patients are particularly</p>	<p style="text-align: right;">Page 25</p> <p>1 disease, not so much pulmonary disease. And the                  2 acquired ones like untreated HIV disease, certainly is                  3 associated with NTM. But things like chemotherapeutic                  4 agents that reduce the patient's immune system                  5 functioning, antirheumatic agents, Kevin Winthrop is                  6 expert on this issue. The drugs that we use for                  7 rheumatoid arthritis and related diseases definitely                  8 put the patient at risk for getting NTM lung disease.</p> <p>9       Transplant immunosuppressive therapies, and                  10 these therapies sort of overlap with other chronic                  11 lung diseases that we've -- use these drugs. And                  12 another important one and probably very                  13 underrecognized is the patient inhaled                  14 corticosteroids. There's now three studies that have                  15 looked at this issue. And you know, ICS therapy is                  16 very, very common in people with airways disease. And                  17 yet, this does seem to pose a risk for developing NTM                  18 infection. So there are these underlying conditions.</p> <p>19       Some other ones are chronic reflux or                  20 aspiration, low-grade aspiration. I already mentioned                  21 the rheumatologic drugs, but the rheumatologic                  22 diseases like Sjogren's and RA, put the patient at</p>

<p style="text-align: right;">Page 26</p> <p>1 risk for getting this type of infection and also                  2 inflammatory bowel disease. But the big question is,                  3 you know, why me? Why now? You know, this is what                  4 patients ask us, like, "Hey, I have this underlying                  5 disorder or I don't. But why all of a sudden do I                  6 have NTM lung infection." And we really believe it's                  7 kind of a two-hit hypothesis that the patient is                  8 predisposed for reasons like I just mentioned and then                  9 they're exposed because these organisms are in the                  10 environment, in the soil and in the water. So in the                  11 right side are scenarios where the patient has a                  12 predisposition and the exposures there, the person                  13 gets actual infection with the bacteria.                  14 So those are the patients at risk. And then,                  15 you know, they come to us sometimes with imaging                  16 studies, sometimes without. But we really need a CT                  17 scan to confirm the diagnosis of pulmonary NTM.                  18 Although the findings are not totally specific, there                  19 are some hints in these CT images that suggest that                  20 the patient may have NTM infection. And I'll show you                  21 some representative images. There's fibronodular                  22 changes in the lungs, what the radiologists often</p>	<p style="text-align: right;">Page 28</p> <p>1 associated with the bronchiectasis.                  2 The thing about this though is that this is                  3 not diagnostic of NTM. Other infections can cause                  4 this type of a radiographic abnormality. But it is at                  5 least a suggested finding and should lead to                  6 laboratory testing. And that's the third part of the                  7 triad of diagnosing this disease, so you have the                  8 patient's clinical symptoms, you have the imaging, and                  9 then you the lab. And, you know, these two types of                  10 mycobacterial now the biggest ones in the U.S. about                  11 80 percent of our patients have mycobacterium avium                  12 complex, MAC, and a smaller number 10 or so percent,                  13 mycobacterium abscessus complex. You can see within                  14 that there's subspecies. One of the problems that we                  15 have is that the clinical labs are not totally                  16 attentive to providing every last detail on these                  17 culture results.                  18 Another important message is that these                  19 patients, many of these patients don't just have NTM                  20 infection, and this complicates obviously how we treat                  21 them. This is data from our U.S. bronchiectasis                  22 registry that showed a significant number, 23 to 52</p>
<p style="text-align: right;">Page 27</p> <p>1 refers to as tree-in-bud nodularity or bronchiolitis                  2 that suggest NTM patients with fibrocavitary disease.                  3 One of the features of the radiographic imaging is                  4 that there is often a waxing and waning, because this                  5 disease is characterized by mucus plugging, and                  6 difficulty clearing the airways.                  7 So on the left hand panel is an example of                  8 what we would characterize as a fibronodular disorder.                  9 You can see sort of that diffused nodularity, I wish I                  10 can point it out, but I'm sure you can see that                  11 there's mucus plugging in those areas and on the right                  12 side of the -- right up below -- I am sorry the right                  13 middle lobe, right lower lobe. Whereas the size of CT                  14 on the right shows a patient who has that kind of                  15 finding but also has a cavity. You can see that in --                  16 on the left lower lobe, there. So these are the                  17 typical radiographic findings, this is -- I know                  18 people struggle with this concept of tree-in-bud                  19 nodularity, but this is what a tree-in-bud looks like.                  20 If we go outside, we see some more. And you can see                  21 on the CT scan, why the radiologist has adopted that                  22 term. There's mucus probably in the small airways</p>	<p style="text-align: right;">Page 29</p> <p>1 percent of the patients who've had NTM infection with                  2 bronchiectasis, also had another organism like                  3 pseudomonas. Some of these patients are co-infected                  4 with staph aureus, some with H. flu, stenotrophomonas,                  5 so this is one of the difficulties of designing                  6 clinical trials into NTM, because many of these                  7 patients have other organisms there. It can be                  8 difficult to tell really kind of what's driving their                  9 symptoms.                  10 You know, a key thing is to get respiratory                  11 symptoms, and you know this is easier said than done                  12 in many circumstances. There's sort of been a                  13 downplaying of sputum cultures in the world of                  14 pulmonary medicine, the adult pulmonary medicine, but                  15 we need these in order to make the diagnosis. And                  16 some patients like the CT scan on top, you know, we                  17 have kind of just nodular disease are not very                  18 productive where patients with the more extensive and                  19 cystic and cavitary disease, it's often fairly easy to                  20 get them to cough up a nice sputum specimen.                  21 We have some tricks but they're not -- in the                  22 clinical treatment of this disease is that, you know,</p>



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

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

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

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

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

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

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

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

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

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

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

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

<p style="text-align: right;">Page 34</p> <p>1 bronchiectatic disease, their recommendation is the  2 three oral drugs. Usually in a de novo, you know, the  3 first go around the treatment, they'll give those  4 drugs three times a week. And what's the result of  5 that? In general we talk about 70 percent or so of  6 those patients clear their sputum culture i.e. convert  7 to negative by their own treatment, but unfortunately  8 many patients either relapse or they get infected with  9 a new strain of mycobacterium avium complex. So about  10 a year or so out maybe about 50 percent of the  11 patients are again positive by culture.</p> <p>12 You know, it's very difficult to define what  13 a cure is in this disease. Because again, you're  14 dealing with a microbiologic infection superimposed  15 usually on some chronic lung damage. And so again,  16 the notion of -- this is not a urinary tract infection  17 that, you know, have a positive culture and three days  18 of antibiotics makes it negative. It's just not that.  19 Generally again, from the guidelines, the  20 recommendation is to treat with antibiotics for 12  21 months after the sputum converts to negative. So the  22 idea is that we're collecting sputum while the patient</p>	<p style="text-align: right;">Page 36</p> <p>1 patients who have had 6 months of standard oral  2 therapy and are still culture positive. This drug has  3 about a 30 percent success rate and then converting  4 the patient to negative. So you know, for MAC, we  5 just -- you know, we have drugs, we have drugs that  6 the patient can tolerate but the regimen is  7 complicated and the add-on therapy that we have right  8 now amikacin inhaled, has some success but obviously  9 not 100 percent.</p> <p>10 When we think about mycobacterium abscessus,  11 it's even more complex because the regimen requires IV  12 therapy generally upfront. So this means patients  13 receiving home IV antibiotics, the length of time for  14 these treatments is not entirely clear. It's often  15 like as long as the patient can tolerate having the  16 PICC line and getting the antibiotics. And we know  17 that it's very, very difficult, even more difficult  18 than this MAC to clear these infections, even with  19 this complex regimen that I've put up here on the  20 slide.</p> <p>21 We also know that treating these patients  22 does make them feel better, so even if we can't</p>
<p style="text-align: right;">Page 35</p> <p>1 is in antibiotic therapy. And usually this turns into  2 18 -- 15 to 18 months of antibiotic therapy when  3 you're dealing with sort of straightforward MAC.</p> <p>4 If the patient has cavities, if the lung  5 damage is more significant, then the recommendation  6 from the guidelines is daily therapy. And usually  7 with the addition of aminoglycoside, for many patients  8 that means an intravenous aminoglycoside like  9 amikacin. We also used inhaled formulations (ph),  10 we'll hear more about that.</p> <p>11 One of the really big problems, I mean, just  12 think of yourself trying to take this regimen for as  13 long as we're trying to prescribe it. It's difficult  14 for patients to take these treatments, number one; and  15 number two, there's not great enthusiasm in the world  16 of pulmonary and ID physicians to prescribe these  17 things. So there's a couple of studies by a gentleman  18 in (inaudible 0:30:36.2) that show that clinicians  19 generally don't adhere to this guidelines for the  20 treatment regimen.</p> <p>21 We have ones liposomal amikacin that was  22 approved late last year. This is a add-on drug for</p>	<p style="text-align: right;">Page 37</p> <p>1 convert their sputum to negative, they still benefit  2 in terms of quality of life improvement. You know,  3 quickly the toxicities of the standard therapies are  4 legion. We think of macrolides as a fairly benign  5 treatment. But when you have to take it for 18  6 months, patients wind up sometimes with GI symptoms.  7 There's cardiac rhythm issues, QT interval drug and  8 drug/drug interactions, loss of hearing. We know with  9 Ethambutol, there's a risk of developing problems with  10 vision that have to do with optic neuritis. It was  11 about a 10 percent discontinuation rate because of  12 that. Rifampin causes GI hepatic and hematologic  13 abnormalities; and aminoglycosides, auditory,  14 vestibular, renal issues.</p> <p>15 So some of the challenges that we have and  16 hopefully some of the things that we're going to get  17 out of this conference is, you know, what to do if the  18 patient can't tolerate three or more drugs, are two  19 drugs sufficient? What if the patient doesn't want to  20 take the 18 to 24 month therapy, could we come up with  21 a shorter regimen? That's one of the big questions I  22 think that patients have. If the patient has a</p>

<p style="text-align: right;">Page 38</p> <p>1 resistance, if they have MAC that's resistant to                  2 macrolide, you know what are our options there? And                  3 Dave Griffith has published data that show that                  4 mortality with macrolide resistant MAC is similar to                  5 mortality from MDR T).                  6 There's cost issues about patients accessing                  7 these drugs we're constantly, you know, calling the                  8 insurance benefits managers to try to justify                  9 prescribing these drugs and expertise is somewhat                  10 limited. So we need new drugs, with new treatment                  11 regimens, new paradigms, it's a growing patient                  12 population, patients are older maybe sicker, it's                  13 clearly a priority to find something new and better.                  14 We have a paucity of effective and well tolerated                  15 drugs, we're recycling old drugs for new purposes here                  16 and trying to come up with combinations that the                  17 patients can tolerate.                  18 So some of the old drugs for this bug, for                  19 both MAC and abscessus, I've listed here. Linezolid,                  20 tedizolid, tigecycline, possibly some of the new                  21 tetracycline drugs. Clofazimine, again there's                  22 limited data. Clofazimine is not actually on the</p>	<p style="text-align: right;">Page 40</p> <p>1 bad stuff that we want to make sure patients are aware                  2 they shouldn't do.                  3 So I'm just going to conclude by showing this                  4 very nice table that was published late last year by                  5 Wu (ph) that shows where we are with drug discovery                  6 and we'll be hearing more about this. This is clear,                  7 you know, discovery phase up to Phase IV and I just                  8 would say that our patients and this was published in                  9 the animals -- are asking, you know, for preventive                  10 the environmental issues, better diagnostics, the                  11 priority for patients is quality of life. So they                  12 want to improve treatment regimens and they want to                  13 know what their outcomes are going to be.                  14 So I'll just conclude by saying this is a                  15 difficult disease because it's very heterogeneous and                  16 there are patients that, you know, we culture the bug                  17 from but they actually don't have progressive disease.                  18 And then there are some patients who really progress                  19 and go on to one failure and it can be difficult to                  20 prognosticate. So I look forward to hearing more                  21 about what we're going to do next. So thank you very                  22 much and I guess a minute for questions for sure.</p>
<p style="text-align: right;">Page 39</p> <p>1 market but it can be obtained. And the one thing we                  2 think is not effective is the Fluoroquinolones.                  3 So what's in the pipeline? We're going to                  4 hear more today I think, but these are some of the                  5 drugs that have had some case hearings or some limited                  6 enthusiasm for using like the bedaquiline, inhaled                  7 nitric oxide, there's a dry powder form of nitric                  8 oxide, B-lactams and other antibiotics that are                  9 modified to improve the outcomes.                  10 Surgery is sometimes a consideration for                  11 patients with localized disease. But this is a very                  12 small number of patients. I think one thing I wanted                  13 to read, you know, with the FDA there's been a lot of                  14 coverage this week in the local newspapers about stem                  15 cell treatments. I mean, patients are asking about                  16 this all the time in bronchiectasis and in NTM. So                  17 this is a hazard, that some of these things that are                  18 being advertised for patients really. They're totally                  19 unproven and makes me sad when patients, you know, are                  20 willing to spend huge amounts of money for this kind                  21 of stuff like stem cells, like this other conditioning                  22 regimens promise of a cure for bronchiectasis, this is</p>	<p style="text-align: right;">Page 41</p> <p>1 MS. NAMBIAR: Thank you, Dr. O'Donnell. It                  2 was very, very extensive. Thank you. Are there any                  3 questions, clarifying questions for doctor -- yes,                  4 Erica.                  5 MS. BRITAIN: That was a really great talk.                  6 You mentioned how during -- when patients are treated,                  7 sometimes patients with symptoms will get a lot better                  8 but the culture is still positive.                  9 MS. O'DONNELL: Yes.                  10 MS. BRITAIN: Can you give -- I'm trying to                  11 understand what that means. What do you think when                  12 that happens?                  13 MS. O'DONNELL: I mean clearly, sometimes                  14 patients just feel better even if we don't give                  15 antibodies, we give them airway clearance and exercise                  16 even though they're still culture positive. So that's                  17 one of the real challenges, because the culture may                  18 stay positive, the CT scan may get better, the patient                  19 feels better and, you know, how often does that                  20 happen? You know, it varies. Even if you see only                  21 the sickest patients it doesn't happen, but in                  22 patients with kind of mild disease, it's not uncommon.</p>

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<p>1 A lot of patients do feel better, you know, when they                  2 initiate antibiotics too, as long as they tolerate                  3 them. And then it's, you know, it's a struggle to get                  4 patients to continue on those therapies.</p> <p>5 UNIDENTIFIED SPEAKER: I have a question                  6 related to our discussion this afternoon. What -- in                  7 your experience, what fraction of patients are                  8 positive on the sputum culture versus requiring either                  9 a biopsy or BAL (ph)?</p> <p>10 MS. O'DONNELL: So the question is -- can you                  11 get this -- from sputum? I mean see, it really                  12 depends on how hard you try. So in the average                  13 pulmonologist hand, there's still a lot of patients                  14 are getting diagnosed by BAL, because they're not                  15 really inducing sputum's in the office. But like, in                  16 my hands, I rarely do a bronchoscopy because we do our                  17 best to get the sputum. So it's hard to give you an                  18 exact number, but it really depends on your practice                  19 setting I would say.</p> <p>20 UNIDENTIFIED SPEAKER: I just want to make a                  21 brief comment though about the sputum culture                  22 positivity and the symptom improvement. Getting back</p>	<p>1 waxing and waning of the CT. Can you just make a                  2 brief comment about the use of CT for monitoring                  3 response to therapy? Because I guess that might come                  4 up later when we talk about endpoints.</p> <p>5 MS. O'DONNELL: Right, that's a good                  6 question. I mean, how do we monitor these patients                  7 either when they're on therapy or not. And because                  8 obviously, we don't want to overdo imaging, there's no                  9 standard approach I would say to how often we image                  10 patients in follow-up. Neither is there really a                  11 standard approach to how often do we culture them, you                  12 know, either during or after therapy. I think, you                  13 know, people want to limit the exposure to the                  14 radiation. But unfortunately the CT is the best way                  15 to tell. I mean we can sometimes -- if the disease is                  16 significant enough use a plain chest X-ray. So I                  17 would say the answer to that question is, you know,                  18 maybe a 6-month CT therapy and then maybe yearly or 2                  19 years after that, really patient specific. Great                  20 question though.</p> <p>21 UNIDENTIFIED SPEAKER: And maybe just to                  22 follow that up. Much like the microbiological</p>
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<p>1 to your point about the complexity of understanding                  2 what positive cultures mean in patients who are on                  3 therapy where we may see multiple organisms, multiple                  4 different species and not necessarily the species that                  5 was -- that was originally present when we started                  6 therapy. And unfortunately, as you also pointed out,                  7 laboratories in the United States don't help us do                  8 that. There are only a couple places where we can                  9 tease all of that out.</p> <p>10 UNIDENTIFIED SPEAKER: And then we just for                  11 completeness also just emphasize that I think it's our                  12 clinical experience that in most instances, to answer                  13 your question, we do see a concordance between                  14 microbiological response and symptom response in most                  15 instances. And the microbiological response is                  16 something I think we'll address as the day goes on,                  17 quantitatively how many positive, that sort of thing.                  18 But I just want to leave and make sure that we start                  19 from a position that in most instances symptoms and                  20 microbiological response go hand-in-hand, not always.</p> <p>21 UNIDENTIFIED SPEAKER: Great talk, Anne. Can                  22 I quickly ask you a question? You mentioned the</p>	<p>1 response, the radiograph does not often clear even                  2 with successful treatments? So someone feels better,                  3 their sputum clears, they do well, they complete 18,                  4 24 months whatever that is, but they will not have                  5 normal chest X-rays or CT scans at that point. They                  6 very often will have some residual abnormalities. So                  7 I think the expectation that we're going to clear a X-                  8 ray or clear a chest CT scan is a misnomer with or                  9 without therapy.</p> <p>10 UNIDENTIFIED SPEAKER: I've got an answer                  11 too. I would only just clarify too, it depends what                  12 kind of patient is. We all seem to be talking about,                  13 bronchiectatic patients that don't have cavities. But                  14 if patients have cavitory disease whether they have                  15 bronchiectasis or not, you're going to try image at                  16 different intervals and you may be able to just use an                  17 x-ray if it's a cavity you are following. But really                  18 those are the people you're much more worried about                  19 progressing and you might radiologically be more                  20 interested in following them more closely.</p> <p>21 MS. NAMBIAR: Thank you, Dr. O'Donnell. So                  22 we go to the next presentation from Dr. Kim, on the</p>

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<p>1 regulatory perspective on development of antibacterial                  2 drugs for NTM. Dr. Kim is a medical team leader in                  3 the division and leads a team whose portfolio includes                  4 drugs and development for NTM disease. Peter?                  5 DEVELOPMENT OF ANTIBACTERIAL DRUGS FOR NTM: A                  6 REGULATORY PERSPECTIVE                  7 MR. KIM: Good morning. My name is Peter                  8 Kim, and I'll be discussing development of                  9 antibacterial drugs for NTM from a regulatory                  10 perspective. So there is interest in developing                  11 inhaled and oral therapies for the treatment of NTM                  12 lung infections. Approved products include inhaled                  13 liposomal amikacin, as well as clarithromycin and                  14 azithromycin. Regarding inhaled amikacin or arikayce,                  15 received accelerated approval based on sputum culture                  16 conversion. There were limited clinical safety and                  17 effectiveness data, and the indication for use is                  18 currently in a limited population of patients with                  19 refractory MAC lung disease with limited or no                  20 treatment options.                  21 Clinical benefit has not yet been                  22 established. There is a post marketing requirement to</p>	<p>1 inhaled placebo or vehicle control may help in the                  2 attribution of adverse events for the purposes of                  3 blinding trials.                  4 Regarding the surrogate endpoint, as                  5 discussed at the advisory committee meeting on August                  6 7, 2018; key findings from our review of the                  7 literature to support the correlation between the                  8 surrogate endpoint and clinical benefit included.                  9 There were retrospective, nonrandomized studies, which                  10 suggests a higher mortality rate in patients with MAC                  11 lung disease, who remain culture positive despite                  12 treatment compared to those who convert to culture                  13 negative. Some studies are from single centers or                  14 specific subtypes of MAC lung disease, which limits                  15 generalized ability to the overall population.                  16 The main limitation that we noted is that it                  17 is possible that converters are inherently different                  18 from nonconverters in certain disease or patient                  19 characteristics. And hence it is difficult to assess                  20 if sputum conversion is a surrogate for a clinical                  21 outcome.                  22 Some considerations for future development.</p>
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<p>1 conduct a randomized double-blind placebo controlled                  2 clinical trial to assess and describe the clinical                  3 benefit of arikayce in patients with MAC lung disease.                  4 Some of the lessons -- we learned a lot from this                  5 application. And some of these lessons include an                  6 uncertainty as to the relation of a surrogate                  7 endpoints, sputum culture conversion to clinical                  8 benefit in patients with MAC lung disease. We noted                  9 inconsistent results in clinical outcomes between the                  10 Phase 2 and Phase 3 trials. In Phase 2, there was                  11 improvement in the 6-minute walk test distance seen in                  12 the inhaled amikacin arm.                  13 However, in Phase 3, we did not see a                  14 clinical benefit on the measured outcomes such as the                  15 6-minute walk test or in the patient reported                  16 outcomes. There was one error in the printed slides.                  17 The quality of life assessment tool was not the QOL-B                  18 but a different quality of life questionnaire.                  19 Additionally, comparison between study arms on long-                  20 term endpoint was difficult because a large fraction                  21 of patients were allowed to cross over to the                  22 treatment arm. For inhaled therapies, inclusion of</p>	<p>1 So at this point, we have more questions than answers.                  2 But these are some of the issues that we're thinking                  3 about. As Dr. O'Donnell noted, there's a lot of                  4 heterogeneity in the patient population. Which types                  5 of patients should be enrolled? We have questions                  6 regarding trial design, superiority versus                  7 noninferiority, how best to monitor patients during                  8 the study. Questions on clinical endpoints and also                  9 how long to tree-in for -- how long should follow up                  10 occur in these clinical trials.                  11 Regarding patient population heterogeneity,                  12 patients maybe different based on treatment                  13 experience. There are treatment naïve patients and                  14 also those with refractory disease. The disease                  15 manifests differently, nodular bronchiectatic disease                  16 versus fibrocavitary versus mixed picture. The                  17 etiologic organism varies, a patient can have MAC or a                  18 non-MAC NTM. Patients may have underlying comorbid                  19 conditions such as cystic fibrosis or COPD. And it's                  20 possible that response to stay (ph) drugs may vary                  21 based on any or all of the above.                  22 Regarding trial design: so superiority trials</p>

<p style="text-align: right;">Page 50</p> <p>1 are scientifically sound and readily interpretable.                  2 An evidence based noninferiority margin needs to be                  3 established based on the clinical outcome to have an                  4 interpretable noninferiority trial. So currently                  5 demonstrating superiority to standard of care maybe                  6 accomplished by adding a new drug to standard of care                  7 versus standard of care plus placebo or assessment of                  8 a new combination regimen versus standard of care or                  9 placebo. And we'll need to address the contribution                  10 of each component in such a new combination regimen.                  11 How do we monitor patients to determine                  12 clinical benefit? As previously noted, there are                  13 limitations to microbiological results as an outcome                  14 measure. During the discussion of the cases later                  15 today, we'll be considering the feasibility and                  16 acceptability of bonding investigators and patients to                  17 culture conversions status during the trials.                  18 Patients could withdraw for clinical reasons, such as,                  19 increased fatigue, or worsening respiratory symptoms.                  20 But not solely because of failure to convert sputum                  21 culture to negative. This could allow for an unbiased                  22 assessment of whether culture conversion is</p>	<p style="text-align: right;">Page 52</p> <p>1 function or survive; when should such an endpoint be                  2 assessed? More questions, should the endpoint be                  3 assessed on therapy versus off therapy; at 6 months,                  4 12 months, 24 months after initiating therapy? Does                  5 the timing depend on the type of patient? Based on                  6 treatment experience, disease type or underlying                  7 comorbid conditions, should the assessment be based on                  8 a fixed time point or on a summary of clinical outcome                  9 assessment scores over time?                  10 If based on a summary of scores, how                  11 frequently should assessments be made; daily, weekly,                  12 monthly, every 6 months? Regarding duration of                  13 treatment and follow-up, what is the evidence to                  14 support an optimal duration of treatment? Is it based                  15 on clinical benefit? In trials, we note that early                  16 treatment discontinuations may complicate assessments                  17 of long-term follow-up. How long is it acceptable for                  18 patients to be on placebo in the control arm? Does                  19 this depend on the study population?                  20 We hope to cover these concepts in further                  21 detail during the course of our discussions today.                  22 And thank you for your attention. Are there any</p>
<p style="text-align: right;">Page 51</p> <p>1 unacceptable or surrogate for clinical benefit.                  2 In addition, we'd like to hear your thoughts                  3 on avoiding crossover between treatment arms during                  4 trials. Clinical endpoints: so more work needs to be                  5 done to define clinically meaningful endpoints and                  6 assessments in NTM patients. Currently, microbiologic                  7 outcomes are not linked to how patients feel, function                  8 or survive. One option would be a patient reported                  9 outcome. But then the question is, is the PRO fit for                  10 purpose? And this would be assessed based on the                  11 reliability, validity, sensitivity to detect change                  12 and thresholds the meaningful change to the patient.                  13 Beyond PROs, what other clinical outcome                  14 assessments, such as clinician reported, observer                  15 reported, or performance outcomes be more feasible                  16 and/or acceptable. And once again, with any of these                  17 clinical outcome assessment tools, we'll need to                  18 define a clinically meaningful change in NTM patients.                  19 In addition, we'll talk more about these                  20 clinical outcome assessment tools later today.                  21 Assuming that the primary endpoint is designed to                  22 assess direct clinical benefit, how patients feel,</p>	<p style="text-align: right;">Page 53</p> <p>1 clarifying questions? Thank you.                  2 MS. NAMBIAR: Thanks, Peter. So we move on                  3 to the third presentation from Amy Leitman, who is the                  4 director of policy and advocacy at the NTM Info and                  5 Research, a nonprofit advocacy group for patients with                  6 pulmonary NTM mycobacterial disease. Thank you.                  7 PATIENT PERSPECTIVE FOR TREATMENT OF                  8 NTM DISEASE                  9 MS. LEITMAN: Thank you. Good morning. I'd                  10 like to thank the FDA for convening this workshop.                  11 Hang on, what did I press? Here we go. These are my                  12 disclosures. NTM patients experience a variety of                  13 symptoms, side effects and impacts from both. These                  14 include, long delays to diagnosis, often 2 years or                  15 more; lengthy and burdensome treatments. Side                  16 effects, some of them quite severe, and some of them                  17 leaving permanent damage, including hearing or vision                  18 loss, vestibular dysfunction, or renal or hepatic                  19 dysfunction. A few of the more notable symptoms                  20 include severe cough, often producing mucus, extremely                  21 debilitating fatigue and shortness of breath.                  22 At an FDA led, patient focused, drug</p>

<p style="text-align: right;">Page 54</p> <p>1 development meeting in October 2015, the word  2 "fatigue" was mentioned 49 times. 30 of those  3 mentioned were from patients. The word "cough" was  4 mentioned 98 times, 64 of those were from patients.  5 At this same meeting, several patients noted coughing  6 so severe that they have fractured ribs or vertebrae.  7 Patients have noted that the disease is unpredictable  8 and how they feel and function can vary widely from  9 day-to-day. They've also noted social isolation and  10 stigma that comes with a chronic illness and symptoms  11 such as coughing and sputum production. Saying that  12 friends tend to withdraw and for many it places a  13 strain on their families as well.  14       These things can often lead to anxiety,  15 depression and loneliness for the patient at a time  16 when they most need a support system. In advance of  17 this workshop, NTM Info and Research undertook a  18 survey of patients to learn more about their  19 preferences for treatments, outcomes and clinical  20 trials. We worked jointly with the head of medical  21 affairs, at Spero pharmaceuticals to develop questions  22 that would try to elicit useful information from the</p>	<p style="text-align: right;">Page 56</p> <p>1 respondents were female, 8 percent male. Already more  2 than 70 percent currently have an NTM lung infection.  3 For the other nearly 29 percent, some had previously  4 had an NTM lung infection. Those who have never had  5 an NTM lung infection were exited from the survey  6 after that question. About 60 percent were diagnosed  7 more than 3 years ago and one quarter of them are  8 diagnosed 1 to 3 years ago. The vast majority of  9 respondents, 90 percent had MAC; about 18 percent had  10 abscesses. There were a number of respondents that  11 had coinfecting streams. We did not have a chance to  12 fully analyze those data and we will be looking at  13 that in the next wave of analysis.  14       Looking at other infections; just over 1/3  15 have another type of infection along with their NTM.  16 More than half of those with coinfections had  17 pseudomonas and one quarter had aspergillus. And  18 again, some of them had more than one and we will be  19 looking at that information again more closely.  20       Looking at comorbidities, more than 80  21 percent of the respondents had bronchiectasis, which  22 we did not find at all surprising. Some respondents</p>
<p style="text-align: right;">Page 55</p> <p>1 patients.  2       The survey had 57 questions in total, asking  3 for both quantitative and qualitative responses, and  4 used branched logic to follow patients dependent on  5 their previous answers. The survey was reviewed  6 internally by NTM IR staff by several research staff  7 at the COPD Foundation. A researcher at OHSU (ph),  8 and a panel of five NTM patients. Once it was  9 finalized, we distributed the survey through the  10 internet, social media and online patient forms at  11 NTMinfo.org and our Social360 platform which is  12 developed jointly as part of Bronchiectasis and NTM  13 Initiative.  14       The direct reach was approximately 400 --  15 excuse me, 4,500 patients. The survey was opened for  16 just under 3 weeks and we had a total of 465  17 responses. Because of the short time frame from the  18 close of the survey, we analyzed some data that we  19 thought would best inform today's discussions. And  20 now I report on these findings.  21       Respondents ranged in the age from 18 to 94  22 years, averaging 65.9 years old. 92 percent of the</p>	<p style="text-align: right;">Page 57</p> <p>1 likely selected bronchiectasis, plus one of the other  2 comorbidities listed. 84 percent of the respondents  3 have at some point been treated with antibiotics for  4 their NTM infections specifically. 42 percent of  5 respondents are currently on antibiotic treatment for  6 their NTM infection.  7       We use patients to tell us what symptoms  8 they've experienced. We gave them an extensive list  9 to select from, plus an other option that they could  10 fill in. Here we have the top 10 symptoms that were  11 selected, and this is where we start to pick up on  12 some familiar themes that we're going to see  13 throughout. The top three are fatigue, coughing up  14 sputum and dyspnea, which in the survey was worded as  15 shortness of breath with the word dyspnea in brackets.  16 Throughout the survey we worded things in terms that  17 patients would be more likely to understand with the  18 more technically correct medical term in brackets.  19       So those were the symptoms patients  20 experienced. We asked then what were the most  21 bothersome symptoms? And again, there's a familiar  22 pattern. The most bothersome ranked: fatigue, cough,</p>

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

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

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

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

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

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

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

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

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

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



<p style="text-align: right;">Page 62</p> <p>1 Regardless of their other preferences, it remains a  2 priority for them. Given that they associate some of  3 their symptoms with both the illness and the  4 treatment, they might view this outcome as a way to  5 eventually alleviate both by getting rid of the  6 infection and getting off treatment.</p> <p>7 Right under culture conversion, we see a  8 pattern that is probably very familiar by now, fatigue  9 and respiratory symptoms. Here we presented one of  10 three hypothetical clinical trials scenario to  11 respondents, if they had never been treated for their  12 NTM lung disease and have the opportunity to enroll in  13 clinical trial, where they would receive either the  14 investigational new drug or a placebo, what length of  15 time did they think would be reasonable to take a  16 placebo? More than 50 percent felt that it was 6  17 months or less, that number increases to about 65  18 percent when going up to 9 months. Only 6 percent  19 said they felt comfortable with anything over 12  20 months. And only 12 percent said they would feel  21 comfortable with a 10 to 12 month placebo arm.  22 In the second hypothetical scenario, the</p>	<p style="text-align: right;">Page 64</p> <p>1 ethical challenges in terms of being able to enroll.  2 The next series of questions pertaining to  3 respondents who participated in clinical trials had  4 much smaller sample sizes. More than one third of  5 those respondents who participated in clinical trials  6 indicated that it took at least 2 months, and as long  7 as 12 months, to feel a benefit while taking an  8 investigational therapy. This may make the  9 development of a validated PRO tool more challenging  10 as we would need to determine how far out we will need  11 to measure with the tool in order to accurately assess  12 the benefit of the therapy. And that time frame may  13 vary depending on what the tool is measuring.</p> <p>14 We asked patients what they noticed after  15 they started an investigational therapy in a clinical  16 trial? And this chart summarizes the analysis of  17 their responses. Again, we see this familiar pattern  18 of response with fatigue and respiratory symptoms.  19 This is a sample of feedback from patients who were in  20 clinical trials when we asked them what improvements  21 they noticed once they began taking the  22 investigational therapy? These same patients were</p>
<p style="text-align: right;">Page 63</p> <p>1 respondent was asked if they'd already been on  2 treatment? If they had already been on treatment? And  3 would receive either the investigational therapy or  4 placebo, in addition to standard of care, how long did  5 they think was reasonable to be on placebo? At this  6 point, the number of patients willing to go up to 6  7 months drops to about 45 percent. The number of  8 people who'd be willing to go past 12 months is  9 roughly the same as is the number of people who choose  10 not to participate in this kind of clinical trial.</p> <p>11 The third hypothetical asks if the respondent  12 was already on treatment, and will receive either the  13 investigational therapy or a placebo instead of  14 standard of care, what would be an acceptable length  15 of time for placebo? Roughly 50 percent selected up  16 to 6 months, but nearly 30 percent selected they would  17 not participate in such a trial, which is nearly  18 double that of the other two hypotheticals.</p> <p>19 Based on the results on all three scenarios  20 and given that we've already seen previously how  21 challenging it can be to enroll for NTM trials,  22 placebo beyond 6 months presents both practical and</p>	<p style="text-align: right;">Page 65</p> <p>1 asked, what improvements they noticed first? This  2 chart summarizes the analysis of responses with their  3 answers tracking strongly to the preferences that have  4 been expressed by patients in earlier questions and to  5 the symptoms that they experience. This is a sampling  6 of their feedback from those patients who were in  7 clinical trials when asked to report on the first  8 improvement or benefit that they noticed.</p> <p>9 So I guess, we can conclude this with a brief  10 summary of fatigue, cough, dyspnea, sputum. The  11 results of this sends some strong messages, fatigue is  12 overwhelmingly a problem for these patients, and  13 fatigue itself is not currently measured as a  14 standalone item. There are validated fatigue  15 assessments available but none have been validated for  16 NTM specifically. But this may present an opportunity  17 to look at these PRO tools to determine whether one of  18 them can be repurposed as a validated tool for NTM.</p> <p>19 Finally, I'd like to thank some people, most  20 important of all the reason we're here today, the MTM  21 patients, those who reviewed the survey and those who  22 took the survey, for taking their time out of a very</p>

<p style="text-align: right;">Page 66</p> <p>1 busy day filled with treatments in airway clearance,                  2 to give us information that we hope will be useful in                  3 drug development.                  4 Stephanie Unis (ph) at NTMIR, who assisted                  5 with data analysis and the data presentation; Kate                  6 Selham (ph) at Spero with whom I partnered on the                  7 survey construction and data analysis; and Emily Hink                  8 (ph) at OHSU, who also served as a reviewer for the                  9 survey before it was finalized; and to the COPD                  10 Foundation, who also reviewed the survey and helped                  11 distribute it to patients, and with whom we partnered                  12 on with so many successful initiatives. Thank you.                  13 MS. NAMBIAR: For questions. Amy thank you                  14 very much for sharing the results, and many thanks on                  15 our behalf as well to the NTM patients who                  16 participated in the survey, I think, very useful                  17 information.                  18 We have a couple of minutes, so I want to                  19 make sure if any members of the audience that might                  20 have questions for any of the three speakers from this                  21 morning, no?                  22 UNIDENTIFIED SPEAKER: Amy? It looked liked</p>	<p style="text-align: right;">Page 68</p> <p>1 certainly an important symptom, the gastric symptoms                  2 were certainly an important concern for patients, we                  3 did see quite a bit of that reporting. So it would                  4 not surprise me to find that a number of them had                  5 developed C. diff.                  6 UNIDENTIFIED SPEAKER: I'll comment on that.                  7 I haven't been doing this as long as Dave, he's a lot                  8 older than me, but I've -- what have you got? I've                  9 been doing this 15 or 16 years, I've created one                  10 C.diff case in my entire career. And maybe that's                  11 because I don't use Forcolons (ph). Dave is wild                  12 about Forcolons. I don't know what everyone else's                  13 experience is, but it's just not something we see.                  14 UNIDENTIFIED SPEAKER: Right it's a frequent                  15 side effect, of course, of erythromycin which -- and                  16 I'm like you, I don't know that I've had a documented                  17 C.diff case in 25 years.                  18 UNIDENTIFIED SPEAKER: The other comment I                  19 made Amy and great public -- great survey, and of                  20 course we partnered on a lot of surveys like this. I                  21 will just say in terms of the acceptability of                  22 placebo, it really depends on -- it's a hard question</p>
<p style="text-align: right;">Page 67</p> <p>1 the numbers on the patients that responded to                  2 questions related to clinical trials is relatively                  3 small. Do you know what the total number was like in                  4 those?                  5 MS. LEITMAN: I think it was either 16 or 18,                  6 it was a very small sample size, which we would like                  7 to actually conduct a separate survey that's targeted                  8 only to clinical trials patients. We -- one of the                  9 things we're trying to figure out is how do we target                  10 those patients specifically. So that's something                  11 we're going to be working on. Because we think it's                  12 important to get a bigger sample size for those.                  13 UNIDENTIFIED SPEAKER: Hi, Mary Antego (ph)                  14 with Cistern (ph). I was always impressed how little                  15 C.diff we saw on these patients with diarrhea despite                  16 very broad spectrum antibiotics. Amy, did you drill                  17 down into the causes of diarrhea? Was this simply                  18 related to the antimicrobial or was there C.diff also?                  19 MS. LEITMAN: We don't see a lot of mention                  20 of C.diff specifically but we did see a lot of                  21 mention of diarrhea. I don't know how much how much                  22 the patients are being tested for C. diff, but it's</p>	<p style="text-align: right;">Page 69</p> <p>1 to ask someone on a survey. And having, you know,                  2 placebo controlled trials on going where a lot of the                  3 patients are cite to be on placebo and they actually                  4 want to be on placebo for as long as possible. So it                  5 really depends on who you're enrolling and what kind                  6 of disease they have of course, and what they're                  7 interested in. So it's a hard question, I think, to                  8 survey people without giving them some scenarios                  9 about, you know, how they might feel or what kind of                  10 disease type they have. So I just offer that as a --                  11 something to consider.                  12 UNIDENTIFIED SPEAKER: It didn't seem to be -                  13 - the survey is not a scientific survey, right? So I                  14 guess I was wondering how representative you thought                  15 it was for the whole population. It would seem like                  16 it was 92 percent female, which where I think we heard                  17 it was like 60 percent female in the broader group.                  18 So I was wondering what you thought about that? And                  19 not just about that but just how representative it is?                  20 MS. LEITMAN: Sure I -- you know obviously we                  21 would like to get more representativeness, but given                  22 the short time frame what we were really trying to</p>

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1 elicit was information on what do these patients want  
 2 to see in terms of outcomes? You know, what are their  
 3 experiences and as much as it's not a scientific  
 4 survey, the results were not at all surprising. It's  
 5 something we've been hearing for -- from October 2015  
 6 now, so 4 years almost. We've been hearing the same  
 7 things. Now we just have a nice little data chunk  
 8 that tells us that yes, these patients that this is  
 9 what they're saying. And we have a, you know, sort of  
 10 a combination of qualitative and quantitative  
 11 responses, that are telling us exactly that. And they  
 12 -- we asked the questions in several different ways to  
 13 see how much difference we got. There really wasn't a  
 14 lot of difference, the responses were consistent.  
 15 So I'm not sure how much different it would  
 16 be with a larger sample size or slightly more diverse  
 17 sample size, I think the experience is going to be  
 18 very similar. But yeah, we would certainly love to be  
 19 able to, you know, to broaden this. There certainly -  
 20 - we'd certainly love to explore the idea of reopening  
 21 the survey and administering it to more patients.  
 22 UNIDENTIFIED SPEAKER: And Amy, you've

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1 thought about this for some time now, in several  
 2 years, were there any particular aspects of this  
 3 survey that were surprising or unexpected?  
 4 MS. LEITMAN: No.  
 5 UNIDENTIFIED SPEAKER: And that's just the  
 6 point I think it's very consistent what our experience  
 7 is and what we hear from patients on a day in day out  
 8 basis.  
 9 MS. LEITMAN: Thank you.  
 10 UNIDENTIFIED SPEAKER: My name is Lee Young  
 11 (ph), thanks for your presentation. I just want to  
 12 know in this TB or NTB -- NTM tests conducted  
 13 simultaneously and whether there are some unnecessary  
 14 test and treatments, especially racial profiling maybe  
 15 forced by -- racial profiling by police or there is  
 16 something some unjust treatment just like a -- they  
 17 try to find something as excuses. You get what I  
 18 mean? Whether this test and --  
 19 MR. COX: Yeah, we appreciate your question.  
 20 I think it's a complicated question you're asking,  
 21 maybe you all can talk at the break and get a little  
 22 more detail.

