

Capital Reporting Company  
Patient-Focused Drug Development Public Meeting 10-15-2015

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FOOD AND DRUG ADMINISTRATION

PUBLIC MEETING ON NON-TUBERCULOUS  
MYCOBACTERIAL (NTM) LUNG INFECTIONS  
PATIENT-FOCUSED DRUG DEVELOPMENT

Thursday, October 15, 2015

9:01 a.m.

FDA White Oak Campus

Building 31

Conference Center, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

(866) 448 - DEPO

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| 6 | <p>1 PROCEEDINGS (9:01 a.m.)</p> <p>2 Welcome</p> <p>3 MS. GIAMBONE: Good morning, everyone.</p> <p>4 Thank you, all, for being here. Thank you for</p> <p>5 braving -- we had a really bad commute day, I</p> <p>6 think. There was a lot of traffic on the roads and</p> <p>7 I heard from a lot of you that you had to deal</p> <p>8 with that. Thank you for doing that and for being</p> <p>9 here.</p> <p>10 My name is Soujanya Giambone. I am with</p> <p>11 the FDA, Center for Drug Evaluation and Research,</p> <p>12 Office of Strategic Programs. On behalf of all of</p> <p>13 my FDA colleagues, I'd like to welcome you to</p> <p>14 today's patient-focused drug development meeting</p> <p>15 on Non-Tuberculous Mycobacterial Lung Infections,</p> <p>16 NTM Lung Infections.</p> <p>17 We're just very thankful that you're</p> <p>18 here, and we're looking forward to a really great</p> <p>19 day of learning from you and listening to you and</p> <p>20 your perspectives. What I'd like to do is just</p> <p>21 spend a few minutes going over the agenda and a</p> <p>22 few housekeeping remarks, and then we'll go ahead</p>   | 8 |
| 7 | <p>1 and get started.</p> <p>2 We're going to start the day today with</p> <p>3 some FDA presentations. My FDA colleagues will</p> <p>4 provide an overview of the Patient-Focused Drug</p> <p>5 Development initiative, background on NTM and</p> <p>6 current treatment options. Then I'll come back</p> <p>7 and provide an overview of the discussion format.</p> <p>8 We have two topics for today as you</p> <p>9 know. Topic 1 is on the most significant symptoms</p> <p>10 of NTM lung infections and how they impact your</p> <p>11 daily life. Topic 2 is on patient perspectives on</p> <p>12 current approaches to treating NTM.</p> <p>13 For each topic, we have a panel</p> <p>14 discussion, followed by a group discussion, and we</p> <p>15 take a break between each of those discussion</p> <p>16 topics. Then we'll break for lunch. Then in the</p> <p>17 afternoon, we have a scientific workshop with some</p> <p>18 really great experts in the field that will be</p> <p>19 presenting a range of presentations on NTM lung</p> <p>20 infections, and the epidemiology, and clinical</p> <p>21 trial design and so forth. So it should be a very</p> <p>22 interesting discussion.</p>                                    | 9 |
| 6 | <p>1 A few housekeeping items. Restrooms are</p> <p>2 back out into the lobby. If you make a right and</p> <p>3 go all the way down the hallway, you'll see the</p> <p>4 restrooms there. We also have a kiosk that you</p> <p>5 may have seen out in the foyer area. Again, it</p> <p>6 sells basic coffee, sandwiches, snacks, and so</p> <p>7 forth, so please make yourself comfortable. If</p> <p>8 you need to get up and stretch, if you need to go</p> <p>9 grab a snack or if you need to use the restroom,</p> <p>10 please feel free to do so. We want you to be as</p> <p>11 comfortable as possible.</p> <p>12 Next thing, you can feel free to pre-</p> <p>13 order your lunch if you're -- we have that 45-</p> <p>14 minute lunch break in the middle. But during</p> <p>15 break, if you'd like to, you're welcome to go and</p> <p>16 just let them know what you'd like to order, and</p> <p>17 they'll have it all ready for you if you don't</p> <p>18 want to have to wait too long in line.</p> <p>19 All right. I do have a few notes down</p> <p>20 here, so I'm just going to go through them for</p> <p>21 some of the reminders. The shuttle bus that some</p> <p>22 of you may have taken, the NTM shuttle bus that</p> | 8 |
| 7 | <p>1 brought many of you here, it's going to leave at</p> <p>2 5:15 p.m.</p> <p>3 sharp. If you're going to be taking the</p> <p>4 bus back, please be sure to be there by 5:15.</p> <p>5 Next, just a reminder that we do have</p> <p>6 the screens around the room so you can feel free</p> <p>7 to look at any of the screens. We're going to do</p> <p>8 some polling questions throughout the day. We're</p> <p>9 going to have the presentations, of course. You</p> <p>10 can feel free to look along to any of these slides</p> <p>11 and that'll be great.</p> <p>12 This meeting is being transcribed and</p> <p>13 recorded. In about a week or two weeks or so, the</p> <p>14 transcript and the recoding of the meeting will be</p> <p>15 available on the meeting website. Right after the</p> <p>16 meeting, we'll have the slides for the scientific</p> <p>17 workshop. They're already posted up there for the</p> <p>18 second half of the day, the scientific workshop.</p> <p>19 You'll be able to find the slides there.</p> <p>20 I'd been given a notice that you can</p> <p>21 just go to Google, google.com, and search "FDA</p> <p>22 NTM" and the very first link that comes up will</p>                                 | 9 |