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1 UNIDENTIFIED SPEAKER: Thank you.  
 2 MR. COX: Okay. Thank you.  
 3 MS. NAMBIAR: Maybe we will take a comment  
 4 from Dr. Proschan and then break.  
 5 MR. PROSCHAN: Yes, I was a little bit  
 6 surprised that, you know, patients ranked so high the  
 7 outcome of culture conversion, and I wonder what do  
 8 you think the explanation for that is, because that's  
 9 something they wouldn't necessarily even feel, right?  
 10 MS. LEITMAN: Sorry, are you asking for an  
 11 explanation of how they reported culture conversion?  
 12 MR. PROSCHAN: No, why the patients felt  
 13 that, that was so important to?  
 14 MS. LEITMAN: Sure, well, so the symptoms  
 15 make them feel really lousy, the treatments make them  
 16 feel really lousy, I think a lot of them view getting  
 17 rid of the infection means they alleviate treatment  
 18 and they can alleviate some of the symptoms, I think  
 19 that's their hope. Certainly their -- if they culture  
 20 convert, they're not taking the antibiotics, and the  
 21 antibiotics have some really brutal side effects. So,  
 22 I mean, I think that's one of the main reasons why

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1 they view it as so important. And you know, I think  
 2 like anybody else who's dealing with the serious  
 3 chronic illness, they're probably -- they're facing  
 4 their own mortality and a lot of them are very  
 5 frightened. And they would like to see something  
 6 that's going to clear the infection and, you know, for  
 7 -- and we did see some qualitative feedback that said,  
 8 you know, I would like to know that I'm going to live  
 9 a normal lifespan or that I'm not going to die young.  
 10 So I think all of those things factor in.  
 11 MR. COX: Yeah, I'll just --  
 12 MR. PROSCHAN: Did you ask them that? I  
 13 didn't see that question up there about fear of death?  
 14 MS. LEITMAN: We do not ask them that  
 15 specific question.  
 16 MR. COX: I'll just add a comment too, I mean  
 17 turning your cultures negative is your road towards  
 18 someday stopping therapy, which is what you're saying.  
 19 And you know, without that it's very hard to stop  
 20 anyone's therapy for very long. So I think patients -  
 21 - and we've done these same service with Amy and we've  
 22 got this patient center outcome workgroup and panel

<p style="text-align: right;">Page 74</p> <p>1 for a long time for years, patients understand that                  2 their, you know, best shot at getting off the                  3 antibiotics is to turn their cultures negative, and                  4 have them negative for a long time, so that they can                  5 stop. So that's the path, it's progress, and it's a                  6 path towards treatment, completion, or stopping.                  7 UNIDENTIFIED SPEAKER: It might actually be                  8 more simple than that, and that's they believe that is                  9 the cause of all of the problems that they have. So                  10 if you get rid of that, it will -- but I will also                  11 tell you that patients are not the only ones that                  12 persevere on what's in the micro cultures, I know                  13 this discussion is not about antimicrobial resistance,                  14 but in the world of inhaled antibiotics, we hear                  15 repeatedly great fear about any bugs that might appear                  16 in a culture because the assumption is always that                  17 it's bad.                  18 UNIDENTIFIED SPEAKER: I'll just add a                  19 comment to that. If you do any survey in any disease,                  20 usually the top answer from patients will be cure.                  21 And I think a lot of patients will equate getting rid                  22 of the bugs, with cure. And the second aspect will</p>	<p style="text-align: right;">Page 76</p> <p>1 sampling, some other way to make an assessment about                  2 microbiological response other than conventional old                  3 sputum culture data? I think that's going to be dated                  4 with the new platforms that are available. And I                  5 think we collectively should begin to explore, are                  6 there better more sensitive and more specific measures                  7 of microbiological assessment and response than what                  8 we have right now because right now it's terrible.                  9 UNIDENTIFIED SPEAKER: Yeah. Just with                  10 respect to the timing of a potential clinical endpoint                  11 the survey suggests that among patients who are going                  12 to have a symptomatic response, you see it within                  13 about 6 months, does that coincide with the experience                  14 of the clinicians on the panel?                  15 UNIDENTIFIED SPEAKER: Yes, 3 months. I                  16 agree with you all, 3 to 6. 3 is the minimum, I                  17 think, in my mind.                  18 MS. NAMBIAR: Okay. So I think with that                  19 we'll take a break. We're running a few minutes late                  20 so maybe if we can reconvene in about 10 or 15                  21 minutes, and we should get started with the second                  22 session. Thank you.</p>
<p style="text-align: right;">Page 75</p> <p>1 be, I think if you asked a lot of my patients, they                  2 would put culture conversion very high, because I                  3 asked them about to submit cultures at every visit.                  4 And I talk to them about their culture results at                  5 every visit. And so it gets very much ingrained in                  6 their heads that this is very important.                  7 UNIDENTIFIED SPEAKER: I will say that in                  8 some of the qualitative responses with that as well,                  9 we also -- that, you know, our patients are -- they                  10 educate themselves very well about their disease. And                  11 we did see several patients responding, you know, if                  12 it can't get rid of the bug at least reduce the amount                  13 of bacteria. So they understand the difference                  14 between, you know, reduction of bacterial load and                  15 culture conversion.                  16 UNIDENTIFIED SPEAKER: And I might just also                  17 make a comment and or a plea that I think we need to                  18 think more broadly about this culture conversion. And                  19 I think standard culture conversion by microbiological                  20 responses Dr. O'Donnell said, sometimes we can get a                  21 sputum. So I think we need to think more broadly.                  22 Are there other technical aspects, PCR, some other</p>	<p style="text-align: right;">Page 77</p> <p>1 BREAK                  2 SESSION 2: TRIAL DESIGN CONSIDERATIONS AND CHALLENGES                  3 FOR NTM DISEASE                  4 LESSONS LEARNED FROM COMPLETED NTM TRIALS AND                  5 IMPLICATIONS FOR FUTURE TRIALS                  6 MR. SULLIVAN: Here are some of the learnings                  7 that Insmed has gained based on the clinical trials                  8 that we've conducted in patients with NTM lung                  9 disease. I'll begin with a brief overview of the                  10 clinical trials that we've conducted, then address                  11 these four specific topics.                  12 We observed that culture conversion, as                  13 defined in our pivotal trial, did in fact seem to                  14 predict durable microbiologic response. That is the                  15 maintenance of sputum culture negativity throughout                  16 the remaining course of treatment and out to 3 months                  17 after having stopped all NTM therapy.                  18 We observed that the study population was                  19 very heterogeneous despite the fact that these studies                  20 were conducted in a subset of MAC patients who are                  21 considered to be refractory to available therapy. And                  22 we believe that this heterogeneity introduces noise,</p>

<p style="text-align: right;">Page 78</p> <p>1 which can make it more difficult to detect the  2 treatment effect of an investigational drug. We found  3 that the 6-minute walk test was not a reliable clinic  4 trial endpoint for various reasons.  5 And finally, we believe that drug  6 tolerability issues may confound the assessment of  7 clinical benefit during the course of treatment.  8 So first, a brief description of the NTM  9 trials. There were three trials conducted with  10 Amikacin Liposome Inhalation Suspension or ALIS in  11 patients with NTM. Today I will discuss the first two  12 listed here which were the randomized trials. And  13 much of the data that I will present will be from the  14 pivotal Phase III study, Study 212. This was the  15 largest study and it included only patients with MAC.  16 Whereas the Phase II study included both MAC and  17 abscessus patients.  18 So first a brief overview of the designs of  19 the trials. The Phase II study, Study 112, was a  20 randomized, double-blind, placebo-controlled trial of  21 ALIS in patients with NTM lung disease who are  22 persistently culture positive on treatment. In</p>	<p style="text-align: right;">Page 80</p> <p>1 The pivotal study, Study 212, was a  2 randomized open-label multicenter study in adult  3 patients with MAC lung disease who are persistently  4 culture positive for at least 6 months while on a  5 guideline based multidrug treatment regimen. Patients  6 were randomized two to one to either ALIS 590  7 milligrams once daily, plus their multidrug regimen or  8 to their multidrug regimen alone.  9 The primary endpoint was sputum culture  10 conversion by month 6. In this study sputum culture  11 conversion was rigorously defined. Each month two to  12 three samples were obtained. In order to achieve  13 culture conversion, all samples had to be negative for  14 3 consecutive months. This primary endpoint was  15 considered to be a surrogate endpoint for the purposes  16 of marketing approval in the United States under the  17 Accelerated Approval regulations.  18 Once the month 6 sputum cultures results were  19 available for the last patient enrolled, the database  20 was locked and the primary and key secondary endpoints  21 were analyzed. Patients in either arm who achieved  22 the primary endpoint and remained culture negative</p>
<p style="text-align: right;">Page 79</p> <p>1 contrast to the subsequent pivotal study, this study  2 enrolled both patients with MAC and patients with M.  3 abscessus.  4 Another significant difference is that this  5 study enrolled both patients with and patients without  6 underlying cystic fibrosis. The overall objective was  7 to evaluate the safety, efficacy and tolerability of  8 ALIS versus placebo when added to a background  9 multidrug regimen.  10 The randomized, double-blind treatment period  11 was 84 days in duration. After the double-blind  12 phase, patients entered into an open-label phase where  13 they received ALIS plus their background multidrug  14 regimen for another 40 to 84 days. Patients were then  15 followed for an additional 12 months off of ALIS.  16 This study failed to demonstrate statistical  17 significance on its primary endpoint, which was a  18 semiquantitative measure of micro bacterial burden in  19 the sputum at day 84. However, other study findings  20 prompted Inmed to continue development. And I will  21 share some of the data from this study in a few  22 moments.</p>	<p style="text-align: right;">Page 81</p> <p>1 through month 6 continued in the study to complete  2 their course of treatment, which was 12 months  3 following their conversion date.  4 Patients who did not achieve culture  5 conversion through month 6 were enrolled in Study 312.  6 Following completion of 12 months of treatment, after  7 having achieved culture conversion patients in Study  8 212 stopped all MAC therapy. These patients were then  9 assessed at 3 months and through 12 months off all  10 antibiotic therapy.  11 Study 212 met the primary endpoint with a  12 higher proportion of patients treated with ALIS  13 achieving culture conversion by month 6. The absolute  14 difference between the treatment groups was 20.1  15 percent. And this finding was highly statistically  16 significant. This study demonstrated the treatment  17 with ALIS converted significantly more patients than a  18 multidrug regimen alone within 6 months.  19 Here you see the most common adverse events  20 in Study 212. Respiratory adverse events were the  21 most commonly reported category, and these included  22 dystonia, cough, bronchospasm and hemoptysis. All of</p>

<p style="text-align: right;">Page 82</p> <p>1 the adverse events listed here were more frequently                  2 reported in ALIS-treated patients than in the control                  3 group.                  4 The first observation from Study 212 was that                  5 sputum culture conversion by month 6 seemed to predict                  6 a durable microbiologic response. Once again, here's                  7 the design the 212 study. The results that I just                  8 showed you were for the primary endpoint of 6 months.                  9 Patients who met the primary endpoint continued on                  10 their assigned treatment for a complete course.                  11 What we found was that patients who converted by month                  12 6 using the rigorous definition of culture conversion                  13 deployed in the study tended to maintain their                  14 negative sputum cultures throughout the course of                  15 treatment and even 3 months after stopping treatment.                  16 These are the interim data which were                  17 discussed at the FDA Advisory Committee meeting held                  18 last August. As of a cutoff date of April 2018,                  19 durability results were available for 48 of the 65                  20 patients on ALIS who achieve culture conversion by                  21 month 6, and for 7 of the 10 patients who achieved                  22 culture conversion on the multidrug regimen alone.</p>	<p style="text-align: right;">Page 84</p> <p>1 study population was very heterogeneous.                  2 Although balance between treatment groups,                  3 there was significant variability in the baseline                  4 characteristics of the overall population. For                  5 instance, in regard to the number of drugs in the                  6 background regimen some patients were on two and some                  7 are on four or more. Likewise, approximately one-                  8 third of the patients were on a drug other than a                  9 ethambutol, macrolide or rifamycin.                  10 There was also wide variability in the                  11 specific multidrug regimens that were used. In this                  12 slide E stands for ethambutol, M for macrolide, R for                  13 rifamycin and O for any other medication deemed to be                  14 a component of the background regimen by the                  15 investigator. Fifty-five percent of patients were on                  16 the classic combination of macrolide, rifamycin and                  17 ethambutol. But the remainder were on various other                  18 combinations.                  19 Similarly, the duration of the diagnosis of                  20 MAC was quite diverse. The inclusion criteria                  21 required patients to have failed to obtain negative                  22 sputum cultures after a minimum of 6 months. But</p>
<p style="text-align: right;">Page 83</p> <p>1 As you can see 81.3 percent of patients who                  2 achieved culture conversion on ALIS had remained                  3 culture negative throughout their course of treatment                  4 and through 3 months after having stopped all MAC                  5 treatment. In contrast, none of the patients who                  6 achieved culture conversion on their Multidrug regimen                  7 alone had remained culture negative at this time                  8 point.                  9 More complete study data which will be                  10 described at the upcoming American Thoracic Society                  11 meeting are consistent with these data, suggesting                  12 that culture conversion by month 6 predicts durable                  13 culture conversion. The implication of these data for                  14 future studies is that early microbiological                  15 assessments may be informative in regard to longer-                  16 term microbiologic outcomes.                  17 The next observation I would like to share                  18 with you relates to the nature of the study                  19 population. What we found was that despite the fact                  20 that we focused our Phase III study on a specific                  21 subset of NTM patients. Only those with MAC and who                  22 were refractory to guideline-based treatment. The</p>	<p style="text-align: right;">Page 85</p> <p>1 there were patients who had had their MAC lung disease                  2 for 20 to 30 years. What I've shown you so far is the                  3 diversity of various descriptive baseline                  4 characteristics in our study population.                  5 There was also significant baseline                  6 variability in regard to metrics that might serve as                  7 potential outcome variables. For instance, here we                  8 see great diversity in the baseline scores on the St                  9 George's Respiratory Questionnaire in Study 212. Both                  10 a total score and the symptom score domain. Both of                  11 these have a range of 0 to 100. What you can see is                  12 that the four cortiles on these scores span almost the                  13 entire range of possible scores. Some patients are                  14 severely impaired and some have little room for                  15 improvement from baseline.                  16 In the Phase II study we didn't use the SGRQ,                  17 but you can see the same phenomenon on the QOL-B which                  18 was the patient-reported outcome instrument we used in                  19 that study. The data are shown here for the entire                  20 study population on the left, and only for the MAC                  21 patients on the right. Again, some patients were                  22 severely impaired at baseline and some have very</p>

<p style="text-align: right;">Page 86</p> <p>1 little room for improvement.</p> <p>2 I'll say a bit more about the 6-minute walk</p> <p>3 test in a moment. But here I just like to point out</p> <p>4 the significant diversity in our study population in</p> <p>5 terms of their baseline 6-minute walk test distance.</p> <p>6 Some patients showed severe impairment and others had</p> <p>7 values seen in healthy subjects. The point here is</p> <p>8 that even among the subset of MAC patients who are</p> <p>9 refractory to guideline-based treatment, there is</p> <p>10 significant heterogeneity in the clinical phenotype.</p> <p>11 In general, decreasing heterogeneity in a</p> <p>12 study population will increase study power and assay</p> <p>13 sensitivity, the ability of a clinical trial to</p> <p>14 demonstrate a treatment effect if one is present. So</p> <p>15 the implication of these observations for future</p> <p>16 clinical studies is that effort should be made to</p> <p>17 limit relevant heterogeneity in the study population.</p> <p>18 Now, I would like to say a little more about</p> <p>19 the 6-minute walk test. Because early on we were</p> <p>20 intrigued with the possibility that this might be a</p> <p>21 means to demonstrate a direct clinical benefit early</p> <p>22 in the course of treatment. This notion was driven by</p>	<p style="text-align: right;">Page 88</p> <p>1 I already showed you the data on the left</p> <p>2 side of this slide demonstrating the wide variability</p> <p>3 in terms of the baseline 6-minute walk test distance</p> <p>4 in the study population. There were patients who had</p> <p>5 very poor 6-minute walk test distances as well as</p> <p>6 patients who had performed so well at baseline that</p> <p>7 there was little room for improvement.</p> <p>8 The right side of this slide shows the</p> <p>9 variability in terms of the treatment response during</p> <p>10 the first 6 months of the study. The change from</p> <p>11 baseline to month 6, which you can see is that there</p> <p>12 were patients who had dramatic declines as well as</p> <p>13 patients who had dramatic improvements in this</p> <p>14 measure.</p> <p>15 This degree of variability both at baseline</p> <p>16 and during the course of treatment make it challenging</p> <p>17 to demonstrate a treatment effect in a clinical trial.</p> <p>18 There are other challenges in regard to the use of 6-</p> <p>19 minute walk test as an important clinical endpoint in</p> <p>20 NTM trials. First of all, the 6-minute walk test is</p> <p>21 not a test that is typically performed clinically to</p> <p>22 assess NTM patients nor is it something that is</p>
<p style="text-align: right;">Page 87</p> <p>1 the findings in our Phase II study in which the 6-</p> <p>2 minute walk test had been included as an exploratory</p> <p>3 endpoint.</p> <p>4 So what we saw in the Phase II study was the</p> <p>5 treatment with ALIS was associated with an apparent</p> <p>6 benefit on 6-minute walk distance. Even as early as</p> <p>7 day 84. Shown here are the 6-minute walk test results</p> <p>8 from that study. The mean difference between</p> <p>9 treatment groups in the change from baseline to day 84</p> <p>10 was 47 meters. Although the nominal P value had to be</p> <p>11 interpreted with caution, since this was just an</p> <p>12 exploratory endpoint, the results were intriguing</p> <p>13 enough that we decided to include the 6-minute walk</p> <p>14 test as a secondary endpoint in the subsequent pivotal</p> <p>15 trial.</p> <p>16 Unfortunately, in the pivotal trial there was</p> <p>17 no apparent effect of treatment with ALIS on the 6-</p> <p>18 minute walk test distance at month 6. So what</p> <p>19 happened? Why did the signal on 6-minute walk test</p> <p>20 looks so different between the two studies? We think</p> <p>21 there are a number of challenges to the use of 6-</p> <p>22 minute walk test as an endpoint in NTM trials.</p>	<p style="text-align: right;">Page 89</p> <p>1 typically used in the clinical practices of many of</p> <p>2 the physicians who care for these patients.</p> <p>3 Therefore, study sites may not have ready</p> <p>4 access to a satisfactory test course and site</p> <p>5 personnel may have limited experience with its</p> <p>6 conduct. Another factor to consider is the presence</p> <p>7 of underlying structural lung disease. The underlying</p> <p>8 lung disease in these patients, often bronchiectasis</p> <p>9 and COPD may be an important factor in their</p> <p>10 performance, A factor which would remain even after</p> <p>11 the infection is cleared, thus putting a ceiling on</p> <p>12 the potential benefit of even successful anti-</p> <p>13 microbial therapies.</p> <p>14 In addition, the clinical course of COPD and</p> <p>15 bronchiectasis often varies with episodic worsening.</p> <p>16 This variability unrelated to the NTM disease activity</p> <p>17 may introduce further noise on the endpoint. It's</p> <p>18 also possible that the benefit of treatment maybe most</p> <p>19 profound among patients who achieve microbiologic</p> <p>20 success. If the study population is one in which</p> <p>21 microbiologic success is less common, for instance in</p> <p>22 already treatment refractory population, the observed</p>

<p style="text-align: right;">Page 90</p> <p>1 effect size maybe blunted.</p> <p>2 Finally, significant physiologic benefit may</p> <p>3 not occur early in the course of treatment. If</p> <p>4 durable microbiologic cure is necessary before</p> <p>5 significant physiologic benefit can be achieved, the</p> <p>6 current very lengthy -- treatment courses for this</p> <p>7 disease introduce challenges in regard to complete</p> <p>8 follow up in clinical trials and the impact of missing</p> <p>9 data.</p> <p>10 Lastly, I'll introduce the topic of drug</p> <p>11 tolerability and how it may impact the assessment of</p> <p>12 clinical benefit in the trial. We know that the</p> <p>13 assortment of existing drugs used to treat NTM have</p> <p>14 certain safety and tolerability issues which can be</p> <p>15 quite challenging for patients. Nonetheless, we use</p> <p>16 these drugs because we think that the goal of</p> <p>17 ultimately curing the infection is worth the cost.</p> <p>18 And that once treatment is complete, if the infection</p> <p>19 can be eradicated, the patient will feel better off.</p> <p>20 So what does this mean for clinical trials?</p> <p>21 We have some evidence from our trials that suggests</p> <p>22 that the burden of the multidrug regimen itself in</p>	<p style="text-align: right;">Page 92</p> <p>1 It's certainly important for a trial to</p> <p>2 collect data to inform and understanding of the safety</p> <p>3 and tolerability of an investigational drug during the</p> <p>4 course of treatment. But if the primary goal of the</p> <p>5 PRO assessment is to characterize the ultimate</p> <p>6 clinical benefit that a patient will derive following</p> <p>7 a course of treatment, a PRO assessment following</p> <p>8 completion of treatment may be a more relevant index.</p> <p>9 So I'll end with this list of four learnings</p> <p>10 that we derived from our clinical trials in patients</p> <p>11 with NTM lung disease. The implications for future</p> <p>12 trials are early microbiologic findings may predict</p> <p>13 for later microbiologic outcomes. Attempt should be</p> <p>14 made to limit study population heterogeneity. The 6-</p> <p>15 minute walk test may not be a useful endpoint in NTM</p> <p>16 lung disease trials. And attention should be paid to</p> <p>17 the most appropriate timing of clinical outcome</p> <p>18 assessments. Thank you.</p> <p>19 MR. CHALMERS: Thank you very much. So we're</p> <p>20 going to have a full discussion of all these</p> <p>21 presentations during the panel discussion between</p> <p>22 11:00 and 12:00. But we have time for a couple of</p>
<p style="text-align: right;">Page 91</p> <p>1 addition to the burden of the disease may be captured</p> <p>2 in patient reported outcome measures.</p> <p>3 Here we show the St. George's Respiratory</p> <p>4 Questionnaire data from Study 212. Although not</p> <p>5 validated for use in NTM, the generally accepted</p> <p>6 threshold for a minimally important difference in</p> <p>7 other respiratory diseases is four units on this</p> <p>8 instrument. Shown here are the percentages of</p> <p>9 patients who achieved this threshold when assessed at</p> <p>10 their end of treatment visit, and when assessed 3</p> <p>11 months off all treatment. For both the SGRQ symptom</p> <p>12 score and the total score we observed that more</p> <p>13 patients achieved a change equal to or greater than</p> <p>14 the MID once they had been off treatment for 3 months.</p> <p>15 Similarly, in Study 112 with a PRL instrument</p> <p>16 was the QoL-B we saw some evidence of improvement in</p> <p>17 the scores 1 month after cessation of drugs. Similar</p> <p>18 to the existing investigational drugs -- similar to</p> <p>19 the existing drugs, investigational drugs may be</p> <p>20 associate with certain tolerability issues. And</p> <p>21 tolerability issues may impact patient reported</p> <p>22 outcome scores during treatment.</p>	<p style="text-align: right;">Page 93</p> <p>1 clarifying questions, if anyone has any, please.</p> <p>2 UNIDENTIFIED SPEAKER: So I guess slide 11</p> <p>3 seemed like a really important slide. And I'm not</p> <p>4 sure I understood everything that was going on in that</p> <p>5 slide. Could you just walk us through that?</p> <p>6 MR. SULLIVAN: Back button is not working.</p> <p>7 Is there anyone who can help me get back to the slide</p> <p>8 presentation? I'm hitting back. Oh now I got it,</p> <p>9 yeah. Play. Okay. So 11. Okay.</p> <p>10 So this is data that we had shown at the</p> <p>11 advisory committee meeting. And this is looking at of</p> <p>12 the patients who at that time we had data who had</p> <p>13 achieved the primary endpoint culture conversion by</p> <p>14 month 6. And we had data out to this time point, 3</p> <p>15 months after stopping.</p> <p>16 So for instance, in the ALIS column there</p> <p>17 were 65 patients who -- we had -- who had converted at</p> <p>18 month 6 and 48 of them had already gone all the way to</p> <p>19 that 3-month time point. And of those 48, 81 percent</p> <p>20 maintain their negativity through the course of</p> <p>21 treatment and then having been off all drugs for 3</p> <p>22 months.</p>



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<p>1 UNIDENTIFIED SPEAKER: But I guess I'm more</p> <p>2 interested in the others --</p> <p>3 MR. SULLIVAN: Yes.</p> <p>4 UNIDENTIFIED SPEAKER: The other side. So</p> <p>5 I'm trying to understand. So 10 -- what's the 7,</p> <p>6 what's the 10 or what's the zero?</p> <p>7 MR. SULLIVAN: So the other side are patients</p> <p>8 who -- there were 10 patients in the trial, initial</p> <p>9 randomization who achieved culture conversion on the</p> <p>10 multidrug regimen, on their background Regimen. But</p> <p>11 if you follow those, we -- when we got data on seven</p> <p>12 of those who had made it all the way so far to the 3</p> <p>13 months off, and none of them maintained it. So I</p> <p>14 think a comment had been made of the adviser to be</p> <p>15 that it certainly looks predictive on an effective</p> <p>16 drug, but how do we explain the fact that zero of</p> <p>17 seven. And so it may be that even despite the rigor</p> <p>18 of our definition of culture conversion, meaning we</p> <p>19 thought when we called you culture converted, you</p> <p>20 really were because there were several specimens for</p> <p>21 many months. But despite that rigor, if they were out</p> <p>22 -- if these were refractory patients who are only</p>	<p>1 your point. I think that if anything this would</p> <p>2 underestimate the ultimate benefit. Now we'll talk</p> <p>3 later about what this is a surrogate for. This -- in</p> <p>4 this study, the 6 months was a surrogate for 3 months</p> <p>5 off. But given what we've seen here, you might be</p> <p>6 fooled. You would look at the 29 percent versus 9</p> <p>7 percent who achieved culture conversion at month 6 and</p> <p>8 say that's going to predict the magnitude of benefit.</p> <p>9 But if the patients on the control group have sort of</p> <p>10 false positive, in other words, it's only going to</p> <p>11 underestimate the treatment effect, the long-term</p> <p>12 treatment effect.</p> <p>13 MR. CHALMERS: I suspect we're going to have</p> <p>14 a long discussion about culture conversion and what it</p> <p>15 means during the panel discussion. So in the interest</p> <p>16 of time I'm going to -- so the next presentation is</p> <p>17 going to be by Kevin Winthrop, who you've already met,</p> <p>18 from Oregon Health and Science University on trial</p> <p>19 design considerations and examples. Kevin's</p> <p>20 background, he's a professor of public health and</p> <p>21 infectious diseases at Oregon Health and Science</p> <p>22 University and very heavily involved in multicenter</p>
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<p>1 treated with MDR, it didn't hold.</p> <p>2 UNIDENTIFIED SPEAKER: All right. So your</p> <p>3 title is it that month 6 result predicts, is that not</p> <p>4 necessary -- you're saying maybe that's not true in</p> <p>5 the other group?</p> <p>6 MR. SULLIVAN: Well, the numbers are with 7,</p> <p>7 I think if you combine them you would still say of the</p> <p>8 58, the percentage would still be pretty high if you</p> <p>9 said irrespective of their treatment.</p> <p>10 UNIDENTIFIED SPEAKER: Please.</p> <p>11 UNIDENTIFIED SPEAKER: Yeah, but I bet you</p> <p>12 would see a statistically significant difference</p> <p>13 between those two --</p> <p>14 MR. SULLIVAN: Yeah.</p> <p>15 UNIDENTIFIED SPEAKER: -- durable. So I mean</p> <p>16 what you want with a surrogate endpoint is you want to</p> <p>17 be able to predict what the difference between arms</p> <p>18 would be on the real endpoint of interest. And so if</p> <p>19 there's a different relationship between the surrogate</p> <p>20 and the ultimate endpoint of interest in the two arms,</p> <p>21 that's a problem for being a good surrogate.</p> <p>22 MR. SULLIVAN: I think that -- I understand</p>	<p>1 NTM trials. Thanks Kevin.</p> <p>2 TRIAL DESIGN CONSIDERATIONS AND EXAMPLES</p> <p>3 DR. WINTHROP: Good. Thanks. Thanks James.</p> <p>4 So I want to thank doctors Nambiar and Cox for holding</p> <p>5 this. And I thank you for coming to our symposium</p> <p>6 meeting in November in Oregon. It was a long to go</p> <p>7 for you and for following it up with this is exactly</p> <p>8 what we need to be doing so. So thank you for</p> <p>9 bringing us together.</p> <p>10 I was asked to just give some general and</p> <p>11 maybe some specific ideas around what's been done.</p> <p>12 And of course Dr. Sullivan just outlined what's been</p> <p>13 done in the Insmed development program. So I won't go</p> <p>14 into too much detail around their program, but I think</p> <p>15 some of this is largely theoretical. I showed Dave my</p> <p>16 talk, he said it was provocative, it was funny, but it</p> <p>17 was only half true.</p> <p>18 So I will do my best to point out the parts</p> <p>19 that are half true. And then, you know, some of the</p> <p>20 things are there really just to make people think and</p> <p>21 hopefully stimulate discussion in the next hour.</p> <p>22 So my disclosures, I already disclosed. Although I</p>

<p style="text-align: right;">Page 98</p> <p>1 had forgot a few and so they're all up there for you                  2 now.                  3       So we're at the stalemate and this is why we                  4 need to all come together. We have companies looking                  5 for advice and physicians giving advice and FDA                  6 looking for advice and trying to give advice. And                  7 whose move is it next? So I think, you know, I don't                  8 know who's going to make the first move after this                  9 conference, but I think we'll all be better informed                  10 and someone's going to move and we'll get out of the                  11 stalemate. So currently approved therapies are                  12 really, there's just two. And if you look in their                  13 label, Azithromycin is labeled for disseminated MAC in                  14 patients with HIV, it's very specific and also very                  15 specific it says in combination with ethambutol.                  16       For Clarithromycin it also mentions                  17 disseminated MAC in patients with HIV, but there's no                  18 mention of companion drugs. So these of course --                  19 there's quite a bit of data in the Clarithromycin                  20 label outlining how it was evaluated in the context of                  21 disseminated MAC in HIV decades ago. So this is all                  22 we have approved for NTM. And of course the approval</p>	<p style="text-align: right;">Page 100</p> <p>1 some ideas why I think that's true. Our outcome                  2 measures of course we're going to probably spend 10                  3 hours debating our outcome measures, but some ideas of                  4 what's been done and maybe things we can consider in                  5 the future. And then trial lengths. And I think we                  6 all want shorter trials and patients want shorter                  7 trials.                  8       So in terms of patients in the disease state.                  9 So some simple ideas here. One problem we've had                  10 particularly in bronchiectasis trials, which is a                  11 related area is that we enroll patients maybe that                  12 aren't at the greatest capacity change. So for RCTs                  13 what we really -- if we want to study therapy, we want                  14 to enroll people who are going to change with the                  15 therapy, so we can measure difference with therapy.                  16       Another general idea is when you're studying                  17 the safety and efficacy of a drug it's a lot easier to                  18 understand it if it's being used in monotherapy. If                  19 it's being layered on to a study with four other drugs                  20 in one arm and three other drugs in the other arm, so                  21 it's just totally different. I mean all you're                  22 figuring out is the safety and efficacy of that drug</p>
<p style="text-align: right;">Page 99</p> <p>1 here is very specific to the setting that we're not                  2 even talking about today. This is disseminated MAC in                  3 HIV and this is not pulmonary MAC which essentially is                  4 not in HIV related disease almost at all. I mean                  5 there's a few HIV patients that get this, but it's                  6 99.9 percent non-HIV and it's limited to pulmonary                  7 NTM.                  8       See what did I do there? Current NTM --                  9 these are the current RCTs. And this was already                  10 highlighted. And I think Anne showed a nice slide.                  11 This is just if you go to clinical trials.gov, this is                  12 what's registered. I'll make some comments about some                  13 of these trials that are ongoing use them as examples                  14 but suffice to say there looks like there's kind of a                  15 lot going on, at least compared to say 5 years ago                  16 this slide was pretty much blank, that's encouraging.                  17       So considerations and examples. So I want to                  18 talk a bit about patient selection and disease state,                  19 follow-up some of Dr. Sullivan's comments about when                  20 to measure things. The treatment exposure groups who                  21 really need to think hard about, I'll just tell you I                  22 think we need placebo control trials and I'll give you</p>	<p style="text-align: right;">Page 101</p> <p>1 in the context of the other drugs.                  2       Then there is -- this is a big issue. It's,                  3 you know, you say this, you learn this in med school.                  4 If someone walks in the ER, they're sick or they're                  5 not sick, figure it out in a second. And if they're                  6 sick, they go down a different pathway than if they're                  7 not sick. When we enrolled patients in clinical                  8 trials, mostly what we're talking about here is we're                  9 talking about people who aren't that sick. Yes, they                  10 have all the symptoms Amy just described but they're                  11 not dying, they're not people with cavitory disease or                  12 have "consumption" and need to start therapy right                  13 away. It's a different -- that's a different type of                  14 person. And those types of people are probably not                  15 suitable for clinical trials, because they're too                  16 sick.                  17       So what is the standard of care. Anne                  18 outlined this in her talk. And, you know, Chuck and I                  19 stand up and talk about this a lot. Most of our                  20 patients who come in even if they're symptomatic, but                  21 they're not cavitory patients and about 20 percent of                  22 patients have cavities, the other 80 percent don't.</p>

<p style="text-align: right;">Page 102</p> <p>1 They have symptoms but you take some time to sort them                  2 out. You do not start them on antibiotic therapy                  3 right away. There's a lot of reasons for that.                  4 Most patients need to work on other things like                  5 clearance and bronchial hygiene. They need to develop                  6 an exercise routine. They need to eat better, they                  7 need to try to gain weight, there's a lot of things to                  8 work on before you start layering on three or four                  9 antibiotics many of which have adverse events. Many                  10 of which cause people not to want to eat or they get                  11 diarrhea like Amy mentioned, it makes weight gain                  12 difficult, et cetera. So you need to educate the                  13 patient about the drugs, what to expect and how to                  14 manage the side-effects. All those things take 3 to 6                  15 months. So you have a window of time if you're                  16 planning a trial where you can enroll patients who                  17 have symptomatic, pulmonary MAC, noncavitary disease                  18 to work on some of these things and randomize people                  19 to a drug in active arm and a placebo arm. And again,                  20 the exception is those that are sick.                  21 So what is the natural history of pulmonary                  22 MAC. And we -- the first part is actually fully true.</p>	<p style="text-align: right;">Page 104</p> <p>1 stable are certainly are listed there. I have a                  2 question mark around clearance and bronchial hygiene,                  3 it's just simply because we don't have a lot of data                  4 or prospective data looking at that, but an                  5 observational cohort certainly having cavitary disease                  6 being too skinny make these ideas of stability less                  7 likely.                  8 So if you're fit, if you're a good weight,                  9 you have noncavitary disease, you're much more likely                  10 to remain stable for some time period. So let's talk                  11 about -- so really we talk about two groups of people                  12 for these trials, refractory disease. So the intimate                  13 program focused on refractory disease. So these are                  14 my thoughts about refractory disease.                  15 This is an arbitrary definition. We kind of                  16 came up with it as a group because we looked at the                  17 data. And again this is observational study data from                  18 largely institutions. But around 10 or 20 percent of                  19 people depending on which series you look at don't                  20 convert by 12 months into therapy. So we've decided                  21 to call these people refractory. They're refractory                  22 to guideline-based therapy or whatever we're giving</p>
<p style="text-align: right;">Page 103</p> <p>1 It's not half true. And this comes from our studies,                  2 it comes from Ted Marisa's (ph) studies, Becky                  3 Trevor's (ph) studies. And we've looked population-                  4 wide in various places in the U.S. and Canada and                  5 it's, we see the same phenomenon. About 50 percent of                  6 people who meet disease criteria start therapy in the                  7 next 3 to 5 years. And the other 50 percent never do.                  8 And there's various reasons why they don't.                  9 They might die, they might have other severe diseases                  10 that just preclude consideration of treatment of this,                  11 i.e. lung cancer is a good example. And then you can                  12 see the other reasons. Ten or 15 percent of patients                  13 actually convert to negative spontaneously, probably                  14 just with better bronchial hygiene and exercise. And                  15 then another about quarter patients remain stable for                  16 years.                  17 How many years is years? Well I tell my                  18 patients, you know, some day you will progress, but it                  19 could be in 10 years, it could be in 5 years. And so                  20 the data where they followed people out 3 to 5 years                  21 after diagnosis. About 20 to 25 percent of people                  22 will stay stable. And factors associated with staying</p>	<p style="text-align: right;">Page 105</p> <p>1 them, which is usually the drugs that were already                  2 outlined by Anne and by Eugene.                  3 So we came up with that definition and then                  4 we kind of debated 6 months to 12 months, and in fact                  5 there's a publication that I cite in here on a                  6 subsequent slide where we just decided 6 months was                  7 long enough before we felt like we would want to try                  8 something else.                  9 So the benefit of studying refractory                  10 patients is that you can actually power studies with                  11 patients who are taking background multidrug therapy.                  12 Meaning you could have a comparator arm that actually                  13 people aren't actually real antibiotics that should be                  14 active because the placebo group in this group is                  15 unlikely to change. They've already been on therapy                  16 for 6 to 12 months, having converted their sputum and                  17 still don't feel good. They're probably not going to                  18 change a whole lot. So if you add a drug and causes a                  19 little bit of change, you're hopefully going to find                  20 that statistically. So you can actually power that                  21 study.                  22 The con of this is that measurable change in</p>

<p style="text-align: right;">Page 106</p> <p>1 both the placebo group and the new therapy group could  2 be quite minimal. And I just wrote M. abscessus an  3 example. I treat a lot of M. abscessus and pretty  4 much all those people, and this is subspecies  5 abscessus. Pretty much all those people were  6 refractory. And I put new drugs on all the time, and  7 I don't see any change, they're still refractory.  8       So if I were doing a study and I had some  9 abscessus patients on three drugs and they're  10 refractory and I just chose some other drug to study,  11 if I added it, I don't think I'd see any change at  12 all. That's the risk of studying that group of  13 people, refractory disease. So I won't go through  14 this. Dr. Sullivan already went through their design.  15 And they did show some benefit. And you can see there  16 was some benefit. Again it was very small in the  17 placebo group as expected as people probably aren't  18 going to change much.  19       So what about treatment naive patients? So  20 my bias is this is where we should be focusing. This  21 is the group that has the greatest capacity to change.  22 It's easier to measure change, you can measure change</p>	<p style="text-align: right;">Page 108</p> <p>1 see with the power assumptions below, if we assume 35  2 percent of conversion in the clofazimine and 10  3 percent spontaneous conversion of placebo arm. You  4 only need 102 people to do this study, 51 in each arm.  5 So there's no active comparator. This is a placebo  6 comparator.  7       If you do a multidrug active comparator  8 trial, you can see this at the bottom with a circle, N  9 equals 500. It's a totally different story from a  10 investment standpoint for patients, resources and time  11 and statistical power. So this is a multi-drug active  12 comparative trial that we've been funded through  13 Precorian (ph), it's a large study that involves our  14 consortium and our trials network up to 35 sites. And  15 we're comparing two drugs versus three drugs,  16 azithromycin and ethambutol verses azithromycin,  17 ethambutol or rifampin. It's a simple question. Are  18 these regimens equivalent?  19       So this is actually noninferiority design  20 which helped us a little bit on power but not much,  21 and culture conversion and tolerability at 12 months  22 outcome measures. And again, we're assuming about 85</p>
<p style="text-align: right;">Page 107</p> <p>1 more quickly and sooner. The trial doesn't have to be  2 as long. You can actually power these studies against  3 placebo, that's the benefit.  4       The con is that it's difficult to power the  5 study with an active comparator. If you take two  6 groups of people and you put them both on effective  7 therapy and 85 percent of people convert their sputums  8 and get better in each arm, you got to have a huge  9 study to show a difference.  10       So here's one example. This is the FDA R1  11 sponsored Clofazimine trial that many of us in this  12 room are participating in. It's a Phase II RCT, its  13 placebo-controlled. It's clofazimine monotherapy  14 versus sugar pill. You have to be a non-cavitary  15 patient, you're supposed to be "stable" which is a  16 hard thing to define. But we all know when we see it.  17 There have symptoms but they're not that sick, and  18 they're not that excited about taking antibiotics to  19 be honest.  20       Outcome measures or culture conversion at 24  21 weeks, which I'll make some comments about. We're  22 also looking at a semi-quantitative culture. You can</p>	<p style="text-align: right;">Page 109</p> <p>1 percent of conversion in each group because we think  2 both these regimens are active. And we think based on  3 observational data that's probably what we're going to  4 see. So again, you need a very large study to do  5 this.  6       Okay. Let's switch to outcome measures.  7 Efficacy, we were talking about the microbiologic  8 outcome. We'll be talking more about it. We have  9 some thoughts. I have some thoughts on QOL or quality  10 of life. And I'll mention some of the other things  11 here as well. So one question I have for the group  12 was actually a big please. Can we define culture  13 conversion with two consecutive sputums and not three?  14 This was the results of our voting. This is our NTM  15 that consensus statement part of the European -- joint  16 European-Japanese-U.S. guideline effort. And we came  17 up with some definitions about "cure" and different  18 aspects of therapy. And one was culture conversion.  19 You can see the voting there.  20       So choice number two -- I don't know if I  21 have a thing -- yeah, I do have a thing. But choice  22 number two you can see is the question was finding of</p>

<p style="text-align: right;">Page 110</p> <p>1 at least two consecutive negative cultures collected  2 at least four weeks apart. They got six votes. And  3 then number four is finding of at least three  4 consecutive negative cultures at least 1 month apart.  5 So that got six votes also. So they tied, six versus  6 six. And when we did a tiebreaker and in the  7 tiebreaker you can see that the one down below, which  8 was seven before (ph) got nine. And that was if, you  9 know, three consecutive cultures over, it's really  10 over 2 months that would be considered culture  11 conversion.  12 Here's an example of the Bedaquiline program,  13 in fact I'm not going to say much about TB because I  14 don't think we should even think about TB when we  15 think about these trials, but their culture conversion  16 definition was two. This is a registration trial and  17 led to approval and they used two over a month time  18 period. In fact, there's a number of TB trials that  19 have used two consecutive negative cultures over a  20 month time period.  21 So one question is do two consecutive  22 negatives predict three? I think the Insmed data</p>	<p style="text-align: right;">Page 112</p> <p>1 treatment duration for a particular regiment. What is  2 the minimum time I need to give this to someone, is it  3 12 months? Or I guess how long do I stick negative  4 after 12 months versus how long we going to stay  5 negative after 18 months, and it may be just the same.  6 Lastly semi-quantitative cultures, we've done  7 them. Dave's published a nice analysis showing it  8 predicts conversion. I think it does. There's also a  9 idea of time to conversion and we could talk about  10 that as a potential micro outcome measure.  11 Okay. Quality of life. We can just march  12 right through this. So we just submitted a response  13 to the FDA R1 and I know others in the room did as  14 well, looking at developing or further honing quality  15 of life questionnaires in bronchiectasis but also the  16 NTM component of bronchiectasis.  17 We've worked a lot with RSS or the  18 respiratory questionnaire the QoL-B for years. It's  19 undergone quite a bit of refinement and study. Dr.  20 Chalmers, I mean Patrick, lots of us in this room have  21 been using this in various studies on our own or  22 together and show good internal consistency, test-</p>
<p style="text-align: right;">Page 111</p> <p>1 probably says yes to that. And I think there's other  2 data that probably says yes to that. Concept of  3 sustainability while on treatment, this is important.  4 If you put someone on an antibiotic and they convert,  5 you'd like to know that they stay converted. We all  6 know that that's not always true, even with our  7 current regimens that aren't improved, certain people  8 pop up passes time here time again, but in general  9 we'd like to know that there's some sustainable effect  10 what's being used. This idea of durability of  11 treatment. I think I'm not sure what the clinical  12 relevance of this is. The infection rate from the  13 environment or the re-infection rate is so high, it's  14 50 percent in 3 years. I'm not sure that is where the  15 patient came from. Did they come from a placebo group  16 and they were negative or they came from a active drug  17 group in negative.  18 We learned 3 years ago half of them are going  19 to be positive again. So I'm not a big fan of this  20 durability measure and I don't think it tells us a  21 whole lot. I think the durability studies could be  22 done and the main utility is defining the optimal</p>	<p style="text-align: right;">Page 113</p> <p>1 retest reliability, convergence and some  2 responsibility in bronchiectasis but still need some  3 refinement, which we hope to do, particularly with  4 regards to defining the minimal important difference.  5 And the big question is, is it useful in NTM  6 bronchiectasis? There's very little study in MTM  7 bronchiectasis with this tool. The questions of one  8 to measure are huge, and I think Eugene was getting at  9 that. And I'm going to show you some more thoughts on  10 that in a second.  11 And lastly, the NTM module. This is a module  12 that was developed years ago with help from NTM IOR  13 and others and patient panels, in terms of defining  14 the symptoms that are important to these patients.  15 And they're all the same symptoms that Amy just  16 mentioned today. This module takes into account  17 fatigue, along with a number of other things. It  18 certainly needs to be refined and needs to be tested.  19 I'd say it's something that that looks promising but  20 needs longitudinal evaluation.  21 The QoL-B and NTM, again has received very  22 little study. We are presenting this at ATS. This</p>

<p style="text-align: right;">Page 114</p> <p>1 comes out of our biobank, and it's a small -- it's a  2 preliminary analysis in terms of the number of people.  3 But we looked at people who start therapy. And then  4 12 months later we looked at them again. And the  5 people who started therapy, their quality of life  6 improved.  7 And it seemed to correlate with culture  8 conversion. But, you know, when you look at the  9 people who improved, it's really the people who had  10 the ability to improve, the people who felt like crap  11 to begin with. The people who felt pretty good at  12 start don't improve. So that speaks to the point I  13 think Dr. Sullivan was trying to make, measure people  14 who have the capacity to change.  15 In the last bullet there you'll see the  16 people who'd already started therapy more than 3  17 months ago, they didn't change at all. In fact, their  18 change had already occurred and it had occurred before  19 we started measuring them. So there is this 3 to 6  20 month window, I believe as Chuck and I were saying  21 where there is a change to be anticipated and it's  22 measurable.</p>	<p style="text-align: right;">Page 116</p> <p>1 you're not really seeing much change because people  2 are at baseline.  3 Now I have thoughts about that. I mean, not  4 everyone's the same. There's heterogeneity just like  5 Eugene said, people who are heavily colonized with  6 pseudomonas, you know, they may be more susceptible to  7 whatever therapy you're giving them as compared to  8 someone who's not colonized with pseudomonas. And  9 James is doing some great work looking at this. And  10 we hope to work with him further looking at basilar  11 burden, et cetera.  12 I think those same concepts are true in NTM.  13 So in NTM, it's different. You don't have this  14 baseline exacerbate, baseline exacerbate thing. What  15 you have is this kind of gradual long slide down. And  16 at some point that gradual long slide down you decide  17 to treat someone.  18 So let's say you start your treatment there.  19 And they tend to stabilize this first 3 months. They  20 may even improve. But you can see the delta here as  21 if you haven't treated them, it's very small. So in 3  22 months the question is how much change can you really</p>
<p style="text-align: right;">Page 115</p> <p>1 So I was on the plane. And I was very  2 squeezed in. I mean, the guy next to me was a lot  3 bigger than me. And the lady next to him had an  4 emotional support dog, with a little jersey on that  5 said, "Number 9 Emotional Support Dog," with a round  6 thing on it. Anyway, I'm allergic to dogs. You can  7 tell I'm a little stuffed up today. So thanks, Delta.  8 Actually, I was in Alaska.  9 But anyway, here's what I think. The top  10 line is -- so this is bronchiectasis. This is our  11 problem. When you look back at all the bronchiectasis  12 trials, it's amazing to me that lots of them have  13 measured quality of life and people who shouldn't have  14 a change in quality of life. Because we measure them  15 at baseline. We enroll them at baseline, their  16 quality of life kind of just stays the same. When  17 they exacerbate they feel worse. And then they go  18 back to baseline.  19 And so if our trial is 3-month long or 6  20 months or whatever, it will never exacerbate. You  21 kind of just stay on this plateau. Maybe there's a  22 little up and down here and there. But by and large,</p>	<p style="text-align: right;">Page 117</p> <p>1 measure? And if you imagine the dotted line below,  2 this is someone we've -- actually this is someone we  3 haven't treated. So the solid line keeps going down.  4 There's very little change or drop in the 3-month  5 window. Someone you have treated here, they may  6 stabilize and then just gradually improve over months  7 or years. And they'll probably get back to about  8 their baseline but maybe not quite.  9 So it really depends on your time window and  10 when you choose to measure these patients. And not to  11 mention there's the issue that was also just mentioned  12 about your therapies. Giving a respiratory therapy  13 may cause respiratory symptoms. And so if you're  14 measuring respiratory symptoms, it may not be the best  15 time to do it while they're actually taking therapy.  16 So the last three columns about this, pulmonary  17 function test generally show no change during therapy,  18 they're mostly fixed due to the underlying lung damage  19 of bronchiectasis or emphysema. The 6-minute walk  20 test took me 1 minute to walk to the bathroom. I  21 would bathe and it took me like 6 minutes to walk  22 back. So that just tells you what I think of it.</p>

<p style="text-align: right;">Page 118</p> <p>1 It's very operator dependent. There's a lot  2 of heterogeneity. There's problems that were already  3 outlined by Dr. Sullivan. I think exercise capacity,  4 one thing we just put into our grant submission is  5 we're going to give everyone Fitbits. I think you can  6 probably measure overall activity and steps and  7 functionality based on something like that, some real-  8 world daily measurement. And I talk about that with  9 my patients. We don't usually give them Fitbits in  10 clinic but we do talk about the overall daily energy  11 output in terms of what they're doing from an exercise  12 standpoint.  13 So my last point I'll talk is just to  14 emphasize this. NTM is not TB. TB is curable.  15 Culture conversion has a definition and it's a  16 surrogate for cure. Cure has a definition and it's  17 contagious, you have to treat it. You can't let  18 people with TB go untreated. So placebo-controlled  19 studies are out of the question.  20 NTM is an infectious disease but it's not  21 contagious. It behaves more like a chronic  22 inflammatory disease like an autoimmune disease. I</p>	<p style="text-align: right;">Page 120</p> <p>1 flu (ph) or from their pseudomonas. And we think,  2 well maybe I'm actually a little better or worse, 3  3 months later the treatment bud's gone. So it's hard  4 to understand how that correlates with culture  5 sometimes.  6 And then clinical meaningfulness. I think  7 every question here is going to say yes, culture  8 conversion has meaning, it means you're on the road to  9 being able to stop someone's treatment. So lastly, I  10 think we need better outcomes measures. I gave this  11 plea in Oregon, and I'm going to give it again really  12 quick here as my time runs out. But I think we should  13 think about disease activity. We need some sort of  14 index that incorporates subjective science, subjective  15 feelings, patients and physician input, and something  16 that's meaningful to the patient and the physician.  17 So the analogy I -- what I've looked towards is  18 rheumatology, literature. They've done this with  19 chronic inflammatory drug disease. We're dealing with  20 chronic inflammatory airway disease. They have a  21 composite measure that requires 20 percent improvement  22 in both physician and patient global assessments, a</p>
<p style="text-align: right;">Page 119</p> <p>1 like to use rheumatoid arthritis as my analogy.  2 Treatment is really guided by disease activity and by  3 patients, patient input. It's generally not curable,  4 although it's usually suppressible.  5 My experience with therapy is almost everyone  6 feels better with therapy or at least stabilizes.  7 They don't continue to go downhill except for maybe 10  8 or 15 percent of people that are refractory. And then  9 relapse/re-infection is common after therapy,  10 particularly in the nodular bronchiectatic patients  11 it's around 50 percent from Dave's data and similar  12 from other experiences elsewhere.  13 Lastly, culture conversion is only part of  14 the story. And I hear lots of comments about culture  15 conversion. It doesn't always correlate with how  16 patient feels or functions, but I think it generally  17 does and does not always correlate with radiographic  18 change. A lot of our patients' radiographs improve  19 and they get worse and then they improve again and  20 then they get worse. And it's because a lot of times  21 we're seeing things that aren't necessarily MAC on the  22 radiograph. They get treatment buds (ph) from the H</p>	<p style="text-align: right;">Page 121</p> <p>1 functional measure, a pain scale and an inflammatory  2 objective measure, inflammatory measure.  3 We've submitted a grant that we hope to do  4 this with everybody in this room, that, you know, we  5 have a provision of disease activity score. And we're  6 using kind of all the things we're talking about.  7 Inflammatory markers, cultural results, symptom scores  8 from NTM module, the respiratory scores, and the QoL-  9 B, CT scan results, and then physician visual analog  10 scale and patient VAS scores. So how do you feel on a  11 zero to 10 today? These are the kinds of things that  12 all the other chronic inflammatory diseases use. And  13 I think that might be applicable here.  14 It drives with our patient-centered panel and  15 a patient-centered research priority that was  16 published that I think Amy mentioned. And this was as  17 part of a precory (ph) funded initiatives, a  18 developing composite measure of disease activity  19 severity that actually reflects how patients feel and  20 function is the top priority for patients.  21 So in summary, NTM trials. Placebo  22 controlled trials, you can power, they're ethical if</p>