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| <p style="text-align: right;">10</p> <p>1 take you to the slides. Under "Meeting<br/> 2 Materials," you can go there, and you'll see the<br/> 3 slides for the scientific workshop.</p> <p>4       Okay. On that note, let me ask my FDA<br/> 5 colleagues to please introduce yourself.</p> <p>6       DR. FARLEY: Sure. I'm John Farley,<br/> 7 deputy director of the Office of Antimicrobial<br/> 8 Products at CDER.</p> <p>9       DR. NAMBIAR: Good morning. Sumathi<br/> 10 Nambiar, director of the Division of Anti-<br/> 11 Infective Products, CDER FDA.</p> <p>12       DR. TOERNER: I'm Joe Toerner, the<br/> 13 deputy director for safety in the Division of<br/> 14 Anti-Infective Products at FDA CDER.</p> <p>15       DR. SHAMSUDDIN: Hala Shamsuddin,<br/> 16 medical officer, Division of Anti-Infective<br/> 17 Products.</p> <p>18       DR. DANIELS: Selena Daniels, reviewer<br/> 19 with clinical outcome assessment staff here at<br/> 20 CDER.</p> <p>21       DR. GOLDSMITH: Jonathan Goldsmith. I'm<br/> 22 the associate director of the Rare Diseases</p> | <p style="text-align: right;">12</p> <p>1 the rest of the day, you'll probably hear that<br/> 2 abbreviated as NTM because it's a pretty long<br/> 3 name.</p> <p>4       As I mentioned, I'm from the Office of<br/> 5 Anti-Microbial Products within the Office of New<br/> 6 Drugs here at FDA. Within our office, the<br/> 7 Division of Anti-Infective Products reviews anti-<br/> 8 bacterial drugs, including products that can help<br/> 9 manage and treat NTM lung infections. This<br/> 10 afternoon, the panel discussion will be chaired by<br/> 11 Dr. Sumathi Nambiar, the director of that division<br/> 12 who is seated to my left.</p> <p>13       We, here, at FDA are very happy to see<br/> 14 so many patients and patient advocates in the<br/> 15 audience. We know a number of you, and we're<br/> 16 looking forward to getting to know all of you in<br/> 17 the course of the day.</p> <p>18       I also understand that we have many more<br/> 19 folks joining us on the Web. For those of you in<br/> 20 the room, we particularly appreciate you, not only<br/> 21 putting up with Washington traffic but then<br/> 22 putting up with a security system similar to that</p>                 |
| <p style="text-align: right;">11</p> <p>1 Program in the Office of New Drugs, CDER.</p> <p>2       MR. BONA: Jim Bona, the Office of<br/> 3 Orphan Products Development.</p> <p>4       DR. MULLIN: Good morning. I'm Theresa<br/> 5 Mullin. I direct the Office of Strategic Programs<br/> 6 in the Center for Drugs.</p> <p>7       MS. GIAMBONE: Thank you. We have some<br/> 8 colleagues over here.</p> <p>9       DR. EGGERS: Sara Eggers, in the Office<br/> 10 of Strategic Programs.</p> <p>11       MS. CHALASANI: Meghana Chalasani, the<br/> 12 same office.</p> <p>13       MS. THOMPSON: Graham Thompson, same<br/> 14 office.</p> <p>15       MS. VAIDYA: Pujita Vaidya, same office.</p> <p>16       MS. GIAMBONE: Thank you. Now, I'd like<br/> 17 to turn it over to Dr. Farley for his opening<br/> 18 remarks. Opening Remarks - John Farley</p> <p>19       DR. FARLEY: Good morning, everybody. I<br/> 20 want to welcome everyone to this meeting on<br/> 21 Patient-Focused Drug Development for Non-<br/> 22 Tuberculous Mycobacterial Lung Infections. For</p>   | <p style="text-align: right;">13</p> <p>1 that you would face at an airport when you arrived<br/> 2 today. At least, they didn't hopefully make you<br/> 3 take off your shoes.</p> <p>4       Today's meeting is one in a series of<br/> 5 FDA's patient-focused drug development meetings,<br/> 6 and Dr. Theresa Mullin will be talking about this<br/> 7 initiative in more detail in a few minutes. What<br/> 8 our division here has done a couple of times,<br/> 9 which we found really helpful, is to have experts<br/> 10 that we invite through the whole day, so the<br/> 11 thought leaders in the country.</p> <p>12       Then this afternoon, once they've heard<br/> 13 from patients, we get to talk about clinical trial<br/> 14 design and moving drug development forward during<br/> 15 the latter half of the day, we found that to be a<br/> 16 very useful discussion and a useful way of moving<br/> 17 forward.</p> <p>18       As most of you know, NTM or non-<br/> 19 tuberculous mycobacteria represent over a 150<br/> 20 different species of naturally occurring organisms<br/> 21 that are found in water and soil. In some people,<br/> 22 these organisms infect the airways and lung</p> |

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| 14 | <p>1 tissue, and that can cause inflammation in the<br/>2 respiratory system. Symptoms include chronic<br/>3 cough, shortness of breath, fatigue, and a range<br/>4 of other symptoms that we'll be talking about this<br/>5 morning.<br/>6       Diagnosis of NTM lung disease is often<br/>7 delayed because the symptoms are similar to other<br/>8 lung diseases like emphysema or bronchitis. Dr.<br/>9 Hala Shamsuddin will provide a bit more background<br/>10 on the disease and treatment options for you in a<br/>11 few minutes.<br/>12       This is a very important meeting for us.<br/>13 We fully understand that NTM lung infections are a<br/>14 serious condition and that there is unmet need for<br/>15 patients.<br/>16       It's FDA's responsibility to ensure that<br/>17 the benefits of a drug outweigh its risks.<br/>18 Therefore, having this kind of dialogue is<br/>19 extremely valuable for us. What we hear from you<br/>20 today can help us understand how patients view the<br/>21 benefits, as well as the risks of treatments for<br/>22 NTM lung infections.</p>                        | 16 | <p>1 treatments for NTM and some ways forward to meet<br/>2 those challenges.<br/>3       I know there are a lot of<br/>4 representatives from industry, academia, and<br/>5 others in the room and on the Web. I want to<br/>6 thank you again for being here and being a part of<br/>7 this important discussion.<br/>8       Now, I'll turn the microphone over to<br/>9 Dr. Theresa Mullin who will talk about our broader<br/>10 efforts in patient-focused drug development.<br/>11 Presentation - Theresa Mullin<br/>12       DR. MULLIN: Thank you, John.<br/>13       Good morning, everyone. I want to echo<br/>14 Dr. Farley in welcoming you here today, and I'm<br/>15 glad you were able to get here on time. I know I<br/>16 got snagged in the traffic a little bit myself.<br/>17       I'm going to take a few minutes to tell<br/>18 you about this Patient-Focused Drug Development<br/>19 Initiative. This meeting is one that we are able<br/>20 to organize and provide as part of that<br/>21 initiative. As John was saying, one of the most<br/>22 fundamental responsibilities of FDA is to ensure</p>   |
| 15 | <p>1       We particularly want to hear from you<br/>2 today about the different ways your symptoms<br/>3 affect your daily life. It is also important to<br/>4 hear what you value in a treatment for NTM<br/>5 infections and what you would like to see in<br/>6 future treatments for you.<br/>7       It's important to remember that FDA is<br/>8 just one part of the drug development process.<br/>9 We, at FDA, do not develop drugs or conduct<br/>10 clinical trials. Drug companies, often working<br/>11 with researchers or patient communities, are the<br/>12 ones who conduct trials and submit applications<br/>13 for new drugs to us.<br/>14       However, we work closely with these drug<br/>15 companies throughout their drug development<br/>16 process, and what we hear from you this morning<br/>17 will be helpful to companies, as well as ourselves<br/>18 as clinical trials for new NTM treatments are<br/>19 planned.<br/>20       This afternoon, we will have a panel of<br/>21 experts specifically discussing some challenges<br/>22 with the design of clinical trials to evaluate new</p> | 17 | <p>1 that the benefits outweigh the risks of a drug<br/>2 that we approve or allow to be on the market.<br/>3       Part of that decision is looking at the<br/>4 clinical context, as we call it, which is to say<br/>5 how severe is this condition, what is the impact<br/>6 on the patient's life, what other treatments that<br/>7 are already available so that we're not allowing<br/>8 anything on the market that offers less benefit or<br/>9 more risk and is not offering as much to the<br/>10 patient as what may already be available.<br/>11       Those two components are questions we're<br/>12 going to be probing extensively this morning in<br/>13 our meeting: the impact of the disease on your<br/>14 life and what you're doing today to treat your<br/>15 condition and how well that's work or not working<br/>16 for you.<br/>17       We realize that the patient's<br/>18 perspective on benefit/risk was absolutely<br/>19 critical because patients have that unique<br/>20 perspective of experiencing any benefit that there<br/>21 is to gain from a drug and also experience the<br/>22 harm. So their perspective on benefit risk is</p> |