<p style="text-align: right;">Page 122</p> <p>1 you don't involve people with cavities. You can look  2 at drugs as monotherapy or as multi-drug therapy  3 combinations. And I think you can show efficacy in as  4 little as 3 to 4 months with a number of the outcome  5 measures that were just mentioned. And I do think  6 disease activity should be something we consider and  7 work together to formulate a case definition for.  8 So my last slide, the quote, "Figure out a drug  9 safety/efficacy first, approve it, and then figure out  10 how best to use it." You can see the citation that  11 was me.  12 Last shown, Alaska Air, Seat 10F, and that  13 was after I had a discussion with emotional support  14 dog. But we often mess up the ideas of registrational  15 studies with strategy trials. And once that idea is  16 approved, we can do the strategy trial to figure out  17 how best to use it. And I think those are separate  18 concepts, and we should try to keep them separate.  19 Phase III trials, I agree generally should  20 reflect how you think a drug should be used post-  21 approval, and this will have impact as well as the  22 idea of drug resistance.</p>	<p style="text-align: right;">Page 124</p> <p>1 somewhere at 12 to 16 weeks. So I think this is  2 doable with shorter trials.  3 And if you switch people over, I'm not sure  4 why there's resistance to this idea, you do in all the  5 other diseases, but you can certainly take people on  6 placebo and after your primary outcome measures you  7 can switch them to an active drug and see what happens  8 to them. And I'll tell you what's going to happen to  9 them. This is what's going to happen to them.  10 You got placebo up top, you've got active drug down  11 below, disease activity has fallen, you switch the  12 placebo group at month 3 to active drug, and within a  13 month they look exactly like the treatment group. And  14 that's what you're going to see if you do this with  15 NTM. And it's nice to see, it's reassuring, and it  16 allows you to collect more safety data.  17 Last slide, a small trial to prove efficacy  18 with focused patient populations and vested clinicians  19 who are experts and a good drug, you can always do a  20 larger trial later to prove safety that's cheaper and  21 easier. This is one thought particular as an orphan  22 disease, we don't -- I don't think we need to do two</p>
<p style="text-align: right;">Page 123</p> <p>1 Now given a drug where there's no known issue  2 of resistance, maybe you can give that drug in  3 monotherapy. Giving a drug where you're worried about  4 acquired resistance, monotherapy is probably not a  5 good idea. And then the strategy trials I just  6 mentioned, you can figure out how to use things later.  7 Here's a simple study design. Rheumatology is full of  8 dozens and dozens of these examples. You have someone  9 with high disease activity, you give them placebo, or  10 you give him one of your two doses of your compound.  11 This is a JAK inhibitor called baricitnib. And you  12 follow them out for a certain time period you have  13 rescue available for people who aren't responding.  14 This is very simple design.  15 There's my very simple design. This was also  16 from a different plane flight. But I think you can do  17 the same thing, randomize people to drug or drugs  18 versus placebo. You can have your primary outcome  19 measure at 24 weeks if you're talking about 6 months  20 culture conversion. But I think we can look to see  21 who's converting sooner than 6 months, and I think  22 some of the other outcome measures we can measure</p>	<p style="text-align: right;">Page 125</p> <p>1 Phase III trials that show the same thing. I think  2 it's impossible. I think we need one Phase III trial  3 that's doable and short. It shows efficacy and  4 safety. And then we can refine some of ideas about  5 how to use the drug later, and we can do larger safety  6 studies later.  7 That was it. Thank you to everyone here who  8 I work with. Cheers.  9 UNIDENTIFIED SPEAKER: Thank you very much,  10 Kevin. We're running a little bit behind. But we've  11 got time for one clarifying question if there's any  12 questions. Looks like your talk was perfectly clear.  13 Thank you, Kevin. So the final presentation is from  14 Dr. Chen. The title is, Use of Patient-Reported  15 Outcome Measures in NTM Trials.  16 USE OF PATIENT-REPORTED OUTCOME MEASURES  17 IN NTM TRIALS  18 MR. CHEN: Good morning. So actually with  19 the wonderful presentation from Dr. Sullivan, Dr.  20 Winthrop and Dr. Leitman, I don't think I need to be  21 here. Actually it's just that it's been -- actually  22 it's shown that that we all have thinking the same</p>



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1 thing we all are thinking important things in, I mean  
 2 other than just the cultural conversion but what's the  
 3 outcomes and that's my job. So I'm only here to just  
 4 emphasize that FDA are thinking about the same thing.  
 5 Usually, that's what we do. So I just want  
 6 to mention that the brief introduction about COA  
 7 staff. We are in the office on new drug in CDER. Our  
 8 mission is to promote and develop and implement of  
 9 patient-focus endpoint measure in medical product  
 10 development to describe clinical benefit in labeling.  
 11 This is an overview of my presentations.  
 12 But we have seen many discussion this morning  
 13 about how outcomes majors in this NTM space and I  
 14 think it's very clear. So actually I will just jump  
 15 over a lot of my slides. I don't need to be repeat  
 16 the same information. Now given this great  
 17 presentation this morning. Maybe just a few thing  
 18 that I just like to point out. So from FDA's  
 19 perspectives how we measuring clinical benefit.  
 20 We focus on, you know, (inaudible 0:56:04.6)  
 21 internal pump, patient feel, function or survived.  
 22 Now we know that biologic endpoint doesn't really tell

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1 us how a patient feel, function or survive. So we  
 2 have the need of outcome, other outcome measure, what  
 3 we call the clinical outcome assessment. And we have  
 4 seen discussion this morning quality of life,  
 5 symptoms, functions and even the not very good 6-  
 6 minute walk test. Those are one of the outcome  
 7 assessments.  
 8 And so speaking of which, here are the four  
 9 major type of clinical outcome assessment. We  
 10 actually for the NTM probably the most relevant and  
 11 important one will be the PRO Patient-Reported  
 12 Outcomes studies, the symptom or function reported by  
 13 the patient themselves. (Inaudible 0:56:57.0)  
 14 clinician reported outcome that may be also useful as  
 15 maybe including like say, for example, is the  
 16 activities that Dr. Winthrop just proposed. There's  
 17 also performance outcomes and that's the infamous 6-  
 18 walk test is performance outcome. And also so the  
 19 report the outcome is used when the patient can now  
 20 report the outcomes by themselves within the pediatric  
 21 patients.  
 22 This one new model of outcomes that also that

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1 Dr. Winthrop just mentioned, I will repeat that we  
 2 have been able to qualify to classify into one of  
 3 these four is the one in the pattern now with this  
 4 actual risk state, digital house technology tool.  
 5 These other new type of outcomes that you wear. It's  
 6 like wearable like Fitbit like (inaudible 0:57:48.9).  
 7 This may be able to use your monitoring your daily  
 8 activities, your sleep, your physical functions.  
 9 So these are the type of the COAs and these  
 10 could be -- in NTM space this could be any one of  
 11 them. We can consider all of them or just one. But I  
 12 think it is the framework that we will be discussing  
 13 today which will be the better outcomes. Now as I  
 14 mentioned, the patient-reported outcome is probably  
 15 the most relevant and important one because the  
 16 patient are able to report about their own symptoms  
 17 with their functions, their daily activities. For  
 18 example cough, shortness of breath, fatigue as Amy  
 19 mentioned this morning.  
 20 Fit-for-purpose that we need instruments that  
 21 is fit-for-purpose and the definition of fit-for-  
 22 purpose is that fit-for-purpose instruments is a

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1 conclusion that the level of validation associated  
 2 with the tool is sufficient to support this conduct we  
 3 use. Pretty general and here's the more expanded  
 4 definitions of fit-for-purpose COA as is probably for  
 5 its intended including the study design patient  
 6 populations is valid and reliable, is measuring a  
 7 concept that are clinical relevant, important to the  
 8 patients and from the FDA's perspective also can be  
 9 communicated in the level, in a way that is accurate,  
 10 interpretable and not misleading.  
 11 And in 2009 FDA had published a patient-  
 12 reported outcome guidance, laid out the general  
 13 principle in develop a fit-for-purpose clinical  
 14 outcome assessments. What about NTM space? Actually  
 15 we've been hearing a lot, I'm just -- I don't need to  
 16 repeat all these symptoms that we heard from 2005  
 17 Patient Focus Drug Development Meeting and also what  
 18 Amy presented this morning.  
 19 There is a roadmap that regarding how you  
 20 develop a fit-for-purpose instruments. The first step  
 21 is understanding the disease of the condition. I  
 22 think we pretty much have a lot of information about

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1 knowledge to that. They are too -- this slide is too  
 2 small to read, they are in FDA's website. But I want  
 3 to point out what is the most important one is at the  
 4 bottom of this roadmap engage FDA early and through  
 5 our medical develop -- product development. And that  
 6 is the point I want to emphasize by showing this  
 7 slide.  
 8 We are willing to collaborate, to work with  
 9 you to develop a fit-for-purpose outcome assessment.  
 10 Now, the system we worked at has been mentioned a  
 11 couple of times. They are all patient reported  
 12 outcome instruments and ensuring the result not maybe  
 13 (inaudible 1:01:02.1). And actually my first reaction  
 14 is actually maybe the choice is not sensitive enough.  
 15 So this is something that we also we want to discuss  
 16 in the panel and in this afternoon. How can we  
 17 develop a more sensitive instrument for the patient  
 18 who seems not able to improve but actually that  
 19 because we don't have a good tool.  
 20 So considering for developing the PRO in NTM  
 21 understanding the natural history -- we have seen a  
 22 lot presented this morning. I think we have good

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1 understandings. Symptom PRO, we know Function PRO, we  
 2 know (inaudible 1:01:44.0) function of PRO that we can  
 3 use or we can developed while doing my patient  
 4 functions, I mean patient functioning in daily life.  
 5 As Amy mentioned, actually it is also social,  
 6 psychological. They feel depressed, they feel  
 7 isolated. This may be, you know, something that is  
 8 also relevant and important to the patients. So not  
 9 just physical functions. So what do the patient say?  
 10 These are all we can take into considerations. These  
 11 considerations, I would just skip over them. These  
 12 are the way that you can engage us in terms of the  
 13 COA, the patient-reported outcome that you  
 14 individually can go through the IND/NDA/BLA Pathway  
 15 that we've been talking a lot about this morning.  
 16 However, there's another two pathway that you  
 17 can engage FDA in terms of developing appropriate fit-  
 18 for-purpose PRO or COAs. There's DDT, the Drug  
 19 Development Tool, COA qualification pathway, you can  
 20 submit your proposal for qualifications. There's  
 21 another pathway is nonbinding nonformal discussion  
 22 between FDA and you is what we call the CP, critical

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1 path innovation meeting pathway that you have a great  
 2 idea.  
 3 For example like Dr. Winthrop's is the  
 4 activity for NMT, that would be a great -- the CPE  
 5 meeting will be a great way to communicate to talk  
 6 about this disease activities and then we can go from  
 7 there. So I just want to present the way to talk to  
 8 us that we will love to work with them about this  
 9 COAs.  
 10 The conclusions, we encourage the development  
 11 and implementation of patient-reported outcomes  
 12 assessment in clinical trial especially in NTM space.  
 13 Patient input is the critical importance and  
 14 understand what we are able to measure. And then keep  
 15 in mind is that we do want to improve the symptoms.  
 16 We want to withhold, we want to improve the function  
 17 or we want to improve both or cure what have you.  
 18 Early communication with FDA is important. In this  
 19 website link now you can go find for more information,  
 20 including the qualification program and the CPIMs.  
 21 Thank you.  
 22 MR. CHALMERS: So I think we now move on to

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1 the panel discussion part of the morning. And I think  
 2 we're going to get some questions. So these are the  
 3 questions that FDA would like the panel to focus on  
 4 over the next hour of discussion. So it's organized  
 5 into three real overarching questions. What patient  
 6 population should be prioritized for clinical trials,  
 7 what the clinical symptoms, signs or measures should  
 8 be incorporated into outcome assessments and clinical  
 9 trials. And then assuming that the primary endpoint  
 10 is designed to assess direct clinical benefits, when  
 11 should it be assessed. So without further ado, open  
 12 the floor to questions.  
 13 PANEL DISCUSSION  
 14 UNIDENTIFIED SPEAKER: James, is it possible,  
 15 I might make a comment about Kevin's presentation?  
 16 MR. CHALMERS: About the percentage of  
 17 truthfulness.  
 18 UNIDENTIFIED SPEAKER: No, it's a superb  
 19 presentation, very thought-provoking and I think  
 20 excellent. But I disagree in a fundamental way with  
 21 Kevin about curability. And I would use our own data  
 22 that we have generated to discuss that. It is true

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1 that in our data with nodular bronchiectatic patients,  
 2 within 3 to 4 years, about half have a microbiologic  
 3 occurrence, but two things. Half don't.  
 4 So to dwell on the half that have reoccurred  
 5 is misleading. But the other important thing is that  
 6 of the 50 percent who have their microbiological  
 7 occurrence, 75 percent are new genotypes. And so in a  
 8 sense, this is -- these people require we think  
 9 isolate. So another perspective is that for the  
 10 genotype that the patient was treated for initially,  
 11 there is, if you will, cure and that the patient then  
 12 because of the underlying structural lung disease  
 13 reacquires another infection.  
 14 I think -- I don't want that to get lost. I  
 15 believe it is an infectious disease. And I would be -  
 16 - I would certainly welcome other comments that is  
 17 treatable and in a real way curable. I don't want --  
 18 I don't want to -- I think it's easy to become  
 19 nihilistic because we have all of these complicating  
 20 factors. We have underlying bronchiectasis, we have  
 21 multiple organisms, and we -- all of these, there's an  
 22 interplay of so many factors. But we are able to

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1 produce cure for some patients, many patients.  
 2 MR. WINTHROP: Dave, I agree with everything  
 3 you just said. But that's all a joke. No, I do. I  
 4 actually agree. But I think in terms of, I would just  
 5 rephrase -- I guess I would shoot back that in terms  
 6 of trial design and development, this the issue of  
 7 cure is less of what we should be talking about.  
 8 Because cure takes a long time to effectuate and your  
 9 data, as you just said, a lot of people who are cured  
 10 get reinfected. And it's pretty high percent, and  
 11 it's within a pretty short time period.  
 12 So in terms of trial design and studies, you  
 13 know, if we focus on cures and outcome, we're never  
 14 going to make any headway at all. So, yeah, but well,  
 15 I guess that was my point.  
 16 UNIDENTIFIED SPEAKER: So I also just want to  
 17 clarify that of these 25 to 50 percent of people that  
 18 we're talking about that do have another infection and  
 19 we say that most of those are reinfection, it does not  
 20 equate to pathogenic infection in all those patients.  
 21 So we start over.  
 22 And again, maybe 50 percent of those will

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1 need to be treated similar to our original group. But  
 2 just because we say they have a new organism does not  
 3 mean that they have a pathogenic organism like they  
 4 had initially.  
 5 UNIDENTIFIED SPEAKER: Well, I disagree with  
 6 both David and Kevin. No, what I hear though, there's  
 7 tension in that we're discussing, which is, is this an  
 8 infectious disease or not? So if it's an infectious  
 9 disease, we think about curing infections. And if  
 10 it's a chronic inflammatory disease, we think about  
 11 improving how the patient feels. I mean -- but see,  
 12 it turns out as both. And I think that's why we're  
 13 struggling a little bit, because we need to address  
 14 both of those issues. And I think if we could show  
 15 better to everyone that there was a correlation, then  
 16 the discussion would be over.  
 17 So I think somehow we need to think about how  
 18 we better document correlation with the micro biologic  
 19 response to how patients feel and function.  
 20 UNIDENTIFIED SPEAKER: I agree with that.  
 21 I'd add to it, I mean, just use a clinician, when you  
 22 enter into treating these people, I mean, you don't

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1 tell them you're going to cure them. I mean, I never  
 2 tell them that. Like, I think that's -- I mean, I  
 3 tell them we might cure it, we might get rid of it,  
 4 but we're going to make you feel better number one.  
 5 And we're going to suppress -- we're going to get rid  
 6 of as much of it as we can. And that's what I say.  
 7 And then if we do get rid of it, you might  
 8 get it back. So I mean, you have to understand that  
 9 as a patient going into treatment that this is more  
 10 like your RA man. I can put it in remission and I can  
 11 stop your treatment. You may stay in remission  
 12 forever, or it may bounce back on you.  
 13 UNIDENTIFIED SPEAKER: You think you spend  
 14 too much time with rheumatologist. But I disagree, I  
 15 just think it's important to know that there's more  
 16 than one -- more than one -- what am I trying to say -  
 17 - approach to this. Tim, help me out here.  
 18 UNIDENTIFIED SPEAKER: Just if I could, I  
 19 wonder if there are different patients in whom when  
 20 they come in the clinic, you think my goal here is I  
 21 think I can cure this, but others you just know --  
 22 UNIDENTIFIED SPEAKER: That's a great point.

<p style="text-align: right;">Page 138</p> <p>1 There's heterogeneity which you were talking about in                  2 the talk, and I was mentioning absolutely, yeah. And                  3 there are people that you think you probably could                  4 cure and you may go for that and you tell them that,                  5 but then there's other people that you're not.                  6 UNIDENTIFIED SPEAKER: So could do you think                  7 you could design a trial, you know, with inclusion                  8 criteria for the appropriate endpoint? So for this                  9 type of phenotype, my endpoint is going to be, I'm                  10 aiming for cure. For this...                  11 UNIDENTIFIED SPEAKER: Yes, so I mean I'll                  12 just tell you what I think, I know this from our                  13 population-based data in Oregon. We've seen it. We                  14 followed people out for 9 years. And people with                  15 bronchiectasis get it back, people with COP and                  16 emphysema only, not bronchiectasis, you can actually                  17 cure them. And they don't get it back. And their                  18 rate of getting it back is super miniscule compared to                  19 some of the bronchiectasis.                  20 Does it happen? Sure, if they have an                  21 existing cavity, they can get re-infected. But if you                  22 can close your cavity or if you can treat them, cure</p>	<p style="text-align: right;">Page 140</p> <p>1 need to come up with some sort of maintenance                  2 strategy.                  3 UNIDENTIFIED SPEAKER: What you're speaking                  4 to is the broader goals of what are the objectives of                  5 therapy? And, you know, this is a perfect point to                  6 highlight the fact that it may be different for                  7 different stages of disease. What you define as cure                  8 and a treatment inexperienced population is a                  9 completely different thing than what your expectation                  10 and definition of cure might be in a treatment                  11 experienced patient. So I think that in terms of the                  12 broader goals for both populations we need to step                  13 back and as a group consider what are the objectives                  14 of therapy and are they different in Phase II, Phase                  15 III, different populations.                  16 UNIDENTIFIED SPEAKER: Yeah, I totally agree,                  17 and I would just say, look, I agree with what Dave                  18 said. But I don't think the word cure enters into a                  19 discussion around clinical trial design for phase two                  20 and three. And I -- it's a concept we can debate and                  21 we can define, but it shouldn't enter into this                  22 because to affect cure takes way too long. And we</p>
<p style="text-align: right;">Page 139</p> <p>1 them, you're much more likely to cure that person.                  2 The caveat being you got to get them early. If you                  3 get them late and they've got too much involvement,                  4 it's impossible.                  5 UNIDENTIFIED SPEAKER: Well, I know this is,                  6 you know, we're mincing words here. But again, they                  7 reacquire organisms. And as Shannon said, that isn't                  8 treatment failure and they are successfully treated                  9 for a specific episode. I don't know what you want to                  10 call that.                  11 UNIDENTIFIED SPEAKER: But I think we have to                  12 be unsatisfied with the current treatment regimen                  13 because, right, I mean it's 50 percent at best. And                  14 so I think in answer to some of these questions, you                  15 know, treatment naïve is probably where we need to                  16 start, but we need to blow up the treatment paradigm I                  17 think. And we need to maybe, you know, decide who                  18 we're going to treat and then treat them super                  19 aggressive for 3 months or something. You know, add                  20 another jug, add something.                  21 And the standard therapy is not working then                  22 I think with regards to this reinfection, we probably</p>	<p style="text-align: right;">Page 141</p> <p>1 cannot do studies of new drugs that take that long to                  2 go cure someone and then have them get infected anyway                  3 later. So I, you know --                  4 UNIDENTIFIED SPEAKER: (Cross talk).                  5 UNIDENTIFIED SPEAKER: I know. You wanted to                  6 make the point that this is infectious, we can care,                  7 which I agree with. We can't --                  8 UNIDENTIFIED SPEAKER: And I think -- I mean                  9 we really need to clarify that we're really talking                  10 about microbiological response, not a cure. That is,                  11 we don't do bronchoscopy, we don't do biopsies, we                  12 don't do an aggressive evaluation to know is that                  13 organism cleared. I think when we have culture                  14 conversion by standard sputum analysis, does that mean                  15 that I can find any MAC at that point if I look really                  16 hard by bronchoscopy or biopsy or something. And the                  17 answer is probably not. So I think we just need to                  18 also be very clear about the terminology and then                  19 where that patient is.                  20 And I would feel much better about a                  21 microbiological assessment rather than or culture                  22 conversion is even better than cure. Cure implies a</p>

<p style="text-align: right;">Page 142</p> <p>1 whole different -- so but treatment is in most  2 instances again in parallel. So you're saying that  3 there may be instances where we don't have a  4 microbiological response and yet patients feel a lot  5 better. I don't know that that happens a lot. And  6 I'd like to -- I mean I would as part of the clinical  7 study try to determine what that means microbiological  8 response discordant with what their clinical symptoms  9 are.  10 I think that that's a pivotal part especially  11 for the naïve patients. And we understand for nodular  12 bronchiectatic disease as was mentioned, I mean 85, 90  13 percent clearance rates for sure I think are easily as  14 established with thrice weekly therapy.  15 MR. CHALMERS: Erica?  16 MS. BRITAIN: Yeah, I keep thinking about it  17 as that the outcome shouldn't separate the micro and  18 the clinical. You could say the best outcome is  19 someone who's successful on both. The worst outcome  20 is someone who is not successful on either and where -  21 - how you want to call the discordant ones, I'm not  22 sure which is worse, which is better being -- I would</p>	<p style="text-align: right;">Page 144</p> <p>1 we think ultimately what we're trying to do here for  2 patients, we're trying to improve the patient's  3 overall condition, trying to make them feel better,  4 we're trying to make them live longer, we're trying to  5 have a more functional.  6 And so I think, I mean, you know, I agree  7 with you. We have to be very thoughtful as we're  8 talking about microbiologic response versus clinical  9 response. But I think a key thing here is to try and  10 think about how we understand what's going on  11 clinically with the patient. Is the patient better  12 off, and if so, how?  13 MR. CHALMERS: Bruce?  14 MR. TRAPNELL: Yeah, I think the discussion  15 around cure is really centered on two different  16 things. Cure the infection, what David's comments and  17 cure the patient in terms of the risk of reinfection,  18 propensity for disinfection. So have to pick which  19 thing we're talking about and focus on that, you know,  20 from a trial standpoint, well, you have to have  21 something specific that you can measure. And there  22 are future -- the patient's future risk of reinfection</p>
<p style="text-align: right;">Page 143</p> <p>1 think being -- having a good result on clinical and  2 not a good result on culture is better than having a  3 good result on culture and nothing on clinical. But  4 it seems like one way to approach this is not to  5 divorce them but to put them together into one  6 outcome.  7 MR. CHALMERS: Okay. Ed.  8 MR. COX: Yes. So when I think about  9 surrogate endpoints and, you know, their development  10 and how we usually get to them. Usually what you have  11 is a trial where you actually show a clinical benefit.  12 So you've established clinical benefit and in that  13 same trial you also have collected the data for the  14 surrogate and you look to be able to show that that  15 surrogate, you know, appears to be associated with the  16 clinical outcome. You know, there's also an  17 understanding that it's on the causal pathway that's  18 important.  19 And ideally you've got that repeated across a  20 few different trials. And that allows you to come to  21 a firm conclusion that the surrogates you're seeing is  22 actually associated with clinical benefit. You know,</p>	<p style="text-align: right;">Page 145</p> <p>1 may be linked to that underlying disease in a way that  2 allows you to cure an infection as David is saying.  3 But the patient is not cured in the sense of their  4 risk of reinfection or reemergence.  5 UNIDENTIFIED SPEAKER: But I would just  6 argue, this isn't any microbial discussion. And so  7 really the infection is the primary focus. I think  8 it's a lot to expect of an antibiotic to have an  9 effect on their underlying susceptibility for  10 reinfection unless we're talking about suppressive  11 therapy or secondary prophylaxis.  12 MR. TRAPNELL: I couldn't agree more. I  13 think there's two different ways the word cure is  14 being used, with reference to the patient and the risk  15 for whatever's going to happen in the future and  16 specifically about a particular infection at any given  17 time. So we just have to be cleared which thing we're  18 talking about as we go forward so not confused.  19 UNIDENTIFIED SPEAKER: I agree those  20 thoughts. And I think Tim said it on the -- hit it on  21 the head. I think we should A) just stop talking  22 about cure, because I don't even know what we're</p>

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

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

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1 patients, you expect to see a benefit within  
 2 3 month.  
 3 MR. WINTHROP: I expect to see the start of  
 4 that benefit around 3 months. I mean, because I think  
 5 some people actually get worse the first 2 weeks you  
 6 start a treatment because they start killing bugs,  
 7 they have more inflammation, maybe their cough gets  
 8 worse. And then they tend to level out and they can  
 9 start feeling better. But I would pick 3 months as  
 10 kind of my minimum. I don't know what my colleagues  
 11 think, but.  
 12 UNIDENTIFIED SPEAKER: Okay. I would just  
 13 show -- point out that David actually has data in that  
 14 regard from the study that was in the blue journal in  
 15 2015 and a treatment-naïve patient population where  
 16 they looked at predictors of ultimate microbiologic  
 17 effect at 12 months. And so reduction in colony  
 18 counts predicted that, but also a reduction in  
 19 symptoms predominantly cough at 3 months was  
 20 predictive of what we're seeing at 12 months. So I do  
 21 think within that 3-month period that you're seeing  
 22 culture conversion in the majority of treatment-naïve

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

<p style="text-align: right;">Page 150</p> <p>1 where the endpoint was symptoms at 6 months and you'd                  2 be confident that that's sufficiently predictive that                  3 long-term outcome would be affected?                  4 UNIDENTIFIED SPEAKER: Well, I have a                  5 question about that specifically regarding 1H (ph),                  6 treatment-naïve versus treatment refractory because                  7 now we're talking about predicting that seeing an                  8 improvement in symptoms at 3 months with the                  9 treatment-naïve population is somewhat predictive of                  10 culture conversion. So if we're going to look at a                  11 clinical trial that treats treatment-naïve patients                  12 and I think that might be beneficial because they                  13 might end up with less lung damage. But then when we                  14 get to the end of the clinical trial, we're talking                  15 about labeling and, you know, indications for that                  16 drug. What's the label look like?                  17 I mean or is it also going to be approved for                  18 refractory patients and then conversely, you know,                  19 what happens when you're studying a drug for                  20 refractory patients, can you then say it can be used                  21 to treat treatment-naïve patients if we know that                  22 treating a patient whose treatment-naïve might be able</p>	<p style="text-align: right;">Page 152</p> <p>1 prioritize clinical trials going forward, So I think                  2 it's not that whether we -- one population is                  3 preferred over the other. I think given where our                  4 knowledge is right now and what would be the, you                  5 know, in terms of prioritizing do -- should we focus                  6 on treatment-naïve.                  7 I mean we heard from Kevin that there are                  8 some advantages and maybe focusing on treatment naïve                  9 population at this point. But does that necessarily                  10 translate into treatment effect on in a refractory                  11 population. I think is very hard to answer. Again,                  12 the endpoints you choose -- the timing of the                  13 endpoints all of that would really be dictated by the                  14 patient population that you plan to study.                  15 UNIDENTIFIED SPEAKER: I don't know that                  16 those two populations need to be one or the other. I                  17 think their advantages are both. It depends on the                  18 drug. I think it depends on whether or not we've got                  19 adequate preclinical data to show effect, which I'm                  20 not sure we really have animal models that give you a                  21 definitive answer of that.                  22 And I think it depends a lot on how much</p>
<p style="text-align: right;">Page 151</p> <p>1 to help them get a better result?                  2 UNIDENTIFIED SPEAKER: And that's a valuable                  3 question for translation from an early efficacy read                  4 that one might be looking for in Phase II study in                  5 order to, you know, figure out if you have a drug                  6 worth pursuing, worth extending into a long study that                  7 could potentially run as long as 8 years. And then                  8 moving into Phase III and a different population, a                  9 treatment refractory population. So, you know, one of                  10 the questions for this group is how does that                  11 translate an early efficacy look in one patient                  12 population to Phase III or to your point if we study                  13 only in treatment-naïve because it's the cleanest, how                  14 does that translate to treatment refractory patients                  15 and labeling?                  16 UNIDENTIFIED SPEAKER: So in terms of your                  17 question regarding labeling, I mean in general the                  18 label reflects the population that was studied in the                  19 clinical trials.                  20 So I think this question is more to do with,                  21 you know, that there is an unmet need right now and                  22 then we're looking at feasibility, how should we</p>	<p style="text-align: right;">Page 153</p> <p>1 money you have to spend on your first in target                  2 disease trial. So I think if you've got somewhat                  3 shaky animal data to invest a lot of money into a                  4 large study and treatment-naïve patient population, we                  5 really don't have an effect -- an idea of what this is                  6 going to do in human disease, may not be a preferable                  7 way to go for a given drug. It may be for another                  8 drug where you have some experience already in other                  9 diseases showing effect or showing safety.                  10 UNIDENTIFIED SPEAKER: So I'm not sure if                  11 there's a requirement to lump them or separate them,                  12 but I think we've heard that there's enough                  13 differences between these patient populations such as                  14 the endpoint, the timing might be different so then                  15 there are difficulties in combining them into one                  16 patient study.                  17 UNIDENTIFIED SPEAKER: So I have something                  18 that's really important as you're designing this and                  19 considering, if you're going to have a placebo arm, a                  20 true placebo arm, I would not study that in a                  21 treatment refractory group.                  22 UNIDENTIFIED SPEAKER: We haven't heard any</p>

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1 comments yet on whether to put CF and non-CF patients  
 2 in the same trials, which is question number three.  
 3 UNIDENTIFIED SPEAKER: No.  
 4 UNIDENTIFIED SPEAKER: No.  
 5 UNIDENTIFIED SPEAKER: I have my own bias.  
 6 UNIDENTIFIED SPEAKER: No.  
 7 UNIDENTIFIED SPEAKER: So answers is no,  
 8 because they're so different.  
 9 UNIDENTIFIED SPEAKER: No.  
 10 UNIDENTIFIED SPEAKER: Does anyone disagree  
 11 with that?  
 12 UNIDENTIFIED SPEAKER: No.  
 13 UNIDENTIFIED SPEAKER: I'm going to take that  
 14 one on that. So there's -- well, first I just want to  
 15 make one comment about treatment refractory and what  
 16 worries me about studies in this population that  
 17 they've already proven they're not, well,  
 18 microbiologically responsive to the therapy. One  
 19 question is are you actually getting drug to the bug?  
 20 And if you're not, adding another drug isn't going to  
 21 expect to improve upon that. It's particularly a case  
 22 of cavitory disease.

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1 So in the CF versus non-CF, you know, James  
 2 made it clear why they sort of targeted a specific  
 3 population in the Phase III study with Liposomal  
 4 Amikacin. There was a small subset of CF patients in  
 5 there. And they didn't seem to have the same robust  
 6 response. And that's a decision moving forward, but  
 7 you still have to come forward as explaining why that  
 8 population is different and would not be responsive to  
 9 a therapeutic treatment.  
 10 I can tell you that when we've done the  
 11 numbers, looking at CF studies only, you got a  
 12 feasibility problem in terms of how many patients you  
 13 could actually study. So the CF Foundation is  
 14 actually investing a large sum of money into the  
 15 investigation of NTM, obviously their interest is in  
 16 the CF population, but fully committed to if there are  
 17 therapies that are beneficial to those that don't have  
 18 CF, that's okay with them. So in our discussions we  
 19 actually are contemplating whether to include non-CF  
 20 patients in our therapeutic trials. But I haven't  
 21 heard anybody throw up a reason why they couldn't be  
 22 enrolled in a study.

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1 UNIDENTIFIED SPEAKER: My concern is power.  
 2 How do you power that kind of study if the CF -- if  
 3 the CF population is already having trouble enrolling  
 4 studies? And we've already seen how difficult it is  
 5 to enroll in a non-CF population. Once you get, you  
 6 know, done with a study, you have to start stratifying  
 7 the data out and looking at the two different  
 8 populations. And once you stratify the data, you  
 9 start losing power. So you really have to overpower  
 10 at the study. What does that look like? How do you  
 11 power that study? I'm concerned about that.  
 12 UNIDENTIFIED SPEAKER: You would have them  
 13 all in one big group as part of your primary analysis  
 14 that would do an analysis afterwards.  
 15 UNIDENTIFIED SPEAKER: You can't stay with  
 16 primary analysis.  
 17 UNIDENTIFIED SPEAKER: The issue isn't so  
 18 much that there's a reason why they wouldn't respond,  
 19 but that they might respond differently or the  
 20 assessment of their response might be different, you  
 21 know, the instrument might...  
 22 UNIDENTIFIED SPEAKER: And I think --

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1 heterogeneity into already a very heterogeneous group,  
 2 the NCF and non-NCF, we've even burned enough times  
 3 with the bronchiectasis experiences. So I would be  
 4 inclined as far as NTM goes to try to keep that sorted  
 5 out at least initially because if for no other reason  
 6 heterogeneity. The other aspect of this, we have to  
 7 also be clear about say treatment-naïve. It's not  
 8 just about even culture conversion microbiological  
 9 response, but time, shorten that interval. Why should  
 10 we have 12 months, 18 months, 24 months of therapy.  
 11 So having a new strategy to shorten therapy  
 12 and then look at durability would be a sufficient  
 13 endpoint in itself. So it may be that the culture  
 14 conversion rate is the same but I can do what I do now  
 15 and say 12 or 18 or 24 months in 3 or 6 or 9 months.  
 16 And that would be a tremendous benefit for patients in  
 17 cost.  
 18 UNIDENTIFIED SPEAKER: Just to repeat, the  
 19 variability that is what we're all concerned about  
 20 with all the heterogeneity. And as you introduce  
 21 different patient populations you increase the  
 22 variability of the response in a small patient



<p style="text-align: right;">Page 158</p> <p>1 population, which just gets larger and larger,                  2 requires stratification, harder to stratify, more                  3 sites around the country. It's best to be get an                  4 answer and then study whatever we want to study and                  5 what's appropriate to study in the right population.                  6 UNIDENTIFIED SPEAKER: Yeah. And I agree, I                  7 mean I think you'd be -- you could incorporate them,                  8 you could deal with it, you could, you know,                  9 randomize, equaling each groups and minimize --                  10 there's ways to deal with for trial sample. But I                  11 disagree with Patrick, I think you can totally power                  12 the studies in CF if you do placebo controlled trial.                  13 So you have to enroll the right patients that you                  14 think is ethical to enroll placebo weighing. But I do                  15 think those patients are out there and you could power                  16 study with, you know, 50 to 75 CF kids.                  17 And it depends on your outcome measures too,                  18 but I think you, you know, if you look at bacillary                  19 outcomes, particular through the quantitative and you                  20 look at your patient-reported outcomes, CFQR, things                  21 like that, I think you can do it but --                  22 UNIDENTIFIED SPEAKER: If you can get it down</p>	<p style="text-align: right;">Page 160</p> <p>1 outcomes that, for example, maybe for the treatment-                  2 naïve the main primary outcome should be cultural                  3 conversion but for the refectory we should looking at                  4 how patient feel, function, these outcomes. So if we                  5 -- if different outcomes is more appropriate for                  6 different subpopulation should we then actually                  7 combine them into the same study? So that's my                  8 question for you.                  9 UNIDENTIFIED SPEAKER: Goes back to the                  10 objectives of therapy, you can -- I think you can                  11 think of these as three different subsets of patients.                  12 Because the -- what the patient is most interested in                  13 if they're a CF patients or if they're a treatment                  14 refractory patient with macro or treatment-naïve                  15 patient may be completely different priorities. And,                  16 you know, defining those outcome specific to that                  17 patient population at which you're going to see a                  18 response may be a cure associated with some clinical                  19 improvement in less fatigue in the treatment-naïve                  20 population. In the treatment-experienced population,                  21 they are looking for a clinical response on treatment                  22 period that makes their quality of life improved. So,</p>
<p style="text-align: right;">Page 159</p> <p>1 to 50 to 70, I would agree with you.                  2 UNIDENTIFIED SPEAKER: Yeah.                  3 UNIDENTIFIED SPEAKER: The worry is that it                  4 is exceeding that. I just want to make a comment that                  5 the issue with bronchiectasis was that the temptation                  6 was there is CF and there is non-CF bronchiectasis.                  7 And I think a big failure of our trials is the                  8 assumption that non-CF bronchiectatic patients will                  9 respond similar to bronchiectasis patients. But now                  10 is for learning is that there's multiple endotypes and                  11 multiple phenotypes and trying to hash out which of                  12 those patients are most likely to respond.                  13 And so to just start thinking nodular                  14 bronchiectasis is going to be the model is going to                  15 fit that, I'm not so sure that that's right. I think                  16 Kevin has a point that you're looking for the                  17 population that is likely to demonstrate ability to                  18 change is what you're after.                  19 UNIDENTIFIED SPEAKER: Yeah. I'd like to add                  20 to that because that's my area, I mean in terms of CF                  21 versus non-CF, even for the treatment-naïve versus the                  22 refectories NTM, are we still talking about the same</p>	<p style="text-align: right;">Page 161</p> <p>1 you know, I think it goes to the same extent to the CF                  2 patients as well. But these needs to be separately                  3 defined.                  4 UNIDENTIFIED SPEAKER: And I think this                  5 begins to raise the question of is it statistically or                  6 methodologically possible to use one, two, three or                  7 four different outcomes as any one of those four as a                  8 positive study. So if you say that I'm going to pick                  9 a PRO or a sputum or FEB1 or something else and you'll                  10 take any of those four then -- and the question I                  11 guess I would go to the maybe FDA and the stance folks                  12 from a methodological problem is that is that legal                  13 essentially.                  14 UNIDENTIFIED SPEAKER: Yeah, I'll start and                  15 then Erica is going to fill in. So, you know, in a                  16 field where you're still trying to figure out what's                  17 the best endpoint, what's changing, I mean that sounds                  18 like where you want to do sort of a Phase II study.                  19 And you want to see if you can figure things out. Now                  20 Phase II is hard sometimes because the numbers are                  21 small. So unless the change is dramatic you may not                  22 see too much. But, you know, ideally you want to try</p>

<p style="text-align: right;">Page 162</p> <p>1 and figure out what it is that you're measuring before                  2 you get into a Phase III trial.                  3       And then as Erica will tell us in just a                  4 minute, you know, if you do start to go in with                  5 multiple different endpoints, then, you know, there's                  6 multiple different ways that you can win then there                  7 are certain additional sort of statistical, you know,                  8 you have to divide your alfa across the multiple                  9 different ways you can win because as you have more                  10 different ways you can win that the likelihood of                  11 winning by chance alone is greater, but Erica is going                  12 to help us with that okay.                  13       MS. BRITTAIN: Okay. We already said it but,                  14 no, I mean it is legal if it -- I think that was a                  15 question, was it is legal. Yes, it's legal but you                  16 have to do it in a very -- in a conservative way so                  17 that you're not cheating. I guess the potential                  18 downside is it end up interpretable depending on how                  19 you do it.                  20       UNIDENTIFIED SPEAKER: So I guess just a                  21 quick comment...                  22       UNIDENTIFIED SPEAKER: It may increase your</p>	<p style="text-align: right;">Page 164</p> <p>1 does lead to interpretation issues but it's something                  2 to consider.                  3       UNIDENTIFIED SPEAKER: But I think what we                  4 heard this morning was that some patients have coughs,                  5 some patients don't, so if your primary outcome is                  6 cough, you lose a significant chunk of your patients                  7 who could not improve. The same with exercise                  8 capacity. So in some ways it makes complete sense to                  9 measure multifactorial outcomes.                  10       UNIDENTIFIED SPEAKER: I think I'd like to                  11 make a plug for a recent FDA guidance, the multiple                  12 endpoints guidance is very instructive in this regard                  13 and walk-through all the different ways you can                  14 handle, well to whether it's a composite and so forth,                  15 and it's actually really good read if you're                  16 interested.                  17       UNIDENTIFIED SPEAKER: Yeah, I mean, that's                  18 why I make this pitch for a combined outcome measure                  19 for all these reasons. And you know look at the ACR                  20 20, and the ACR 50, and the ACR -- so ACR 20 is 20                  21 percent improvement across those five measures. So                  22 you don't have to improve in each of them. In fact</p>
<p style="text-align: right;">Page 163</p> <p>1 sample size too considerably, so if you can...                  2       MS. BRITTAIN: They could, right.                  3       UNIDENTIFIED SPEAKER: If you can pick a best                  4 way before you get into Phase III, your sample size,                  5 you know, won't balloon incredibly because you're                  6 going to win, you're going to win many different ways.                  7       UNIDENTIFIED SPEAKER: So the way I heard                  8 Tim's question was not to have four primary outcomes                  9 but was to have a kind of composite of multiple                  10 outcomes where one is response. And if you think                  11 about it, most PROs are a composite. They take cough                  12 and breathlessness and sputum and they give you a                  13 final score. And I think what I picked up was Tim was                  14 saying, well you could have an improvement in 6-minute                  15 walk or an improvement in call for, and they make one                  16 outcome and that would be...                  17       MS. BRITTAIN: Right. So that's similar to                  18 what I was trying to say before, that you don't                  19 necessarily have to have separate outcomes and then do                  20 a multiple comparisons which is the penalty that Ed                  21 was referring to. But you could set it up so that                  22 your outcome is just inherently multifactorial. That</p>	<p style="text-align: right;">Page 165</p> <p>1 you might have even got worse in one of them. But                  2 overall you've had this overall improvement. And                  3 that -- and then statistically you don't have these                  4 multiple comparison issues. And of course this                  5 doesn't help we don't have a combined outcome measure.                  6 Now I have this provisional I wrote on a plan, but,                  7 you know, I think we should commit ourselves to                  8 developing it, that's what I think we should do.                  9       UNIDENTIFIED SPEAKER: Right so we're talking                  10 about 2 very different things. I mean you can have a                  11 composite end point. And it is correct that                  12 oftentimes, you know, PRO instruments look at multiple                  13 different domains in multiple different, you know,                  14 things that they're assessing. And that's all fine.                  15 So I think we need to be really clear about what we're                  16 talking about because we're talking about composite                  17 endpoints or PRO instrument that's measuring a variety                  18 of different things. It's then coming out to a single                  19 score. Yeah, that's, you know, quite common, so --                  20 and it's very different in the multiple endpoint                  21 issue.                  22       UNIDENTIFIED SPEAKER: So, you know, I think</p>

<p style="text-align: right;">Page 166</p> <p>1 the more you make things tailored to the specific  2 patient the better from the standpoint that you're  3 measuring whether that patient improved and the worse  4 in terms of figuring out what the effect of the drug,  5 you know, is. So, you know, for particular patient  6 that -- for them, you know, the fact that they used to  7 be active might be the most important thing.  8 So for them a change in their physical  9 activity, you know, would be huge. And so conceivably  10 you could say, okay, at baseline what's the most  11 important thing to you, what would, you know, if you  12 change in this area what would be the most important  13 one.  14 And you could actually say, you know, okay,  15 for this patient it's a change in this. And if you  16 did that at baseline you'd have a valid test. But  17 then at the end of the day, you know, it'd be kind of  18 difficult. You'd say, okay, this drug help patients  19 improve in what was most important to them. But the  20 fact is it was different for different patients. So  21 that becomes hard to, you know.  22 But could I just -- you know, you guys</p>	<p style="text-align: right;">Page 168</p> <p>1 And if that's the case, what would be the set  2 of symptoms or signs that we'd be interested in? Is  3 there a PRO that we can use today? And then if so, if  4 we were to measure it at 3 months or 6 months, and we  5 saw a clinical benefit 3 months or 6 months, how long  6 will we anticipate that clinical benefit would  7 continue beyond that 3 to 6 months for anyone?  8 UNIDENTIFIED SPEAKER: Well, so there's a lot  9 of questions there, but I'll just -- I'll take the  10 first one and that I -- and I said in my talk, I  11 would enroll noncavitary patients. And that's how I  12 would write it in your inclusion criteria. Because if  13 you said nodular bronchiectatic, it means they have to  14 have nodules in bronchiectasis.  15 And not everyone has bronchiectasis. So I  16 think this is this about whether you can use a  17 placebo. And I don't think you can use a placebo when  18 people have cavitary disease, so I would exclude those  19 individuals.  20 MR. DALEY: But just to take that thought  21 maybe one step further, so if you are using a  22 microbiologic outcome, then using your argument</p>
<p style="text-align: right;">Page 167</p> <p>1 actually needed statistical help before and didn't  2 realize it with the stratification and then the CF.  3 You know, what's really important is whether there is  4 a treatment difference in CF and non-CF. So the fact  5 that it's adding variability is not a problem at all.  6 If you're going to do a stratified analysis, which  7 doesn't mean what I think many people at this table  8 think it means.  9 Stratified analysis means you're going to  10 compute the treatment effects separately in these  11 different groups but then you will combine them, you  12 know, and so you will not necessarily lose power if  13 the effective treatment is the same in CF and in non-  14 CF. That's really the important question is, is the  15 effective treatment the same in those two groups?  16 UNIDENTIFIED SPEAKER: Can I ask a question?  17 Okay. And so we have we have all kinds of questions  18 about the population and when to study and what to  19 study. But like if we had to design a trial tomorrow,  20 and I'm getting the sense it might be in a  21 bronchiectatic nodular group in general, I'm getting  22 that sense possibly.</p>	<p style="text-align: right;">Page 169</p> <p>1 earlier you want to get people who can have change.  2 So the people who have the greatest chance of change  3 are those with the highest bacterial load, right?  4 UNIDENTIFIED SPEAKER: Yeah.  5 MR. DALEY: So because not nodular bronchiectatic  6 disease has a lower bacterial load. So now we've  7 already set the curve maybe against us a little bit on  8 the microbiologic outcome.  9 UNIDENTIFIED SPEAKER: Yeah, I agree with  10 Chuck completely. So I think you're going to do  11 cavitary patients, which I'm all for, you just can't  12 have a placebo -- you can have placebo-controlled  13 trial but you've got have two active arms, like you  14 can't have just placebo. That's -- I mean ethically I  15 don't think we could do that.  16 UNIDENTIFIED SPEAKER: And what about if -- I  17 mean you mentioned if you are looking at micro, I mean  18 I get the point about the high micro count, but how  19 about if you wanted to look at clinical as your  20 primary endpoint, so that's a clinical outcome and  21 let's say it's a PRO?  22 UNIDENTIFIED SPEAKER: Chuck is right, those</p>