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| 18 | <p>1 extremely important.</p> <p>2 Before we started this initiative in</p> <p>3 2012, we didn't really have a systematic way to</p> <p>4 collect that information. We have a patient</p> <p>5 representative program, which is extremely</p> <p>6 valuable, but that really allows us to get one</p> <p>7 person really to -- one or two to provide and</p> <p>8 speak for the whole community. And we know there's</p> <p>9 a lot of diversity of experience in the patient</p> <p>10 communities for each disease.</p> <p>11 So this initiative allows us a more</p> <p>12 systematic way to collect that information, to</p> <p>13 hear from a broader set of patients, a community</p> <p>14 of the people who are experiencing a disease and</p> <p>15 the people who are care partners for those people</p> <p>16 with the disease.</p> <p>17 We started this initiative. We</p> <p>18 committed to do at least 20 such meetings. This</p> <p>19 is the 17th meeting. We're going to be doing more</p> <p>20 20 because it's been so valuable. We're trying to</p> <p>21 do as many as we are able to do with the available</p> <p>22 folks that we have on our staff. Each one focuses</p> | 20 |
| 19 | <p>1 on a particular disease and tries to really</p> <p>2 systematically go at getting that kind of input.</p> <p>3 We began, as I said, in September of</p> <p>4 2012. We put out a Federal Register notice with</p> <p>5 about 40 diseases where we asked input on which</p> <p>6 should we focus on, which diseases should we focus</p> <p>7 on. We got about 4,500 comments from the public</p> <p>8 on that list, and we got many more nominations of</p> <p>9 diseases.</p> <p>10 We've worked with the divisions to try</p> <p>11 to come up with a list that we are working through</p> <p>12 for this initiative, and we've been learning an</p> <p>13 awful lot about how to do this and how to actually</p> <p>14 allow for others to do it as well, collect this</p> <p>15 kind of information.</p> <p>16 Here's a snapshot for you of the</p> <p>17 diseases that we are covering over this five-year</p> <p>18 period. As you can see today, we're doing the</p> <p>19 non-tuberculous mycobacterial lung infections as</p> <p>20 our meeting focus today.</p> <p>21 In each of these meetings, we focus, as</p> <p>22 I said, on those questions related to impact of</p>           | 21 |