<p style="text-align: right;">Page 170</p> <p>1 people get better. I mean we're talking about cure.                  2 And I already said I don't think we should ever say                  3 that word again today. But you can cure those people.                  4 UNIDENTIFIED SPEAKER: You said it.                  5 UNIDENTIFIED SPEAKER: They have fevers, they                  6 have night sweats, they're weight losing, they're                  7 being -- they have consumption basically, so you can                  8 measure improvements in all those...                  9 UNIDENTIFIED SPEAKER: So the clinical change                  10 should be present also?                  11 UNIDENTIFIED SPEAKER: Yeah.                  12 UNIDENTIFIED SPEAKER: Kevin, you showed data                  13 with the QoL-B that the only patients in your                  14 observational cohort who got better had a score less                  15 than 70, so would you advocate enrolling patients with                  16 a minimum symptoms score?                  17 MR. WINTHROP: Yeah, it's a really good idea.                  18 I mean if that's going to be your primary outcome                  19 measure, a part of it, then I think you got to enroll                  20 the people who might change. So having some                  21 exclusionary criteria around that or at least a                  22 priority statistical analysis plan that takes into</p>	<p style="text-align: right;">Page 172</p> <p>1 the goal of therapy I think, Angela as you had pointed                  2 out, I think as long as you're a priority clear about                  3 that, what you're trying to do for a specific                  4 population I think some things we'll need to go back                  5 to Phase II and some things we'll be ready to go right                  6 at Phase III.                  7 UNIDENTIFIED SPEAKER: And I think just                  8 because it's Phase II doesn't mean that we don't want                  9 to use the clinical endpoint for that early efficacy                  10 read.                  11 UNIDENTIFIED SPEAKER: Could you imagine                  12 abandoning the micro endpoint and just be on clinical                  13 and do 3 months of therapy and be satisfied and let us                  14 figure out how long to treat them in the long run?                  15 And where I'm going with that is if I ask the docs in                  16 the room, if it's 6 months, your patient says I feel                  17 great, their x-ray was better, and they still were                  18 positive, would you change your therapy? And then                  19 when I look at the treatment refractory patients and                  20 they're on drug for 6 years on average, if it wasn't                  21 working doing something, why didn't the docs just stop                  22 it out completely?</p>
<p style="text-align: right;">Page 171</p> <p>1 account would be key, I think.                  2 UNIDENTIFIED SPEAKER: Or you might be able                  3 to stratify depending on multiple endpoints and just                  4 stratify for patient enrollment, whether it's by                  5 symptoms score and even which one of the domains                  6 versus culture conversion in the context of a nodular                  7 bronchiectatic patient versus otherwise. Because if                  8 you have a large bacterial burden or bacillary burden                  9 and someone fibrocavitary disease, and you use a drug                  10 that's not going to at all get to that cavity, it                  11 doesn't really matter at all. You're not going to be                  12 any further along and having any positive impact                  13 there. And that's predictable. So even though you                  14 got the right population for that particular drug                  15 whatever that example would be would be a poor choice.                  16 UNIDENTIFIED SPEAKER: So I guess a more                  17 broader question are -- do we still need to do more                  18 Phase II or are we ready for Phase III, because if                  19 we're ready for Phase III we need a clinical endpoint.                  20 UNIDENTIFIED SPEAKER: And I think the easy                  21 answer is, yes, I think it's both. It depends on                  22 circumstance and what you want to start with and what</p>	<p style="text-align: right;">Page 173</p> <p>1 UNIDENTIFIED SPEAKER: There is an issue                  2 though with coinfection with these patients, because                  3 we're talking about antibiotics. So in a                  4 bronchiectasis patient who I put on multiple broad                  5 spectrum antibiotics, if they feel a lot better but                  6 they still contrapositive it may be something else                  7 that I'm treating, it may be the pseudomonas or                  8 something else.                  9 UNIDENTIFIED SPEAKER: And I mean we do that                  10 all the time in the NTM world. I mean, patients don't                  11 have a micro biological improvement yet they feel much                  12 better and we're inclined to continue therapy. And I                  13 think we'd be inclined not to stop therapy in that                  14 particular group we just extended. And we do that all                  15 the time day in day out.                  16 UNIDENTIFIED SPEAKER: So how long have you                  17 extended the -- what's the determining factor?                  18 UNIDENTIFIED SPEAKER: Well, it depends on                  19 how -- and that's something we should -- that would be                  20 based on symptoms and sometimes it goes on for years.                  21 UNIDENTIFIED SPEAKER: Sometimes forever. I                  22 mean, think of your abscessus patients, I mean, they</p>

<p style="text-align: right;">Page 174</p> <p>1 don't change -- your goal is stability, I mean, that's                  2 the goal, it's not to make them better. The goal is                  3 to keep them from getting worse. And that's true for                  4 some of the MAC patients too, it depends on how severe                  5 a disease is. But that's a win. And you don't need                  6 to make them better, include a sterum (ph) your way.                  7 If you can do that, that's fantastic. Your win is to                  8 keep them from getting worse.                  9 UNIDENTIFIED SPEAKER: Understood. And I                  10 mean I -- yeah, we want patients to feel better. But                  11 for designing the clinical trial, it can't go on                  12 forever, right? We have to have like defined                  13 endpoints either 3 months 6 months or what not. And                  14 then we need to know what that means a little bit                  15 longer term for that patient as well when they're off                  16 therapy perhaps.                  17 UNIDENTIFIED SPEAKER: Borrowing from other                  18 fields perhaps. As Kevin's alluded to with the                  19 rheumatology study, as you know from the oncology                  20 world we look at endpoints that are progression-free                  21 survival, right. And so extending that to this                  22 population for every treatment refractory and looking</p>	<p style="text-align: right;">Page 176</p> <p>1 UNIDENTIFIED SPEAKER: That's right.                  2 UNIDENTIFIED SPEAKER: Well, covering the                  3 benefit perhaps (cross talk).                  4 MR. WINTHROP: So then it gets to -- when to measure                  5 and what not. But again we're now back to talking                  6 about refractory patients. So I think refractory                  7 patients is a very separate group. And to me I try to                  8 say in my talk, there is -- the reasons to choose                  9 whether you're going to study treatment refractory or                  10 naive have to do with what your -- how active you drug                  11 is, what your competitor is and what type of patient                  12 you're putting -- you know, when you're going to                  13 measure your success. And those are the reasons to                  14 choose one or the other.                  15 UNIDENTIFIED SPEAKER: So how would you                  16 respond to Peter's question, Kevin?                  17 MR. WINTHROP: My question, what I would say                  18 is that we should spend the rest of today talk about                  19 how to treat treatment-naïve people, that's what I                  20 think. Because I think if you show benefit to                  21 treatment-naive, you have -- what you want to show is                  22 you have an active drug that works and is safe. So,</p>
<p style="text-align: right;">Page 175</p> <p>1 at delay and disease progression, period, as opposed                  2 to a different goal for therapy with the treatment-                  3 naive population I think is where we're trying to get                  4 to in the treatment refractory.                  5 UNIDENTIFIED SPEAKER: Patrick, so would you                  6 suggest palliative therapy? It's -- you say we take                  7 microbiology out as an endpoint. I can make people                  8 feel better without antibiotics. Is -- I'm curious                  9 what -- are you completely dissociating this as an                  10 infectious disease?                  11 MR. FLUME: No, but I'm saying you're making                  12 them feel better with antibiotics.                  13 UNIDENTIFIED SPEAKER: But your endpoint was                  14 making feel better, which is of course is paramount.                  15 But I can make them feel better without giving them                  16 antibiotics.                  17 UNIDENTIFIED SPEAKER: Yeah, you can also                  18 make them feel worse giving them antibiotics,                  19 seriously. It's hard to...                  20 UNIDENTIFIED SPEAKER: Gene actually showed                  21 slide that showed the thing that made them feel the                  22 best was stopping the drugs altogether.</p>	<p style="text-align: right;">Page 177</p> <p>1 you know, focus on people that have the capacity to                  2 change, show that there's benefit. Then you can do                  3 studies later and salvage therapy and, you know,                  4 treatment refractory patients to figure out how best                  5 to treat them in combination with other drugs that's                  6 already failing.                  7 UNIDENTIFIED SPEAKER: So I tend to agree                  8 with you that it's going to be very hard to show                  9 symptom benefits in people with refractory disease.                  10 But I think we've heard from a number of people                  11 including Amy and the patients earlier. The big                  12 advantage of a salvage regimen is to be able to allow                  13 you to stop it earlier. So is the end stop therapy                  14 earlier? And then patients may feel better than the                  15 comparator who are still on drugs. Is there a way we                  16 can design timing of PROs to compare or to capture the                  17 benefit of a microbiological response in that we can                  18 stop drugs and patients feel better once the drugs                  19 have stopped rather than assessing the endpoint at 12                  20 months when they're both still on drugs and you will                  21 not show a difference?                  22 UNIDENTIFIED SPEAKER: This is key, I mean</p>

<p style="text-align: right;">Page 178</p> <p>1 you're measuring respiratory symptoms and you give                  2 them something that makes the respiratory symptoms                  3 worse. You got to think of that.                  4 UNIDENTIFIED SPEAKER: And I think if you                  5 have a platform that you're doing this in real time                  6 rather than intermittently every month, every other                  7 month, every 3 months, something like that, I mean                  8 with new platforms and the data analysis that's                  9 available, you know, every day or every other day and                  10 do continuous development, I think that that's                  11 probably where the opportunity lies to get a little                  12 bit better representation, whether I'm really having a                  13 positive impact on symptom control. So we -- I think                  14 those platforms are close to being available.                  15 UNIDENTIFIED SPEAKER: And just -- hearing                  16 the discussion to about, you know, can you, you know,                  17 use the PRO to measure some of the adverse effects of                  18 the antibiotics, I mean there's always two sides of                  19 the equation, there is a benefit side and a risk side.                  20 And so, you know, I hear the part about wanting to                  21 stop the antibiotic sooner because of the, you know,                  22 adverse effects that they're causing, and that makes</p>	<p style="text-align: right;">Page 180</p> <p>1 balance the equation here on benefit and risk.                  2 UNIDENTIFIED SPEAKER: No, I agree Dr. Cox.                  3 I just think it plays into when you measure. So I                  4 think if you have a 6-month trial and you're stopping                  5 6 months, sure you measured 6 months, but you should                  6 also measure a month later no matter what drug you're                  7 studying. And because that benefit, the clinical                  8 benefit of the drug may be much more apparent a month                  9 later than it is the day you're stopping drug due to                  10 those antibiotics associated adverse effect.                  11 UNIDENTIFIED SPEAKER: So we may see clinical                  12 benefit 1 month after stopping the drugs, but then how                  13 long does that clinical benefit typically last in your                  14 clinical experiences?                  15 UNIDENTIFIED SPEAKER: 10 days.                  16 UNIDENTIFIED SPEAKER: Well no, that goes                  17 back to the paper that that we talked -- that our                  18 paper from 2015. Now, it wasn't -- it didn't involve                  19 an inhaled antibiotic, but patients who -- patients                  20 were better at 6 months and that predicted                  21 microbiologic outcome, that predicted both clinical                  22 and microbiologic outcome. So I recognize that we --</p>
<p style="text-align: right;">Page 179</p> <p>1 total sense. But, you know, it's still somehow we                  2 have to figure out what's going on in the benefit side                  3 of the equation too, you know, are, you know, are we                  4 providing clinical benefit to the patient?                  5 UNIDENTIFIED SPEAKER: I guess the point is                  6 the benefit might be the microbiological benefit that                  7 you can stop drugs earlier in patients over the course                  8 of 24 months will feel better because they got off                  9 drugs earlier.                  10 MR. COX: Well, yeah, no, I get that. I                  11 think the part that we're missing here is that                  12 changing their microbiology, changing their culture is                  13 actually providing them with clinical benefit, that's                  14 what we need. And if in fact you're treating them                  15 with antimicrobial and making their cultures go                  16 negative helps them, you know, it slows disease                  17 progression, you know, physiologically they can                  18 function better, they feel better, they have less                  19 fatigue, they have less cough, whatever that may be.                  20 It seems that we really need to understand what that                  21 clinical benefit is because obviously, you know, these                  22 therapies do have adverse effects and we're trying to</p>	<p style="text-align: right;">Page 181</p> <p>1 you tossed in a complicating factor which is in an                  2 irritating substance that people are inhaling. But I                  3 do think at 6 months -- but, you know, when you're                  4 talking about the kind of outcomes though you're way                  5 beyond a 3-month and 6-month trial. And what I think                  6 about as multi drug resistant TB, again not to -- we                  7 don't want to talk about TB, people are miserable the                  8 entire time they take much medicines for MDRTB, and                  9 then they're better. I don't know exactly (cross                  10 talk).                  11 UNIDENTIFIED SPEAKER: And I think maybe the                  12 answer to your question, Peter, my experience is that                  13 if patients do respond and we finish our course of                  14 therapy that that response is sustained for at least                  15 3, 6, 12 months minimum before they get re-infected or                  16 re-symptomatic. And then we address that question                  17 that Shannon brought up about do they need to be re-                  18 treated again.                  19 Usually that's not within the first year.                  20 And then there are always exceptions and that sort of                  21 thing. But for the most part if somebody's really had                  22 a favorable response, completes a full course of</p>

<p style="text-align: right;">Page 182</p> <p>1 therapy, it's generally sustained for at least a few                  2 months, 3, 6, 12 months before they started having                  3 symptoms, sometimes even longer periods than that.                  4 UNIDENTIFIED SPEAKER: I mean one thing we                  5 haven't discussed is the co-infection issue, and, you                  6 know, should we really be studying a totally clean MAC                  7 population with no identifiable co-infection because,                  8 you know, a lot of the drugs we looked at -- and                  9 that's why CF complicates it too, because we know they                  10 have pseudo moments, right?                  11 UNIDENTIFIED SPEAKER: Yeah.                  12 UNIDENTIFIED SPEAKER: So we haven't really                  13 figured that question out either. And maybe we'd be                  14 better off with a very pure NTM-only population.                  15 UNIDENTIFIED SPEAKER: One thing you just                  16 said, I'm sorry, you were just talking about when a                  17 patient gets, completes a course of therapy and then                  18 they could be clean for the next 6 months, 9 months, 2                  19 years. You know, we're hearing conversations about a                  20 6-month course of therapy. And you just said, you                  21 know, when a patient completes a course of therapy, I                  22 imagine your course of therapy is not 6 months.</p>	<p style="text-align: right;">Page 184</p> <p>1 to do a trial, it may be very helpful to be quite                  2 specific about exactly what it is you're trying to --                  3 UNIDENTIFIED SPEAKER: We're trying to make                  4 the patient feel better, function better and survive                  5 better.                  6 MR. TRAPNELL: And want -- and have them live                  7 long and be (cross talk)                  8 UNIDENTIFIED SPEAKER: Yeah, yeah, and -- but                  9 remember here that the hypothesis is that the bacteria                  10 that's in their lungs is what's causing them troubles,                  11 and that's what's making, you know, the patient have                  12 difficulties. And so treating that should result in                  13 the patient feeling better, function better or                  14 surviving longer. You would hope to see a correlation                  15 between the patient having a clinical benefit and the                  16 change in those cultures from that trial.                  17 MR. TRAPNELL: So it sounds to me like you're                  18 talking about treating the infection that they have at                  19 the time they enter the trial?                  20 UNIDENTIFIED SPEAKER: Yeah.                  21 MR. CHALMERS: Is there question from the                  22 floor.</p>
<p style="text-align: right;">Page 183</p> <p>1 UNIDENTIFIED SPEAKER: Right now, I mean we                  2 would use guideline-based 12 months sputum negativity                  3 as a full course, whatever that is. Sometimes that                  4 takes, you know, 15 months, 18 months something like                  5 that. But 12 months of sputum negativity is what the                  6 current standard is based on the guideline.                  7 MR. CHALMERS: So Bruce has been waiting a                  8 while to make a point.                  9 MR. TRAPNELL: I just wanted to clarify our                  10 target of the discussion is, are we -- is the outcome                  11 measure discussion-centered on treating an infection                  12 or the risk of the patient getting re-infection in the                  13 future?                  14 UNIDENTIFIED SPEAKER: That's treating an                  15 infection.                  16 MR. TRAPNELL: Because that might help our                  17 discussion, specific outcome measures if we're really                  18 clear about that distinction.                  19 UNIDENTIFIED SPEAKER: So I mean we want to                  20 make the patient feel better, function better and                  21 survive longer.                  22 MR. TRAPNELL: Of course, but if you're going</p>	<p style="text-align: right;">Page 185</p> <p>1 MS. COHEN: Hi, yeah, thanks very much.                  2 It's Kera Cohen (ph) from Johns Hopkins. Just -- I'm                  3 not sure why there's such doubt about the                  4 microbiologic outcomes for patients who are treatment                  5 naive with their first episode of MAC. We all take                  6 care of these patients and they tend to -- once you                  7 put them on treatment, if they're going to respond you                  8 see a response within 3 to 6 months for symptoms, but                  9 you generally tend to see that with their culture data                  10 as well, that they're -- they may not go from culture                  11 positive to culture negative which is a dichotomous                  12 end point.                  13 But we definitely see their time to                  14 positivity of their culture decreased, their bacterial                  15 burden. They may go from AFP smear positive to smear                  16 negative. And there's other data that are telling us                  17 that killing these bacteria and decreasing their                  18 bacterial burden is helping improve their symptoms.                  19 UNIDENTIFIED SPEAKER: And that wouldn't be a                  20 problem.                  21 UNIDENTIFIED SPEAKER: We agree. We agree.                  22 Yeah, I mean if in fact the trial can show, you know,</p>

<p style="text-align: right;">Page 186</p> <p>1 the reduction in microbiology, you know,                  2 microbiological counts, microbiological cultures and                  3 that correlates well with the clinical improvement                  4 then that shouldn't be an issue, the clinical                  5 improvement will be there.                  6 UNIDENTIFIED SPEAKER: Chuck made the point                  7 about concern that we would enroll patients with too                  8 low a bacillary burden to really be able to                  9 demonstrate that benefit, how do we get around that?                  10 UNIDENTIFIED SPEAKER: Well, yeah, but I had                  11 pushed because I wanted to not lose track of                  12 something. And said -- and that's about co morbid or                  13 co-pathogens. I mean if we start getting a really                  14 tight definition of what treatment naive is and then                  15 we say that 30 to 50 percent of the people who we know                  16 are going to be co-infected can't be enrolled in the                  17 study, we get into really a nonviable situation.                  18 So I would say -- and we know the people                  19 enrolled in studies become infected during the course                  20 of the study with copathogens like Pseudomonas. So I                  21 would say that it would be nice to have that clean.                  22 But I think in practicality it'd be very difficult to</p>	<p style="text-align: right;">Page 188</p> <p>1 considerations. I understand the appeal of the                  2 treatment-naive patient population with being able to                  3 do placebo controlled studies with a single drug. But                  4 the issue is that, especially, as you get patients                  5 enrolling with higher bacillary burdens, those                  6 monotherapy trials have been done before and issues of                  7 resistance developing a relatively early on is an                  8 issue.                  9 If you set a 3-month endpoint for the trial                  10 or a 6-month endpoint for the trial and you plan to                  11 stop your single drug then you've got the issue of                  12 dormancy and potential for true relapse for recurring                  13 not reinfection. So it's a bit more complicated than                  14 that.                  15 You know, if you're going to try to get                  16 around resistance, you're talking about putting                  17 multiple drugs on, you've got interacting affects of                  18 that. One of the appeals of the treatment refractory                  19 population is that they are already on those multiple                  20 drugs. But I understand that there are differences.                  21 I just want to make sure that those other factors are                  22 taken into account if we're moving the day's</p>
<p style="text-align: right;">Page 187</p> <p>1 require no co-pathogens at the beginning of therapy.                  2 And because it will change during the course of                  3 therapy.                  4 In terms of the -- well, you know, I come                  5 from TB where something is very clear to me that's                  6 different between TB patients and NTM is TB patients                  7 have a very consistent microbial load. If they're                  8 smear positive in three specimens, at least two or                  9 three will be.                  10 In NTM it's all over the place. The                  11 variability from sputum to sputum is significantly                  12 different than TB patient. So in TB patients we know                  13 that it's just -- if they come on the first 3                  14 specimens, it's very consistent bacterial load no                  15 matter how many times you check it, but with NTM it's                  16 not. So when we start getting these less sick                  17 patients, with less extensive disease, we recognize                  18 that bacterial load will be lower. I mean that's just                  19 I think that's a fact. You agree?                  20 UNIDENTIFIED SPEAKER: I agree. Yeah, I                  21 agree.                  22 UNIDENTIFIED SPEAKER: I mean two other</p>	<p style="text-align: right;">Page 189</p> <p>1 conversation toward a treatment-naive patient                  2 population.                  3 UNIDENTIFIED SPEAKER: Yeah, no, I think                  4 those are right on, and I tried to touch on it. I                  5 think you could do a monotherapy placebo-controlled                  6 trial, but you could do also multidrug combination.                  7 It's just the -- it's a lot harder to do, right? You                  8 have to justify the combination, you have to produce                  9 preclinical data that says this makes sense. So it's                  10 just a bit longer of a pathway. But if you're really                  11 worried about resistance of your particular drug. I                  12 mean it seems like that's what you want to do. And if                  13 it extreme, you want your drug used -- to be used                  14 with, you know, drug A, B, C then that's probably what                  15 you're going to do because it's going to be in your                  16 label.                  17 I mean, maybe the best way to do it is the                  18 three-arm study where you have placebo, you have a                  19 mono-therapy wing for some time period anyway to learn                  20 about the drug and you have another exposure group                  21 that's multidrug exposure group that you think your                  22 best regimen is. I mean you could think of lots of</p>



<p style="text-align: right;">Page 190</p> <p>1 permutations of this, but.</p> <p>2 MR. CHALMERS: We're running into lunch, so</p> <p>3 our colleagues have been standing here for a while</p> <p>4 waiting to ask questions.</p> <p>5 MR. NOLE: Jeff Nole (ph) with Cupex (ph).</p> <p>6 So rather than a dichotomous variable, could you look</p> <p>7 at a categorical analysis of the combination? So the</p> <p>8 best outcome would be eradication and improvement in</p> <p>9 symptoms. And at the other end of that spectrum would</p> <p>10 obviously be worsening of symptoms which might be due</p> <p>11 to the disease or the drugs and then eradication. So</p> <p>12 that would allow -- and then you'd look for a shift to</p> <p>13 the right of those categories as the case may be.</p> <p>14 Could that be acceptable as a potential analysis?</p> <p>15 UNIDENTIFIED SPEAKER: So that was what I</p> <p>16 suggest previously as something to consider. And I</p> <p>17 would consider an ordinal outcome where the best</p> <p>18 outcome is improvement on both. On the -- and the</p> <p>19 worst outcome is failure on both. And then you'd have</p> <p>20 to decide how you order the discordant ones. So those</p> <p>21 are the four possibilities.</p> <p>22 If you did that though I think you would</p>	<p style="text-align: right;">Page 192</p> <p>1 UNIDENTIFIED SPEAKER: Well, I mean there's</p> <p>2 the issue of demonstrating the effect of each</p> <p>3 individual drug in the combination, if it's</p> <p>4 problematic to treat a drug with any individual drug</p> <p>5 because of resistance concerns. And you may not be</p> <p>6 able to establish it clinically. I think the question</p> <p>7 is, could there be -- given it is an infectious</p> <p>8 disease, could there be a constellation of in-vitro</p> <p>9 and in-vivo animal models studies that could be done</p> <p>10 to demonstrate that each of the elements of the</p> <p>11 combination actually do contribute in the petri dish</p> <p>12 in the animal models and so forth that that would give</p> <p>13 you enough confidence that each drug is actually</p> <p>14 contributing to the clinical fact in the clinical</p> <p>15 trial because you're unable to do it in the clinical</p> <p>16 setting.</p> <p>17 MS. NAMBIAR: And I think some of these</p> <p>18 questions will come up during the case study this</p> <p>19 afternoon, so I'm hoping after lunch we can clarify</p> <p>20 that. Thank you.</p> <p>21 MR. CHALMERS: Okay. Well thank you to all</p> <p>22 of the panelists for a lively discussion, enjoy your</p>
<p style="text-align: right;">Page 191</p> <p>1 really have to also look at individual -- the clinical</p> <p>2 outcome by itself and micro outcome but itself. But</p> <p>3 if we really think the right way to do this is the</p> <p>4 clinical outcome, I don't know if that's the way to</p> <p>5 go.</p> <p>6 MR. CHALMERS: So final point before lunch.</p> <p>7 UNIDENTIFIED SPEAKER: Yes. So I have a</p> <p>8 comment and a question. So I think in treating any</p> <p>9 infection, I just want to agree with David, in</p> <p>10 treating any infection you have to treat the infection</p> <p>11 you have, right, whether it's a catheter infection.</p> <p>12 We don't usually say, oh -- but they will get another</p> <p>13 catheter infection in a year.</p> <p>14 So I think, you know, microbiologically, you</p> <p>15 follow this and you can tell whether it's a new</p> <p>16 infection a re-infection. So I just want -- but I</p> <p>17 actually wanted to ask, it seems like people are</p> <p>18 considering additional one drug to -- what would it</p> <p>19 look like? What would these clinical trials look like</p> <p>20 if you had a completely new regimen that you want to</p> <p>21 compare in naive patients with what's there?</p> <p>22 MR. CHALMERS: Does anyone want to take that?</p>	<p style="text-align: right;">Page 193</p> <p>1 lunch. But back at 1:00 for the public comments and</p> <p>2 other case studies.</p> <p>3 LUNCH</p> <p>4 FORMAL PUBLIC COMMENTS</p> <p>5 UNIDENTIFIED SPEAKER: Should we do it?</p> <p>6 UNIDENTIFIED SPEAKER: Sure.</p> <p>7 UNIDENTIFIED SPEAKER: Okay. Welcome</p> <p>8 everybody back from lunch. And we'll start out the</p> <p>9 afternoon session with the opportunity for public</p> <p>10 comments.</p> <p>11 UNIDENTIFIED SPEAKER: One of the presenter's</p> <p>12 -- the one who is talking.</p> <p>13 UNIDENTIFIED SPEAKER: Okay. Do we -- do we</p> <p>14 have our --</p> <p>15 UNIDENTIFIED SPEAKER: I have the names.</p> <p>16 UNIDENTIFIED SPEAKER: Yeah. And do we have</p> <p>17 --</p> <p>18 UNIDENTIFIED SPEAKER: We have slides.</p> <p>19 UNIDENTIFIED SPEAKER: -- some degree of</p> <p>20 organization here?</p> <p>21 UNIDENTIFIED SPEAKER: Yeah, we have.</p> <p>22 UNIDENTIFIED SPEAKER: Okay. So I think our</p>

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<p>1 first public commenter, is it -- and you'll help me</p> <p>2 with the pronunciation when you get to the podium, but</p> <p>3 I'll try. So Gyanu Lamichhane --</p> <p>4 MR. LAMICHHANE: 100 percent correct.</p> <p>5 UNIDENTIFIED SPEAKER: -- from Johns Hopkins</p> <p>6 University. And please reintroduce yourself so we</p> <p>7 learn the correct pronunciation please.</p> <p>8 MR. LAMICHHANE: Hi. I'm Gyanu Lamichhane.</p> <p>9 UNIDENTIFIED SPEAKER: Okay.</p> <p>10 MR. LAMICHHANE: I am a basic scientist at</p> <p>11 Johns Hopkins University in the Division of Infectious</p> <p>12 Diseases in the Department of Medicine. And our lab</p> <p>13 has been working on NTMs for the last 6-plus years,</p> <p>14 and among NTMs, we focus on abscessus primarily and</p> <p>15 we've also done a little bit of work on the -- on</p> <p>16 mycobacterium avium. And between these two NTMs, we</p> <p>17 focus on the molecular vulnerabilities in the</p> <p>18 synthesis of the cell wall: if you can destroy the</p> <p>19 cell wall, these bugs die.</p> <p>20 So our work has been around that. And we do</p> <p>21 from very basic work, but with the focus on</p> <p>22 translation, so from the bed to the bench back to the</p>	<p>1 the in vitro work that we've done initially and then</p> <p>2 we also have some vivo data to share with you as well.</p> <p>3 So what we did was we took a total of 206 combinations</p> <p>4 of beta-lactams with a couple of rifamycins and beta-</p> <p>5 lactam inhibitors and tested them initially in vitro</p> <p>6 against ATCC 19977, which is the Mab reference strain,</p> <p>7 in a checkerboard assay, which is kind of the standard</p> <p>8 method for determining whether or not there's synergy</p> <p>9 that exists between two drugs.</p> <p>10 So we preferentially chose cephalosporins</p> <p>11 that were oral bioavailable, but didn't require more</p> <p>12 than twice daily dosing just to kind of ease</p> <p>13 administration in patients, and then several of the</p> <p>14 carbapenems that were available not necessarily in</p> <p>15 this country, but in other places in the world they</p> <p>16 have been used since those seem to be more efficacies</p> <p>17 against Mab in general among the beta-lactams.</p> <p>18 We also looked at the rifamycins because</p> <p>19 rifabutin has been shown to have some activity. And</p> <p>20 just a couple of others as well, but they hadn't been</p> <p>21 tested in synergy -- synergies as well. And then a</p> <p>22 couple of the beta-lactams inhibitors.</p>
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<p>1 bed kind of work. And you will hear about this in the</p> <p>2 next set of slides what we have done so far. And Liz</p> <p>3 will present that, Liz Story-Roller. She's a fellow</p> <p>4 in our division and in our lab and she's done this</p> <p>5 translational work, but based on very basic science.</p> <p>6 And before I leave, I would like to thank the</p> <p>7 organizers for putting this thing together and</p> <p>8 allocating time to share so that we could share our</p> <p>9 findings.</p> <p>10 MS. STORY-ROLLER: So I just want to say</p> <p>11 thank you for letting me share some of the research</p> <p>12 that I've done over the past 2 years with you guys.</p> <p>13 And so what we're going to be focusing on is using</p> <p>14 Dual beta-lactam combinations for treatment of M.</p> <p>15 abscessus specifically.</p> <p>16 And so there's been a lot of press towards</p> <p>17 trying to repurpose currently available antibiotics,</p> <p>18 as you guys know, in order to see if maybe we could</p> <p>19 more quickly and rapidly get combinations that are</p> <p>20 actually therapeutics against M. abscessus, especially</p> <p>21 in the setting of drug resistance.</p> <p>22 So I just wanted to talk very quickly about</p>	<p>1 So this is actually in a table form of the</p> <p>2 synergistic combinations that I just showed you on the</p> <p>3 checkerboard assay. So we find 24 total combinations</p> <p>4 that did exhibit synergy based on the Fractional</p> <p>5 Inhibitory Concentration Index, which is kind of a</p> <p>6 mathematical version of how you would determine how --</p> <p>7 the degree to which combination is able to be</p> <p>8 synergistic against a bacteria.</p> <p>9 And so we have the drugs that are listed on</p> <p>10 the left hand side. The table on the left are -- you</p> <p>11 know, we're looking at MIC of the single drugs by</p> <p>12 themselves and then the MICs that are extrapolated</p> <p>13 based on if they're in combination together using the</p> <p>14 FICI to mathematically determine those.</p> <p>15 And on the left, those are the drugs that</p> <p>16 hypothetically bring the MICs within a therapeutic</p> <p>17 range. Unfortunately, the CLSI breakpoints for</p> <p>18 abscessus really are only available for cefpodoxime</p> <p>19 and imipenem. So we just used those as surrogates and</p> <p>20 extrapolated the rest of the breakpoints based on</p> <p>21 those for the (inaudible 0:05:26) respectively.</p> <p>22 The table on the right were combinations that</p>

<p style="text-align: right;">Page 198</p> <p>1 didn't quite bring the MICs down to the -- within the  2 therapeutic range. But as you see, a lot of them had  3 very high MICs to begin with. And so even though  4 there was, you know, several log decrease in MIC for a  5 lot of them, it just was not enough to kind of bring  6 them within that range that we'd like to see.</p> <p>7       However, it's possible that the addition of  8 additional agents either non beta-lactams as we  9 usually use, you know, multidrug therapy against  10 abscessus might potentially bring those within a range  11 that we'd be able to have therapeutic effect.</p> <p>12       The other thing to note is that there are a  13 couple of agents that are not currently FDA approved  14 for use in the U.S. Biapenem actually showed to have  15 -- seemed to have a good amount of efficacy against  16 Mab in vitro and then also in preliminary in vivo  17 studies that I'll talk about.</p> <p>18       And in addition to faropenem and tebipenem --  19 and tebi actually is a recently started Phase III  20 trials for us UTI. So that's exciting and those are  21 both orally bioavailable.</p> <p>22       So that's a -- and I'll go on to this one.</p>	<p style="text-align: right;">Page 200</p> <p>1 seems like a potentially viable system that we could  2 potentially use for additional studies down the road.</p> <p>3       And so our lab -- and Emily Maggioncalda in  4 our lab has kind of headed this, where we're using an  5 aerosolized Mab pulmonary infection in a  6 immunocompromised mouse. It's immunocompetent  7 C3HeB/FeJ mouse that's immunocompromised with  8 dexamethasone or cortisone. And that seems to work  9 the best, where we're able to, you know,  10 immunocompromise them enough to have a sustained  11 pulmonary infection. And then they do develop these  12 caseating granulomas after cessation of --  13 immunocessation in the expressive therapy and then  14 kind of reconstitution of the immune system.</p> <p>15       So it's not perfect. It's, you know --  16 especially, in the CF population and people with  17 bronchiectasis, it's -- the lung physiology is much  18 more robust and potentially more difficult to treat  19 those infections. However, it's something that we  20 could potentially use, you know, as an initial model  21 to go forward with this.</p> <p>22       And so I can't show you the data because it's</p>
<p style="text-align: right;">Page 199</p> <p>1 Just very briefly, we wanted to look at drug  2 resistance frequency in regards to the frequency of  3 development of spontaneous drug resistance mutants in  4 each individual drug plus when they're using  5 combination, because it will be something that will be  6 important when we're thinking about new therapies to  7 try to increase the longevity abuse in the clinical  8 setting. We like to decrease, you know the occurrence  9 of resistance.</p> <p>10       And so, as you see, there's a definite  11 decrease in the rate of resistance with all of the  12 combinations. Some did better than others, especially  13 among the cephalosporins. They seem to have a pretty  14 good decrease in the amount of resistance that we're  15 seeing, which is, you know, promising.</p> <p>16       And so the last slide. I just want to talk a  17 little bit about -- because kind of already mentioned  18 as the discussion has been had, you know, about we  19 really do need, you know, a mouse model or at least  20 some of kind of animal model for these pre-clinical  21 studies. And this is very, very preliminary data.  22 We've only done a couple of studies so far. But it</p>	<p style="text-align: right;">Page 201</p> <p>1 so unfortunately under review currently, but we took  2 five of our in vitro synergistic combinations and  3 tested them in this system. And we did show that --  4 we did find that they seem to be very effective  5 against Mab, at least the ATCC we're referencing. And  6 so that's quite promising in terms of potential future  7 studies as well.</p> <p>8       And so it seemed like maybe we might be able  9 to get complete eradication of the infection within,  10 you know, 5 to 7 weeks using these combinations. And  11 so there's a lot more work to be done, but it's  12 something that we could potentially use, you know, for  13 future studies as well. So that's it. Thank you and  14 happy to answer any questions.</p> <p>15       UNIDENTIFIED SPEAKER: Thank you.</p> <p>16       UNIDENTIFIED SPEAKER: Can I ask why you  17 choose -- which of the rifamycins? Did you use some  18 rifabutins, some rifapentine and some rifampin with  19 your combinations?</p> <p>20       MS. STORY-ROLLER: So we tested all of the --  21 all three of them against all of the other beta-  22 lactams. Rifabutin seemed to have the greatest</p>

<p style="text-align: right;">Page 202</p> <p>1 activity against M. abscessus, but we use kind of TB 2 as the stepping out point. So we have seen some 3 activity with rifapentine and rifampin. 4       However, they had not been tested in a dual 5 beta-lactam setting against Mab, and so we just wanted 6 to see if there was potentially any synergy that might 7 exist among, you know, those other agents plus -- and 8 we did see, you know, in especially the earlier 9 generation of cephalosporins that there was some 10 degree of synergy, but maybe not enough to bring it 11 within that therapeutic range with the MIC there. 12       UNIDENTIFIED SPEAKER: Great. Thanks. And 13 now our next speaker. Ho Namkoong, welcome to the 14 podium. 15       MR. NAMKOONG: Okay. Thanks for giving me 16 chance to talk today. I am Ho Namkoong at the -- a 17 postdoc at NIH right now. And I am doing research on 18 the host genetics (ph) on primary NTM infection and 19 bronchiectasis. And I am primarily physician 20 background in Japan and I came to the United States 21 one year ago. And yes -- oh, yes, last few weeks ago 22 very casually I applied for this public comment</p>	<p style="text-align: right;">Page 204</p> <p>1       And based on these situations, in my 2 university in Japan, Keio University Hospital, we plan 3 a prospective observation study that has been 4 conducted from June of 2012. And the study includes 5 adult patients with diagnosed or suspected with NTM 6 lung diseases and are registered according to the 7 ATS/IDSA 2007 statements. And we collected clinical 8 data and the pulmonary function test, CAT scan and 6- 9 minute walk, SF-36 and SGRQ and the patient's DNA 10 samples and the plasma. 11       And also in addition to one, yes, prospective 12 cohort, we studied to -- we studied a collaborative 13 register in Japan, so NTM B registry in Japan. So 14 based on the INBOX (ph) study and also NTM and B 15 registry in United States, so we studied collaborative 16 study with, yes, these -- about 15 institutions and 17 now registered 800 patients. 18       And based on these situations, my first 19 comment is about international joint clinical research 20 and trials. So as I introduced here -- so many 21 Japanese clinicians and researchers are making efforts 22 to be ready for the international clinical research.</p>
<p style="text-align: right;">Page 203</p> <p>1 session, but so surprised to see this session, so. 2 Yeah. 3       Anyway, I would like to address today two 4 major comments. And some comments are very public, 5 but some, yes, comments are very personal request to 6 clinicians and the researchers and patient support 7 group and the drug company, yes, attending this 8 conference. 9       And before I'll commence, I'd like to 10 introduce Japanese NTM clinical situations and also 11 research situation in Japan. In Japan, the incidence 12 and the mortality of NTM is increasing, as you know. 13 And we -- yes, a few years ago, we performed a 14 biological study -- study and which reported that 15 incidence rate of NTM was 14.7 per 100,000 person 16 years and suggesting that -- so Japan is one of the 17 highest incident countries. And the MAC lung disease 18 is the most common form of NTM pulmonary infection in 19 Japan. So generally causes slowly in Japan and in the 20 immunocompetent host and that compromised 90 percent 21 of NTM. And also the mortality of MAC already 22 increases that of the tuberculosis in Japan.</p>	<p style="text-align: right;">Page 205</p> <p>1 And as you know, when coming to the, yes, clinical 2 research, the sample size is very important. So, yes. 3 So when you think about the clinical trials or 4 clinical studies think about, yes, joint program with 5 Asian countries such as Japan and Korea. 6       And my second comment is about this platform. 7 I'm very surprised to see that -- or to see that 8 clinicians and the researchers and the patient group 9 and the drug companies sit at the same table and that 10 this situation very, very unbelievable for the Asian 11 countries. So if you have a chance just -- I'd like 12 to introduce this platform, but if you guys have a 13 chance to, yes, collaborate with other countries as a 14 global leader so I'd like you to introduce this 15 platform. Thank you. 16       UNIDENTIFIED SPEAKER: Okay. Thanks for your 17 comments. 18       MR. NAMKOONG: Any questions? 19       MR. LAMICHHANE: Any quick questions? All 20 right. Thank you very much. And Khalid Dousa if you 21 are here, if you'll find your way to the podium. 22 Seeing nobody moving, I'm thinking Khalid is not here.</p>

<p style="text-align: right;">Page 206</p> <p>1 All right. Well, that closes our public comment  2 period and I will now turn the microphone over to the  3 Karen and Patrick. Thank you.  4           SESSION 3: CASE STUDIES  5           MS. HIGGINS: Hi. Good afternoon. So I'm  6 Karen Higgins and I'll chair this session with Patrick  7 Flume. So in this session, session 3, FDA will  8 present two case studies to help frame this  9 afternoon's discussion. Please note that these are  10 hypothetical cases. The intent is to bring about a  11 robust panel discussion around the clinical  12 development challenges such as the control used in the  13 trial; the endpoints, including the use of clinical  14 outcome assessments; the timing of the endpoint  15 assessments and the durations of therapy.  16           When Dr. Hiruy, a FDA medical officer, is  17 describing these cases, think about what additional  18 information is needed in order to design and conduct  19 this type of study and what aspects are more or less  20 feasible.  21           So Dr. Hiruy will present each case study,  22 and after each case, it will be followed by an</p>	<p style="text-align: right;">Page 208</p> <p>1 part of drug development. However, for the purposes  2 of today's discussion, we will mainly focus on  3 assessment of efficacy of these hypothetical drugs  4 with the assumption that the drugs mentioned in the  5 cases have acceptable safety profile.  6           The case studies present broad topics and  7 ideas, and this was done purposely to spur discussion  8 on key topics such as clinically-oriented primary  9 endpoint and time of assessment of such endpoints.  10           As part of the discussion around clinically-  11 oriented primary endpoints, the case will refer to  12 clinical outcome assessment tools such as patient-  13 reported outcomes. Today's case study discussions  14 will not focus on the process of validation of these  15 tools. As you heard from my colleague, Dr. Chen,  16 earlier, the FDA has a dedicated team to help with the  17 development and validation of such tools.  18           In the case studies, our main focus for the  19 discussion will be the contents of such assessment  20 tools. We will assume that the clinical assessment  21 tools mentioned are fit-for-purpose, meaning they have  22 been studied and validated for patients with pulmonary</p>
<p style="text-align: right;">Page 207</p> <p>1 academic and industry perspective. Dr. Hiruy,  2           PRESENTATION OF HYPOTHETICAL CASE STUDY #1:  3           DEVELOPMENT OF A NOVEL DRUG AS AN ADD-ON TO A  4           BACKGROUND REGIMEN FOR TREATMENT OF PULMONARY MAC  5           DISEASE  6           DR. HIRUY: Good afternoon. We will be  7 presenting two case studies as you heard. We want to  8 emphasize once again that the study -- the case  9 studies are hypothetical and are not intended to cover  10 every developmental stage and requirement for specific  11 drug program.  12           There should not be a head to head comparison  13 of the two cases either. Our intent is to discuss two  14 patient populations in the pulmonary MAC disease  15 spectrum. Although non-clinical work is an integral  16 part of a drug development program, for the purposes  17 of these case discussions, we will primarily focus on  18 the clinical programs with the assumption that the  19 necessary non-clinical work has been successfully  20 completed and the development program has transitioned  21 to the clinical space.  22           Similarly, safety assessment is a critical</p>	<p style="text-align: right;">Page 209</p> <p>1 MAC disease.  2           With that, we will move on to our first case  3 discussion of Drug X: Novel Drug Developed as Add-on  4 to a Background Regimen for Treatment of Refractory  5 Pulmonary MAC Disease. The background regimen will be  6 referred to as BR in the subsequent slides.  7           So Drug X is an oral formulation of a new  8 molecular entity with a novel mechanism of action. It  9 has shown potent in vitro activity against M. avium,  10 intracellulare and abscessus. Pre-clinical prove of  11 concept murine models demonstrated bacterial load  12 reduction with the addition of Drug X to the  13 background regimen compared to background regimen  14 alone.  15           Several Phase I studies were completed in  16 healthy volunteers, including first-in-human,  17 randomized, double-blind, placebo-controlled study to  18 assess safety, tolerability, PK of single and multiple  19 ascending doses.  20           Drug X was also noted to get into the lung  21 tissue with quantification of Drug X in the epithelial  22 lining fluid. Potential drug-drug interaction with</p>

<p style="text-align: right;">Page 210</p> <p>1 anti-infectives used for treatment of MAC disease such                  2 as clarithromycin and rifampin were also evaluated.                  3 Main adverse event noted during these studies was                  4 gastrointestinal, nausea, abdominal discomfort, which                  5 were mild to moderate in severity.                  6 A dose ranging Phase II trial was done                  7 comparing three dose of -- three doses of Drug X as an                  8 add-on to background regimen versus background regimen                  9 plus placebo in patients with refractory pulmonary MAC                  10 disease. Refractory pulmonary MAC disease was defined                  11 as failing to achieve three consecutive negative                  12 monthly sputum cultures after 6 months of ATS/IDSA                  13 guideline based multidrug regimen. The primary                  14 endpoint for the Phase II was a proportion of patients                  15 with culture conversion at month 6.                  16 Secondary endpoints encompassed a new PRO and                  17 an existing PRO, Quality of Life Bronchiectasis                  18 respiratory module modified for patients with NTM.                  19 Microbiological assessment of sputum culture                  20 conversion, functional assessment with 6-minute walk                  21 test and treatment emergent adverse events and serious                  22 adverse events.</p>	<p style="text-align: right;">Page 212</p> <p>1 blinded to treatment assignment and culture conversion                  2 as long as patients remained clinically stable and                  3 rescue therapy was not deemed necessary.                  4 The primary endpoint was a PRO at month 16.                  5 The secondary endpoints included culture conversion at                  6 the end of treatment as well as off treatment to                  7 assess durability of culture conversion,                  8 sustainability of improvement in PRO during the off                  9 treatment and follow up at month 19 and 24, changes                  10 from baseline 6-minute walk distance at end of                  11 treatment and end of study. Assume the sample size of                  12 the trial was adequate to show clinical meaningful                  13 difference in the PRO between the two arms with a 90                  14 percent power.                  15 The results showed Drug X plus background                  16 regimen met the pre-specified primary endpoint of                  17 meaningful improvement in PRO compared to background                  18 regimen plus placebo. However, there was no                  19 significant difference in culture conversion at month                  20 16. There was no -- there was also no significant                  21 difference in reported treatment-emergent adverse                  22 events, serious adverse events and mortality between</p>
<p style="text-align: right;">Page 211</p> <p>1 Overall, the result of the trial showed the                  2 20 milligram dose was the -- had optimal efficacy and                  3 safety profile, and hence, that dose was chosen for                  4 the Phase III trial.                  5 Moving forward to the Phase III trial, the                  6 trial also focused on the same patient population as                  7 the Phase III, namely patient with refractory MAC                  8 disease. The Phase III was a multicenter, double-                  9 blind, randomized trial comparing Drug X plus                  10 background regimen to background regimen plus placebo                  11 was at 2:1 randomization scheme. The background                  12 regimen adhered to ATS/IDSA guideline, but varied                  13 based on investigator's discretion and patient's                  14 characteristics such as prior therapy and concomitant                  15 medication.                  16 Study duration was 16 months on treatment and                  17 8 months off treatment follow-up period. Monthly                  18 clinical and microbiological assessments were carried                  19 out for the 16 months while on treatment, followed by                  20 every 3 months assessment from months 16 to 24. No                  21 study arm cross-over was permitted.                  22 Of note, investigators and patients remained</p>	<p style="text-align: right;">Page 213</p> <p>1 the two arms.                  2 We have three main questions for the panel.                  3 The first one is asking about the knowledge gap in our                  4 understanding of the patient population, including the                  5 definition of refractory pulmonary MAC disease. In                  6 the literature currently refractory population is                  7 defined as those that failed culture conversion after                  8 6 months of multidrug regimen.                  9 Is it clinically appropriate to include all                  10 types of pulmonary MAC patients who failed to convert                  11 after 6 months of treatment or do we still need to                  12 think about the disease subtypes?                  13 How about the knowledge gap regarding primary                  14 endpoints to assess direct clinical benefit for this                  15 patient population? For example, development of a new                  16 symptom-based or functioning-based PRO. Or is there                  17 an existing PRO that can be modified and used in this                  18 population? And what about the idea of timing of                  19 assessment of such clinically-oriented endpoints and                  20 length of trial?                  21 We also want a discussion around the                  22 feasibility of making clinical decisions based solely</p>

<p style="text-align: right;">Page 214</p> <p>1 on patient's clinical status without sputum culture                  2 results. How about limiting cross-over from the                  3 control arm to test arm? And the feasibility of                  4 standardizing the background regimen is also another                  5 discussion point we would like to have.                  6 For all the existing knowledge gaps, how can                  7 we address them? And finally, despite these knowledge                  8 gaps, what can be done to move forward to design                  9 scientifically sound clinical trials for patients with                  10 pulmonary MAC disease? This concludes the first case                  11 study presentation.                  12 MS. HIGGINS: Thank you, Dr. Hiruy. So Dr.                  13 Chalmers from the University of Dundee will give a                  14 academic perspective.                  15 ACADEMIC AND INDUSTRY PERSPECTIVES ON                  16 CASE STUDY #1                  17 MR. CHALMERS: Thank you very much. So the                  18 questions we were asked to address in the case study                  19 are very similar to the questions that we were asked                  20 to address in the panel study before lunch. So I                  21 think we have to accept that if 30 of the world's                  22 leading experts didn't come to a consensus before</p>	<p style="text-align: right;">Page 216</p> <p>1 There's a really great example of this, which                  2 is in bronchiectasis in the RESPIRE trials, which were                  3 trials of inhaled ciprofloxacin. They did two PROs,                  4 the SGRQ and the Quality of Life Bronchiectasis                  5 questionnaire.                  6 In the same trial, the SGRQ improved and QOL-                  7 B did not despite the fact they measure virtually the                  8 same thing. And it's all determined by the relative                  9 weight you give to chronic bronchitis symptom versus                  10 breathlessness, for example.                  11 So I think we run the risk if we use tools                  12 that were developed for other disease like the SGRQ                  13 that we're measuring the right symptoms, but we're                  14 weighing them in a way that means that they won't                  15 detect response to NTM therapy. So I think that's the                  16 first sort of key point.                  17 The other issue is about the recall period.                  18 So a lot of these tools recall symptoms over, for                  19 example, a week. But you heard from Amy that the --                  20 one of the things the patient says is their symptoms                  21 go up and down very frequently. So if you have a PRO                  22 that detects symptoms over a week in a disease that</p>
<p style="text-align: right;">Page 215</p> <p>1 lunch, it's unlikely I'm going to give you the secret                  2 to this disease in the next 5 minutes. So I'm going                  3 to very briefly make a few comments, then open for the                  4 rest of the panel.                  5 I'm going to focus quite a bit on the                  6 contents of the potential assessment tool because I                  7 know that was -- you mentioned in the introduction                  8 that's the key thing you want to focus on. We                  9 obviously have existing tools like the QOL-B and the                  10 QOL-B NTM module and the SGRQ. The concern I have                  11 with all of the existing tools and the reason I think                  12 we probably need to develop a new tool is not that                  13 they don't incorporate all of the things that we need                  14 in an NTM tool.                  15 So we heard from Amy earlier, I think we                  16 could all name the dominant symptoms in pulmonary NTM.                  17 They are cough, sputum, breathlessness, fatigue. It's                  18 -- the really key issue is how they are weighted in                  19 these particular PROs, how much relative importance is                  20 given to each one. And in those tools that have been                  21 developed for different disease, they generally give                  22 weights to different symptom.</p>	<p style="text-align: right;">Page 217</p> <p>1 people are taking treatment for 24 months, we're going                  2 to lose an awful lot of information. So that's                  3 another thing we need to take into account in                  4 developing a PRO.                  5 The other -- another issue is when we analyze                  6 the primary outcome. So in a lot of trials, we pick a                  7 defined time point, 12 months or 16 months or 24                  8 months, and say that's when we're going to measure the                  9 quality of life change from baseline.                  10 We have experience again in the                  11 bronchiectasis field that that's not the best                  12 approach. So in the ORBIT trials of liposomal                  13 ciprofloxacin, the outcome was changed at the end of                  14 the final cycle of treatment in a 12-month study,                  15 which ignores all of the information of how the                  16 patients felt during that year while they were on                  17 treatment.                  18 And so in this disease where symptoms wax and                  19 wane, where drug toxicity waxes and wanes depending on                  20 what we do, I think you have to capture all of the                  21 information that happens in between. So we need to                  22 use more sophisticated analyses like repeated measures</p>

<p style="text-align: right;">Page 218</p> <p>1 analyses to look at changes over time. And in fact  2 when you do that in the Orbit studies post hoc, you  3 see differences that are not evident by picking  4 individual time points.  5 I want to pick up again on the point that Tim  6 made earlier about the potential to use a composite  7 endpoint rather than potentially a PRO, although, as I  8 said earlier, PROs are composite endpoints. If we  9 know that some patients feel better in terms of cough,  10 some patients feel better in terms of breathlessness,  11 some patients feel better in terms of fatigue,  12 wouldn't it make sense to develop an endpoint that  13 captures those things using existing questionnaires?  14 So we have, as Amy said, existing  15 questionnaires for fatigue. We have the 6-minute walk  16 test, which is validated. It doesn't work as an  17 endpoint because not everybody has an impaired 6-  18 minute walk test at baseline. But if you took a  19 clinically meaningful improvement in one of those  20 three domains to be a clinical response, you would  21 have an endpoint that would detect different  22 responses, but each of them with equal weights, which</p>	<p style="text-align: right;">Page 220</p> <p>1 microbiological information.  2 So I do have concerns about that, and I'm not  3 sure it would give you that much benefit. I think  4 that's enough probably from me in terms of feedback.  5 MS. HIGGINS: Okay, thank you. Okay. So now  6 we'll have the industry perspective. Dr. Angela  7 Talley is Vice President of Clinical Development at  8 Spero Therapeutics.  9 MS. TALLEY: I guess I'll deliver mine from  10 up here because I made slides. So hi. I'm Angela  11 Talley and Vice President of Clinical Development at  12 Spero Therapeutics in Cambridge. Thank you for the  13 opportunity to offer the industry perspective on the  14 drug development path for NTM.  15 As mentioned -- oh, wait -- let see. Yup, I  16 got it. As mentioned at the start of the session, I'm  17 a full-time employee of Spero. So as I think we've  18 heard earlier today, there's an increasing urgency to  19 determine the utility of new or existing agents and  20 new regimens in the treatment of NTM disease. And  21 from an industry perspective, the opportunity today to  22 outline a feasible and efficient development path for</p>
<p style="text-align: right;">Page 219</p> <p>1 is what regulatory guidance for development of  2 composite endpoints takes into account.  3 One of the other points that was raised was  4 the blinding of sputum cultures during therapy. I can  5 see people having different views on this. I would  6 really struggle I think over a 24-month study to not  7 know what my patient's culture results were.  8 I think you would inevitably in that trail  9 design have a window, an escape valve that the  10 clinicians could say, "But they're clinically  11 unstable. Therefore, I can look at the culture  12 results." And my concern is that lots of clinicians  13 like me would press that escape valve pretty early and  14 allow ourselves to look at the culture results.  15 I'm not sure you get that much benefit by  16 blinding the cultural results, because we don't know  17 for sure even if they change from culture positive to  18 culture negative that they're on active drug, because  19 some patients on placebo in previous trials have  20 converted. But I do think you'll get problems with  21 patients dropping out or clinicians pulling the  22 patients out because they want to know the</p>	<p style="text-align: right;">Page 221</p> <p>1 evaluating novel anti-NTM drug candidates is critical  2 in bringing new, effective agents and treatment  3 regimens to patients.  4 So what does this mean? From the -- for  5 perspective, we'll offer this broad development  6 timeline overview for candidate agents such as Drug X.  7 Drug X was presented in the case study and noted to  8 have demonstrated in vitro activity versus clinically  9 relevant NTM pathogens both in vitro and alone and in  10 combination with other agents in vivo in mouse MAC  11 models.  12 And one key issue here is that for Drug X and  13 other agents is that in general there's poor  14 translation of preclinical data from animal models to  15 efficacy in human. So although the goal today may be  16 defining clinical endpoints in clinical trial design,  17 I'll just note that elucidation of translational data  18 indicative of clinical efficacy in humans is still  19 important to the discussion.  20 And on that note, we and others are exploring  21 the utility of hollow-fiber models for this purpose in  22 order to better define activity of new agents for NTM</p>



<p style="text-align: right;">Page 222</p> <p>1 and model human exposures, resistance potential and to                  2 identify potential partner agents for use in                  3 combination regimens.                  4       So in general, it takes about 3 years to                  5 generate these non-clinical safety and efficacy data                  6 before you go into a Phase I study in humans                  7 evaluating a single and multiple dose to outline the                  8 safety in the human PK of your agent, or in this case,                  9 Drug X. As noted for the drug -- typically,                  10 additional Phase I studies in healthy volunteers are                  11 required to evaluate potential drug-drug interactions                  12 and to generate additional PK data in certain special                  13 populations, as well as to support ongoing dose                  14 selection for use in patients.                  15       The case for Drug X also outlines a Phase I                  16 ELF study, although unlike the bacterial pneumonias,                  17 the utility of this data is unclear for NTM and TB and                  18 not typically included in TB development programs and                  19 it may not be required for NTM agents. Perhaps that's                  20 a question for this panel as well.                  21       From an industry and regulatory perspective,                  22 the non-clinical safety and efficacy and Phase I data</p>	<p style="text-align: right;">Page 224</p> <p>1       So we've been thinking about this a lot, and                  2 the next few slides sort of outline the major                  3 questions that we've struggled with. And the one --                  4 one of them I brought up a couple of times today                  5 already and that is: what is the objective of                  6 treatment for pulmonary NTM? Is it cure? Is cure                  7 possible? Is it stage specific? Is -- durable micro                  8 response up to 24 months, is that a reasonable                  9 objective of therapy? Or shall we focus on                  10 symptomatic improvement and which symptoms? How to                  11 measure them?                  12       Is improvement a delay of disease                  13 progression, as I alluded to earlier, a more                  14 appropriate endpoint in terms of progression free                  15 survival? And again, is it patient specific? What's                  16 the appropriate timing for assessment of the response?                  17 Is there a possibility to define an earlier definitive                  18 primary endpoint in 6-months or less?                  19       So these questions have all been discussed                  20 earlier, but I'll just highlight that they are key                  21 questions to develop the development path in terms of                  22 who do we study, are there different populations</p>
<p style="text-align: right;">Page 223</p> <p>1 collectively constitute a proof of principle for                  2 moving a new agent into the clinic. So for Drug X,                  3 the data leading up to Phase II likely represents 5 to                  4 6 years of development before we finally get to                  5 evaluate this promising new agent in the clinic. From                  6 this point, the approach to demonstration of efficacy                  7 in patients is unclear and is the focus of the                  8 workshop today.                  9       Based on the case outlined for Drug X and the                  10 timeline for similar trials, it would likely take 2 to                  11 3 years to get an early efficacy read for Drug X                  12 supporting further evaluation in Phase III. And                  13 similarly, based on the number of factors and prior                  14 experience delivery of a 200 to 300 patient trial,                  15 Phase III study is likely to extend delivery of this                  16 drug to patients by an additional 5 to 8 years.                  17       So in terms of the assessment of efficacy and                  18 the appropriate development path, I think we have more                  19 questions than answers, we can all agree on that. And                  20 we know from the earlier presentations that this is                  21 generally representative of the current status of our                  22 understanding of development in this field.</p>	<p style="text-align: right;">Page 225</p> <p>1 appropriate for Phase II or pivotal trials, which                  2 endpoints are appropriate to assess benefit.                  3       In this study -- a case study of Drug X,                  4 we're adding on Drug X to standard of care in a                  5 treatment refractory population. It's unclear if                  6 that's the most appropriate population to get an early                  7 efficacy read.                  8       Likewise, the endpoint for Drug X is sputum                  9 conversion at 6 months, but there's a 24-month follow                  10 up. And it's unclear whether a durable response for                  11 phase is relevant -- for a Phase II study, which tends                  12 to be focused on the dose ranging, early efficacy read                  13 and PK.                  14       So the timing feasibility I think is the big                  15 question. What is the minimum treatment duration for                  16 a specific micro clinical endpoint in which we might                  17 detect a meaningful difference? Is it possible that                  18 we can deliver these trials earlier by defining an                  19 endpoint under 6-months so that we can move on to                  20 identifying a drug that's a promising candidate and                  21 move it into a Phase III pivotal trial design?                  22       In terms of the comparators, we struggle with</p>

<p style="text-align: right;">Page 226</p> <p>1 thinking about how to standardize the background  2 regimen in a treatment refractory population,  3 particularly for an early efficacy assessment and  4 looking for a readout in clinical efficacy at 6-  5 months. Is it appropriate to add a single agent on to  6 a potentially failing regimen? And in terms of the  7 monotherapy versus placebo, I think there's similar  8 ethical questions about the utility or length of  9 duration of a placebo.  10       So given all of these feasibility and  11 recruitment challenges, is it possible to take a  12 different approach to study design in terms of a  13 platform trial collaboration? And what other lessons  14 can we draw from other fields? We've heard some  15 examples from the rheumatology field today, but I  16 think there may be others.  17       So again, as we started out this session, we  18 have more questions than answers. But what is clear  19 is that this is a very heterogeneous disease that  20 progresses through a variety of inflammatory states,  21 and depending on where you come in as a patient into  22 this process, the trial designs and endpoints for</p>	<p style="text-align: right;">Page 228</p> <p>1 and I don't know that -- I don't know that that's what  2 you really think. But -- I mean, I -- we have tools,  3 like the NT module was developed, you know, using the  4 standard way of developing these with NTM patients at  5 NTM treatment centers with the help of a patient FAQ.  6 I mean, it's done all that. What's lacking is, you  7 know, perspective evaluation refinement. And I  8 wouldn't -- I wouldn't, you know, ditch it to try to  9 do something new here.  10       And on the bronch side -- I mean, obviously  11 we just spent a grant together. We're working to do  12 this together. I mean, I think there's components of  13 the QOL-B that likely will prove to be very worthwhile  14 and it may be different for different types of  15 patients. And the only way we're going to find that  16 out is with perspective assessments.  17       So I don't know that -- I don't know that I  18 would just start over. I do think there are tools  19 that have been developed in the right disease  20 settings. We just haven't had the chance to look at  21 them prospectively and figure out the minimum  22 important difference and things like that.</p>
<p style="text-align: right;">Page 227</p> <p>1 evaluating a new therapy may differ considerably. So  2 I think that we need to consider at each stage if  3 we're starting treatment of naive patients, that the  4 endpoints' timing and follow up may differ  5 considerably versus a treatment refractory population  6 in terms of this, particularly based on the goals of  7 therapy.  8       So bottom line from an industry perspective  9 and I think for the field in general, there are a  10 number of needs and challenges, obstacles to getting  11 drugs to patients faster. We need a better  12 understanding of the pathophysiology, a better  13 translation of the...  14       MR. FLUME: All right. So we're going to  15 open up to the floor.  16       MODERATED PANEL DISCUSSION  17       (CASE STUDY #1)  18       UNIDENTIFIED SPEAKER: Can I just -- I'll  19 start. So I know you want direct comments on this  20 case study, so I'll try to limit to that. I was going  21 to just pitch back to James, so -- I mean, I don't  22 know that we need to develop new tools from scratch</p>	<p style="text-align: right;">Page 229</p> <p>1       MR. CHALMERS: No. I think there are two  2 ways of developing a tool: you make something from  3 scratch or you modify something that already exists.  4 And most PROs are modifications in some form or  5 another of something that already exists.  6       I think what we have struggled with with PROs  7 has been the responsiveness aspect of the validation.  8 So we often -- we get all these symptoms together and  9 then you measure them in a population with any  10 disease, and sure people with more breathlessness and  11 more cough are sicker and you get what's convergent  12 validity.  13       UNIDENTIFIED SPEAKER: Right.  14       MR. CHALMERS: But it's understanding what  15 changes. That's really important.  16       UNIDENTIFIED SPEAKER: Yeah.  17       MR. CHALMERS: Because then you have a -- in  18 a lot of questionnaires, you have a lot of fixed  19 variables that don't change with treatment, which  20 makes it hard to then show a response. The most  21 useful piece of data we can probably get would be the  22 individual patient response data from some of the</p>

<p style="text-align: right;">Page 230</p> <p>1 completed trials --</p> <p>2 UNIDENTIFIED SPEAKER: Exactly.</p> <p>3 MR. CHALMERS: -- to say what symptom is it</p> <p>4 that actually changes when you treat refractory MAC --</p> <p>5 UNIDENTIFIED SPEAKER: Yeah.</p> <p>6 MR. CHALMERS: -- and then weight your</p> <p>7 questionnaire accordingly --</p> <p>8 UNIDENTIFIED SPEAKER: Yeah. And --</p> <p>9 MR. CHALMERS: -- so that it is possible to</p> <p>10 show a difference.</p> <p>11 UNIDENTIFIED SPEAKER: Exactly. And that's</p> <p>12 the data we've been lacking, right, even outside of</p> <p>13 MAC and just regular old " bronchiectasis" has been a</p> <p>14 challenge, so. So I do think Phase II is a place to</p> <p>15 potentially sort some of that out. And I think this</p> <p>16 morning's discussion, we just -- I don't know, we</p> <p>17 weren't really -- Ken and I were talking. We weren't</p> <p>18 really talking about Phase II and Phase III or Phase</p> <p>19 I. So such type of case study kind of goes through</p> <p>20 that. But I do think that you can potentially address</p> <p>21 some of these issues in your Phase II programs or</p> <p>22 Phase II programs.</p>	<p style="text-align: right;">Page 232</p> <p>1 looking good on the culture endpoint, did those</p> <p>2 patients, you know, have relapses in terms of their</p> <p>3 symptoms after they were off drug? It gives an</p> <p>4 opportunity to understand what that discordance means.</p> <p>5 And one other final question -- one -- this</p> <p>6 is -- you mentioned about the rescue therapy. That I</p> <p>7 assume only works if you're using a binary endpoint.</p> <p>8 I mean, I don't know how you would do -- how you would</p> <p>9 handle those patients otherwise. At least it would</p> <p>10 work much more easily with a binary endpoint. But</p> <p>11 again, I -- my main point is that I think the results</p> <p>12 may not be as discordant as it sound and it's an</p> <p>13 opportunity to understand the discordance.</p> <p>14 UNIDENTIFIED SPEAKER: I think you should ask</p> <p>15 the panel. I mean, how many people at this table</p> <p>16 would approve a drug with those Phase III findings? I</p> <p>17 mean, would anyone here vote yes for that? I mean --</p> <p>18 that's a question to everyone. You have a drug that</p> <p>19 helps your PRO over 18 months, but it doesn't improve</p> <p>20 your vascular burden, at least just measured by binary</p> <p>21 outcome and -- I mean, you're right, maybe it does and</p> <p>22 we just aren't seeing it because of the way it was</p>
<p style="text-align: right;">Page 231</p> <p>1 The other thing I would just say is that I</p> <p>2 don't think we should even talk about this. I think</p> <p>3 we should talk about treatment naive studies. That's</p> <p>4 my thing.</p> <p>5 UNIDENTIFIED SPEAKER: So I wanted to talk</p> <p>6 about the results of the Phase III study because I</p> <p>7 thought that was interesting that you got -- that the</p> <p>8 results were significant with the PRO and not for the</p> <p>9 bacterial -- I mean, the microbiological endpoint.</p> <p>10 So that -- I had all sorts of thoughts</p> <p>11 related to that. One was maybe the power -- maybe the</p> <p>12 PRO was continuous and the microbiological endpoint</p> <p>13 was binary and doesn't have the same power. So just</p> <p>14 because they're discordant at that level, just</p> <p>15 crossing 05 or not isn't necessarily that meaningful.</p> <p>16 Maybe it was -- maybe the culture endpoint was close.</p> <p>17 But also I think it would be -- if that</p> <p>18 happened, that would give you an opportunity to look</p> <p>19 at the data and really dig deep and see: Who are the</p> <p>20 discordant patients? What happened to those patients</p> <p>21 over time? Did those patients who were discordant --</p> <p>22 I mean, who were looking good on clinical and not</p>	<p style="text-align: right;">Page 233</p> <p>1 measured.</p> <p>2 UNIDENTIFIED SPEAKER: Maybe the P value (ph)</p> <p>3 is 0.06. We don't know. I mean, again I think</p> <p>4 there's --</p> <p>5 MR. CHALMERS: It's difficult...</p> <p>6 MS. TALLY: -- (cross talk) subtly there.</p> <p>7 MR. CHALMERS: If it was hypertonic saline,</p> <p>8 you would vote yes. But it's an antibiotic --</p> <p>9 UNIDENTIFIED SPEAKER: Yeah, you're right,</p> <p>10 you're right.</p> <p>11 MR. CHALMERS: -- so it gives you concern,</p> <p>12 yeah.</p> <p>13 UNIDENTIFIED SPEAKER: Ken?</p> <p>14 MR. OLIVIER: I'd like to back up to the</p> <p>15 Phase II for a bit if we could. So the Phase II chose</p> <p>16 a primary microbiological outcome, which I would like</p> <p>17 to vote in favor of: if your drug doesn't kill the</p> <p>18 bug, it's a showstopper. So I agree with all the</p> <p>19 other discussion about the need for clinical outcomes,</p> <p>20 but I think in the Phase II setting that that has to</p> <p>21 be your primary bar to achieve.</p> <p>22 I would like to make an argument for not</p>

<p style="text-align: right;">Page 234</p> <p>1 having a 24-month long Phase II study. This is an  2 expensive process to get through and we're dealing  3 with a limited number of patients. I think the 6-  4 month mark may be a good place to pick that and I  5 think that gives you time to get a feel for your  6 clinical outcome measures, which will be secondary in  7 this case to see how responsive they are and how good  8 you set that. And then you've got to go with what  9 you've got in putting your Phase III trial together.</p> <p>10 I understand all the benefits of continuing  11 to follow these patients longer in a Phase II setting,  12 but if that's going to delay your ability to analyze  13 data from that and get it into a Phase III trial, I  14 think that's difficult to do.</p> <p>15 UNIDENTIFIED SPEAKER: So how long would be  16 the ideal follow up?</p> <p>17 MR. OLIVIER: I would suggest 6 months and  18 then if you need a, you know, additional month, the  19 safety follow up after that. I think that would be  20 reasonable.</p> <p>21 UNIDENTIFIED SPEAKER: I would -- those are  22 exactly what I wanted to say. I mean, for a Phase II</p>	<p style="text-align: right;">Page 236</p> <p>1 be a positive effect.</p> <p>2 And again, just as was expressed earlier as  3 far as part of routine clinical practice, when we have  4 patients that are feeling better with a particular  5 regimen, we're going to continue that independent of  6 their microbiological response. We like to see a  7 favorable response for sure and think that that's an  8 important element. But if somebody went from smear  9 positive to smear negative or quantitatively went from  10 4 plus to 1 or 2 plus and they had a positive clinical  11 response, I think that would justify a positive  12 response rather than set the bar so high that we need  13 to have sputum conversion and to have a positive  14 impact on MIDs and PRO from baseline as opposed to the  15 -- and this is for the refractory individuals who are  16 presumably symptomatic and continuing to progress over  17 that 6-month period.</p> <p>18 So I -- again, my point is that I think we  19 should also look at stabilization and a lack of  20 progression as much as improvement from our baseline.</p> <p>21 UNIDENTIFIED SPEAKER: I too am going to  22 agree with Ken's comment about the Phase II. This is</p>
<p style="text-align: right;">Page 235</p> <p>1 trial to go 24 months, I mean, I think that just shuts  2 down drug development right there. So -- and I do  3 believe also in a microbiologic outcome in that Phase  4 II trial. Even following people this long starts  5 getting to be a problem I think because of just  6 standard of care, what starts to happen in terms of  7 airway clearance, stopping and starting, antibiotics  8 given for other reason. Just the longer you go, the  9 more difficult I think it will be to understand the  10 activity of the drug. So I would vote for a 6-month  11 microbiologic.</p> <p>12 UNIDENTIFIED SPEAKER: Yeah, I agree  13 completely.</p> <p>14 UNIDENTIFIED SPEAKER: And I would just add  15 to the microbiological part of that. It doesn't  16 necessarily mean that there would be sputum  17 conversion, but either stabilization or improvement  18 microbiologically like there would be in clinical  19 symptoms. So the notion of preventing progression.  20 So that if you had some microbiological response,  21 however that is defined, and that the clinical  22 symptoms improved, albeit not resolve, that that would</p>	<p style="text-align: right;">Page 237</p> <p>1 typical of the aerosolized antibiotic studies, where  2 your primary is demonstrating the micro effect and  3 your key secondary is really testing what you're going  4 to take as your primary in the Phase III.</p> <p>5 But I'm going to ask about having a short  6 study in Phase III. First, feasibility. It would be  7 hard to recruit patients to do 16 months and never  8 have access to the drug, if that's why they entered  9 the study in the first place. That would be a  10 recruitment nightmare.</p> <p>11 But since this goal was to try to find a  12 clinical outcome, could you achieve that in 6 months  13 and it doesn't depend upon the micro endpoint. And  14 perhaps you had -- if I could test with all the  15 clinicians up here that in general if you're making a  16 change in regimen, at 6 months you want to make a  17 decision about whether to pivot. And that decision of  18 pivoting to some other therapy is probably based on  19 symptoms and radiographic features, not so much on  20 micro.</p> <p>21 Which means you could shorten that study  22 duration considerably. And I -- if I misquote Kevin,</p>

<p style="text-align: right;">Page 238</p> <p>1 I apologize. But then figure out the regimen later.                  2 You don't need to have a 5-year or a 6-year study to                  3 try to get that done.                  4 UNIDENTIFIED SPEAKER: I agree.                  5 UNIDENTIFIED SPEAKER: So we were just                  6 looking at the day. I mean, your Phase III study                  7 should be 6 months, and that's it. Your primary                  8 outcome should be at 3 or 4 months in. Your Phase III                  9 study should be for 6 months. You cannot study these                  10 drugs for 24 months. You'll never -- we'll never have                  11 new drugs ever, and there's no reason to.                  12 I don't understand -- there is this odd -- I                  13 think it's the elephant in the room. Why do you guys                  14 care about durability response after you stop therapy?                  15 This is not something that we need to care about. I                  16 mean, it's not something you should enter into trial                  17 design and development and running these. And I think                  18 we need to talk about that, because the rate of                  19 reinfection so high.                  20 And, you know, if your question is: if you're                  21 on Drug X and you're on placebo and then you see after                  22 everyone stops how -- what percentage stays converted</p>	<p style="text-align: right;">Page 240</p> <p>1 different versions of durability of response. So why                  2 don't I agree with both of you that after stopping                  3 therapy, remaining culture negative, especially when                  4 we've already heard that they get reinfected.                  5 But this is one of the things we talk with                  6 aerosolized antibiotics studies that you wanted to see                  7 multiple cycles or prolonged course for drugs that are                  8 likely to be used for a very long time, so that you                  9 don't just see a benefit at 2 weeks, you see a benefit                  10 over 6 months of therapy. And that's a different                  11 measure of durability of response.                  12 UNIDENTIFIED SPEAKER: Yeah. So -- I mean,                  13 if you can show a clinical benefit and that happens                  14 during that first 6 month time period, I mean, you've                  15 got something, right? It hasn't answered the question                  16 of how durable that effect will be down the road.                  17 That's a separate question that could be answered.                  18 But if those trials are not, you know, something that                  19 could ever be done, we'll then -- we'll never know.                  20 But, yeah -- I mean, I think where we are, is                  21 we're struggling to show or to find, you know, the                  22 clinical benefit. And we had some discussion over the</p>
<p style="text-align: right;">Page 239</p> <p>1 in each group? Like, I mean, "da," like of course                  2 it's going to be higher in the people that were on the                  3 drug. And so what if it was for 2 months? So what if                  4 it was for 6 months? Like these aren't -- these are                  5 not questions that need to enter into the trial                  6 design.                  7 So we need a 6-month study with primary                  8 outcome measures at 3 to 4 months. And you should be                  9 able to swap people over to your active drug arm. You                  10 don't need to keep people on placebo from 1 to 6                  11 months. That's my opinion and I'd love to hear my                  12 colleagues opinion. But I think that's really                  13 important. Otherwise I don't think we're going to get                  14 new drugs.                  15 UNIDENTIFIED SPEAKER: I tend to agree with                  16 you, especially in the treatment refractory                  17 population. You know, this is a chronic disease state                  18 for most of the patients. So expecting them to have a                  19 durability response off therapy I think is completely                  20 unreasonable in this setting.                  21 UNIDENTIFIED SPEAKER: Let me just ask the                  22 FDA to comment, because I'm sort of seeing two</p>	<p style="text-align: right;">Page 241</p> <p>1 lunch period about, you know, what time period might                  2 you expect to see clinical benefit. And it may not                  3 occur until some later point in time with at least                  4 some of what was discussed as a possibility in the                  5 refractory patient population. But perhaps in the                  6 treatment naive population, maybe you would see                  7 something earlier.                  8 So you would at least -- you know, even                  9 though these two patient populations appear to be                  10 behaving somewhat differently probably because of the                  11 nature of their disease and the chronicity -- I mean,                  12 if you could show a clinical benefit early on in a                  13 particular patient population like the treatment naive                  14 patient population, I mean, that would seem to be a                  15 reasonable thing and you've got, you know, a clinic                  16 benefit at that early time point. So...                  17 UNIDENTIFIED SPEAKER: I'm not sure that...                  18 UNIDENTIFIED SPEAKER: I think one thing we                  19 struggle with is like defining disease progression,                  20 because that's really -- we need like some combination                  21 of culture, symptoms and radiographic findings and we                  22 don't have that. I think that would be the best</p>

<p style="text-align: right;">Page 242</p> <p>1 endpoint. Just like you said, in cancer, you know,                  2 success or failure is based on disease progression.                  3 That's what we really need to figure out.                  4 UNIDENTIFIED SPEAKER: I mean, clinically you                  5 do that, right, with individual patients?                  6 UNIDENTIFIED SPEAKER: But we don't have a                  7 way to do it in a child.                  8 UNIDENTIFIED SPEAKER: Yeah. And so -- and                  9 we were talking about to the extent you could use                  10 clinician judgment at the individual level.                  11 MR. CHALMERS: I mean, that was why I asked                  12 you the question in the first session about CT because                  13 I find when I'm wondering "is this patient                  14 progressing," I put a lot of weight on the CT.                  15 UNIDENTIFIED SPEAKER: I mean, it's a                  16 question...                  17 MR. CHALMERS: And it's a missed opportunity                  18 that in this -- for example, we didn't do CT in the                  19 Phase II in this trial to see is there something you                  20 can see that you could use for progression free                  21 survival, which again is a really attractive --                  22 MR. AKSAMIT: (cross talk) just a little</p>	<p style="text-align: right;">Page 244</p> <p>1 microbiological? And so the question is can we show                  2 lack of progression without necessarily showing a big                  3 symptomatic benefit?                  4 MR. AKSAMIT: Well -- and this is where the                  5 composite endpoint comes in with the lack of                  6 progression and that's exactly what then the                  7 definition is from a radiographic. What do you say is                  8 a lack of progression quantitatively so that you could                  9 use that for clinical trials for the PRO issues and                  10 then microbiological lack of progression, or a slight                  11 improvement or a delta, if you will.                  12 UNIDENTIFIED SPEAKER: Yes. So we think too                  13 about, you know, surrogate endpoints or nonclinical                  14 endpoints. So you're thinking about, you know,                  15 radiographs. You're thinking about microbiology. I                  16 mean, the reason that they tell you something                  17 important is because you know that they correlate with                  18 a clinical effect. And the way that you get that is                  19 from a trial that looks at clinical outcomes and then                  20 starts to look to see what else seems to be going                  21 along with it and that there's a passive physiologic                  22 basis for expecting that that is causally related.</p>
<p style="text-align: right;">Page 243</p> <p>1 bit...                  2 MR. CHALMERS: -- is an attractive concept.                  3 MR. AKSAMIT: And I think that we will know                  4 within 6 months. I mean, in the clinical experiences,                  5 you have a pretty good idea within the first few                  6 months whether somebody is going to respond. There's                  7 a rare individual that gets placed on treatment and                  8 gets better at 9 or 12 months and had no improvement                  9 in the first 6 months. I've not seen that. I would                  10 defer to my other colleagues.                  11 But if people are going to get better, as was                  12 said earlier, they're going to get better in -- you'll                  13 know within the first 3 months. And if you wanted to                  14 extend that to 6 months to be, you know, conservative                  15 about it, that will be all right too.                  16 But you'll know relatively quickly whether                  17 this is going to be a successful regimen clinically.                  18 They'll either feel better or not. You don't have to                  19 wait more than 6 months, 9 months or 12 months.                  20 MR. CHALMERS: But is the issue, Tim, not                  21 that in the refractory population the trials have not                  22 shown major symptomatic benefits, but there are</p>	<p style="text-align: right;">Page 245</p> <p>1 And so -- I mean, the way to get there is to                  2 do the study to look at the clinical outcome and then                  3 see what else is going along with it. And if you've                  4 done that, you know -- I mean, once would be great.                  5 You know, twice starts to firm up those relationships                  6 more. And three and four times, it really starts to                  7 firm them up.                  8 That's what's happened in other fields. I                  9 mean, if we talk about learning from other fields,                  10 that's one of the learnings from other fields and                  11 certainly could translate here. That's challenging, I                  12 get that. But I think that's what we need to think                  13 about, you know, how do we get to understand the                  14 clinical effects on patients and how can we use these                  15 surrogate markers as correlates -- or as, you know,                  16 surrogates I should say of the clinical outcome and                  17 the data that we need to establish the clinical                  18 outcome and then look to see what, you know, is                  19 causally associated with that.                  20 UNIDENTIFIED SPEAKER: All right. Kevin --                  21 if you all could introduce yourself when you...                  22 MR. FENNELLY: Okay. Kevin Fennelly, NIH,</p>

<p style="text-align: right;">Page 246</p> <p>1 NHLBI. Now, unless I've had a postprandial lapse, I'm  2 not remembering what patient group this hypothetical  3 patient would fall in. And I don't think that we've  4 defined today or answered question number one. We've  5 talked a lot about heterogeneity.  6 But I'd like to comment on a patient group  7 that I think has been neglected a bit in our --  8 relatively neglected in our discussions, and that are  9 the COPD patients who have NTM disease. They -- the  10 other Kevin and I had the good fortune to work with  11 some folks in the VA, the Veterans Administration, and  12 we published a study last year, which we had I think  13 over 6,000 NTM cases in the U.S. VA population. Of  14 course over two-thirds of them had underlying COPD.  15 And the remarkable thing is that in the first  16 6 months after diagnosis, there was a 40 percent risk  17 of death. So we haven't talked about mortality as an  18 endpoint, but it exists. It will fall within the 6-  19 month period that you're asking for, or you could even  20 extend it out 12 months.  21 But, you know, it's fairly unambiguous except  22 maybe in Game of Thrones or a few other circumstances.</p>	<p style="text-align: right;">Page 248</p> <p>1 The second issue is -- it's interesting I  2 think -- I asked earlier -- so we -- and I'm not  3 saying -- so when we're looking at the stage where we  4 are with all the new drugs coming -- and this was  5 mentioned in case 2 with all the drugs coming. Should  6 we concentrate on adding drugs one by one to what we  7 have, which, if you did iteratively given how long it  8 takes, you're going to take a couple of decades,  9 right, to switch in, get in? Or should we start  10 thinking "by whatever means"?  11 And Tim from Hopkins presented, you know,  12 ways of trying to combine this. And there are  13 different ways. But shouldn't we be thinking of in  14 MAC and certainly in M. abscessus where standard  15 therapy is, you know? No good, right?  16 So shouldn't we be thinking of building new  17 regimens and taking those now to Phase II and Phase  18 III clinical trials faster? Otherwise it's going to  19 take us decades to just change the MAC regimen, right?  20 So that's my question.  21 UNIDENTIFIED SPEAKER: Well, I'm not really  22 sure how to fully respond to that, but the -- there's</p>
<p style="text-align: right;">Page 247</p> <p>1 And it's of great importance to the patients and their  2 families of course. So I would just urge for us to  3 consider the COPD patients.  4 When I was in Florida, I took care of a lot  5 of these folks. There seemed to be a lot more smoking  6 down there and they usually come in really sick. And  7 you can make them better, they feel much better, and  8 you can prevent progression with treatment.  9 UNIDENTIFIED SPEAKER: Thanks.  10 UNIDENTIFIED SPEAKER: Yeah, so I'm Tohand  11 Ugumbu (ph) from Bela (ph). Two issues. So the first  12 one is the microbiological endpoint. And I think  13 somebody mentioned a very important point. We tend to  14 think of it as either/or, right? But there are tools  15 that are used in the clinic now where you can have a  16 quantitative -- use it as a quantitative measure so  17 that, you know, it's not either/or, right? You know,  18 you can tell if there is a decrease in bacterial data.  19 I know there is a lot of noise in sputum  20 samples. But it doesn't have to be either/or, right,  21 in terms of microbiological outcome. And that might  22 improve the power and reduce sample sizes.</p>	<p style="text-align: right;">Page 249</p> <p>1 developing drugs, there's developing regimens, which  2 are really two different pathways. And if you're  3 talking about combinations, getting into the  4 combination role to find out how these drugs not only  5 interact with each other, but also which one is adding  6 anything to the regimen itself. So...  7 UNIDENTIFIED SPEAKER: Hi. Thanks. It's  8 Kira Kahn (ph) from Johns Hopkins again. And just to  9 the point earlier that James Chalmers raised about the  10 feasibility of blinding clinicians and PIs to cultural  11 results. In my opinion, that's a terrible idea.  12 Patients deserve to know and I as a treating physician  13 deserve to know in particular what the drug's  14 susceptibility pattern is of the background regimen.  15 So if you're blinding us to the culture  16 results to know whose culture positive after several  17 months of treatment in a trial, you're also blinding  18 us to know whose culture positive and who may have  19 developed macrolide resistance, for example.  20 And it's a very different treatment decision  21 for patients whether they are macrolide susceptible or  22 resistant. And I think that patients deserve to have</p>

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1 the best available information about what their  
 2 chances are of achieving a good outcome. And that  
 3 means that we need to have that information at that  
 4 time.  
 5 UNIDENTIFIED SPEAKER: So my experience is  
 6 that doctors aren't getting that many cultures. I'd  
 7 like to hear from people when they are treating, how  
 8 many are getting monthly cultures on their patients or  
 9 how many are getting them every 3 months or every 6  
 10 months.  
 11 UNIDENTIFIED SPEAKER: There's like here  
 12 (inaudible 1:05:20) they get them every like 3 or 4  
 13 days.  
 14 UNIDENTIFIED SPEAKER: I got them about every  
 15 2 months for -- to throw it out there.  
 16 UNIDENTIFIED SPEAKER: Yeah, my sense is --  
 17 you know, taking a lot of patients from out of state,  
 18 we see that the practice will -- our practice is  
 19 monthly or every other month. But it's hugely  
 20 variable on the community. Sometimes it's never, you  
 21 know: "We're going to treat you for 12 months and see  
 22 how you do." So -- not that that's the right thing to

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1 do.  
 2 UNIDENTIFIED SPEAKER: And my guess is that  
 3 there are only a handful of people who are actually  
 4 getting susceptibility testing, period, but certainly  
 5 with any regularity.  
 6 MR. AKSAMIT: Yeah. Yeah, I think that even  
 7 though we would do this monthly, we wouldn't  
 8 necessarily repeat susceptibility testing on a regular  
 9 basis unless there was an indication somebody was  
 10 failing therapy.  
 11 I don't know that that's part of standard  
 12 practice, at least that's not mine. But I think to  
 13 collect every month. And looking not only for  
 14 treatment response with respect to the microbiological  
 15 endpoint, but also is their new a pathogen present.  
 16 Because that's not an infrequent occurrence. They  
 17 have another second NTM show up during primary  
 18 therapy.  
 19 MR. FLUME: But if Kira was speaking to this  
 20 particular case, that would be 24 months of not  
 21 knowing the culture results. So I think most of us at  
 22 6 months would -- if they're still positive and we

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1 knew that, would probably be obtaining susceptibility  
 2 studies at that point.  
 3 MR. CHALMERS: Yeah. And I think Patrick is  
 4 talking about the general NTM population. And this is  
 5 refractory patients, so you're changing therapy on --  
 6 and I think we all would recommend that you should be  
 7 doing more frequent cultures than your normal  
 8 practice. And I think most physicians would end up  
 9 break the blind.  
 10 UNIDENTIFIED SPEAKER: And even if they don't  
 11 do it in their clinical practice, in the setting of a  
 12 clinical trial if there's a macrolide resistance that  
 13 has developed or abscesses (ph) is now growing, I  
 14 think there's some ethical issues about not knowing  
 15 about it.  
 16 MR. CHALMERS: And you'd also have to explain  
 17 it to the patient when you enroll them that for the  
 18 next 24 months we're not going to be able to look at  
 19 anything that goes on in your lungs. Even if your  
 20 normal practice is not to do it very frequently,  
 21 that's going to be a real disincentive to the patient.  
 22 UNIDENTIFIED SPEAKER: But I...