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| <p style="text-align: right;">22</p> <p>1 For example, if we're trying to --</p> <p>2 somebody, a sponsor or patient groups want to work</p> <p>3 together or separately to form patient-reported</p> <p>4 outcome tools that could be used in clinical</p> <p>5 trials to better capture that aspect of your</p> <p>6 experience from your perspective, it helps to</p> <p>7 provide some useful input into that kind of</p> <p>8 further development as well.</p> <p>9 With that, I'll stop and thank you again</p> <p>10 so much for joining us today. And we very much</p> <p>11 look forward to hearing what you have to tell us.</p> <p>12 With that, I'll turn it over. Hala Shamsuddin</p> <p>13 DR. SHAMSUDDIN: Good morning, and</p> <p>14 welcome again for being here. This will be a very</p> <p>15 general overview on NTM lung infections. I will</p> <p>16 be focusing the talk mainly on the disease in the</p> <p>17 United States rather than a global overview, and</p> <p>18 that's mainly due to time restrictions.</p> <p>19 Like I said, this is going to be a very</p> <p>20 brief overview. Non-tuberculous mycobacteria,</p> <p>21 there are more a hundred and fifty species, and a</p> <p>22 handful of them cause human disease. You're going</p> | <p style="text-align: right;">24</p> <p>1 However, the other categories include</p> <p>2 patients with cystic fibrosis, chronic obstructive</p> <p>3 lung disease in smokers, patients who had prior</p> <p>4 tuberculosis, where this NTM may occur in areas</p> <p>5 that were previously involved with TB, and then</p> <p>6 other conditions such as alpha-1 antitrypsin</p> <p>7 deficiency, which results in lung damage, primary</p> <p>8 ciliary dyskinesia where people can't clear their</p> <p>9 secretions, and some people who are immune</p> <p>10 compromised.</p> <p>11 Generally, patients will present with</p> <p>12 cough, but the other symptoms include shortness of</p> <p>13 breath, sputum production, coughing of blood,</p> <p>14 chest pain, fatigue, weight loss, and sometimes</p> <p>15 fever. As you can see, all these symptoms are not</p> <p>16 really unique or specific to NTM lung infections.</p> <p>17 They may occur in patients who have underlying</p> <p>18 lung disease of any cause or any other infection.</p> <p>19 On X-ray, you can find cavities or nodules, and</p> <p>20 generally, there is a positive culture from the</p> <p>21 sputum or the lung.</p> <p>22 How common are these infections in the</p> |
| <p style="text-align: right;">23</p> <p>1 to hear some of the names repeated throughout this</p> <p>2 workshop.</p> <p>3 In the United States, mycobacterium</p> <p>4 avium complex, or referred to as MAC, accounts for</p> <p>5 most of the cases, approximately 70 to 80 percent</p> <p>6 with M. abscessus accounting for most of the</p> <p>7 remainder. The organisms are acquired by</p> <p>8 inhalation from the environment, and water is</p> <p>9 thought to be the main source.</p> <p>10 This is a map of the United States, and</p> <p>11 the darker areas represent areas where there are</p> <p>12 more cases of the disease. As you can see, there</p> <p>13 are more cases along coastal lines.</p> <p>14 Who is at risk for this infection? It's</p> <p>15 generally people who have underlying lung disease</p> <p>16 and/or a genetic predisposition. By and large,</p> <p>17 the major group in the United States tends to be</p> <p>18 patients who have bronchiectasis, which is a</p> <p>19 condition where there is damage and scarring of</p> <p>20 the airways. In that group polls a category of</p> <p>21 patients with a very specific body type. These</p> <p>22 tend to be mainly slender women.</p>  | <p style="text-align: right;">25</p> <p>1 United States? Generally, NTM lung infection is</p> <p>2 what we consider an orphan disease, which means it</p> <p>3 generally affects less than 250,000 people in the</p> <p>4 United States. But there is a general consensus</p> <p>5 that the disease is increasing, both in the</p> <p>6 general population and in patients with cystic</p> <p>7 fibrosis.</p> <p>8 The estimates vary depending on where</p> <p>9 you are geographically, but approximately 8 per</p> <p>10 100,000 people are infected. This number</p> <p>11 increases with age, approximately 20 per 100,000</p> <p>12 people in people older than 50 years of age and to</p> <p>13 47 per 100,000 in those older than 70 years of</p> <p>14 age.</p> <p>15 This is a survey of the prevalence of</p> <p>16 the disease and in how many people is it present.</p> <p>17 In the Medicare population, as you can see, the</p> <p>18 increase is both in men and women.</p> <p>19 Why are NTM lung infections increasing?</p> <p>20 There are several possible reasons. The first is</p> <p>21 probably increased awareness among physicians.</p> <p>22 The other is increased number of susceptible</p>   |

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| 26 | <p>1 individuals. As the population gets older, there<br/>2 are patients with more chronic lung disease; there<br/>3 are more people who are immune compromised; cystic<br/>4 fibrosis patients are surviving longer, and<br/>5 there's possibly increased exposure.<br/>6 I'm going to switch gears to treatment.<br/>7 And we'll hear more about treatment later this<br/>8 afternoon, so I'm not going to go into it in much<br/>9 detail. But briefly, there are no FDA-approved<br/>10 drugs for NTM lung infections. Physicians in<br/>11 practice will use antibiotics that are approved to<br/>12 treat tuberculosis or other bacterial infections.<br/>13 In general, these antibiotics that are<br/>14 used, so called "off label" may be used for longer<br/>15 durations and in different populations than those<br/>16 in which they were approved in. Sometimes the<br/>17 side effect profile may be different.<br/>18 In general, antibiotic combinations are<br/>19 recommended and usually three or more drugs, which<br/>20 may include an injectable drug. But the optimal<br/>21 combination of drugs, the optimal doses, and the<br/>22 optimal duration of both the injectable and the</p> | 28 | <p>1 developing a new drug? There are many. The first<br/>2 one is that disease progression really varies by<br/>3 the underlying lung disease, by the appearance on<br/>4 chest X-ray, and by the infecting organism.<br/>5 A patient who has bronchiectasis and is<br/>6 infected with mycobacterium avium and has nodular<br/>7 disease will have a different disease course than<br/>8 somebody who has cavitory disease or somebody with<br/>9 cystic fibrosis or infected with mycobacterium<br/>10 abscessus.<br/>11 The response to treatment varies. The<br/>12 progression of the disease varies. The treatment<br/>13 response varies. A drug that works for one NTM<br/>14 species and one patient population does not<br/>15 necessarily work in another NTM species or another<br/>16 patient population. It may be difficult to<br/>17 extrapolate from one population to another or from<br/>18 one organism to another.<br/>19 Treatments are lengthy; therefore,<br/>20 trials are lengthy. When trials are lengthy, this<br/>21 poses problems with feasibility. Finally, the<br/>22 endpoints for these trials have not been well-</p> |
| 27 | <p>1 overall treatment regimen have not really being<br/>2 rigorously evaluated. The treatment is lengthy<br/>3 with the goal of therapies achieving negative<br/>4 sputum cultures for 12 consecutive months.<br/>5 In a study from 2004 to 2005, the median<br/>6 number of antibiotics that a patient had required<br/>7 range was 5, with a range of 1 to 10. The median<br/>8 number of treatment days was approximately 8 years<br/>9 with a range that was anywhere between 3 months<br/>10 and 20 years. The cost per patient in a year was<br/>11 approximately \$20,000, but it could go as high as<br/>12 \$70,000. Patients who have M. abscessus were<br/>13 associated with higher treatment cost.<br/>14 The number of antibiotics used is rather<br/>15 large for a long treatment of time, but the side<br/>16 effect profile is also significant. In the same<br/>17 study, the adverse reactions were reported in 50<br/>18 percent of patients for those receiving the<br/>19 commonly used drugs and everybody who used the<br/>20 less commonly used drugs.<br/>21 Now that we've kind of painted a rather<br/>22 grim picture, what are the challenges to</p>                              | 29 | <p>1 defined, and we will hear more about that in the<br/>2 afternoon as well.<br/>3 We will need to define assessments in<br/>4 those clinical trials that occur early in the<br/>5 course so we can get a drug to market sooner<br/>6 rather than waiting at least a year for the sputum<br/>7 to be consistently negative.<br/>8 In conclusion, NTM lung infections are<br/>9 increasing in the United States. The affected<br/>10 populations are mainly patients with<br/>11 bronchiectasis and patients with underlying lung<br/>12 disease. We have no approved FDA therapies for<br/>13 this condition. The currently used treatments are<br/>14 multiple drugs used off label for lengthy periods<br/>15 of time and are associated with significant side<br/>16 effects.<br/>17 We realize that there is a huge unmet<br/>18 medical need, but having said that, we also have<br/>19 many challenges to drug development that<br/>20 hopefully, we will have a chance to discuss<br/>21 further this afternoon. Thank you. Thank you all<br/>22 for coming again. Overview of Discussion Format</p>  |