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1 UNIDENTIFIED SPEAKER: Yeah, I actually  
 2 wanted to make a quick comment about that. Because  
 3 again, we have not had a chance to analyze all of the  
 4 qualitative data from the survey, but I can tell you  
 5 that there was a lot of feedback from patients who  
 6 were not necessarily being treated by one of the more  
 7 expert physicians, so most of the people in this room.  
 8 But their feedback generally is that the  
 9 physicians out in the general community need to be  
 10 better educated about the disease, about how to treat  
 11 it, how to diagnose it.  
 12 So now if you take a potential clinical trial  
 13 patient and say to them, "Well, your physician is not  
 14 going to know what your cultures look like for 2  
 15 years," your enrollment probability -- you're going to  
 16 have like maybe -- maybe a quarter of the patients are  
 17 going to be willing to enroll. I don't see that as  
 18 being ethical and I don't see it as being feasible to  
 19 enroll.  
 20 UNIDENTIFIED SPEAKER: Okay. I'm going to  
 21 just assume that everyone agrees that we're not going  
 22 to be blinded for 16 months, so that we're all into a



<p style="text-align: right;">Page 254</p> <p>1 6-month treatment regimen.</p> <p>2 MR. CHALMERS: Yeah.</p> <p>3 UNIDENTIFIED SPEAKER: But I want to ask</p> <p>4 Chuck to just qualify what do you do then if you have</p> <p>5 a patient who is clinically better on your regimen</p> <p>6 during the MAC and now the culture grows abscesses?</p> <p>7 UNIDENTIFIED SPEAKER: I turn on my clinician</p> <p>8 hat and I make a decision: "Do I think this is harming</p> <p>9 the patient?" Usually, what that would mean is</p> <p>10 collection of additional sputum, because it may have</p> <p>11 been a onetime culture. I'll get a CT scan if we</p> <p>12 haven't already gotten one, assess the patient's</p> <p>13 symptom-wise and just do a clinical assessment. And</p> <p>14 if I think that is hurting them, I will treat them for</p> <p>15 it.</p> <p>16 UNIDENTIFIED SPEAKER: So if you're in a</p> <p>17 clinical trial where -- I realize you can't see what</p> <p>18 I've drawn here -- that they're 6 months in treatment</p> <p>19 and you're given that opportunity to make a change in</p> <p>20 therapy at 6 months or in that open period afterwards</p> <p>21 based upon radiographic findings or clinical findings,</p> <p>22 you have that opportunity to do that.</p>	<p style="text-align: right;">Page 256</p> <p>1 actually.</p> <p>2 UNIDENTIFIED SPEAKER: And in David's</p> <p>3 defense, because I think he's comfortable with a lab</p> <p>4 that he has a lot of confidence. And so you raise a</p> <p>5 really important point that for Dave and those that</p> <p>6 practice at Tyler, they're used to that. It's a</p> <p>7 hammer they've gotten a lot of mileage out of and feel</p> <p>8 very comfortable with. But is that the same hammer</p> <p>9 that we all or that community ID and pulmonary</p> <p>10 physicians have? And the answer is no. So if</p> <p>11 you're...</p> <p>12 UNIDENTIFIED SPEAKER: But I think (cross</p> <p>13 talk) use their lab and that tool failed.</p> <p>14 UNIDENTIFIED SPEAKER: Right. But let me</p> <p>15 just point out that it didn't fail. But that was in a</p> <p>16 treatment refractory population, where presumably the</p> <p>17 variability would be higher. And so I don't discount</p> <p>18 or doubt the results that they got in a treatment</p> <p>19 naive population. I think it probably is helpful</p> <p>20 there in the data or the data.</p> <p>21 But, you know, there can be a lot of</p> <p>22 variability, especially if there are penalties</p>
<p style="text-align: right;">Page 255</p> <p>1 UNIDENTIFIED SPEAKER: At 6 months, yes.</p> <p>2 UNIDENTIFIED SPEAKER: And that clinical hat</p> <p>3 thing you described is going to take about 3 months to</p> <p>4 sort out, right? You're going to get -- you're going</p> <p>5 to get repeated cultures, you're going to get a scan,</p> <p>6 and you're going to see how the patient does. This</p> <p>7 can take 3 months to deal with that, so.</p> <p>8 UNIDENTIFIED SPEAKER: Yeah.</p> <p>9 UNIDENTIFIED SPEAKER: Can I just make a</p> <p>10 quick comment? I've heard a couple of people</p> <p>11 advocating to go back to using the semi-quantitative</p> <p>12 scale as a sensitive tool. And I'd love to hear Ken's</p> <p>13 opinion on this too, but my feeling from practice is</p> <p>14 that it's not the right tool to use in these patients.</p> <p>15 There is too much noise and it's variable on the</p> <p>16 quality of the specimen obtained.</p> <p>17 UNIDENTIFIED SPEAKER: Since David is out of</p> <p>18 the room, we can talk about it freely.</p> <p>19 UNIDENTIFIED SPEAKER: Now, that I said was</p> <p>20 seminal.</p> <p>21 UNIDENTIFIED SPEAKER: Yeah. So, you know...</p> <p>22 UNIDENTIFIED SPEAKER: It was terrible</p>	<p style="text-align: right;">Page 257</p> <p>1 assigned in how that scale is constructed and you have</p> <p>2 a lot of people dropping out, which I think is one of</p> <p>3 the main problems that that showed.</p> <p>4 UNIDENTIFIED SPEAKER: Can I bring the</p> <p>5 conversation to the first point, which is the patient</p> <p>6 population to be studied? And since this case was</p> <p>7 about a refractory case, that's not what I'm getting</p> <p>8 at.</p> <p>9 But if the point is to find patients who are</p> <p>10 likely to change, if you're -- you've got your</p> <p>11 clinical endpoint, can that now be an inclusion</p> <p>12 criteria which defines this? And I'll use as my</p> <p>13 example that in the CF trials were FEV1 can change,</p> <p>14 recruitment patients in those trials has an FEV1</p> <p>15 between X and Y, because those are patients who are</p> <p>16 likely to change.</p> <p>17 So your inclusion criteria not just nodular</p> <p>18 bronchiectasis. Or it could be NTM lung disease</p> <p>19 excluding cavitary disease. But then they also might</p> <p>20 need to have something that -- a cough score of X or</p> <p>21 your PRO score less than Y. So that you increase --</p> <p>22 you enrich your population for effect. That was</p>

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<p>1 intended to be a conversation...</p> <p>2 MR. CHALMERS: So since nobody -- since</p> <p>3 nobody is willing to contradict you, I'll play devil's</p> <p>4 advocate and say, I mean, we have talked a lot about</p> <p>5 not reducing the pool of patients because of the need</p> <p>6 to have generalizable data. And I guess if you say we</p> <p>7 need a QOL-B score less than 60 based on Dr.</p> <p>8 Sullivan's graphs, she'd exclude maybe a third of the</p> <p>9 patients. So the study becomes more difficult to</p> <p>10 enroll.</p> <p>11 So I think that's the argument against it, is</p> <p>12 if you -- again, coming back to this idea of a</p> <p>13 composite, if you said they have to have cough or</p> <p>14 breathlessness or fatigue because your endpoint</p> <p>15 encompasses all of them, then you don't have -- you</p> <p>16 have more generalized ability and you find it easier</p> <p>17 to enroll. Having said that, I think if I were</p> <p>18 designing a study tomorrow, I'd go for A QOL-B less</p> <p>19 than 70.</p> <p>20 UNIDENTIFIED SPEAKER: Yeah, I think that was</p> <p>21 a very important presentation and I think that that's</p> <p>22 a really important lesson from your trials, this idea</p>	<p>1 number. But not everyone was.</p> <p>2 UNIDENTIFIED SPEAKER: Erica, did you want to</p> <p>3 say something?</p> <p>4 MS. BRITTAIN: I think somebody else has</p> <p>5 already said it.</p> <p>6 UNIDENTIFIED SPEAKER: Hi. May I? Hi.</p> <p>7 Christian Campbell (ph) with Johnson &amp; Johnson. So on</p> <p>8 that question of refractoriness, Dr. Daley, what do</p> <p>9 you think would be a reasonable time period to make</p> <p>10 that cut of what constitutes refractoriness that</p> <p>11 belongs in the clinical trial?</p> <p>12 MR. DALEY: Well, I think the trial showed us</p> <p>13 that, I mean, in 6 months. Because if you -- beyond 6</p> <p>14 months if you don't do something, they stay the same.</p> <p>15 I mean, I think it was very powerful from both Phase</p> <p>16 II, Phase III that you have to do something. And if</p> <p>17 you don't, they just stay the same.</p> <p>18 So it could be -- but it's really 4 months.</p> <p>19 We know by really the culture that was taken at 4</p> <p>20 months in the Phase III trial, because that's how you</p> <p>21 -- it was 29 percent at 4 months, because it was by 6</p> <p>22 months. But it had to be obtained at 4 months.</p>
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<p>1 that if you're going to measure something over time,</p> <p>2 they've got to start with it. And if they don't have</p> <p>3 it, then it's not going to work. It's -- it's...</p> <p>4 UNIDENTIFIED SPEAKER: (off mic)</p> <p>5 UNIDENTIFIED SPEAKER: Yeah, it's going to</p> <p>6 always fail. But I would also point out from your</p> <p>7 data that we still haven't defined refractory yet,</p> <p>8 because even though we know what your inclusion</p> <p>9 criteria were at least 6 months, you showed the people</p> <p>10 had been on it for years, had been treated for years.</p> <p>11 Now, I don't think clinically a patient who</p> <p>12 has been on a treatment for 10 years is the same as</p> <p>13 someone who hasn't converted in 6 months.</p> <p>14 UNIDENTIFIED SPEAKER: I agree.</p> <p>15 UNIDENTIFIED SPEAKER: And so I will say --</p> <p>16 and the definition of refractory, we really need to</p> <p>17 tighten that up also.</p> <p>18 UNIDENTIFIED SPEAKER: Yet given that 30</p> <p>19 percent of those patients did convert...</p> <p>20 UNIDENTIFIED SPEAKER: Yeah, it was the</p> <p>21 hardest group you can imagine clinically. And so for</p> <p>22 clinicians, I think we were very impressed by that</p>	<p>1 So I think we know that it's 6 months beyond</p> <p>2 we need to do something. And it may be that it's</p> <p>3 earlier than that, 3 months or 4 months, which we need</p> <p>4 to understand because that would again just tighten up</p> <p>5 shortened durations.</p> <p>6 UNIDENTIFIED SPEAKER: But are you advocating</p> <p>7 putting a length of refractoriness limit on that?</p> <p>8 MR. DALEY: Yes.</p> <p>9 UNIDENTIFIED SPEAKER: It's probably not a</p> <p>10 new term. They're probably still refractory. They're</p> <p>11 just like super refractory. And for the purposes of a</p> <p>12 trial, maybe those are the ones you don't want to</p> <p>13 (cross talk)...</p> <p>14 UNIDENTIFIED SPEAKER: But you just argued</p> <p>15 that if they don't do anything at 6 months, they're</p> <p>16 not going to change?</p> <p>17 UNIDENTIFIED SPEAKER: Well -- so that's</p> <p>18 (cross talk) population. It's -- and I think this</p> <p>19 will be an interesting analysis that maybe you've done</p> <p>20 and haven't presented it: What is the difference in</p> <p>21 the outcome between those who were -- would need like</p> <p>22 6 months versus 3 years? I mean, try to dichotomize</p>

<p style="text-align: right;">Page 262</p> <p>1 or develop it into periods post or years of treatment  2 and then see what the outcomes. So how much does that  3 change?  4 UNIDENTIFIED SPEAKER: Right. I don't have  5 that data, but Kevin seems to. But I think the point  6 is really to -- that you want to pick a population  7 that's going to be sensitive to the treatment effect,  8 if there is one. And it may be that those people who  9 have had the disease for 30 years are not going to  10 even be sensitive to a treatment effect.  11 UNIDENTIFIED SPEAKER: And what Angela said  12 - that then determines probably what you want to see  13 change. I mean, if you're -- if you've had  14 fibrocavitary disease for 15 years, you know, I'd --  15 some of those symptoms are not going to change. It  16 may be cough, for example.  17 UNIDENTIFIED SPEAKER: No, I agree with  18 Chuck. If we're going to really do this type of  19 study, which I've already said I'd recommend against,  20 you'd have to define refractory disease. Because  21 there were -- I mean, your case definition was --  22 there's two different types of people in that study.</p>	<p style="text-align: right;">Page 264</p> <p>1 diagnosed. And that's what I reported. Because so  2 many patients come on and off and then they had sort  3 of a holiday for a while. So the data on actual how  4 many years were you on how many drugs is a little less  5 firm.  6 UNIDENTIFIED SPEAKER: And you have  7 colleagues here, but in the manuscript that was  8 published it described a median of like 3 years of  9 treatment.  10 UNIDENTIFIED SPEAKER: Yes, treatment  11 direction.  12 UNIDENTIFIED SPEAKER: Total treatment.  13 MR. SULLIVAN: That was captured, but what I  14 showed was duration.  15 UNIDENTIFIED SPEAKER: Yeah.  16 UNIDENTIFIED SPEAKER: And while we're doing  17 math, there was another suggestion about changing the  18 definition of culture conversion to even just to how  19 much would that have changed the study results for 212  20 and 312?  21 UNIDENTIFIED SPEAKER: You know, this is not  22 published data, but I think it's been looked at by</p>
<p style="text-align: right;">Page 263</p> <p>1 And there's people who have been on therapy for 6  2 months and still culture positive. And there's people  3 who had a history of that basically and now they're  4 culture positive again. They didn't have to be on  5 therapy at that time. They just had to be on therapy  6 only for the last 12 months or something.  7 So there is kind of two different groups of  8 people in there. And, yeah, they're all like kind of  9 the same people and their balance between arms and I  10 don't think there's any difference between them. But  11 it just -- it serves to Chuck's point that there's  12 really -- this is not something we've fully defined  13 in...  14 UNIDENTIFIED SPEAKER: And, Eugene, can you  15 clarify on the data that you presented? There was  16 duration of NTM diagnosis -- not necessarily therapy,  17 but diagnosis. And my question is, how much therapy  18 did they get? Was that close to the duration of  19 diagnosis or was that completely separate and  20 unassociated type of relationship?  21 MR. SULLIVAN: I think the easiest thing to  22 quantify was self-reported how long -- when were you</p>	<p style="text-align: right;">Page 265</p> <p>1 some of the folks that were involved, and it looked  2 like if you have two, you're likely to have three.  3 UNIDENTIFIED SPEAKER: I mean, that's what  4 your graph -- you know (cross talk)...  5 UNIDENTIFIED SPEAKER: It doesn't give...  6 UNIDENTIFIED SPEAKER: Well, your data shows  7 that if you have three, you're likely to stay  8 negative. So I would think if you had two, that that  9 would be (cross talk).  10 UNIDENTIFIED SPEAKER: Yeah. So it could  11 conceivably be an adequate diagnose of culture of  12 conversation too. We always emphasized how rigorous  13 we were requiring three. It turned out that three --  14 the third one didn't add all that much.  15 UNIDENTIFIED SPEAKER: Path of your primary  16 outcome, you can back of an envelope and do it, right?  17 You can tell that, so.  18 UNIDENTIFIED SPEAKER: No, because they --  19 that's -- only those that had met the definition of  20 three consecutives -- so earliest they could do it  21 would be month 1. But in -- if we're saying 2, you  22 could get it positive and it will be negative in 5 and</p>

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<p>1 6 and have met the criteria and that would not be in                  2 that graph.                  3 UNIDENTIFIED SPEAKER: Well -- but most of                  4 people that met that -- I mean, what was the positive                  5 at 3 months? I mean, you could see it 3 months or 2                  6 months. You could see the majority of those people                  7 that were converters were already identified as                  8 converters at that time, which would imply that if                  9 they have two consecutive, they're going to get a                  10 third, most of them.                  11 UNIDENTIFIED SPEAKER: And just to put this                  12 in perspective. I think just if we look at the data -                  13 - Eugene, as you're here -- we talked about -- so                  14 you've got refractory people that have been on and off                  15 therapy for at least 3 years, for lack of argument.                  16 More than 3 years of therapy on and off in the                  17 refractory disease. They get put on therapy, and                  18 within 3 months, they got signal. I mean, that                  19 answers his question about what's that timeframe...                  20 UNIDENTIFIED SPEAKER: A signal on the micro                  21 --                  22 UNIDENTIFIED SPEAKER: Correct.</p>	<p>1 exposure to drug somewhere around 3 years. So again,                  2 it's in that population.                  3 So two seemed to be reasonable and predicted                  4 three perfectly because three required two. So I'll                  5 just add that color to that. So hopefully that                  6 answers a few more questions.                  7 UNIDENTIFIED SPEAKER: Yeah. No, my question                  8 was just does it go from 30 percent to 35 percent?                  9 UNIDENTIFIED SPEAKER: So --                  10 UNIDENTIFIED SPEAKER: It had to be more.                  11 UNIDENTIFIED SPEAKER: -- it will add about                  12 10 percent to 15 percent more patients.                  13 UNIDENTIFIED SPEAKER: That's not trivial?                  14 UNIDENTIFIED SPEAKER: It's not trivial.                  15 UNIDENTIFIED SPEAKER: And also I think too                  16 it will be much more likely -- I mean, I'm -- I                  17 pitched the two idea. And I think in a treatment                  18 naive group it's probably much more potentially                  19 meaningful than in a refractory population. I mean,                  20 that would be my guess. But...                  21 UNIDENTIFIED SPEAKER: And I'm wondering,                  22 you're saying it raises it about 10 percent. Is that</p>
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<p>1 UNIDENTIFIED SPEAKER: -- not necessarily a                  2 signal...                  3 UNIDENTIFIED SPEAKER: Correct. Exactly.                  4 UNIDENTIFIED SPEAKER: So I just want to just                  5 add to still look -- so Dr. Kevin Minch (ph)                  6 (inaudible 1:20:51) and holds stock in the company.                  7 So a couple of points. So everyone that had three                  8 consecutive negative cultures had two consecutive                  9 negative cultures, right? There's that perfect                  10 correlation, right? You know, so that's the math,                  11 Patrick, you were saying.                  12 So you have a higher proportion that would                  13 have met success if you only required two. So -- and                  14 when you had your first negative culture, it occurred                  15 really around 2 months, right, for the first time. So                  16 you did see some people that had their first negative                  17 culture, but you had some other people that had their                  18 first negative culture a bit later as well too, as                  19 well as in the trial.                  20 So there is that heterogeneity a bit that,                  21 again, in a difficult to treat refractory population                  22 median time of NTM duration of 4 years and a median</p>	<p>1 in both arms?                  2 UNIDENTIFIED SPEAKER: I can go back --                  3 UNIDENTIFIED SPEAKER: I mean, it's probably                  4 to some degree...                  5 UNIDENTIFIED SPEAKER: -- (cross talk) double                  6 check that.                  7 UNIDENTIFIED SPEAKER: Okay.                  8 UNIDENTIFIED SPEAKER: It's a fair question                  9 and I want to go back and just double check the                  10 accuracy. So for the investigational arm at that                  11 time, for sure. But I just want to double check that                  12 and come back to you on that please.                  13 UNIDENTIFIED SPEAKER: Thank you.                  14 UNIDENTIFIED SPEAKER: So if I could ask you                  15 a question before you leave. So in trying to define                  16 the refractory population, is there anything that we                  17 can glean from that? So if the mean or the median is                  18 around 3 years, does that help us? And what's the                  19 variability around that and does that help us any in                  20 defining who's more likely to respond?                  21 UNIDENTIFIED SPEAKER: I think Dr. Sullivan                  22 showed the slide that showed the range of that -</p>

<p style="text-align: right;">Page 270</p> <p>1 again, NTM duration of 4 years was a medium, but you 2 had people that had that diagnosis for 30 years. 3 UNIDENTIFIED SPEAKER: No, not the diagnosis, 4 but -- 5 UNIDENTIFIED SPEAKER: Yeah, the treatment, 6 right. 7 UNIDENTIFIED SPEAKER: -- how long that they 8 were on treatment? 9 UNIDENTIFIED SPEAKER: Again, 40 percent of 10 patients had, you know, 3 or 4 years. We'd have to go 11 back and look at that upper range to give you a sense 12 of how wide it was, but it was pretty significant. 13 And we did see a bit in some of the modeling that 14 we've done that those who tended to be shorter in 15 duration tended to have a higher probability of 16 culture conversion. 17 Again, we're talking, again, the numbers in 18 the study, but it was still very significant. And you 19 saw that treatment effect when you added Alice (ph) on 20 top of the background regimen. You did not see that 21 effect in the control arm, because they were already 22 resistant to treatment, right? As you said, they've</p>	<p style="text-align: right;">Page 272</p> <p>1 UNIDENTIFIED SPEAKER: So then we're back to 2 a longer study, which I had thought we had talked 3 about trying to shorten down. So either we're 4 stopping it at 6 months or we're continuing for 24 5 months in assessing safety and whatever else you need 6 to assess in the long term in the same study. 7 UNIDENTIFIED SPEAKER: So it's tradeoffs, 8 right? So, you know, it, you know, depends on whether 9 you feel you could get a better study by doing 6 10 months in the cross-over. I mean, you'd have to see 11 how the tradeoffs played out. 12 UNIDENTIFIED SPEAKER: And for the shorter 13 study, I mean, it seems like there's maybe some 14 uncertainty or some differences of opinion about the 15 clinical events that would happen during that shorter 16 time period? That's on the efficacy side. 17 UNIDENTIFIED SPEAKER: So I guess something 18 else that we're thinking about is, if the guideline 19 say treat for 12 months from the time of culture 20 negativity, then it would seem that patients would be 21 on therapy roughly 16 months. And so we'd want 22 information with this drug for that 16 months ideally</p>
<p style="text-align: right;">Page 271</p> <p>1 been treated for a very long time, they remain culture 2 negative. 3 But when you added Alice on top of that 4 background regimen, if they were in the lower half of 5 the median -- just choosing the median as an arbitrary 6 binary -- they tend to do culture convert a bit more 7 than those who had been, you know, higher than a 8 median duration. 9 UNIDENTIFIED SPEAKER: I want to next take 10 the question to the limiting cross-over since we've 11 now said we're not going to do a 16-month trial for 12 decision making, and because that was an issue during 13 the advisory panel for Alice. Is that a problem if 14 your endpoint is within 6 months that those patients 15 who were randomized to control would be allowed to 16 rollover into open label extension? 17 UNIDENTIFIED SPEAKER: So obviously, if the 18 primary endpoint is before when the crossover happens, 19 you're okay for the primary endpoint. But it could -- 20 it could complicate assessment of safety and other 21 longer term endpoints that you would want to know 22 about. So it's not a total free lunch.</p>	<p style="text-align: right;">Page 273</p> <p>1 if that's how long its use would be in the clinical 2 practice. 3 I understand people may come off a drug and 4 then get reinfected and go on a drug again, but ideally 5 we want to capture some sense of safety and efficacy 6 over the expected duration of practice, ideally, 7 understanding the -- it sounds like -- in general the 8 people -- everyone here on the panel is saying 6 9 months is what patients would likely tolerate. So 10 then that raises a question for us: How do we get that 11 additional experience beyond 6 months given that 12 guidelines may -- 13 UNIDENTIFIED SPEAKER: Right. 14 UNIDENTIFIED SPEAKER: -- recommend longer 15 therapy? 16 UNIDENTIFIED SPEAKER: Could you imagine a 17 study where patients are randomized to the active 18 versus the control arm for 6 months? At 6 months, the 19 clinician has an opportunity to pivot and say, "I 20 don't know what they're on, but it ain't working and 21 I'm going to change their regimen." So they now are 22 on that arm. And if the patients were doing well,</p>

<p style="text-align: right;">Page 274</p> <p>1 they could remain in the arm that they were in.</p> <p>2       And at some point, you'll break the blind on</p> <p>3 the cultures, because if you're going to adhere to 12</p> <p>4 months of treatment, then you could do that. So your</p> <p>5 treatment arm could continue for 12-plus months, which</p> <p>6 is now based on a micro aspect, but you've already hit</p> <p>7 your primary at 6 months.</p> <p>8       UNIDENTIFIED SPEAKER: And that's essentially</p> <p>9 what 212 was designed going in the 312, is that</p> <p>10 correct?</p> <p>11       UNIDENTIFIED SPEAKER: But it had -- micro is</p> <p>12 the primary...</p> <p>13       UNIDENTIFIED SPEAKER: Yeah, that's -- not</p> <p>14 quite. But I think -- and why do you say fixed at 6</p> <p>15 months? What about if you randomized to active or</p> <p>16 control blinded and the outcome variable is the</p> <p>17 physician and patient deciding, "It's not working. We</p> <p>18 need to get you on a guideline base there." So it's a</p> <p>19 time to event analysis.</p> <p>20       UNIDENTIFIED SPEAKER: It's a treatment</p> <p>21 failure...</p> <p>22       UNIDENTIFIED SPEAKER: Where the event is</p>	<p style="text-align: right;">Page 276</p> <p>1 answer is -- you know, what the guidelines are going</p> <p>2 to say, we don't know. They're going to be out in</p> <p>3 another 3 or 4 years. Is there right? I'm checking</p> <p>4 back on -- but that's why you should just cross people</p> <p>5 over, whether you do it the way Patrick just said or</p> <p>6 the way Eugene said, crossing them over. Like you</p> <p>7 don't need placebo information or control information</p> <p>8 past 6 months, for example, if you have a short term</p> <p>9 trial and your primary outcome measures are in that</p> <p>10 time period.</p> <p>11       So you cross them over and you treat</p> <p>12 everyone. Everyone gets 16 months of active drug. So</p> <p>13 you get the information you want and people are</p> <p>14 treated in accordance with the guidelines.</p> <p>15       UNIDENTIFIED SPEAKER: So I guess then the</p> <p>16 question is, why do they need that full 12 months of</p> <p>17 therapy other than a group of people decided that they</p> <p>18 need 12 months of therapy from culture negativity?</p> <p>19       UNIDENTIFIED SPEAKER: You know, we don't</p> <p>20 think they do.</p> <p>21       UNIDENTIFIED SPEAKER: Okay. I'm just going</p> <p>22 by what's published in the guidelines.</p>
<p style="text-align: right;">Page 275</p> <p>1 treatment failure and such that the physician and</p> <p>2 patient say, "Whatever it is you're on, I don't know.</p> <p>3 You could be on active or you could be on placebo."</p> <p>4       UNIDENTIFIED SPEAKER: I do have that. But</p> <p>5 at 6 months, you've given yourself that opportunity --</p> <p>6 I mean, sure a person could get worse in that 6 months</p> <p>7 and you have to figure out, "Well, why are they</p> <p>8 worse?" But after that 6 months, if your patients on</p> <p>9 your control arm are doing well --</p> <p>10       UNIDENTIFIED SPEAKER: They would stay.</p> <p>11       UNIDENTIFIED SPEAKER: -- you would continue</p> <p>12 with that. If they're on your treatment arm and</p> <p>13 they're doing well, you would continue that. But you</p> <p>14 have that opportunity to pivot from that.</p> <p>15       UNIDENTIFIED SPEAKER: Yeah.</p> <p>16       UNIDENTIFIED SPEAKER: And the only</p> <p>17 difference I'm saying is -- so then your analysis</p> <p>18 would be: at 6 months how many patients of each group</p> <p>19 bailed out? And the only difference with what I'm</p> <p>20 saying is it's not at six months, it's a time to</p> <p>21 event. So it allows that to happen at any point.</p> <p>22       UNIDENTIFIED SPEAKER: Yes. So I think the</p>	<p style="text-align: right;">Page 277</p> <p>1       UNIDENTIFIED SPEAKER: So I was going to come</p> <p>2 in from the guidelines perspective that I don't think</p> <p>3 you need to stick too hard to the guidelines because</p> <p>4 those guidelines are based on no evidence or very,</p> <p>5 very -- and I'll tell you, very low certainty of</p> <p>6 effects.</p> <p>7       So we don't have data on what's the optimum</p> <p>8 treatment. And until we do, we can't really change</p> <p>9 that recommendation based on guideline development.</p> <p>10 So we're stuck until someone does a trial that shows</p> <p>11 us that we don't need to do what we recommended in</p> <p>12 2007.</p> <p>13       UNIDENTIFIED SPEAKER: And we'd love that</p> <p>14 trial. We'd love to see that trial.</p> <p>15       UNIDENTIFIED SPEAKER: Well -- I mean, you</p> <p>16 cross over and over and half the people will stop at</p> <p>17 12 months and half of the people go for 18 months.</p> <p>18       UNIDENTIFIED SPEAKER: The challenges,</p> <p>19 though, I think we have to be careful, because</p> <p>20 primarily we're trying to design the trial to</p> <p>21 demonstrate that the drug works. And if we also try</p> <p>22 to solve another question in the same trial, it gets</p>

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<p>1 really complicated and could ruin both.</p> <p>2 UNIDENTIFIED SPEAKER: So Dr. Cox asked what</p> <p>3 would be the criteria for bailing out?</p> <p>4 UNIDENTIFIED SPEAKER: I think as a clinician</p> <p>5 you'd want to know clinical, how do they feel,</p> <p>6 function or survive. And if those are -- you know, if</p> <p>7 they're failing clinically, you'd bail. And I -- you</p> <p>8 know, we use CT imaging. So I think you couldn't do</p> <p>9 this without having imaging. They're just tied too</p> <p>10 closely together.</p> <p>11 UNIDENTIFIED SPEAKER: Yeah, I agree. I</p> <p>12 mean, I'll just give an example. We are CLO-FaST (ph)</p> <p>13 monotherapy trials, a few people and nothing. We have</p> <p>14 people on monotherapy CLO-FaST, which might also be</p> <p>15 nothing, we don't know. We're going to find out.</p> <p>16 But I had a patient 3 months in and she's had</p> <p>17 no improvement. She actually felt like she was</p> <p>18 coughing more. She was more tired. I scanned her.</p> <p>19 Her scan looked a lot worse. And I pulled her out of</p> <p>20 the trial. That was -- those were my criteria for</p> <p>21 bailing on the...</p> <p>22 UNIDENTIFIED SPEAKER: So could you do it</p>	<p>1 UNIDENTIFIED SPEAKER: So I guess Dr.</p> <p>2 Winthrop, is there a way to quantify your clinical</p> <p>3 intuition into some sort of a clinical outcome</p> <p>4 assessment tool?</p> <p>5 MR. WINTHROP: Yeah.</p> <p>6 UNIDENTIFIED SPEAKER: Yeah.</p> <p>7 UNIDENTIFIED SPEAKER: It's what I was trying</p> <p>8 to do with that thing, that napkin thing I drew on his</p> <p>9 point. I mean, yeah, I look at their sputum. I look</p> <p>10 at their radiograph. I look at their symptoms. I</p> <p>11 look at them and say, "God, they look great, they look</p> <p>12 bad, they look okay." And they tell me they look bad,</p> <p>13 they look great, they look okay.</p> <p>14 And, I mean -- so, you know, you got to</p> <p>15 collect that data prospectively and, you know, see how</p> <p>16 it plays out and how responsive it is to treatment.</p> <p>17 But we don't -- we haven't done that yet, you know,</p> <p>18 with a lot of these things. So I realize we're not</p> <p>19 solving any problems today...</p> <p>20 UNIDENTIFIED SPEAKER: I also think it's</p> <p>21 easier, although it's really quite difficult, as we</p> <p>22 all know, to look at something as to positive clinical</p>
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<p>1 without a surrogate? Because I think what the agency</p> <p>2 is concerned about is if the surrogate -- which in</p> <p>3 this case will be a CAT scan -- if that's driving your</p> <p>4 decision, that's not all that heartening to them. It</p> <p>5 doesn't really reflect a clinical. So could you have</p> <p>6 a bailing criteria that didn't involve some sort of</p> <p>7 surrogate, be it radiologic or microbiological?</p> <p>8 UNIDENTIFIED SPEAKER: Yeah. Well, I think</p> <p>9 what Shannon was saying, what I was trying to backup,</p> <p>10 it was a constellation of -- you know, it's putting</p> <p>11 your clinical hat on. It was a constellation of</p> <p>12 findings that this person is not doing well.</p> <p>13 And you're right. Let's say her scan was</p> <p>14 stable. I probably would have pulled her anyway,</p> <p>15 because she felt terrible and it didn't seem like</p> <p>16 whatever we were doing was helping her.</p> <p>17 So I don't know. I guess you could -- you</p> <p>18 know, you could debate the nuances. But I think those</p> <p>19 -- and you know what? I didn't even look at her</p> <p>20 cultures because I'm blinded. So I didn't really</p> <p>21 care. I just figured she's still culture positive.</p> <p>22 So...</p>	<p>1 outcome, to quantify a negative clinical outcome in a</p> <p>2 rescue. You know, there's no Hy's law with liver</p> <p>3 function test for NTM, you know, to say, "Oh my God,</p> <p>4 you know, my LFT has gone up three to five times I</p> <p>5 repeated it." That that doesn't really exist.</p> <p>6 So I think we're trying to do a lot of</p> <p>7 things. So I think what the -- the focus area of the</p> <p>8 clinical outcome is, you know, looking at the measures</p> <p>9 that we have now and trying to figure out how we can</p> <p>10 tailor those to marry "we live better, live longer,</p> <p>11 live fuller," you know, dictum that we are all trying</p> <p>12 to achieve here.</p> <p>13 UNIDENTIFIED SPEAKER: Yeah. So for a design</p> <p>14 like this, blinding would seem to be particularly</p> <p>15 important, blinding the treatment assignment. Yeah.</p> <p>16 I see heads nodding.</p> <p>17 UNIDENTIFIED SPEAKER: Is our next case the</p> <p>18 abscesses case?</p> <p>19 UNIDENTIFIED SPEAKER: It's a new regimen.</p> <p>20 UNIDENTIFIED SPEAKER: So treatment naive?</p> <p>21 UNIDENTIFIED SPEAKER: Yeah.</p> <p>22 UNIDENTIFIED SPEAKER: All right. I think</p>

<p style="text-align: right;">Page 282</p> <p>1 we've kind of addressed most of these questions for                  2 you all, but we haven't talked about abscesses.                  3 UNIDENTIFIED SPEAKER: One thing, Patrick,                  4 good about this issue of standardizing the background                  5 regimen, because I think we saw a gene slide that                  6 showed, you know, how diverse the background regimens                  7 were. And to me, you know, that raises red flags if                  8 people were on terrible background regimen and you                  9 added a new drug that helped them, it was just the new                  10 drug.                  11 UNIDENTIFIED SPEAKER: Yeah. I mean, yeah, I                  12 chose the efficacy of the new drug whether or not it                  13 was on a wise background. It's hard to do. These are                  14 patients that have been on drugs for many years and                  15 you couldn't change them all over to a standard. I                  16 mean...                  17 UNIDENTIFIED SPEAKER: I mean, it was                  18 agnostic (ph). But, you know, it is a question. You                  19 know, to design a new trial, how are we going to do                  20 this?                  21 UNIDENTIFIED SPEAKER: So I think as long as                  22 your bad background regimen is equally distributed and</p>	<p style="text-align: right;">Page 284</p> <p>1 that mandates appropriate guideline based therapy.                  2 UNIDENTIFIED SPEAKER: That's just because                  3 the new guidelines haven't come out. Anyone wants to                  4 talk about abscesses?                  5 UNIDENTIFIED SPEAKER: I do.                  6 UNIDENTIFIED SPEAKER: I mean, we clear --                  7 it's clearly an unmet need.                  8 UNIDENTIFIED SPEAKER: No, just a quick                  9 question. Is there a timeline for those guidelines,                  10 by the way?                  11 UNIDENTIFIED SPEAKER: We heard 3 to 4 years.                  12 UNIDENTIFIED SPEAKER: Three to four years.                  13 No. The guidelines have been under review for 2                  14 months at each of the four societies that are                  15 sponsoring them, and they are supposed to be back, all                  16 the reviews. Three societies were able to get it done                  17 a little faster than the last society, but they won't                  18 send the reviews until all are in.                  19 So hopefully, perhaps this week they will all                  20 be in. I hope certainly by next week. Then they must                  21 be -- those comments must be addressed, re-reviewed by                  22 the writing committee to see if they agree, then go</p>
<p style="text-align: right;">Page 283</p> <p>1 you're looking to see that your drug is working, I'm                  2 not sure that makes a whole bit of difference.                  3 UNIDENTIFIED SPEAKER: This is not quite the                  4 same thing, but we faced it with our STOP trial, which                  5 is choosing antibiotics for treatment of pulmonary                  6 exacerbations, CF. And we knew we couldn't be                  7 rigorous about the choices, because there's different                  8 bugs that people are treating and there's allergies or                  9 intolerances. But we did make them adhere to an                  10 approach, where, if there's pseudomonas in the                  11 culture, you have to pick two drugs from this table;                  12 and if you have MRSA, you pick from this. So you                  13 could try to at least find some minimum two drug                  14 regimen of what would be acceptable and ideally if                  15 it's MAC, it's got a macrolide as part of the regimen.                  16 MR. CHALMERS: So the counter argument to                  17 that was I think Anne showed this slide in her talk of                  18 the Vaningan (ph) paper, where less than a quarter of                  19 patients worldwide were on the recommended background                  20 therapy for MAC. So again, you run into the                  21 feasibility problem if that data is generalizable.                  22 Most patients are not going to be eligible for a trial</p>	<p style="text-align: right;">Page 285</p> <p>1 back to the societies for a faster review. So a few                  2 months, not years.                  3 UNIDENTIFIED SPEAKER: All right. 15 minutes                  4 on abscesses.                  5 UNIDENTIFIED SPEAKER: What do you want to                  6 talk about?                  7 UNIDENTIFIED SPEAKER: Is it the same                  8 conversation or is there something unique about                  9 abscesses that would be different for this study                  10 design?                  11 UNIDENTIFIED SPEAKER: I think it's different                  12 in a number of ways. One, if you thought you had                  13 trouble with a background regimen with MAC, you're                  14 going to really have trouble with abscesses. And I                  15 think it's much more difficult to think about                  16 monotherapy trials with abscesses.                  17 And the whole issue of what symptoms are                  18 important may be different, particularly if you're                  19 talking about abscesses and cystic fibrosis, where                  20 there tends to be a lot of fever and very acute type                  21 presentations as it progresses and worsens. I think                  22 it's -- in general it's going to be a more difficult</p>



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1 trial design conversation.

2 UNIDENTIFIED SPEAKER: So, yeah, what Ken

3 said. But abscesses is one of the most difficult

4 strains to treat. So if it takes X number of months

5 to see a, you know, microbiological response with MAC,

6 it's going to take -- I would think it would take

7 longer with abscesses.

8 I would think that the trial design will

9 change based on how long you have to measure out not

10 only in a surrogate endpoint, but possibly also in

11 clinical endpoints.

12 UNIDENTIFIED SPEAKER: Yeah, I agree with

13 those thoughts and I think Ken is absolutely right.

14 And I should also just restate that I'm not against

15 studying refractory people. I think we need to do

16 those studies. But for registrational studies, I

17 think they're much more difficult and treatment naive

18 will be much easier.

19 So that being said about abscesses, I would

20 also recommend treatment naive patients, but it brings

21 up a host of things that Ken just mentioned in terms

22 of, you know, you have to be really careful about who

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1 you enroll and, you know, what kind of control arm

2 that you'd allow them to be on.

3 I think if you're going to do a refractory of

4 such trial, the regimen -- background regimen issues,

5 as Ken said, makes it very difficult. I think you go

6 for a treatment naive trial.

7 I think CF and non-CF are different, just

8 like Ken said. I think, however -- this will be my

9 thought -- that there's a lot of abscesses patients

10 out there that behave like MAC patients and they just

11 cook along and they cook along with really minimal

12 disease progression over months and years, and then

13 something happens and they go down the tubes.

14 And I think there is a group of patients out

15 there that you can enroll and you can enroll them into

16 a multidrug regimen versus placebo. And you could do

17 the same type of study we were talking about for MAC.

18 That will be my -- that will be the way I'd do it.

19 UNIDENTIFIED SPEAKER: I wonder if we could

20 put our registries and whatnot together now to just

21 gather some observational data on our -- on how we're

22 treating abscesses and outcome -- you know, something

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1 that we could do within our registries, because it's

2 all over the places, as you say, and people just have

3 opinions on. And that could possibly inform a real

4 term.

5 UNIDENTIFIED SPEAKER: I think we have that

6 data, but I think it's going to be just as you say,

7 it's going to be all over the (cross talk).

8 UNIDENTIFIED SPEAKER: We have to do it more

9 organized than --

10 UNIDENTIFIED SPEAKER: Right.

11 UNIDENTIFIED SPEAKER: -- we have now.

12 UNIDENTIFIED SPEAKER: Right.

13 UNIDENTIFIED SPEAKER: But I think too about

14 -- going back to refractory disease, I mean, that

15 point of my talk. I feel like my refractory abscesses

16 patients they're refractory to everything. Like I

17 don't know that any new drug on the planet is going to

18 change the refractoriness. So I -- again, I would try

19 to enroll patients that you think has a propensity to

20 respond to a therapy.

21 MR. CHALMERS: That's how I think as well. I

22 mean, there's plenty of data now on abscesses biofilms

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1 and CF and bronchiectasis and I start to think about

2 it like pseudomonas infection, that you'll never

3 eradicate your more suppressive therapy.

4 UNIDENTIFIED SPEAKER: And you mentioned

5 registry data. How granular is the registry data?

6 Could it start to be interrogated in a way that might

7 help to inform the development of a clinical outcome

8 assessment?

9 UNIDENTIFIED SPEAKER: I think sort of. But

10 we could certainly put a push on to do a better job in

11 a relatively short fashion to get more data.

12 UNIDENTIFIED SPEAKER: Because if you get an

13 understanding of what's changing when, you know, for a

14 relevant patient population -- and what I mean by that

15 is it's the patient population that would be enrolled

16 in the trial. That may be really important to trying

17 to figure out what will change in 6 months and what

18 would be, you know, a reasonable endpoint to have in a

19 6 months trial.

20 UNIDENTIFIED SPEAKER: Yeah. I mean, I think

21 the U.S. Bronchiectasis Registry -- our registry is

22 not granular enough to answer those questions.

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<p>1 UNIDENTIFIED SPEAKER: Right. And that's</p> <p>2 what I would say...</p> <p>3 UNIDENTIFIED SPEAKER: We'd have to do</p> <p>4 something prospective.</p> <p>5 UNIDENTIFIED SPEAKER: Yeah, yeah.</p> <p>6 UNIDENTIFIED SPEAKER: We'd have to change</p> <p>7 what we're doing.</p> <p>8 UNIDENTIFIED SPEAKER: There is an example of</p> <p>9 that in the CF run out of National Jewish, Colorado,</p> <p>10 is the predict in-patient study. And we predict our</p> <p>11 CF patients who have newly identified NTM. And</p> <p>12 they're just in an observational arm. It's not</p> <p>13 rigorous like with routine study visits. It's tied to</p> <p>14 their routine clinic visits.</p> <p>15 And then if they now get to a position where</p> <p>16 the clinician feels they need to treat them, they go</p> <p>17 into the patient's arm, which is following an</p> <p>18 algorithmic approach for treating for both abscesses</p> <p>19 and for MAC. Again, this is entirely CF patients. I</p> <p>20 think there's 9 or 10 centers now involved and likely</p> <p>21 expansion to more.</p> <p>22 UNIDENTIFIED SPEAKER: But what kind of</p>	<p>1 of inform, you know, where you'd focus in on on</p> <p>2 subsequent development. So, yeah, no. But agree</p> <p>3 completely your comments, yeah.</p> <p>4 MR. CHALMERS: And just to fill in the</p> <p>5 discussion on registry. So in Europe, there's about</p> <p>6 16,000 patients now in the bronchiectasis and NTM</p> <p>7 registry, but only about a thousand of them have NTM.</p> <p>8 But they have annual quality of life bronchiectasis</p> <p>9 questionnaire data. So that could be used to look at</p> <p>10 some aspects of treatment response.</p> <p>11 UNIDENTIFIED SPEAKER: And I would just say</p> <p>12 from the CF registry standpoint, since 2010, there's</p> <p>13 been NTM data in that we've learned a tremendous</p> <p>14 amount about. If the CF Foundation could go one step</p> <p>15 further and put in NTM treatment data in there, I</p> <p>16 think it could be an even more useful tool on a</p> <p>17 greater number of patients that could help address</p> <p>18 some of these time to response and drug differential</p> <p>19 type of questions that we're having.</p> <p>20 UNIDENTIFIED SPEAKER: And how often CFQRs?</p> <p>21 Over 3 months? Is that...</p> <p>22 UNIDENTIFIED SPEAKER: It's not routinely</p>
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<p>1 outcome assessments are they doing regularly? In</p> <p>2 other words, sometimes you have this historical data</p> <p>3 and you're trying to look for what changes when. But</p> <p>4 if you haven't captured the particular instruments,</p> <p>5 it's not that helpful, you know.</p> <p>6 UNIDENTIFIED SPEAKER: Well, I know they're</p> <p>7 getting micro and some laboratory assessments,</p> <p>8 certainly lung function, but I think they're probably</p> <p>9 CFQR.</p> <p>10 UNIDENTIFIED SPEAKER: Okay.</p> <p>11 UNIDENTIFIED SPEAKER: So it's the -- it's</p> <p>12 just clinical data as would be captured during routine</p> <p>13 care, but it doesn't queue the CFQR, which is a</p> <p>14 respiratory questionnaire for CF symptoms every 3</p> <p>15 months. But beyond the CFQR every 3 months, it's just</p> <p>16 clinical data as it would be captured usually in the</p> <p>17 CF registry.</p> <p>18 UNIDENTIFIED SPEAKER: So if that's not a</p> <p>19 validated instrument for NTM or for the abscesses part</p> <p>20 of it, then it's something.</p> <p>21 UNIDENTIFIED SPEAKER: Yeah. It might not</p> <p>22 get you all the way there, but it might help to sort</p>	<p>1 captured, yeah.</p> <p>2 UNIDENTIFIED SPEAKER: Oh, it's not routinely</p> <p>3 captured.</p> <p>4 UNIDENTIFIED SPEAKER: Well, it just so</p> <p>5 happens we have our registry committee meeting on</p> <p>6 Wednesday and Thursday. So I'll bring that up for</p> <p>7 you.</p> <p>8 UNIDENTIFIED SPEAKER: You know anybody</p> <p>9 that's going to that?</p> <p>10 UNIDENTIFIED SPEAKER: Yes, I'll be there.</p> <p>11 BREAK</p> <p>12 PRESENTATION OF HYPOTHETICAL CASE STUDY #2:REGIMEN Y:  13 A NEW DRUG REGIMEN FOR TREATMENT OF NEWLY DIAGNOSED  14 BRONCHIECTATIC NODULAR PULMONARY MAC DISEASE</p> <p>15 MS. HIWOT: Drug regimen for treatment of</p> <p>16 newly diagnosed bronchiectatic nodular pulmonary mac</p> <p>17 disease. Regimen Y is a combination of two</p> <p>18 antimycobacterial drugs. Clinical microbiology</p> <p>19 studies were conducted to rule out antagonistic</p> <p>20 effects in the combination and resistance development</p> <p>21 to the combination. The contribution of each drug was</p> <p>22 demonstrated by hollow-fiber models and animal model</p>

<p style="text-align: right;">Page 294</p> <p>1 studies. Phase 1 studies to assess the safety                  2 tolerability PK of a single and multiple semi-doses                  3 were also completed.                  4 The Phase 2 trial was a randomized double                  5 blind placebo-controlled trial in patients newly                  6 diagnosed with bronchiectatic nodular pulmonary MAC                  7 infection that fulfilled the ATS/IDSA criteria for                  8 pulmonary disease. The study duration was 18 months.                  9 Primary endpoint was culture conversion at month 6,                  10 which was defined as three consecutive negative                  11 monthly sputum cultures without reversion.                  12 Secondary endpoints include changing the new                  13 clinical outcome assessment tool at month 6, 12 and                  14 18; microbiological assessment of sputum culture                  15 conversion at months 12 and 18. Functional assessment                  16 was a 6-minute walk test and quality of life                  17 bronchiectatic respiratory module modified for NTM                  18 patients.                  19 The results showed 45 percent more patients                  20 treated with Regimen Y achieved culture conversion at                  21 month 6 compared to placebo-treated patients. It was                  22 also noted that there were more treatment emergent</p>	<p style="text-align: right;">Page 296</p> <p>1 assessment tool between the two arms was a 90 percent                  2 power.                  3 The result of the study showed that Regimen Y                  4 met the prespecified clinical meaningful improvement                  5 in the COA compared to placebo. Secondary influence                  6 of culture conversion also showed 40 percent more                  7 patients treated with Regimen Y achieved culture                  8 conversion compared to placebo at months 12 and                  9 sustained conversion at months 24, was 20 percent                  10 higher in patients treated with Regimen Y versus                  11 placebo.                  12 There was a higher incidence of GI and                  13 dermatologic treatment emergent adverse events                  14 reported with Regimen Y compared to placebo that no                  15 significant difference and serious adverse events and                  16 mortality.                  17 Similar to case study 1, we have the three                  18 main questions. The first one is regarding our                  19 knowledge gap in our understanding of acceptability of                  20 duration of placebo, using the control arm for the                  21 patient -- this patient population. What the                  22 preferred primary endpoint may be to assess a direct</p>
<p style="text-align: right;">Page 295</p> <p>1 adverse events reported in patients with Regimen Y                  2 compared to placebo. However, the serious adverse                  3 events and mortality were comparable between the two                  4 arms. Based on the Phase 2 data, the program went on                  5 to the Phase 3 trial, which was a multi-center,                  6 randomized, double blind placebo-controlled trial                  7 which included similar patient population to the Phase                  8 2 trial, mainly adults with bronchiectatic nodular                  9 pulmonary MAC infection, who met the ATS/IDSA criteria                  10 for pulmonary disease and were treatment naive.                  11 Study duration was 24 months, 12 months on                  12 therapy and 12 months of treatment. Unblinding and                  13 rescue therapy was allowed only in clinical                  14 deteriorating patients. The primary endpoint was                  15 clinical outcome assessment at months 12.                  16 Secondary endpoints include change in COA at                  17 a later time points, microbiological endpoint of                  18 culture conversion at end of treatment, and 6 months                  19 and 12 months of treatment. And functional assessment                  20 was 6-minute walk at the end of treatment and of                  21 treatment. Sample size for the trial was adequate to                  22 show meaningful difference in the clinical outcome</p>	<p style="text-align: right;">Page 297</p> <p>1 clinical benefit for this patient population, symptom-                  2 based, functioning-based PRO be suitable or with                  3 functional assessment such as 6-minute walk or a PFT                  4 (ph) be appropriate in this treatment naïve population                  5 compared to the previous treatment experience                  6 population. And when should the clinically oriented                  7 primary endpoint be assessed and how long should the                  8 patients be followed?                  9 For the above mentioned points, how can we                  10 address any existing gap? And finally, despite all of                  11 the knowledge gaps, what can be done now for these                  12 patient population to design a scientifically sound                  13 clinical trial? That's the conclusion of the second                  14 case.                  15 MS. HIGGINS: Thank you, Hiwot. So we will                  16 have Charles Daley give the academic perspective and                  17 Dr. Daley's a pulmonologist at National Jewish Health.                  18 ACADEMIC AND INDUSTRY PERSPECTIVES ON                  19 CASE STUDY #2                  20 DR. DALEY: Thank you. And like my colleague                  21 Dr. Chalmers, I do not have slides. The academicians                  22 amazingly came without slides. So let me just</p>

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1 highlight something about this case as we began which  
 2 is different than the previous case. One is this is a  
 3 regimen, not a drug, that we're studying, includes two  
 4 drugs, and it's first placebo versus placebo in both  
 5 the Phase 2 and Phase 3 trial. It's newly diagnosed.  
 6 I guess that's the same as treatment naive. But  
 7 again, I would even argue we haven't really made clear  
 8 what we mean by treatment naive, more on that in a  
 9 moment. And it's nodular bronchiectasis, so that's  
 10 who we're studying here.

11 So in this regimen study, we have some data  
 12 presented, both preclinical, Phase 1. The preclinical  
 13 includes in vitro information; the hollow fiber  
 14 models; animal models. As we're going to be combining  
 15 drugs, this is very important data because we're going  
 16 to have to use this preclinical information to figure  
 17 out which drugs should or shouldn't go together. And  
 18 so I think this is even more important than the data  
 19 from in the first case, that no extra cellular lining  
 20 fluid is mentioned here. It wasn't the first one, but  
 21 I don't think you need it. So I'm glad that it's not  
 22 presented.

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1 The Phase 2 was placebo control, again, two  
 2 drugs versus placebo. And I think this is the same  
 3 discussion we had before. The duration here is 18  
 4 months in our Phase 2 trial. I just don't understand  
 5 why we would need to do an 18-month treatment regimen.  
 6 With culture conversion, it's 6 months. So to me,  
 7 it's 6 months instead of 18 months. They also add the  
 8 clinical assessment tool and it goes all the way out  
 9 to 18 months, but it doesn't start till 6 months. And  
 10 I think we all feel that this actually begins to show  
 11 a difference earlier than that, like at 3 months. So  
 12 I'm not sure why we wait to the end to start making  
 13 that assessment.

14 45 percent improved culture conversion was  
 15 noted. So as compared to placebo, so maybe we'll hear  
 16 from the panel what they think about that. Two drugs  
 17 -- two new drugs, because what we think would happen  
 18 with our standard regimen, but we're not comparing to  
 19 our standard regimen. So is this good? It's better  
 20 than placebo. But as mentioned earlier, saline is  
 21 better probably than placebo. So we need to think  
 22 about kind of what expectations we would have.

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1 The Phase 3 trial also randomized, double  
 2 blind, placebo control, same patient population, here  
 3 I think this issue came up earlier also, and this is  
 4 the idea of blinding to culture status. And here  
 5 we're going to be doing this for 24 months because  
 6 there's 12 months of treatment. So not 12 months be  
 7 on speed of culture conversion, which we talked about  
 8 before, but this is a fixed time treatment, which  
 9 personally I prefer over everyone getting a slightly  
 10 different treatment duration. And the 12 months of  
 11 follow up. And I think that's a reasonable time for  
 12 follow up in Phase 3 trial.

13 But as we've heard, we're going to be blinded  
 14 now for quite a while to culture status. We are going  
 15 to be gathering clinical information along that way.  
 16 And I think that's a long time to treat people without  
 17 some information or are they progressing, are they  
 18 failing or not. But at the same time, I think this  
 19 has to be fairly clearly defined what the rules are of  
 20 pulling out of a trial, and not just let docs make  
 21 that decision. Because that will be -- really it's  
 22 not a randomized process the way doctors think. So I

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1 would want to have clear criteria if we're going to  
 2 have some way to pull out. Otherwise, I don't feel  
 3 comfortable going a year of treatment being blinded.

4 And then the other thing that has come up  
 5 relates to this clinical assessment tool. And I think  
 6 it became very clear to me hearing the discussion  
 7 today that, if you're going to start off with a tool  
 8 that lists let's say symptoms, then you've got to  
 9 enroll the right patients, or you're just not going to  
 10 be able to determine whether people are improving. So  
 11 that's I think is a very important thing is to  
 12 consider the enrollment criteria. The other thing I  
 13 would say is that this is going to take forever. So I  
 14 kind of think this is unacceptable approach. And we  
 15 should be starting to borrow, I think when we get to  
 16 the stage of regimen testing, thinking about adaptive  
 17 designs, other ways to be able to get more information  
 18 over shorter periods of time because this process I  
 19 think is going to be very long. And we've learned  
 20 this already in MDR TB. This is how we started. And  
 21 we've evolved now to some other more interesting  
 22 designs.

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1 Ultimately, I think one of the questions that  
 2 we were asked is about coprimary. And I actually,  
 3 through the discussions today, I almost don't see any  
 4 other way around it. And you know, you don't get a  
 5 home run in these patients. They don't all feel  
 6 better. They don't all have radiographic improvement  
 7 and they don't all convert. But they often improve in  
 8 one of those domains. And clinically is that  
 9 important for the patient? So I do think we should  
 10 rethink how we measure outcomes. And I think this  
 11 idea of using multiple domains is probably the way to  
 12 go. That's it for me.

13 MS. HIGGINS: Okay. Thank you Dr. Daley.  
 14 For the industry perspective, we'll have Ira Kalfus.  
 15 He's the medical director of RedHill Biopharma where  
 16 he oversees the NTM program.

17 DR. KALFUS: I want to thank the panel for  
 18 inviting us. I think it's really been a wonderful  
 19 day. I know I'm the last guy with slides. I won't  
 20 say last but not least, we're an Israeli company. The  
 21 Israeli phrases are (foreign language). "The last is  
 22 the most cherished." It's what I tell my youngest

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1 kid. I'm not sure if that's really the right attitude  
 2 for today. But that's what I'm going with. Screen  
 3 right.

4 So I go with just about everything that's  
 5 been said today. I mean, we know that we have issues  
 6 with heterogeneity in populations. We know that we  
 7 have issues with what a clinical outcome analysis is -  
 8 - a clinical outcome assessment is going to be. We  
 9 also all know that a positive sputum culture that  
 10 turns into a negative sputum culture is beneficial.  
 11 It's beneficial in pneumonia, it's beneficial in  
 12 meningitis, it's beneficial in multiple disease  
 13 states.

14 And it's what our KOLs have told us that when  
 15 they are taking care of these patients, it's  
 16 beneficial for their patients. I think this  
 17 particular case illustrates something different from  
 18 what we've been discussing and these two antibiotics,  
 19 as I understood the case, are known antibiotics, known  
 20 -- drugs with known experience in treating this  
 21 particular patient population treating NTM, although  
 22 in a different -- I apologize, a different patient

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1 population. If it's a macrolite (ph), we saw the  
 2 slides about macrolites are approved. If it's  
 3 erythromycin or verbutin (ph) compound, we know that  
 4 this has been approved in the HIV population.

5 So these are drugs that actually there's a  
 6 fair amount of experience. So I think there's a  
 7 little bit difference in how we can approach the drug  
 8 development. And hopefully, we can actually make this  
 9 go a little bit faster because what I've heard all  
 10 morning is that we need to do this better and faster  
 11 for our patients. There are clinical guidelines out  
 12 there, there are new clinical guidelines that are  
 13 coming. Clinical guidelines or our clinical  
 14 guidelines are not FDA-approved products and what we  
 15 have to do as clinicians is we have to marry our  
 16 clinical experience with the regulatory environment so  
 17 that we can get drugs out for our patients.

18 The defined patient population in this study,  
 19 a naive patient population or a newly diagnosed  
 20 patient population that does not have cavitory disease  
 21 has no currently approved therapy. There is no  
 22 universally prescribed therapy. We saw today the

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1 patients were getting, you know, whatever a doctor  
 2 happens to be prescribing. He may have looked at the  
 3 guidelines years ago, he may have looked at the  
 4 guidelines that morning. Patient I was discussing  
 5 with somebody earlier today, one of the breaks, that a  
 6 patient comes in, isn't feeling that well, so they'll  
 7 change the prescription to an off-guideline  
 8 therapeutic because they think the patient is having  
 9 an adverse events.

10 So right now, even as they're on therapy,  
 11 there is no standard of care that's currently being  
 12 used. And this is a patient population that's an  
 13 orphan disease. There's a significant unmet need and  
 14 we as clinicians have to do something for this  
 15 particular patient population. The clinical outcomes  
 16 assessment is yet as undefined, is invalidated and not  
 17 for the purpose of this talk were to assume that it  
 18 is. We've heard about the top three symptoms, cough,  
 19 dysphonia and fatigue. Everybody agrees that these  
 20 are clinically relevant. And if we can get our  
 21 patients to improve in these symptoms, we will win.

22 But as Chuck (ph) just said, not every

<p style="text-align: right;">Page 306</p> <p>1 patient is going to win on all three of these. And                  2 you have to prospectively, if we're going to have a                  3 clinical outcome assessment, we have to figure out a                  4 way to prospectively to include those patients that                  5 have an outcome that can improve because if they don't                  6 have an outcome that can improve, then we're wasting a                  7 lot of time and effort doing this study.                  8 It may take a long time to demonstrate this                  9 statistical significance. It may take 6 months -- for                  10 sputum culture it may take 6 months for some of the                  11 outcomes we've looked at. We've had discussion as to                  12 how long do we treat people afterwards. I would love                  13 a 6-month study to a primary outcome of sputum with a                  14 clinical outcome. So -- but we know that the                  15 guidelines now talk about an additional 9 months.                  16 Actually, it adds up to 15 months in my math, not 16.                  17 But it's the fourth month is when that first one comes                  18 in plus an additional basically, you know, if you need                  19 12 months total of therapy, it's 12 plus 3, it's                  20 actually 15 month therapeutic. But then we have to                  21 think about whether it's a follow-on and I agree, I                  22 think a 24 months study in this particular patient</p>	<p style="text-align: right;">Page 308</p> <p>1 have that based upon discussions with all the                  2 stakeholders. It's the patients who are in the room,                  3 the patients who aren't in the room. It's the key                  4 opinion leaders and obviously it's the FDA.                  5 And I think that if we took the patient                  6 population that is treated with drugs that are already                  7 approved and on the market, and have safety and                  8 efficacy demonstrated by in previous and different                  9 indications and have a 6-month study that shows that                  10 there's efficacious and they're safety and there's                  11 tolerability, I would argue that that should be a                  12 pivotal study. It should allow for approval. And if                  13 a post-approval commitment is necessary, then that                  14 post-approval commitment for full approval will be                  15 designed based upon the clinical outcomes that come                  16 out of that Phase 2 study because we don't know for                  17 sure which ones are the ones that are going to work,                  18 which ones are going to best measure. And the best                  19 way of doing that is actually like we said earlier                  20 today, we've got to do the work to figure out how to                  21 best define what we're going to be doing next. Thank                  22 you.</p>
<p style="text-align: right;">Page 307</p> <p>1 population that really needs an approved product is                  2 probably too long.                  3 What I was suggesting a population who is                  4 being studied with drugs that are currently approved                  5 and other disease indications and may even be improved                  6 in various indications that are related to this NTM is                  7 I would look at a accelerated subpart H approval. And                  8 I would look at 3 to 6 months. We've heard about 3                  9 months you can start seeing symptomatic improvement.                  10 Certainly 6 months you need for 3 sputums in a row. I                  11 would look at safety and tolerability and I would look                  12 up, you know, because we would have to follow for the                  13 durability of the sputum conversion. We need to                  14 discuss how long we should be treating placebo                  15 patients, but if placebo patients are doing well, I                  16 see no reason why we can't really keep maintaining                  17 patients on placebo if we have to.                  18 We have to consider re-randomization of                  19 responders based upon what data risk committee and                  20 further discussion comes up with this, what would be                  21 necessary to get an approval. And I think we do the                  22 clinical outcome assessment. And I think we need to</p>	<p style="text-align: right;">Page 309</p> <p>1 (Applause)                  2 UNIDENTIFIED SPEAKER: All right. We'll open                  3 the floor to questions or comment.                  4 MODERATED PANEL DISCUSSION                  5 (CASE STUDY #2)                  6 UNIDENTIFIED SPEAKER: I'm just going to make                  7 one quick comment because I have to go. I want to                  8 thank everyone for this. It was excellent. And I                  9 basically disagreed with pretty much everything Chuck                  10 said that the one comment, the caveat would be that I                  11 think we should just study non-cavitary disease. I                  12 don't know that we need to specify that they have                  13 bronchiectasis because that will eliminate a big pool                  14 of patients who have COPD or other underlying lung                  15 diseases that have this. So I'd just be careful of                  16 that. Thanks.                  17 UNIDENTIFIED SPEAKER: I had a question.                  18 We've had talked about the duration of these studies,                  19 and it's challenging that they be long. And one                  20 particular issue I'm concerned about is missing data.                  21 If the endpoint is a change in a COA from baseline to                  22 month 12 in this case, what's your sense of how many</p>

<p style="text-align: right;">Page 310</p> <p>1 patients in the control group might have dropped out  2 because of worsening and so have missing data? And  3 then how best to handle that maybe from the  4 statisticians?  5 MS. BRITTAIN: Well, I guess one compromise  6 is, is if the primary endpoint is relatively early.  7 UNIDENTIFIED SPEAKER: Erica, can you get  8 closer? Thank you.  9 MS. BRITTAIN: Sorry. One possible  10 compromise is if the primary endpoint is relatively  11 early, like 6 months, but that, you know, you're still  12 going to evaluate longer term endpoints with, you  13 know, recognizing that you're going to have more  14 missing data.  15 UNIDENTIFIED SPEAKER: I might also add, I'm  16 just not sure about the premise of this particular  17 study, knowing that standard of care has relatively  18 high conversion rates over short periods of time. I  19 mean, I think most of us would quote minimum 80  20 percent, maybe 90 percent conversion rates, given  21 standard treatment. And so I think compare this to a  22 placebo control, unless there's some other reason to</p>	<p style="text-align: right;">Page 312</p> <p>1 road, or 2 months down the road, and it's something  2 else to think about and if you do start to think about  3 non-inferiority margins, then we need to have a  4 treatment effect, you know, to get to the non-  5 inferiority margin. So we'd have to be able to sort  6 of sort through that and have an evidence base to  7 define the treatment.  8 UNIDENTIFIED SPEAKER: And I would ask what's  9 the goal of a delayed treatment strategy as long as  10 that was defined a priority, I think that that would  11 be possibly, it would have to spelled out up front.  12 UNIDENTIFIED SPEAKER: Yeah. And a delay  13 treatment approach might be to allow you to show  14 superiority over a shorter time period. And then for  15 the patients who didn't get treatment initially, you  16 know, then they would get treatment thereafter. So  17 it'd have to be a delay that people were comfortable  18 with and that would not cause, you know, the patient  19 harm or consequences.  20 UNIDENTIFIED SPEAKER: So these would be  21 symptomatic patients who are candidates for  22 observation, right?</p>
<p style="text-align: right;">Page 311</p> <p>1 do this to shorten this up, I can't envision if the  2 decision was this patient needs treatment to put this  3 person on placebo or and they have expected 45 percent  4 better rate, it seems we're not in alignment with what  5 our current clinical practice is.  6 And I mean, again, I would defer to my  7 colleagues. So, you know, if you had -- rather than  8 placebo, you had standard of care in a non-inferiority  9 and you were looking to shorten the regimen, that  10 would be a whole different set of questions that I  11 would be interested in. If you say, well, I'm going  12 to do this in 2 or 3 months, rather than 6 or 9 months  13 to get to a singular endpoint, then I would -- I'd buy  14 into that. So I think this design would need to be  15 changed substantially for me to buy in.  16 UNIDENTIFIED SPEAKER: Yeah, so just -- I  17 mean a couple of things to think about. I mean, one  18 might be, you know, could you -- would it be ethical  19 and adequately safe to think about a treatment delay  20 strategy, you know? And it might, you know, if you  21 were debating treatment for some period of time, and  22 it was started this month, started a month down the</p>	<p style="text-align: right;">Page 313</p> <p>1 UNIDENTIFIED SPEAKER: I think what you're  2 seeing, Tim, is that this is -- these studies are  3 designed to demonstrate that the drugs -- these  4 regimen works, not designed to compare how it works in  5 comparison to existing guideline base, which are like  6 two different questions. But the regulatory purpose  7 would be to demonstrate efficacy.  8 DR. AKSAMIT: Yeah. And so I mean, again,  9 ethically, you'd be said -- I really wanted -- I think  10 we need to treat this person. You're going to say, I  11 don't know if this treatment works or not, I'm going  12 to give you a placebo. I don't know about that --  13 UNIDENTIFIED SPEAKER: You have to have  14 (cross talk), yeah.  15 UNIDENTIFIED SPEAKER: And it sort of brings  16 us back to the, you know, the basis for the, you know,  17 the clinical desire to treat the patient. I mean, is  18 there evidence that shows that, in fact, if you delay  19 treatment, you didn't treat that patient immediately  20 that, you know, there would be consequences to the  21 patient? And if so, what are they and that sort of  22 thing?</p>

<p style="text-align: right;">Page 314</p> <p>1 MS. HIGGINS: Mike, you want to say 2 something? 3 MR. PROSCHAN: So I'm a big believer in 4 avoiding non-inferiority trials whenever possible. 5 It's almost always better if it's ethical to do a 6 placebo-controlled trial. And you know, all the 7 things that should hurt you in a clinical trial 8 actually can help you in a non-inferiority trial, like 9 people crossing over to the other, you know, 10 treatment. And so, you know, I think if you can avoid 11 that, and it's ethical, I think you want to. Also if 12 you're talking about, you know, 90 percent with the 13 standard regimen, then a non-inferiority margin, a 14 realistic non-inferiority margin, I don't think 10 15 percent to me is non-inferior. If it's 90 versus 80, 16 that's a pretty big difference. And the smaller your 17 non-inferiority margin, of course, the higher your 18 sample size. So I think, you know, avoid them 19 whenever possible, non-inferiority. 20 MS. BRITTAIN: Right. Also, with the non- 21 inferiority, given how much is sort of unknown about 22 the clinical outcome, you really cannot do, at least</p>	<p style="text-align: right;">Page 316</p> <p>1 wouldn't, you know, you wouldn't go back and do the 2 individual drugs in a clinical trial. So that's sort 3 of the idea. 4 UNIDENTIFIED SPEAKER: But in TB, you 5 wouldn't have a placebo comparison to it. I mean, 6 that's -- it's a little confusing. When you get done 7 with this design, where do you position these two 8 drugs? 9 UNIDENTIFIED SPEAKER: So in TB, you're 10 right, you would show a dramatic effect over what 11 would be current standard of care. And the issue is 12 standard of care is already very effective, then it's 13 hard to show a dramatic effect over standard of care. 14 So then you're faced with the question of is it 15 ethical to either delay treatment, or to have a 16 placebo group for some period of time? And that I 17 think was what we were sort of coming back to. 18 UNIDENTIFIED SPEAKER: Or is it better than 19 standard of care, better in the sense of medicines 20 that were better well-tolerated, or could do it for 21 over a much shorter period of time rather? And that 22 would be a big deal and the patients would buy into</p>
<p style="text-align: right;">Page 315</p> <p>1 at this point, I don't see how you could do the 2 clinical outcome with non-inferiority. 3 UNIDENTIFIED SPEAKER: Yeah, I guess I don't 4 know what you would do with these two drugs when 5 you've got done. 6 UNIDENTIFIED SPEAKER: So maybe I'll just try 7 and fill in a couple of lines here. So, you know, I 8 think this is in part sort of an idea that's come from 9 the TB world. And in the TB world, if you have 10 patient populations where the available therapies are 11 not very good, you know, there is the possibility to 12 show something dramatic like, you can treat MDR and 13 XDR TB like you can treat drug-sensitive TB. And in 14 that setting, you'd go in not with one drug, but you 15 would go in with a combination. And you know, the 16 idea is, is that you'd show the value of each of the 17 components with other pieces of data, and you wouldn't 18 necessarily do like a full factorial design. So the 19 idea with going in with a regimen is to essentially 20 achieve a big advance. You know, all of a sudden, you 21 can treat patients and you can have a dramatic 22 improvement. And you know, it's so dramatic that you</p>	<p style="text-align: right;">Page 317</p> <p>1 that. And I think we would advance the field if we 2 could make what arguably is a 15 or 18-month regimen 3 now 6 months and still have similar outcomes. That's 4 a big deal. 5 UNIDENTIFIED SPEAKER: You also... 6 UNIDENTIFIED SPEAKER: But that's not this 7 design. So you would then be using historical 8 controls compared to what you're studying here. 9 UNIDENTIFIED SPEAKER: But you also could 10 have better -- theoretically, you could have better 11 compliance and better adherence with a prescribed 12 approved product as opposed to currently what is being 13 used in the community. If it's a combination product 14 that was a single capsule that had a combination of 15 both products, where you actually couldn't make an 16 alteration to what the product was. 17 UNIDENTIFIED SPEAKER: I think... 18 UNIDENTIFIED SPEAKER: So I mean, this would 19 be the first step. It would show that this regimen is 20 effective the first time we've shown that. And then 21 you could do a subsequent trial would say, well, let's 22 do one head-to-head and try to see how different it</p>



<p style="text-align: right;">Page 318</p> <p>1 is. But this would be the cleanest way to say this                  2 regimen is better than placebo. And the second                  3 question is, but how's it compared to some other                  4 regimen?                  5 UNIDENTIFIED SPEAKER: I mean, the only                  6 patients you put in a placebo-controlled trial, I                  7 don't think you're going to see a big bang, you know,                  8 because these are on sick patients that, you know, we                  9 would feel comfortable watching. So I'm with Tim and                  10 Ken over there. I think what we need is a shorter                  11 duration of therapy and you know, a good upfront                  12 response.                  13 UNIDENTIFIED SPEAKER: So it sounds like the                  14 group is leaning towards the active controlled trial.                  15 And then the question is could you show superiority or                  16 a significant treatment shortening? And then when the                  17 other thing too is, we'd still want to see the                  18 clinical benefit here to tell us that we're actually                  19 doing something somewhere in this mix.                  20 UNIDENTIFIED SPEAKER: Yeah, and that -- I                  21 think you're then shifting the non-inferiority to --                  22 because the end of your sentence was could we do</p>	<p style="text-align: right;">Page 320</p> <p>1 speaking, patients are dropped out of the analysis.                  2 And so when you see high reports of treatment success,                  3 you ask why did 50 percent of the patients get                  4 excluded from the analysis? And I'll bet my nickel                  5 that the actual culture conversion rate is probably                  6 closer to 50 percent.                  7 UNIDENTIFIED SPEAKER: Can I just sort of                  8 stir the pot here a little bit? Right? Nobody throw                  9 chairs at me. Okay. So we talked a little bit about                  10 the refractory patient population, and part of the                  11 discussion there was is that it was going to take, you                  12 know, a long period of time in order to see a clinical                  13 effect. So there was some, you know, at least among                  14 some folks, and then there was, you know, some people                  15 thought that within, you know, the first 3 to 6                  16 months, we could actually show a clinical effect in                  17 the refractory patient population with the correct                  18 clinical outcome assessment. So that's sort of one                  19 piece. Here, too, if we think about the naive                  20 population, I thought one of the ideas was, you know,                  21 that in the naive population, we would in fact be able                  22 to see a treatment effect earlier on.</p>
<p style="text-align: right;">Page 319</p> <p>1 shorter treatment and have similar outcomes? So we'd                  2 have to have some way of saying, yes, you've got                  3 similar outcomes which is non-inferiority, which is                  4 the same problem. I think we can't solve two things                  5 at once. We can't change the duration of the regimen                  6 and add drugs and try to make a clean trial.                  7 UNIDENTIFIED SPEAKER: It may be an approach                  8 that just doesn't fit too well here. I mean, we were                  9 trying to think of other ideas and things that we                  10 could drive from other areas. But this may be one --                  11 you know, sometimes we learn from other areas why                  12 something doesn't necessarily work too well in a                  13 different area. There may be regions, you know, the                  14 disease is different, the biology is different, you                  15 know, there may be other factors. But that's the                  16 value of the discussion.                  17 UNIDENTIFIED SPEAKER: So there were several                  18 pieces to that. One is the feasibility about a                  19 placebo-controlled trial and then the regimen versus                  20 drug analysis. But I will go on record as saying I                  21 don't believe there's an 85 percent culture conversion                  22 rate. My review of the literature, generally</p>	<p style="text-align: right;">Page 321</p> <p>1 Now, if we can't get to non-inferiority                  2 because we haven't been able to define the treatment                  3 effect in the treatment naive population, maybe that's                  4 possible, but it's eluded us so far. Then the                  5 question is, is what is the design here? And if it's                  6 superiority, it could be challenging if standard of                  7 care is highly effective already to show superiority                  8 over something that's highly effective. And here I                  9 saw you raise your hand, is there something else I'm                  10 missing here? Whatever, help me correct or fill in                  11 the gaps. But so where does that leave us?                  12 UNIDENTIFIED SPEAKER: I wouldn't want to be                  13 accused of not wanting to throw chairs.                  14 UNIDENTIFIED SPEAKER: But I agree with you.                  15 UNIDENTIFIED SPEAKER: I'm sure I agree with                  16 him. I like that. I mean, it's because I do think                  17 standard of care is at least modestly, at worst, you                  18 know, effective. So I think we have a pretty good                  19 regimen. We just -- it's too long and there are too                  20 many side effects of what we're using at the moment.                  21 UNIDENTIFIED SPEAKER: But I'm not -- I                  22 haven't heard that we can define a treatment effect</p>

<p style="text-align: right;">Page 322</p> <p>1 for the treatment naïve population.</p> <p>2 UNIDENTIFIED SPEAKER: Well, I think here we</p> <p>3 might use or weigh more heavily on a microbiological</p> <p>4 response in addition to these clinical response, so</p> <p>5 we're looking at a different clinical...</p> <p>6 UNIDENTIFIED SPEAKER: But that's sort of</p> <p>7 getting back toward the start of our problem though,</p> <p>8 right?</p> <p>9 UNIDENTIFIED SPEAKER: Exactly.</p> <p>10 UNIDENTIFIED SPEAKER: Because we haven't</p> <p>11 shown the clinical benefit linking to the</p> <p>12 microbiological effect.</p> <p>13 UNIDENTIFIED SPEAKER: Correct.</p> <p>14 UNIDENTIFIED SPEAKER: Now it's time for the</p> <p>15 chair, right?</p> <p>16 UNIDENTIFIED SPEAKER: No, I...</p> <p>17 MS. HIGGINS: Thanks. I know that -- you</p> <p>18 know, I don't want to be accused of not wanting new</p> <p>19 drugs because I desperately think we need new drugs</p> <p>20 for this disease. But it sounds like one of the</p> <p>21 things that we need is a trial of our current standard</p> <p>22 triple drug therapy for MAC thrice weekly, with</p>	<p style="text-align: right;">Page 324</p> <p>1 care does. So it can actually impede the subsequent</p> <p>2 development of additional therapies that could benefit</p> <p>3 patients. So a very fair point and the trial design</p> <p>4 you talk about could be helpful.</p> <p>5 MS. HIGGINS: Thank you. Can we go back to</p> <p>6 the question of the enrolling patients who are</p> <p>7 symptomatic, but candidates for observation in this</p> <p>8 sort of study design? And Tim, I hear you having some</p> <p>9 objections to that. But that is essentially I guess</p> <p>10 the more conservative, protecting against resistance</p> <p>11 manner of the monotherapy versus placebo control, as</p> <p>12 is going on right now for the Clofazimine study.</p> <p>13 MR. AKSAMIT: So I think, again, the starting</p> <p>14 position is a little bit different. If we have a</p> <p>15 cohort of individuals, let's say they're not so sick,</p> <p>16 we can either observe them or give them monotherapy</p> <p>17 Clofazimine, for example, but they're not so sick.</p> <p>18 That's a different group then that group that comes in</p> <p>19 and we say, there's no doubt what the diagnosis is,</p> <p>20 there's no doubt that they're symptomatic enough, we</p> <p>21 need to do some treatment, in which case then we're</p> <p>22 going to commit them to a placebo as opposed to the</p>
<p style="text-align: right;">Page 323</p> <p>1 treatment duration as the primary thing that we're</p> <p>2 looking at. So a trial that shows beyond culture</p> <p>3 conversion, do we need people to go 3 months beyond</p> <p>4 culture conversion on that regimen, 6 months beyond</p> <p>5 culture conversion, 9 months, 12 months to see whether</p> <p>6 -- and the outcome there would be relapse, meaning</p> <p>7 that you have the same bacteria that we were treating</p> <p>8 from time zero that we later identified, meaning that</p> <p>9 we didn't fully eradicate that in that person. Not</p> <p>10 re-infection meaning another species identified at a</p> <p>11 later time point.</p> <p>12 UNIDENTIFIED SPEAKER: Yeah, that could be an</p> <p>13 informative trial because if you had longer duration</p> <p>14 being associated with improved clinical outcomes, you</p> <p>15 know, you've answered a very important question, in</p> <p>16 essence, the longer duration being superior to the</p> <p>17 shorter duration. So, yeah. And I mean, it is</p> <p>18 challenging in a field where, you know, you don't have</p> <p>19 all the evidence that you want for what has already</p> <p>20 been adopted a standard of care because it makes</p> <p>21 follow-on studies that much more difficult because you</p> <p>22 haven't really defined exactly what the standard of</p>	<p style="text-align: right;">Page 325</p> <p>1 first group which aren't so sick. You say, "Okay,</p> <p>2 yeah, we can watch them versus the monotherapy."</p> <p>3 That's a different group and I don't have any</p> <p>4 hesitation about that.</p> <p>5 UNIDENTIFIED SPEAKER: Can I push just a</p> <p>6 little bit on that? Would it be possible to take</p> <p>7 those patients, I mean obviously there's a spectrum</p> <p>8 here. So you've got the ones that you'd be</p> <p>9 comfortable waiting on, and those that you'd not be,</p> <p>10 and then you've got, you know, a gray area where</p> <p>11 you're still putting the category of not being</p> <p>12 comfortable, but, you know, maybe there's a little bit</p> <p>13 more gray there. Could you monitor patients in a way</p> <p>14 that would allow you to be comfortable holding off for</p> <p>15 a little bit in this sort of gray area of where you</p> <p>16 might want to treat to keep patients out of trouble?</p> <p>17 DR. O'DONNELL: I mean, that is basically</p> <p>18 what we do in practice, right? We see the patient,</p> <p>19 they're not super-sick, but then we usually do</p> <p>20 something like airway clearance. And that we would</p> <p>21 have to sort of standardize that, I think, which is</p> <p>22 super difficult.</p>

<p style="text-align: right;">Page 326</p> <p>1 UNIDENTIFIED SPEAKER: And I think that  2 that's the key Anne brings up is as long as for the  3 clinical trial means different than clinical practice,  4 where we get started and look at the patient, take the  5 holistic kind of approach and say, okay, we're ready  6 to pull the trigger and treat or not treat. For  7 clinical trial design, we really need to have  8 objective criteria that guide us, yes, treat, don't  9 treat. And so we're comparing similar groups I think.  10 UNIDENTIFIED SPEAKER: And I'm going to agree  11 with you it'd be better to have the standard  12 approaches. But if you -- I mean if -- as long as it  13 was not antimicrobial, and you destilted (ph) it in  14 both arms and you were blinded and it was a  15 superiority design, I see Erica saying yes, I'm  16 thinking that maybe you'd still have something that  17 would be informative.  18 MS. BRITAIN: But if you have a binary, if  19 your endpoint is going to be binary, and you have a --  20 this decision that someone does need treatment is made  21 in a blinded fashion, it seems like that would be the  22 solution to the ethical dilemma.</p>	<p style="text-align: right;">Page 328</p> <p>1 UNIDENTIFIED SPEAKER: The missing piece in  2 here, so getting back to Dr. Cox's repeated request  3 that we need a clinical outcome to measure is, it's  4 one thing to say this is what you get when you use the  5 antibiotics, but also what do you get when you do  6 airway clearance? In terms of how much that will  7 change, and then with the addition of antibiotics?  8 UNIDENTIFIED SPEAKER: Well, and in that case  9 that you raise an interesting point because that then  10 becomes standard of care for that population, right?  11 If you're -- have a population that are candidates for  12 observation, and they don't want to go on treatment  13 right away, then in the absence of a trial, that would  14 be their standard of care.  15 DR. MELNICK: Yeah, David Melnick from Spero.  16 You guys sort of stole my points here, you know, if  17 the goal here is to come up with a superiority design  18 to demonstrate that a new agent has activity against  19 the drug, is the concern about a placebo-controlled  20 trial the ethical concern of withholding treatment  21 because I think we're in the situation that you  22 pointed out, where, you know, patients are symptomatic</p>
<p style="text-align: right;">Page 327</p> <p>1 UNIDENTIFIED SPEAKER: Yes, I think Tim's  2 issue was entirely the ethics of withholding therapy  3 from a patient for a while, but you've got some  4 patients who come in and they're asymptomatic and  5 you're really not putting them on therapy, you're  6 going to just observe those. You may have some  7 patients who come in that you want to treat day 1, but  8 that usually is because they've got cavitory disease  9 on radiographs. And so you've got the people in  10 between and as Anne has suggested, we don't start with  11 antibiotics, we start with the other things, treating  12 the underlying condition, treating their  13 bronchiectasis.  14 And so you could be randomizing those  15 patients then to be getting that approach plus placebo  16 versus that approach plus your active drug. And I  17 think at that point, 6 months doesn't seem too long.  18 UNIDENTIFIED SPEAKER: We heard 3 to 6 months  19 earlier this morning as well. So could you define a  20 period or an efficacy endpoint, clinical outcome at 3  21 months that was more definitive, at which point you  22 could reassess and potentially work in (cross talk).</p>	<p style="text-align: right;">Page 329</p> <p>1 candidates for therapy. You know, they've been  2 observed, you're going to -- you know, and then  3 randomize them in both arms, either to receiving a  4 placebo or the drug. I mean, is the concern, the  5 ethical concern about maintaining those patients on  6 placebo for 6 months because the conversation seemed  7 (cross talk).  8 UNIDENTIFIED SPEAKER: Kind of a clinical  9 issue more. You know, it's kind of like you're facing  10 the patient one-on-one. And it's very difficult for a  11 patient to -- for us, I think, to say 6 -- we're going  12 to wait 6 months, when, you know, it looks like they  13 really need the antibiotic. This is just not very  14 black and white, these patients.  15 UNIDENTIFIED SPEAKER: So that would be upon  16 us to define a clinical endpoint at 3 months, or  17 sooner than 6 months, that 4 to 6 months, that could  18 allow that assessment to be sooner and definitive.  19 UNIDENTIFIED SPEAKER: Well, I think that the  20 thing that's slowing us down the most right now is we  21 don't have a clinical outcome assessment.  22 UNIDENTIFIED SPEAKER: Correct.</p>

Page 330	<p>1 UNIDENTIFIED SPEAKER: Exactly.</p> <p>2 UNIDENTIFIED SPEAKER: And to do it right</p> <p>3 from the start is going to take a while. So how could</p> <p>4 we design -- to your question earlier, how -- if we</p> <p>5 had to design tomorrow, what would we do? And I'm</p> <p>6 wondering though, could we take this distilled (ph)</p> <p>7 assessment and use that as the -- so rather than a</p> <p>8 clinical outcome assessment, but the doctors decision</p> <p>9 that you're here, I don't -- wouldn't normally treat</p> <p>10 you right now, I would watch you and I'm going to</p> <p>11 watch you as part of this trial, I'm going to see you</p> <p>12 every hour. Don't worry, when I think you need to get</p> <p>13 treated, I will initiate treatment, but you'll be</p> <p>14 randomized to during that time.</p> <p>15 UNIDENTIFIED SPEAKER: And...</p> <p>16 UNIDENTIFIED SPEAKER: I think it would help</p> <p>17 us because we have this Clofaz (ph) versus placebo</p> <p>18 trial starting --</p> <p>19 UNIDENTIFIED SPEAKER: Yeah.</p> <p>20 UNIDENTIFIED SPEAKER: -- to know what -- how</p> <p>21 that goes before we take on another placebo-controlled</p> <p>22 trial.</p>	Page 332	<p>1 would find that very acceptable. And frankly</p> <p>2 understanding that this may in fact based on the Phase</p> <p>3 2 studies, or in the pre-studies to understand that if</p> <p>4 after 6 months, they may not need any treatment at</p> <p>5 all. And that would be enough justification to say,</p> <p>6 okay, let's proceed with placebo controlled study with</p> <p>7 standard of care airway clearance and see what happens</p> <p>8 at that 6-month period knowing I'm not going to put</p> <p>9 that person in a position to not receive what I would</p> <p>10 consider best care of macrolite-based regimen at that</p> <p>11 point.</p> <p>12 And if you're following them regularly, then</p> <p>13 at any moment, you could say you've gotten worse now,</p> <p>14 you need to come off randomized treatment and go on</p> <p>15 real treatment. And you could consider -- conceivably</p> <p>16 do that for a long time. And the endpoint the time</p> <p>17 too I think that's better to me, I know it's</p> <p>18 statistically more powerful than at 6 months, how many</p> <p>19 have gone on versus how many haven't, I would probably</p> <p>20 prefer a time to event.</p> <p>21 UNIDENTIFIED SPEAKER: But the...</p> <p>22 UNIDENTIFIED SPEAKER: If you're going to</p>
Page 331	<p>1 UNIDENTIFIED SPEAKER: So if we did the</p> <p>2 superiority study, though, with that front end, and</p> <p>3 somebody that wasn't really sick, if I had somebody</p> <p>4 that I knew needed to be treated and I needed to give</p> <p>5 them best care, it would be -- I'd be hard pressed now</p> <p>6 to at least give them an arm of placebo. It just</p> <p>7 wouldn't be the thing to do.</p> <p>8 UNIDENTIFIED SPEAKER: Right.</p> <p>9 UNIDENTIFIED SPEAKER: Right.</p> <p>10 UNIDENTIFIED SPEAKER: On the other hand, if</p> <p>11 you said -- and this patient comes in, I don't know if</p> <p>12 you're going to need to be, you know, on treatment or</p> <p>13 in this gray zone, if you will, and say we could</p> <p>14 justify treatment or a placebo in addition to standard</p> <p>15 of care with just chest physio, airway clearance, all</p> <p>16 that sort of thing and do that for 6 months, and</p> <p>17 knowing that I'm not going to lose macrolite, I'm not</p> <p>18 going to create macrolite resistance, or put that</p> <p>19 patient in a difficult spot as far as not responding</p> <p>20 to standard of care should that need arise at a later</p> <p>21 date, I'd be okay with that. And that would clearly</p> <p>22 be something that for a 6 month period would -- I</p>	Page 333	<p>1 borrow from other fields for a moment, the</p> <p>2 rheumatology, early HIV days, you know, it's not that</p> <p>3 we think you should go on therapy and we're not doing</p> <p>4 it, it's that we don't know actually when the right</p> <p>5 point is to start therapy. It could be that patients</p> <p>6 would benefit from earlier intervention all around and</p> <p>7 that this current practice of monitoring patients with</p> <p>8 pulmonary hygiene and that sort of thing is not</p> <p>9 sufficient and we're actually doing harm to patients</p> <p>10 by not starting therapy sooner. Therefore, when</p> <p>11 you're sitting in front of a patient, and you're not</p> <p>12 presenting it like I'm withholding a therapy from you,</p> <p>13 but actually, we're doing a study because we don't</p> <p>14 know we need to further elucidate the pathophysiology</p> <p>15 of this disease. It could be of great benefit to stop</p> <p>16 the inflammation in your airways that may be occurring</p> <p>17 at this stage in your disease.</p> <p>18 UNIDENTIFIED SPEAKER: But the risk of this</p> <p>19 study is we're testing two hypotheses. So one is the</p> <p>20 efficacy of the drug, the other one is the effect of</p> <p>21 early intervention in relatively mild MAC disease. So</p> <p>22 it's positive. It's no problem. We know the drug</p>

<p style="text-align: right;">Page 334</p> <p>1 works. If it's negative, we don't know whether that's                  2 because the drug combination lacks activity or because                  3 the patients didn't require treatment. And Tim was                  4 cautious in only putting in the patients that didn't                  5 really need treatment.                  6 MR. AKSAMIT: I think you have to define                  7 right now what you mean by positive or negative, or                  8 working and not working. If it's a microbiological                  9 sputum conversion, there's no positive or -- I mean,                  10 you'll know whether the antibiotic combination worked.                  11 If it's a combination of a clinical outcome                  12 assessment, and we're giving pulmonary toilet and                  13 we're giving respiratory care, it's very hard to                  14 define a priority without first doing that study what                  15 will define a positive endpoint for that -- from that                  16 perspective.                  17 UNIDENTIFIED SPEAKER: I mean the tension                  18 here is you want to prove some new drug or new drug                  19 combination works, right? Microbiologically,                  20 presumably, versus what we face in the clinic, which                  21 is (audio gap) and we can't tell on day 1 which                  22 patient is going to progress and which patient</p>	<p style="text-align: right;">Page 336</p> <p>1 clinical benefit here. I mean, ultimately. Now,                  2 maybe you're not measuring the right thing, maybe                  3 you're not measuring it at the right time, maybe it's                  4 going to take longer. But if all you've done is alter                  5 the culture, and there's no demonstrable clinical                  6 advantage to the patient, I'm not sure that it's worth                  7 doing that.                  8 UNIDENTIFIED SPEAKER: So I just want to go                  9 back a little bit further to how we're defining the                  10 population for the study. Are we defining the, you                  11 know, in this theoretical situation, are we defining                  12 the population as just a positive MAC culture, or are                  13 we defining the population as positive MAC culture and                  14 meets criteria -- ATS/IDSA criteria for beginning                  15 treatment?                  16 UNIDENTIFIED SPEAKER: You know, I think we                  17 would have to start with the position that they would                  18 fulfill criteria, but even fulfilling ATS criteria at                  19 the moment, doesn't in itself warrant treatment in all                  20 those cases.                  21 UNIDENTIFIED SPEAKER: So at that aquapoised                  22 (ph), then would it be okay if you had a population</p>
<p style="text-align: right;">Page 335</p> <p>1 doesn't. That's what we really need. I think what                  2 Karen said was real important, I mean why do we really                  3 want to know right now, we want to know who to treat,                  4 right, number 1, with antibiotics. And number 2, we                  5 want a shorter regimen, or that's what the patients                  6 want, like a built-up shorter regimen.                  7 UNIDENTIFIED SPEAKER: If I could just                  8 respond to James, I think that's a real concern that                  9 there, you know, we might -- it might not be a                  10 sensitive assay because these patients never go on.                  11 That's sort of why I would favor not a 6-month time                  12 point. (Audio gap).                  13 UNIDENTIFIED SPEAKER: By clearing exercises                  14 in one arm, and then the other arm, you did airway                  15 clearing, and then you gave an antibiotic. And there                  16 was no difference in the clinical outcome. But the                  17 patients who got the antibiotic had more clearing of,                  18 you know, their microbiological culture, you know, but                  19 you had no effect on the clinical outcome. I'm not                  20 sure what you're doing there. I mean, you're altering                  21 the culture. We know antibiotics can change people's,                  22 you know, cultures. You'd really want to show a</p>	<p style="text-align: right;">Page 337</p> <p>1 who met ATS/IDSA criteria for starting treatment, is                  2 there aquapoise to randomize them to treatment versus                  3 placebo?                  4 UNIDENTIFIED SPEAKER: In a gray zone group,                  5 my position would be yes. And I think it comes down                  6 to I think if we had a better clinical assessment                  7 tool, something that would be very sensitive, not                  8 necessarily even specific, but sensitive enough to                  9 pick up signal for treatment that is we're making the                  10 chronic fatigue and dyspnea better, or one of those                  11 three better, in addition to microbiological response,                  12 then I'm onboard. That's...                  13 UNIDENTIFIED SPEAKER: And then I have                  14 another question. So in clinical experience in these                  15 -- this particular patient population, when you clear                  16 their culture, are they symptomatically better?                  17 UNIDENTIFIED SPEAKER: Generally, yes. Not                  18 always, but generally. And you want to -- I mean...                  19 UNIDENTIFIED SPEAKER: I just had a                  20 clarification comment. There's -- in the ATS                  21 criteria, that's a criteria for diagnosis. There are                  22 no clear criteria for when to start treatment.</p>

<p style="text-align: right;">Page 338</p> <p>1 UNIDENTIFIED SPEAKER: I just don't think  2 this is the unmet need that we -- I mean, that sort of  3 philosophically, there's the unmet needs that we've  4 heard about, I don't think this type of study  5 addresses that.  6 UNIDENTIFIED SPEAKER: And that's in contrast  7 to the unmet need of a shorter, better regimen.  8 That's a big unmet need for the current standard of  9 care.  10 UNIDENTIFIED SPEAKER: And the other unmet  11 need in this population is less toxic therapy.  12 UNIDENTIFIED SPEAKER: That's exactly --  13 because, you know, there's a reason, one of the  14 reasons that we don't treat everybody is because we  15 recognize that the morbidity of the drugs that we use.  16 And some of that is benign sort of nausea, diarrhea  17 stuff, but you know, we've all seen visual toxicity,  18 hearing issues, the -- these meds are hard to take.  19 And that's why, you know, you think about it, we're  20 using drugs to treat MAC that are really basically  21 would use to TB, nobody treating TB is talking about  22 the toxicity of their drugs. Maybe you guys are, but</p>	<p style="text-align: right;">Page 340</p> <p>1 standpoint for the most part they're relatively  2 similar. But would you rather take something 4 months  3 or 9 months?  4 UNIDENTIFIED SPEAKER: In the background  5 there too is we've got a pretty good idea of the  6 effective treatment for latent TB and sort of  7 preventing, you know, recurrence of TB, which helps  8 us. That's our foothold.  9 MR. FENNELLY: Kevin Fennelly, NIH. So since  10 you guys brought up TB, so I've spent a fair amount of  11 my career studying cough and TB. And one of the  12 things that we observe in treating TB patients is that  13 -- it's if -- if we're using a good regimen, their  14 cough often goes down pretty quickly. And so I have a  15 question for the panel and for the FDA, and that is  16 we've talked about the heterogeneity a lot. So why  17 don't we get real narrow and pick something that we  18 can measure both subjectively and objectively? So, in  19 2019, there are two devices out there that will  20 measure cough frequency, we can measure the urge to  21 cough by doing inhaled capsaicin studies, and it would  22 be fairly clean. Patients who are wracked with cough</p>
<p style="text-align: right;">Page 339</p> <p>1 in general, you're pulling the trigger pretty quick,  2 but we have a lot of angst about it in our NTM  3 patients, because, you know, you're going to put a 80-  4 year-old woman on this therapy. So you want to be as  5 certain as you can be that it's actually going to  6 provide benefit. So I think there is a clear need for  7 something better in this patient population and  8 shorter as well.  9 UNIDENTIFIED SPEAKER: And part of what I  10 think I'm hearing is, is that we don't really have the  11 benefit well characterized here. I mean, compared to  12 TB, I mean in TB, the benefit is well characterized.  13 And then there's also the issue of, you know, the  14 contagiousness of the disease to others. But it feels  15 like here part of the issue is not just the toxicity,  16 the multiple meds, but also, you know, not really  17 having a really strong handle on the benefit side.  18 UNIDENTIFIED SPEAKER: And I want to resist  19 going back to the TB analogies, but I'm going to go  20 back there in LTBI, so, you know, 4 months of rifampin  21 versus 9 months of isoniazid or the 3HP now regimen, I  22 mean those are regimens that from an efficacy</p>	<p style="text-align: right;">Page 341</p> <p>1 usually want treatment, they're really uncomfortable.  2 So would a trial where the patient population were  3 patients with severe cough from their NTM disease,  4 would that be acceptable?  5 UNIDENTIFIED SPEAKER: So, I mean, it sounds  6 like what you're trying to do is put a construct  7 together where cough is at the clinical endpoint. So  8 I mean, a couple of things; I mean, we've also heard  9 in the discussion the heterogeneity of the disease,  10 and that some patients have cough, some people have,  11 you know, cough with sputum production. Some people  12 have shortness of breath, other people have fatigue.  13 So, I mean, you're proposing to use just the cough  14 population, and look for reduction in cough.  15 UNIDENTIFIED SPEAKER: We want a clinical  16 outcome. So a clinical outcome is cough, and study  17 those patients.  18 UNIDENTIFIED SPEAKER: So theoretically that  19 sounds possible. It sounds like you're focusing in on  20 a small portion of the population and one particular  21 manifestation of the disease.  22 UNIDENTIFIED SPEAKER: Yeah, I don't think</p>