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| 30 | <p>1 MS. GIAMBONE: Thank you to my FDA<br/>2 colleagues for your presentations. What I'd like<br/>3 to do now is go over the discussion format. As I<br/>4 mentioned earlier, we have two topics that we're<br/>5 going to be diving into today.</p> <p>6 Topic 1 is on the most significant<br/>7 symptoms of NTM lung infections and how they<br/>8 impact you in your daily life. What we're<br/>9 listening for here is what are the symptoms that<br/>10 are most important to you, that matter most to<br/>11 you, and how do they affect your ability to do<br/>12 activities? Is there something that you can't do<br/>13 as fully as you would like or you can't do at all<br/>14 because of the symptoms that you experience?</p> <p>15 We also want to hear how your symptoms<br/>16 have evolved or changed over time. Tell us what<br/>17 it's like on a good day, on an average day, and on<br/>18 your bad days. What do those symptoms look like?<br/>19 How has your symptoms impacted your life, not just<br/>20 physically but emotionally, socially? What are<br/>21 all the different ways that your symptoms have<br/>22 impacted you?</p>        | 32 |
| 31 | <p>1 In topic 2, we're going to be listening<br/>2 to patient perspectives on their approaches to<br/>3 treating NTM lung infections. Here, what we're<br/>4 listening for is what are you currently doing to<br/>5 treat the NTM lung infection; how well is it -- or<br/>6 is it working; or if not, what's not working about<br/>7 it? What are the downsides that you're<br/>8 experiencing because of your treatment regimen,<br/>9 and what would you look for in an ideal treatment?</p> <p>10 We're also in topic 2 going to have a<br/>11 scenario slide that we'll present to patients to<br/>12 hear your immediate thoughts on participating in a<br/>13 clinical trial. We're going to put some<br/>14 information up and talk to you for a few minutes<br/>15 about what are the first things that come to mind.</p> <p>16 We are going to have a portion in our<br/>17 afternoon session in the scientific workshop<br/>18 that's going to go on to greater detail on<br/>19 considerations of clinical trial designs and so<br/>20 forth, but we want to first hear some thoughts<br/>21 from you on what matters to you in clinical<br/>22 trials.</p> | 33 |