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<p>1 it's so small.</p> <p>2 UNIDENTIFIED SPEAKER: Okay.</p> <p>3 UNIDENTIFIED SPEAKER: Well, it's...</p> <p>4 UNIDENTIFIED SPEAKER: I think it's 80</p> <p>5 percent of patients cough. So I think it's the same</p> <p>6 issue with a clinical instrument, which is, if you're</p> <p>7 going to measure cough, they need to have cough. And</p> <p>8 how would you measure cough though? I think this is</p> <p>9 the most difficult part of this is cough is so</p> <p>10 prevalent, and particularly with inhaled agent. So</p> <p>11 how would you measure cough again?</p> <p>12 UNIDENTIFIED SPEAKER: There are two</p> <p>13 instruments available now that are devices that will,</p> <p>14 you know, attach to the body, kind of like a Holter</p> <p>15 monitor with for cardiology, and you measure 24-hour</p> <p>16 cough frequency. And you could do that periodically,</p> <p>17 you know.</p> <p>18 UNIDENTIFIED SPEAKER: And what if the</p> <p>19 patient still said I have a terrible cough, and this</p> <p>20 isn't helping my cough?</p> <p>21 UNIDENTIFIED SPEAKER: You could -- there are</p> <p>22 subjective tools that, you know, you can use analog</p>	<p>1 there are certain cardinal symptoms associated with</p> <p>2 the disease that if you can find the top two, you</p> <p>3 know, according to Amy's presentation, that was</p> <p>4 fatigue and cough, and it -- and find a way to work</p> <p>5 that into an outcome assessment, an early outcome</p> <p>6 assessment, in the absence of a PRO -- a validated</p> <p>7 PRO, or a PRO that most focuses on those two.</p> <p>8 UNIDENTIFIED SPEAKER: And what I meant by</p> <p>9 the small population was if you were going for</p> <p>10 patients that exclusively only had cough because I'm</p> <p>11 guessing that they also have, you know, fatigue and</p> <p>12 dyspnea and I think that'd be really tough.</p> <p>13 UNIDENTIFIED SPEAKER: Measure the content...</p> <p>14 UNIDENTIFIED SPEAKER: Missing anything? I</p> <p>15 do want to come back to the -- that we've picked out</p> <p>16 the PRO, but it needs to be one that also not just to</p> <p>17 find something that can be measured, and they'd have</p> <p>18 to find the population that would be responsive. And</p> <p>19 so is there a need perhaps for just an observational</p> <p>20 study of these patients with an existing PRO?</p> <p>21 UNIDENTIFIED SPEAKER: You guys want to talk</p> <p>22 about the -- how we develop outcome assessment tools,</p>
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<p>1 scale or the Liester (ph) cough questionnaire,</p> <p>2 Leicester Cough Questionnaire.</p> <p>3 UNIDENTIFIED SPEAKER: They've been used</p> <p>4 successfully in Phase 2 studies of cough-suppressing</p> <p>5 medication. So they are sort of validated.</p> <p>6 UNIDENTIFIED SPEAKER: But it hasn't been</p> <p>7 successful...</p> <p>8 UNIDENTIFIED SPEAKER: Yeah, and these</p> <p>9 devices are being used in FDA-approved studies. So</p> <p>10 it's not like it's something new.</p> <p>11 UNIDENTIFIED SPEAKER: But it had -- you</p> <p>12 brought up TB, you know, it hasn't been successful in</p> <p>13 TB trials. So looking at clinical symptoms...</p> <p>14 UNIDENTIFIED SPEAKER: No, there's -- well, a</p> <p>15 different -- there's two different groups that have</p> <p>16 used ambulatory cough monitors and TB.</p> <p>17 UNIDENTIFIED SPEAKER: No, I mean cough</p> <p>18 assessment, the cough scales.</p> <p>19 UNIDENTIFIED SPEAKER: Oh, yeah, but I mean,</p> <p>20 I'm just talking about getting a 24-hour cough</p> <p>21 frequency. It's just an idea, just trying to...</p> <p>22 UNIDENTIFIED SPEAKER: No, but to your point</p>	<p>1 sort of the various steps along the way?</p> <p>2 UNIDENTIFIED SPEAKER: So the observational</p> <p>3 study, the PRO, will be able to tell us whether the</p> <p>4 PRO, the council evaluating this in the PRO is</p> <p>5 important, relevant to the patients. Unless the</p> <p>6 patients get worse or get better, we are -- we won't</p> <p>7 have the data to know whether they -- the instrument</p> <p>8 is sensitive to that change. You know, because if</p> <p>9 they -- I heard that it being -- it will be stable for</p> <p>10 quite a while, maybe they will get worse. But we know</p> <p>11 -- we don't know if the score -- if they get better,</p> <p>12 the score will be, you know, going up as showing that.</p> <p>13 So that power will probably still to</p> <p>14 (inaudible 0:55:16.7) to see a PRO still need to have</p> <p>15 a clinical trial. Now, we can observe in that patient</p> <p>16 that have not improved. I do have the question about</p> <p>17 -- about the PRO because I heard many times that the</p> <p>18 patient not have different symptom, shortness of</p> <p>19 breath, fatigue and cough. For example, we have a</p> <p>20 instrument which requests three questions and there's</p> <p>21 a -- they talk about heterogeneity and we need to</p> <p>22 evaluate patient depending on what symptom they have.</p>

<p style="text-align: right;">Page 346</p> <p>1 So my question for the panelists that is there no  2 concerned -- or should we be concerned that, for  3 example, patient at the baseline have very severe  4 cough. So we say, okay, for this patient, we will  5 evaluate a cough. At the end of the trial, the coughs  6 get better, but their shortness of breath or their  7 fatigue got worse, do we need to worry about that? So  8 if we need to worry about that, then we probably need  9 to evaluate all important symptoms, not just based on  10 what the symptom they have at the baseline. That's  11 one question.  12 The second question I heard about, I also  13 heard that the patient need to be symptomatic at the  14 baseline so that we can see improvement at the end.  15 That's one scenario. But also I heard that the one of  16 the treatment goal is that the patient not getting  17 worse, that they remain stable. So if they are  18 remaining stable, then they don't need to be  19 symptomatic at the baseline, and they just don't have  20 a symptom in that again they don't have a symptom, so  21 there's these two different patient populations. One  22 final comment, I heard about this study design, vision</p>	<p style="text-align: right;">Page 348</p> <p>1 individual items, and maybe it's a matter of rescoring  2 some of the instruments that are available to a very  3 small subset of items that actually work because I'm  4 not that familiar with this condition, but I've been  5 looking at the scales that are available. And just on  6 their face, some of them have items that are clearly  7 not going to move with treatment and so I don't know  8 that we need to develop something new, it may be a  9 matter of using the data, we have to try to combine  10 something into a better score that we can use.  11 UNIDENTIFIED SPEAKER: So I'll just -- I'll  12 briefly comment on that because I made a similar point  13 during my short presentation. There's no question  14 that there are data sets already with item level data.  15 So in this med (ph) clearly will have item level data.  16 And we've done some item level analyses of some of the  17 unsuccessful bronchiectasis trials. And I alluded to  18 it a little bit in my discussion that you see in some  19 of these studies that the cough domains get better and  20 the breathlessness get worse. And so the average  21 score is the patient looks as if they've not improved.  22 But on the subjective question in the database of</p>
<p style="text-align: right;">Page 347</p> <p>1 for vision, I think about that. But I also hear that  2 we don't have endpoints. You know, so it's very  3 difficult for me to think about all these studies done  4 without an endpoints. So that's all my questions.  5 MS. HIGGINS: So to the question about  6 whether we need observational study to evaluate  7 clinical outcome assessments, I guess I would want to  8 ask first, the existing instruments that have been  9 used previously have scores that are based on  10 combining a bunch of different symptom items and  11 impact items and tolerability items into a single  12 scale score, and they're not working well. But some  13 of these items are very specific to cough and  14 shortness of breath and things that probably will work  15 well. Is there existing -- are there existing data  16 that will allow us to look at the item level changes  17 on the very narrow specific cough, shortness of  18 breath, outside of these scale scores that are not  19 very good in this context for looking at clinical  20 benefit?  21 And so in early studies, if you've used the  22 QLLB (ph) respiratory domain, looking at those</p>	<p style="text-align: right;">Page 349</p> <p>1 would the patient like to remain on treatment, and the  2 answer is yes which suggests that the patient valued  3 the improvement in cough more than they didn't like  4 the change that they've reported in some of the other  5 domains. And so we need to adjust the weighting I  6 think of some of these to more match what's important  7 to patients.  8 MS. HIGGINS: Right. And I think the survey  9 that was done helps with the (audio gap). Based on  10 James' comment, wouldn't a joint decision by the  11 patient and the physician in terms of the need for an  12 alternate therapy be a reasonable clinical endpoint  13 and in terms of the time to failure in that setting?  14 What is that joint decision based on?  15 UNIDENTIFIED SPEAKER: It's, I mean,  16 obviously it would be multi-factorial, but for some --  17 one patient, it could be like my cough isn't there  18 anymore, or I or my cough has come back. I, you know,  19 I don't care that the sputum is positive, I'm  20 achieving benefit. I don't want to change, whereas  21 the clinician is uncertain something.  22 UNIDENTIFIED SPEAKER: Yeah, the clinical</p>



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<p>1 endpoint becomes the patient walking in and saying, I                  2 feel lousy, I want off this therapy, take me out of                  3 the trial. And that becomes the time to event                  4 analysis. And it's I think perhaps a reasonable                  5 reflection of the way the patient feels.                  6 UNIDENTIFIED SPEAKER: So the challenge...                  7 UNIDENTIFIED SPEAKER: And it brings in the                  8 physician's assessment, we've talked about this --                  9 UNIDENTIFIED SPEAKER: Yeah.                  10 UNIDENTIFIED SPEAKER: -- historic (ph)                  11 assessment of my patients doing well or not.                  12 UNIDENTIFIED SPEAKER: Right. The one                  13 challenge I see with that is that it at a data level                  14 score level, we won't know if those decisions are made                  15 because of tolerability issues or lack of efficacy.                  16 But -- and so I think we need to be able to clearly                  17 define how those decisions to change treatment are                  18 made or to treat and be able to measure those. These                  19 global assessments are really difficult to interpret                  20 at the end of the day. We don't know if the decision                  21 to change treatment or to treat was based on the                  22 culture alone in those cases and that doesn't get us</p>	<p>1 unrelated, but I mean, if treatment gets rid of some                  2 of those other things, that is making the patient feel                  3 better, and that's, you know, improving their quality                  4 of life.                  5 UNIDENTIFIED SPEAKER: Yeah. So, you know,                  6 in this -- in that example, again, I'll just over-                  7 generalize, so that per same person comes in, has                  8 cough, and now they've got pseudomonas, they get                  9 treated for their pseudomonas. And 10 days later,                  10 after they get treated for their pseudomonas, they                  11 come back and say, hey, I feel great again. And                  12 they're still on their same treatment for the MAC,                  13 say, that's been there all along, just that we treated                  14 the secondary issue that caused cough. And again, it                  15 was completely removed from the therapeutic for the                  16 primary therapy of the MAC.                  17 UNIDENTIFIED SPEAKER: But I'm saying that                  18 how do you know that the treatment for the MAC isn't                  19 going to have an effect on those other things as well?                  20 UNIDENTIFIED SPEAKER: And it's possible. So                  21 again, in this example, where somebody stated been on                  22 MAC therapy for a month or 2 or 3 or 6 months, and</p>
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<p>1 to having any information on the clinical benefit.                  2 UNIDENTIFIED SPEAKER: And I would caution                  3 just a little bit to that's overweighed the specific                  4 domains. And let's take cough as a example, and as it                  5 was just shared, so we have a patient that's on some                  6 therapy comes in, says my cough is terrible, I want to                  7 get off this therapy, well, it turns out that they've                  8 now got pseudomonas or they've got a sinus infection,                  9 or they've got some other reason they have coughs.                  10 It's not that their cough isn't worse, it's not that                  11 they don't feel badly, but it's two true and unrelated                  12 type of issues. So we have to be a little bit                  13 cautious not to overweight cough and attribute with a                  14 great deal of specificity that symptom of cough. And                  15 in fact our experience clinically is just as was                  16 shared about this heterogeneity, and that holds true                  17 for the symptoms as well, that we if we overweight                  18 that then that's going to be a problem. So we have to                  19 just be a little cautious going into this and                  20 assigning too much weight to give us spurious results                  21 essentially.                  22 UNIDENTIFIED SPEAKER: You say it's</p>	<p>1 comes in analysis, I feel crummy because my cough is                  2 worse. And that person has the impression I think my                  3 MAC is back and so I just want to come off therapy,                  4 and then you -- we make our assessment and lo and                  5 behold, well, it's not because they have a bacterial                  6 exacerbation or they have a sinus infection, which can                  7 be taken care of very easily. And the symptoms they                  8 have 3 months or 6 months that they attributed to                  9 their MAC coming back wasn't in fact the MAC at all                  10 and something else. We treated in a very simple and                  11 easy way. Those symptoms go away and they'll say,                  12 "Okay, I'll stay on the MAC treatment now."                  13 UNIDENTIFIED SPEAKER: Right. So I mean, it                  14 sounds like, you know, that's one of the issues with                  15 having the patient have a big say in the outcome. And                  16 I think, you know, what I would worry about is this                  17 conflict between, you know, you give them the results                  18 of the culture, there's -- it was expressed earlier                  19 they have to give them the results of the culture.                  20 I'm worried that that can have a big effect on their                  21 PRO. You know, maybe they felt great until you told                  22 them that that they're, you know -- you know, I would</p>

<p style="text-align: right;">Page 354</p> <p>1 like to get those PROs before giving them the                  2 information about the culture.                  3 MS. HIGGINS: Okay. Can I address...                  4 UNIDENTIFIED SPEAKER: I just want to weigh                  5 in on that. I was thinking about that earlier, when                  6 we were talking about the blinding and I completely                  7 agree. I would say you don't want to give the PRO,                  8 have them administer it before any of the other                  9 assessments, before the 6-minute walk if you're going                  10 to do that, because you don't want anything to bias                  11 their -- how they feel -- how they think they feel,                  12 and I agree that giving them their results of their                  13 culture could actually have an impact. We're worried                  14 earlier that it can be the other thing, that if the                  15 sputum results were -- it's a conversion that                  16 happened, then we might artificially think they're                  17 better --                  18 UNIDENTIFIED SPEAKER: Yeah.                  19 UNIDENTIFIED SPEAKER: -- because of that                  20 result.                  21 UNIDENTIFIED SPEAKER: And just for the                  22 record, so with the PRO and the culture, so if</p>	<p style="text-align: right;">Page 356</p> <p>1 bronchiolectasis. And I think that's going to be some                  2 noise in the system that is unavoidable.                  3 UNIDENTIFIED SPEAKER: I also think when you                  4 start measuring multiple outcomes like fatigue and                  5 cough, I think we're going to have to remember -- and                  6 maybe the best thing is to measure those things                  7 together, but we're always going to face the fact that                  8 the cough contributes to the fatigue. And that's                  9 something we saw -- I was reading our PFDD transcript                  10 recently and the patients described the cough as                  11 exhausting. And if you think about -- if you're                  12 talking about a cough that causes them to fracture                  13 bones, and that's what it does sometimes, that is the                  14 nature of the cough they're experiencing, it is                  15 exhausting for them. And they do it constantly and                  16 sometimes it's, you know, sometimes -- a lot of times                  17 they just cough, and sometimes they have to do it on                  18 purpose to clear their lungs. So it's they really                  19 almost have no choice. Those things are going to                  20 confound measurements, no matter what, I'm not sure                  21 how to get around that. That's not my area of                  22 expertise. That's why a lot of you are here. But I</p>
<p style="text-align: right;">Page 355</p> <p>1 somebody comes in for say a study clinic visit, they                  2 collect the sputum and do their 6-minute walk test,                  3 that sputum will be available up to 2 months later.                  4 So it would not be in real time for sure.                  5 UNIDENTIFIED SPEAKER: But still it could be                  6 -- they might be affected by the one from before. But                  7 it seems like it might be okay. Some of the designs                  8 people didn't like the MD not knowing the sputum                  9 result. So maybe there could be, you know, the MD                  10 could have the -- the health professional could have                  11 the sputum result in a patient not for a possibility.                  12 UNIDENTIFIED SPEAKER: (Off mic). Six month                  13 (off mic).                  14 UNIDENTIFIED SPEAKER: I think in the                  15 scenario we were talking about where these are sort of                  16 mild patients might not -- you could conceivably --                  17 UNIDENTIFIED SPEAKER: Yeah.                  18 UNIDENTIFIED SPEAKER: -- keep everyone                  19 blinded. I think you bring up this point of the non-                  20 specificity of the symptoms and we're always going to                  21 face that there may be underlying COPD that gets a                  22 little worse that, you know -- or a flare of the</p>	<p style="text-align: right;">Page 357</p> <p>1 think no matter how sensitive the tool is, we're                  2 always going to have that confounding factor.                  3 UNIDENTIFIED SPEAKER: I have a question for                  4 the clinicians. In this less sick population, where                  5 you have less lung damage, is there any other                  6 functional assessment that can be done to follow these                  7 patients in addition to PRO or on its own?                  8 UNIDENTIFIED SPEAKER: When we pulmonary                  9 function tests, you know, there are things we do, but                  10 the PFTs are not very sensitive at all. So...                  11 UNIDENTIFIED SPEAKER: Yeah. To make it                  12 short, the answer would be no.                  13 UNIDENTIFIED SPEAKER: Yeah.                  14 UNIDENTIFIED SPEAKER: (Cross talk).                  15 UNIDENTIFIED SPEAKER: It -- really the PROs                  16 would be the main thing if -- I mean we -- obviously                  17 in clinical practice, it's not a formalized PRO, it's                  18 like how you're doing kind of thing, right?                  19 UNIDENTIFIED SPEAKER: Yeah.                  20 MR. CHEN: So instead of the pulmonary                  21 function, the symptoms that we know this, we have                  22 difficulty evaluating the symptoms that they are all</p>

<p style="text-align: right;">Page 358</p> <p>1 inter correlated, and we didn't know how to weight  2 that and I don't think it will -- I also think it will  3 be difficult to weight by the degree of bother because  4 the degree of bother is different for different  5 patients, some patient more bothered by shortening of  6 breath, some people -- some patient more bothered by  7 fatigue. So the weightings is used -- I think usually  8 we will see, you know, based -- the instrument should  9 be based on what is most relevant and important to the  10 patient. But instead of symptoms, that because of the  11 cough, because of the shortening of breath, can we  12 measure their activity to their daily functions, that,  13 you know, rather than a 6-minute walk test at one time  14 point, but how about ask them to say, you know, are  15 you able to run a mile, walk up 10 flight of stairs,  16 what is useful to ask them to do, physical function  17 PROs, daily activity PRO?  18 UNIDENTIFIED SPEAKER: I think the PRO that  19 asks them those kinds of questions about daily  20 functions would be more useful. But again, looking at  21 patient feedback, and again -- (audio gap) and stop  22 and rest. It takes them several days to do a couple</p>	<p style="text-align: right;">Page 360</p> <p>1 UNIDENTIFIED SPEAKER: They're not, but we  2 have to consider developing tools that are going to  3 work across a broader spectrum.  4 UNIDENTIFIED SPEAKER: Right. I understand  5 that. But I think, you know, when we're talking about  6 enrolling patients, milder patients, our tools are  7 different.  8 UNIDENTIFIED SPEAKER: Not different, but  9 different results.  10 UNIDENTIFIED SPEAKER: You mean -- I think  11 your survey probably represents a somewhat skewed  12 population.  13 UNIDENTIFIED SPEAKER: Probably does. But  14 again, we're going to end up dealing with refractory  15 patients at some point in clinical trials.  16 UNIDENTIFIED SPEAKER: Right. Now...  17 UNIDENTIFIED SPEAKER: And if the tool isn't  18 going to measure, you know, across multiple patient  19 populations, then, you know, then we're looking at  20 developing multiple tools for multiple patient  21 populations, it becomes an even more complex issue.  22 UNIDENTIFIED SPEAKER: But it does seem to be</p>
<p style="text-align: right;">Page 359</p> <p>1 of loads of laundry. Those kinds of things that we  2 would walk into the house and think nothing of doing,  3 they have to plan and sometimes they have to plan days  4 in advance. And if they're having a bad day with  5 their lungs, they are not going to be able to do it.  6 If the weather is not good, they might not be able to  7 do it. So if they see improvements over time in just  8 their basic daily functioning tasks, that also might  9 be a measurement. We may not consider those things  10 important like, oh, great, I did a load of laundry  11 today. For us, that's not a big deal. For someone  12 who's unable to do that, for someone who's unable to  13 walk across one room, for someone who's unable to walk  14 up one flight of stairs, a change in that measurement  15 for them might be very significant. And I don't think  16 we can tell them if it's not significant, if it is  17 important to them.  18 UNIDENTIFIED SPEAKER: But I think -- I mean  19 you -- it's a little bit of a skewed population you're  20 talking the more severe patients, we're also  21 discussing real mild patients that we might want to  22 intervene on. And they're not having those issues.</p>	<p style="text-align: right;">Page 361</p> <p>1 advantageous to measure something, you know, daily,  2 rather than have it, you know, they had the 6-minute  3 walk test on a bad day for them, you know...  4 UNIDENTIFIED SPEAKER: I mean, that's why the  5 Fitbit idea?  6 UNIDENTIFIED SPEAKER: Yeah. Yeah.  7 UNIDENTIFIED SPEAKER: Something along those  8 lines, some activity monitor (cross talk).  9 UNIDENTIFIED SPEAKER: Right.  10 UNIDENTIFIED SPEAKER: Yeah, just a comment  11 on the Fitbit, though. I had 893 steps today. So  12 it's a bad day.  13 (Laughter)  14 UNIDENTIFIED SPEAKER: I just wanted to make  15 one comment to your original question, because the --  16 yes, the NTM therapy can have other benefits and I'll  17 just pick the MAC providers as an example. It's a  18 common therapy in bronchiectasis. So they could get  19 additional benefits from a drug like that that's  20 unrelated to the effect on the MAC.  21 MS. YANG: Thank you. My name is Lee Yang  22 (ph). I heard you the whole day and I think we are</p>

<p style="text-align: right;">Page 362</p> <p>1 going to the -- (audio gap). There's nothing to do                  2 with TB or NTM. So I would like you to be -- pay                  3 attention. You are going to provide a health care.                  4 You are not going to (inaudible 1:13:55.4) something                  5 misleading cost and consequences related to the                  6 disease or health prevention. Instead you were to                  7 focus on the healthcare. So something is misleading,                  8 you have to get rid of it, for instance the fatigue.                  9 Now if you go to some people, which are providing some                  10 to people to (inaudible 1:14:19) and they already                  11 have, so there are more instance.                  12 DR. FLUME: All right, let me interrupt you                  13 for a moment, because if -- I'm not understanding the                  14 question completely and we can talk about this                  15 afterwards, but we are talking about -- (audio gap).                  16 MS. YANG: -- to pay attention to healthcare.                  17 So instead of the healthcare, you are talking about                  18 something else. They allow them to make the excuses.                  19 DR. FLUME: Okay. Thank you.                  20 MS. YANG: So now, I still have the other                  21 point that you just mentioned now, I want you to                  22 redirect your attention. So instead of like false</p>	<p style="text-align: right;">Page 364</p> <p>1 correction. This is the word you are talking about.                  2 I mean not us too long ago -- (audio gap). This is                  3 that we are talking about system problem. And then                  4 you just learn the system direct to where you should                  5 go. I would like you to -- and I respect you as a                  6 medical health professional, what I try to say is that                  7 this is not on a medical direction problem. They also                  8 offer socialist workers --                  9 DR. FLUME: Ma'am?                  10 MS. YANG: -- and provide or nobody have any                  11 health -- any kind of credentials.                  12 DR. FLUME: Ma'am, I'll stop by and talk a                  13 little bit later with you, okay? We appreciate you...                  14 MS. YANG: (Cross talk).                  15 DR. FLUME: Excuse me, ma'am. Ma'am, we                  16 appreciate your comments.                  17 MS. YANG: (Cross talk). I was from your --                  18 that information. So you had (cross talk).                  19 DR. FLUME: Please do.                  20 MS. YANG: Yeah. That would be good. If you                  21 can just give me a bit in a thought.                  22 DR. FLUME: I will stop by in a moment and</p>
<p style="text-align: right;">Page 363</p> <p>1 constant consequences, now you got to view the right                  2 decision, this is healthcare. This is not something                  3 for you to mislead, you go to wrong direction.                  4 DR. FLUME: Okay. Thank you. You may...                  5 MS. YANG: So let me point something you just                  6 mentioned not too long ago, so you have fresh memory.                  7 So I would like you to say that this is like                  8 (inaudible 1:15:23.2) or how much you want to know                  9 decision and I would like to tell you a lot of                  10 veterans, a lot of (inaudible 1:15:25), they are sent                  11 to mental hospital or rehab center by the month, or 6                  12 months or even longer. And they transfer --                  13 DR. FLUME: Okay.                  14 MS. YANG: -- to the different institution.                  15 DR. FLUME: Let me interrupt you there                  16 because I think we're getting off track, we're talking                  17 about (cross talk).                  18 MS. YANG: Yes. I said you are getting off-                  19 track.                  20 DR. FLUME: NTM therapy -- I'd be happy to                  21 talk to you after the session.                  22 MS. YANG: No. I would like you to my</p>	<p style="text-align: right;">Page 365</p> <p>1 talk with you, okay? But...                  2 MS. YANG: I'm ready to go and I'm not going                  3 to spend anymore.                  4 DR. FLUME: Then I will come and talk with                  5 you right now.                  6 MS. YANG: And I even mentioned, I hope you                  7 sent to the FDA director, okay?                  8 DR. FLUME: All right. Dr. Cox and thank                  9 you. Have we addressed all of the questions for the                  10 panel? I just want to make sure that -- because we                  11 are going to come to time where we need to wrap it up.                  12 MS. HIGGINS: I think there were some                  13 questions in case 1 that perhaps in the treatment --                  14 in the refractory case were potentially more                  15 applicable to here. But we also have that follow-on                  16 overall questions for both cases. So I don't know if                  17 that's -- you're moving on to that or wanted to go                  18 back and...                  19 DR. FLUME: I don't recall that we had other                  20 questions to follow on. I have one question that came                  21 in from the webcast I do want to get to before we                  22 close. But do we have other questions that we had to</p>

<p style="text-align: right;">Page 366</p> <p>1 follow on? These are the questions to you.</p> <p>2 UNIDENTIFIED SPEAKER: Yes.</p> <p>3 UNIDENTIFIED SPEAKER: These are the same</p> <p>4 question.</p> <p>5 UNIDENTIFIED SPEAKER: (Off mic).</p> <p>6 DR. FLUME: From the first case.</p> <p>7 UNIDENTIFIED SPEAKER: We're asking couple of</p> <p>8 bulleted items from the previous...</p> <p>9 MS. HIGGINS: Right, yeah. So I don't think</p> <p>10 we got through all of the questions from the last</p> <p>11 case.</p> <p>12 DR. FLUME: Which one did we not get to?</p> <p>13 MS. HIGGINS: In terms of the feasibility of</p> <p>14 standardizing the background regimen, some of these</p> <p>15 things...</p> <p>16 UNIDENTIFIED SPEAKER: Is it possible bring</p> <p>17 up slide 12, questions for panel from the prior case?</p> <p>18 Is there anyone from AV here? Thank you. For case</p> <p>19 study 1.</p> <p>20 MS. HIGGINS: So while we're waiting for</p> <p>21 that, I have a question that I'm -- in going back and</p> <p>22 forth between these two cases, what we heard in the</p>	<p style="text-align: right;">Page 368</p> <p>1 automatic -- there would be no grounds to know for</p> <p>2 sure that those two separate different situations have</p> <p>3 any connection. They may and there may be benefit in</p> <p>4 both.</p> <p>5 MS. HIGGINS: Yeah, I guess, I should have</p> <p>6 asked it in a slightly different way, which would be</p> <p>7 how would one potentially translate that data as</p> <p>8 informative from a treatment naive population into a</p> <p>9 treatment refractory population. And I guess the same</p> <p>10 would extend to an approval in one of those</p> <p>11 populations in use of the -- (audio gap).</p> <p>12 UNIDENTIFIED SPEAKER: Right.</p> <p>13 UNIDENTIFIED SPEAKER: For what we've heard,</p> <p>14 it does seem like they have two very different patient</p> <p>15 populations.</p> <p>16 UNIDENTIFIED SPEAKER: Yeah.</p> <p>17 UNIDENTIFIED SPEAKER: So it would be very</p> <p>18 hard for you to extrapolate what you've seen in the</p> <p>19 Phase 2 to design your Phase 3 trial for a totally</p> <p>20 different patient population. And I think the same</p> <p>21 would hold for, you know, approval. I mean the</p> <p>22 approval really will depend on what population you</p>
<p style="text-align: right;">Page 367</p> <p>1 first case was that for -- in the case of a Phase 2</p> <p>2 study, where you're looking for an early efficacy</p> <p>3 readout, that a placebo-controlled study design would</p> <p>4 be potentially feasible in a treatment naive</p> <p>5 population. And in -- if you're saying that it's more</p> <p>6 difficult in the Phase 3 study design in a treatment</p> <p>7 naive population versus placebo, what about in the</p> <p>8 treatment refractory Phase 3?</p> <p>9 And the question that I'm wondering about is</p> <p>10 the translation of data for -- from a Phase 2 in a</p> <p>11 treatment naive population to efficacy in a Phase 3 in</p> <p>12 a treatment refractory population? Do we think that</p> <p>13 there are particular difficulties in translating data</p> <p>14 from the early Phase 2 efficacy read in a treatment</p> <p>15 naive population to an ultimate pivotal study in a</p> <p>16 treatment refractory population?</p> <p>17 UNIDENTIFIED SPEAKER: Yeah. So short answer</p> <p>18 I think would be yes. I mean, they're completely two</p> <p>19 separate questions clinically.</p> <p>20 MS. HIGGINS: Yeah.</p> <p>21 UNIDENTIFIED SPEAKER: And I am -- as a</p> <p>22 clinician, I'm not sure that I would extrapolate an</p>	<p style="text-align: right;">Page 369</p> <p>1 study.</p> <p>2 MS. HIGGINS: Right.</p> <p>3 UNIDENTIFIED SPEAKER: And Angela, would you</p> <p>4 be looking for a clinical practice or an expanded</p> <p>5 indication from the FDA for that -- and to answer your</p> <p>6 question --</p> <p>7 DR. TALLEY: Well...</p> <p>8 UNIDENTIFIED SPEAKER: -- because in</p> <p>9 practice, it's done all the time.</p> <p>10 DR. TALLEY: I think it gets...</p> <p>11 UNIDENTIFIED SPEAKER: And we do a lot of</p> <p>12 things that are applied to situations where the</p> <p>13 efficacy has been shown in a completely separate</p> <p>14 issue, and then we clinically still use it, just</p> <p>15 because there's no data there.</p> <p>16 DR. TALLEY: Yeah.</p> <p>17 UNIDENTIFIED SPEAKER: But you're looking for</p> <p>18 a broader indication that that then isn't embraced by</p> <p>19 the FDA, and that's what I think would be the sticking</p> <p>20 point.</p> <p>21 DR. TALLEY: Yeah, I mean, either questions</p> <p>22 are relevant. I think ultimately it comes down to a</p>

<p style="text-align: right;">Page 370</p> <p>1 question of what data does a clinician need to be                  2 convinced in terms of the utility of a new agent or of                  3 a standard of care.                  4 UNIDENTIFIED SPEAKER: Another study?                  5 UNIDENTIFIED SPEAKER: So I do have a sort of                  6 follow up comment. And we heard a lot of discussion                  7 about why the Phase 2 trial shouldn't be long and I                  8 think we get that because it's not feasible. But if                  9 there is so much uncertainty around what is an                  10 appropriate outcome assessment, and we're cutting                  11 short the Phase 2 trials. We're really not going up                  12 to the point where we think we're going to see the                  13 benefit on the clinical outcome, then I think we are                  14 taking a big risk in moving into Phase 3 trials and I                  15 sort of wanted the committee to opine on that because                  16 I -- that's been bothering me. I mean, everyone seems                  17 to think we need a clinical outcome assessment. We                  18 don't exactly what it is. We think it might be 3                  19 months, it might be 6, it might be longer. We're                  20 going to cut short our Phase 2 at 6 because beyond                  21 that is not feasible. And then we're going to design                  22 our Phase 3 trial based on very limited information</p>	<p style="text-align: right;">Page 372</p> <p>1 UNIDENTIFIED SPEAKER: So I guess that's the                  2 question is what lessons have we learned from these                  3 other trials, right, that we could apply here?                  4 UNIDENTIFIED SPEAKER: I think the key lesson                  5 is that you have your clinical endpoint and a                  6 population that will respond to it. So if for                  7 example, in the bronchiectasis trials, if you're going                  8 after exacerbations and your placebo group has an                  9 exacerbation rate half of what you dreamed it would                  10 be, it's not a surprise that it didn't result in a win                  11 for the study. So a key here is it's not just what                  12 the end point is, is you got to have a population that                  13 will be changed by it.                  14 UNIDENTIFIED SPEAKER: In the Phase 2, we                  15 really haven't gone out long enough because right now                  16 I think there's a lot of uncertainty because we -- in                  17 the first place, we haven't defined what the clinical                  18 outcome assessment tool is, right?                  19 UNIDENTIFIED SPEAKER: Right.                  20 UNIDENTIFIED SPEAKER: I think we have a                  21 general feel that maybe months 3, we have some ideas,                  22 some people think it might be month 6. But what if</p>
<p style="text-align: right;">Page 371</p> <p>1 that we've collected in Phase 2. So just wondering                  2 how we can tie all that together.                  3 UNIDENTIFIED SPEAKER: I mean, I think this                  4 is where we've been burned in the bronchiectasis                  5 trials that we have killed bug in Phase 2. But no                  6 clinical benefit, you know, and then they flame out in                  7 Phase 3. So, you know, I think we take a risk if we                  8 don't have more information. I'm looking at Ken                  9 because we -- you know, this issue of like, kill the                  10 bug -- and that's the proof-of-concept, but it's                  11 failed now in multiple Phase 3 trials for...                  12 DR. OLIVIER: I didn't mean to imply that                  13 that is all you need.                  14 UNIDENTIFIED SPEAKER: No, I'm not (cross                  15 talk).                  16 DR. OLIVIER: But if it doesn't do that, then                  17 I don't see the point of going forward is all I was                  18 trying to say. I think the Phase 2, you've got to                  19 collect some information that will give you a hint                  20 about what's important to move on to measure in Phase                  21 3, that's going to relate to clinical outcomes. And                  22 maybe 6 months isn't long enough to do that.</p>	<p style="text-align: right;">Page 373</p> <p>1 you are stopping the trial -- the Phase 2 trial                  2 earlier, you haven't gone long enough where you                  3 actually have the potential to see this clinical                  4 benefit, then how can you appropriately design your                  5 Phase 3 trial? I think that's the question.                  6 UNIDENTIFIED SPEAKER: I think what I'm                  7 hearing or what I'm thinking is that 6 months seems to                  8 be the magic timeframe which we would make a decision                  9 about whether we need to change our approach to                  10 treating the patient. So if -- I'll think two                  11 different patient populations; one is whom they're                  12 symptomatic, and you're trying -- your goal is to                  13 improve their symptoms. And the other is to try and                  14 prevent worsening. So those are two different                  15 populations, you're looking at two different                  16 approaches to what that clinical endpoint would be.                  17 But I think, and I hear repeatedly, 6 months is that                  18 sweet spot, that if you don't have it by 6 months,                  19 you've got to do something different. And if you see                  20 it before 6 months, well, terrific. So if you're                  21 doing a micro endpoint at 6 months, you'll collect                  22 your clinical data in the interim there.</p>

<p style="text-align: right;">Page 374</p> <p>1 UNIDENTIFIED SPEAKER: I guess one of the                  2 things we talked about was the trade off of -- so I                  3 think you're implying that the Phase 2 study is for 6                  4 months. But the primary endpoint of a pivotal trial                  5 is going to be at 18 months, you don't really have                  6 that data. And I guess earlier I had voiced I am                  7 concerned about having the primary endpoint being at                  8 18 months because of so much missing data and then                  9 there was the possibility of entertaining a trade off                  10 where okay, we would we would have the primary                  11 endpoint at 6 months for purposes of having robust                  12 data set. And then...</p> <p>13 UNIDENTIFIED SPEAKER: I mean, I don't even                  14 know to say that 18 months is the correct timing. I                  15 mean, that's also based on no data. So are we better                  16 served because there's so much uncertainty here in                  17 doing more work in Phase 2, so that we then don't, you                  18 know, like, I think the point Dr. O'Donnell made,                  19 we've seen in bronchiectasis trials that selection of                  20 the endpoint might have been the problem. So I --                  21 really I cannot tell you that 18 months is the right                  22 endpoint because I have no more information than</p>	<p style="text-align: right;">Page 376</p> <p>1 that's based upon expert judgment, but not a lot of                  2 data and we're always going to wonder is this 12                  3 months of culture negativity necessary and why are we                  4 even doing that and -- but I really worry if we try to                  5 answer that question and whether a drug works in the                  6 same trial, it's going to make it really messy.</p> <p>7 MR. CHEN: I have a related question, I think                  8 I heard earlier. So suppose that we can refine QOL-B                  9 to make it more sensitive in term of a score or adding                  10 different items, maybe the changes, I heard that the                  11 patient actually starting feeling better minimum at 3                  12 months and then they probably -- most of them will                  13 feel better at 6 months. So in a Phase 2 trial, 6                  14 months Phase 2 trial, is that sufficient time to                  15 validate that refined PRO endpoints?</p> <p>16 UNIDENTIFIED SPEAKER: I think we might be                  17 underselling how valuable 6 months would be. I mean,                  18 I take the analogy of the bronchiectasis studies, but                  19 there the Phase 2 is at 28 days out of a treatment                  20 that you'll get for 20 years, whereas this is 6 months                  21 out of a treatment you'll get for 18 months. So to my                  22 mind, it's not that bad. And most of the treatment</p>
<p style="text-align: right;">Page 375</p> <p>1 anybody else has. So --</p> <p>2 UNIDENTIFIED SPEAKER: That's pointed out.</p> <p>3 UNIDENTIFIED SPEAKER: -- how can we make a                  4 more learned effort to get to a right endpoint, be it                  5 the definition of the endpoint or the timing of the                  6 endpoint? Or even if it's time to enrich, which I                  7 know is your preferred approach, how do we define that                  8 event? What exactly are the components of that event?</p> <p>9 UNIDENTIFIED SPEAKER: That's the challenge.</p> <p>10 UNIDENTIFIED SPEAKER: I think that's the                  11 issue.</p> <p>12 UNIDENTIFIED SPEAKER: It's called patient --                  13 or physician-inpatient global assessment kind of a                  14 thing.</p> <p>15 UNIDENTIFIED SPEAKER: Right.</p> <p>16 UNIDENTIFIED SPEAKER: So that -- that thing                  17 is perfect. I just put that out there because in the                  18 absence of a current validated instrument that might                  19 be the most facile way to at least proceed.</p> <p>20 UNIDENTIFIED SPEAKER: Sure.</p> <p>21 UNIDENTIFIED SPEAKER: But I think, you know,                  22 Ed made the point, when you have a standard of care</p>	<p style="text-align: right;">Page 377</p> <p>1 response you'll see at least in the treatment naive                  2 patients is within the first 3 to 6 months. So you                  3 would expect that if you're not seeing a symptomatic                  4 improvement after 6 months, then some patients will                  5 feel better after that, but you should get a large                  6 chunk of the response within that period of time. So                  7 I don't think this is quite the same as the                  8 bronchiectasis...</p> <p>9 MR. CHEN: Right. So a 6 month Phase 2 trial                  10 is sufficient for us to evaluate the PRO outcomes that                  11 we're trying to use for Phase 3 trials. So the only                  12 question would be if a Phase 3 trial is a longer,                  13 saying not 18 months, but by 12 months, at the PRO,                  14 you see evaluated at 6 months in Phase 2 trial and do                  15 we expect the -- how the patient feel the clinical                  16 outcomes will be last more than 6 months that -- so in                  17 the 12 months Phase 3 trial, we still see the                  18 sustained improvement after 6 months using that PRO?</p> <p>19 UNIDENTIFIED SPEAKER: Maybe improvement,                  20 then stabilization rather than continuing...</p> <p>21 MR. CHEN: Right. So okay. Yeah, for                  22 example, we see improvement starting at 3 months and</p>

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<p>1 then month six, but then it probably won't go higher                  2 up, but that improvement would stay, you won't go                  3 getting worse, go back down?                  4 UNIDENTIFIED SPEAKER: Probably.                  5 MR. CHEN: Probably.                  6 UNIDENTIFIED SPEAKER: It makes sense                  7 according to the biology just now and once you get                  8 sputum culture conversion, the antibiotic then can't                  9 keep improving your quality of life because it's dealt                  10 with the issue that -- it was there to deal with. But                  11 it shouldn't go down.                  12 UNIDENTIFIED SPEAKER: I think what we really                  13 need that we don't have is some kind of progression of                  14 disease composite, yeah, scorecard or something for                  15 the longer trials, particularly the refractory                  16 patients.                  17 DR. FLUME: To make sure that we finish on                  18 time here, there was one question that came in over                  19 the web with respect to abscesses. We need a                  20 combination regimen to advance to clinical trial. So                  21 the question is do we have such a promising regimen to                  22 move forward? And if so please share the drugs and</p>	<p>1 summarize this very complicated and interesting                  2 discussion. I may not necessarily have them in the                  3 right order of research. I just wrote them up as all                  4 of you were talking. So I think one important message                  5 that at least I heard during this discussion this                  6 morning and during the case studies is that there is                  7 certainly a recognition that we need a clinical                  8 outcome assessments tool. We don't have one readily                  9 available, one that's perfect. Whether it's only                  10 going to be a patient-reported outcome or there could                  11 be some component of a clinician-reported outcome. I                  12 think we need to have further discussion around it.                  13 UNIDENTIFIED SPEAKER: And we talked some,                  14 I'll throw in a little bit here, too. We talked some                  15 too about the survey that showed the cough fatigue and                  16 shortness of breath and that seems to be what we're                  17 hearing from everybody is sort of the key things that                  18 we're seeing as clinical symptoms that patients are                  19 reporting.                  20 UNIDENTIFIED SPEAKER: Yeah. And then --                  21 yeah, and there was discussion around whether we need                  22 to start from scratch with new tools, or I think</p>
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<p>1 combinations.                  2 (Laughter)                  3 UNIDENTIFIED SPEAKER: I thought that this                  4 was going to be covered at the next meeting.                  5 UNIDENTIFIED SPEAKER: That's what Kevin                  6 said.                  7 UNIDENTIFIED SPEAKER: What?                  8 UNIDENTIFIED SPEAKER: I'm not sure how to                  9 answer that. We all have that regimen. It's just a                  10 different one. I mean, we -- this is -- I mean                  11 abscesses is another whole day. I mean, it's just                  12 such a complex discussion, you know, but I was looking                  13 -- (audio gap) the SGRQ in abscesses patients from --                  14 (audio gap) -- but I think our patients get better as                  15 Tim said earlier. I mean, so I would proceed. So one                  16 of the action items should be -- (audio gap).                  17 DR. COX: Do you want to tackle the summary?                  18 UNIDENTIFIED SPEAKER: So Ed gave me the                  19 toughest job like a few minutes ago, so I'm going to                  20 try.                  21 (Laughter)                  22 UNIDENTIFIED SPEAKER: So I'm going to try to</p>	<p>1 there's a preference to maybe use or modify existing                  2 tools because I think there are some existing tools,                  3 but probably they need some more work. There was                  4 discussion around what would be the appropriate timing                  5 of the endpoint, whether we choose an endpoint in a                  6 fixed time-point or whether we -- the preferred                  7 approach would be a time-to-event analysis. I think                  8 there was some degree of agreement that an earlier                  9 time-point for a clinical outcome assessment would be                  10 optimal, whether it's 3 months or 6 months, I think                  11 still needs further discussion. And even for a time-                  12 to-event analysis, one would need to define the                  13 components of what exactly constitutes the event.                  14 Yeah. Sorry?                  15 UNIDENTIFIED SPEAKER: So we talked some too                  16 -- we were sort of just trading this back and forth,                  17 but we talked some too about enrolling the patient                  18 population that, you know, has manifestations of                  19 disease so you can actually see a response. You know,                  20 Dr. Sullivan showed us some interesting slides about                  21 the variability of various different characteristics                  22 of the patients in the trial that they enrolled.</p>



<p style="text-align: right;">Page 382</p> <p>1 UNIDENTIFIED SPEAKER: Then regarding the  2 patient population where the one would study a  3 treatment naive population or a refractory population,  4 I think there was a preference that one would start  5 with the treatment naive population. But there was a  6 fair bit of discussion around the feasibility of doing  7 placebo-controlled trials in this patient population.  8 But I think where we ended up was it might be possible  9 for us to define a patient population in whom it  10 should be ethical and to conduct a placebo-controlled  11 trial.  12 There was discussion around the potential  13 need for outcome assessment tools that might be  14 different depending on the specific patient population  15 because treatment naive patient population is  16 definitely different from that of a refractory  17 treatment population. I think we heard clearly that  18 NI trials are not the preferred options, superiority  19 trials are the preferred options for this clinical  20 condition. We have -- we will -- we think identifying  21 an evidence-based treatment effect would be very  22 difficult for this disease, which then makes the NI</p>	<p style="text-align: right;">Page 384</p> <p>1 endpoint. We -- I think we didn't go into a lot of  2 discussion around it, but I think certainly other  3 disease areas, we've had this discussion, and one has  4 to be very careful in combining efficacy and safety  5 endpoints. But again, something that we have to work  6 on. So I think there's a very interesting and robust  7 discussion. I think the main message is we as a group  8 have a lot of work to do. I don't think we have  9 answers to all the problems. But this is a good place  10 to start and I think there's enough momentum here and  11 interest that I think if we as a community work  12 together, we should be able to find ways to design  13 these trials and get patients the medications they  14 need.  15 DR. COX: Agree very much. And I want to,  16 you know, thank everybody for really rolling up their  17 sleeves, all the work that's been done so far. And  18 you know, the continued interest and commitment to  19 continue to develop therapies for patient with NTM and  20 I think it's really important. And you know, like  21 many areas in infectious diseases, there's some  22 significant challenges here. But from those</p>
<p style="text-align: right;">Page 383</p> <p>1 trials very difficult to justify.  2 There was discussion about potential use of  3 registry data or data from existing clinical trials to  4 better understand what improvements and symptoms might  5 be seen with treatment in these patients. And then  6 there was also I think a very clear message that in  7 our hypothetical examples, the duration of the Phase 2  8 trials was too long and certainly would not be  9 feasible in terms of development programs. So Phase 2  10 trials would certainly have to be shorter. But -- and  11 that the clinical outcomes, it might be possible to  12 measure them in these trials as well because somewhere  13 by month 3 to 6 we should see fair degree of clinical  14 improvement in these patients. Did I capture them  15 all, Ed?  16 DR. COX: Medication tolerability.  17 UNIDENTIFIED SPEAKER: Yeah, I think there  18 was --  19 DR. COX: Events.  20 UNIDENTIFIED SPEAKER: Yeah, I think there  21 was some discussion around adverse events  22 tolerability, how one might include that in the</p>	<p style="text-align: right;">Page 385</p> <p>1 challenges can certainly come rewards as far as  2 improving the care of patients. So we're very  3 grateful. Thank everybody.  4 UNIDENTIFIED SPEAKER: Yeah.  5 DR. COX: Wish them well for the travel and  6 all.  7 SUMMARY AND CLOSING REMARKS  8 UNIDENTIFIED SPEAKER: Right. So thank you,  9 everybody. Thank you for everybody -- every member of  10 the audience that was here to listen and for those of  11 you that participated. Many thanks to all members of  12 the panel for your keen interest, and I think it's  13 really contributed a lot to the discussions today. So  14 we thank you all for that.  15 Amy, we do thank you for bringing the voice  16 of the patient forward to this meeting. I think  17 that's really appreciated. And many thanks to Sunita  18 for having coordinated and put this workshop together.  19 We really appreciate that as well. Wish you all safe  20 travels and I'm sure you'd hear from us soon. So  21 thank you.  22 (Applause)</p>

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