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| <p style="text-align: right;">34</p> <p>1 do some questions in just a little bit, and you<br/> 2 can use your clickers to respond to those<br/> 3 questions.<br/> 4       For those of you on the Web, you can<br/> 5 also participate in these polling questions by<br/> 6 answering them through the webcast. For those of<br/> 7 you on the Web -- we have about I believe 70 or so<br/> 8 people on the Web so we have a very active Web<br/> 9 session going right now.<br/> 10       We can't see you, Web participants, but<br/> 11 you're a very, very important part of this<br/> 12 meeting. We encourage you to continue providing<br/> 13 your thoughts through the webcast. Periodically,<br/> 14 I'll check in with my colleagues to provide a<br/> 15 summary of what we're hearing on the Web.<br/> 16       We also, towards the end of each topic<br/> 17 discussion, will go to the phones, and we'll hear<br/> 18 some of the people joining us on the webcast<br/> 19 provide their thoughts over the phone.<br/> 20       Last but not the least, a very, very<br/> 21 important part of our discussion, another way that<br/> 22 we would like to hear from you, is through this</p>   | <p style="text-align: right;">36</p> <p>1 Center Director, we have the Professional Affairs<br/> 2 and Stakeholder Engagement team, PASE, which has<br/> 3 been collaborating with us to provide outreach for<br/> 4 this meeting and help with getting so many of you<br/> 5 here, so thank you for that.<br/> 6       We do have some discussion ground rules<br/> 7 for today. This meeting is really about the<br/> 8 patients and the caregivers to do the talking<br/> 9 today. We really have so much to learn from you,<br/> 10 and we are looking to you to really lead that<br/> 11 dialogue.<br/> 12       FDA is here to listen. We will be in<br/> 13 listening mode. We know that there is academia,<br/> 14 industry, other government agencies here, and this<br/> 15 meeting is very important to you, too. We just<br/> 16 ask that you stay in listening mode.<br/> 17       The discussion is going to stay -- we're<br/> 18 going to do our best to stay on topic. The<br/> 19 discussion is on symptoms and treatments. We know<br/> 20 that there's many aspects to treating NTM lung<br/> 21 infections, and we're not going to be able to<br/> 22 address all of those aspects in this meeting.</p> |
| <p style="text-align: right;">35</p> <p>1 public docket. The public docket, you see the<br/> 2 website here, and you'll also find it on the<br/> 3 slides once they're posted on the Web.<br/> 4       But this docket will be open for two<br/> 5 months after this meeting, so until December 15th.<br/> 6 It's really a great way to continue the dialogue.<br/> 7 I encourage all of you to -- you know, if there's<br/> 8 something that you didn't get to share here or if<br/> 9 there's something else that comes to mind, please<br/> 10 submit those comments in the public docket.<br/> 11       They are all part of this meeting<br/> 12 record, and after you submit all your comments, we<br/> 13 will go through and read each and every one of<br/> 14 those, and they will be incorporated into our<br/> 15 summary report. Anybody is welcome to comment, not<br/> 16 just patients and patient representatives.<br/> 17       I would like to share some additional<br/> 18 resources at the FDA that will be very useful for<br/> 19 you. One is the FDA Office of Health and<br/> 20 Constituent Affairs, which we call OCHA. You have<br/> 21 their contact information here.<br/> 22       Then the other is within the Office of</p> | <p style="text-align: right;">37</p> <p>1       So whatever else comes to mind that's<br/> 2 outside the scope of topic 1 or topic 2, we ask<br/> 3 that you share those during the open public<br/> 4 comment period, which we took registration for.<br/> 5 There's a signup sheet out on the registration<br/> 6 desk, and we'll take registration up through lunch<br/> 7 break. We'll see how many people sign up, and<br/> 8 then we'll see how much time each speaker will<br/> 9 have.<br/> 10       Again, I'm going to put another plug-in<br/> 11 for the public docket, another place to continue<br/> 12 submitting your remarks that you didn't get to say<br/> 13 today. The views expressed today are personal<br/> 14 opinions, and on that note, respect for one<br/> 15 another is paramount.<br/> 16       Finally, let us know how the meeting<br/> 17 went for you today. We're going to be passing out<br/> 18 evaluation forms probably during break time.<br/> 19 They're very important to us, so please fill them<br/> 20 out and let us know what worked and didn't work.<br/> 21       All right. First, what we would like to<br/> 22 do is do some polling questions. You should all</p>      |

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| 38 | <p>1 have a clicker, patients and patient<br/>2 representatives. Those of you on the panel, you<br/>3 have it too. Okay. So let's do our first one to<br/>4 practice. Where do you live? Press A for within<br/>5 the DC Metro Area or B for outside of the DC Metro<br/>6 Area.<br/>7 (Polling audience.)<br/>8 MR. THOMPSON: Yes, it looks like it's<br/>9 bugged, so maybe just do a show of hands or<br/>10 something for now.<br/>11 MS. GIAMBONE: Oh, okay. Okay. It<br/>12 looks like we're having a little bit of technical<br/>13 difficulty.<br/>14 MR. THOMPSON: We're good now.<br/>15 MS. VAIDYA: No, we're good. The<br/>16 computer was just frozen.<br/>17 MS. GIAMBONE: Oh, we're good. We're<br/>18 good. Okay. If you see this and this between us<br/>19 over here, you'll know what's going on. Okay, so<br/>20 it looks like it's working. Let's see the<br/>21 results.<br/>22 MS. VAIDYA: It's a little slow --</p>  | 40 | <p>1 Okay. All right. For your age, press A<br/>2 for younger than 18; B, 18 to 30; C, 31 to 50; D,<br/>3 51 to 60; E, 61 to 74; or F, 75 or greater.<br/>4 Yes?<br/>5 AUDIENCE MEMBER: Is this just for<br/>6 patients or do you want everybody in the room?<br/>7 MS. GIAMBONE: This is just for patients<br/>8 and patient representatives, yes, and caregivers.<br/>9 Oh, just patients for this one; well, unless<br/>10 you're a caregiver answering on behalf of a<br/>11 patient.<br/>12 (Polling audience.)<br/>13 Okay. It looks like just about half of you in the<br/>14 room are within that 61 to 74 age group. But it<br/>15 looks like we have a very nice distribution of<br/>16 folks between 18 to 75 or greater.<br/>17 Okay. Again, for patients or caregivers<br/>18 answering on behalf of a patient, are you male of<br/>19 female?<br/>20 (Polling audience.)<br/>21 Okay. It looks like mostly all of you in the room<br/>22 are female or you are here representing a female.</p>  |
| 39 | <p>1 MS. GIAMBONE: Oh, it's a little slow.<br/>2 Just like traffic today because of that water main<br/>3 break; it's a little slow.<br/>4 MS. VAIDYA: Why don't we go to the Web<br/>5 first? Sorry.<br/>6 MS. GIAMBONE: Okay.<br/>7 MR. THOMPSON: So on the Web, we have<br/>8 about 91 percent outside of DC and 9 percent from<br/>9 inside the DC Metro area.<br/>10 MS. GIAMBONE: I think we can do a show<br/>11 of hands, right? Oh, there it is. So it looks<br/>12 like most of you actually -- the majority of you<br/>13 came from outside the DC Metro area, so thank you<br/>14 for being here. For all of our local neighbors,<br/>15 thank you also for being here.<br/>16 Let's go on to the next question. Have<br/>17 you ever been diagnosed as having an NTM lung<br/>18 infection? Press A for yes or B for no.<br/>19 (Polling audience.)<br/>20 Okay. It looks like over two-thirds of you in the<br/>21 room said yes, so we are going to hear some really<br/>22 great perspectives from you all today. Thank you.</p> | 41 | <p>1 What is the length of time since your<br/>2 NTM diagnosis: A, less than one year ago; B, 1 to<br/>3 2 years ago; C, 2 to 5 years ago; D, more than 5<br/>4 years ago; or E, I'm not sure?<br/>5 (Polling audience.)<br/>6 Okay. It looks like about half of you in the room<br/>7 have been diagnosed for more than five years. But<br/>8 again, it looks like we have several of you that<br/>9 are within this range of newly diagnosed to about<br/>10 2 to 5 years ago.<br/>11 All right. What is your underlying lung<br/>12 condition? A, cystic fibrosis; B, bronchiectasis<br/>13 -- and I apologize if I mispronounce anything --<br/>14 C, COPD or emphysema; D, her lung disease; E, a<br/>15 condition that's not mentioned here; or F, I don't<br/>16 know?<br/>17 (Polling audience.)<br/>18 Okay. So almost over 70 percent of you<br/>19 voted for B, followed by let's see -- and it seems<br/>20 that we do have some other -- we have a little bit<br/>21 of everything here. We'll make sure that when we<br/>22 hear from you during the group discussion, if you</p> |

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| 42 | <p>1 can also maybe mention what that underlying lung<br/>2 condition is if you identify that you had another<br/>3 lung disease or a condition not mentioned here.<br/>4       Okay. Then can I just see what we heard<br/>5 on Web?<br/>6       MR. THOMPSON: The Web results are<br/>7 pretty much the same as it was in the room. Panel<br/>8 1 - Comments on Topic 1<br/>9       MS. GIAMBONE: Okay, great. All right.<br/>10 So on that note, I would like to get started with<br/>11 our panelists for topic 1. You'll just press the<br/>12 red button on your microphone when it's your turn<br/>13 to speak, and when you're done, you just press it<br/>14 to turn it off again. We're going to start with<br/>15 Katie.<br/>16       MS. KEATING: Good morning, everyone. I<br/>17 thank you from the bottom of my heart for paying<br/>18 attention to NTM. This has been a dream of mine<br/>19 for the past 14 years. I was 39 years old when I<br/>20 started not feeling well, and I've been dealing<br/>21 with this for a long time.<br/>22       I am speaking on behalf of a lot of</p>   | 44 | <p>1 different doctors throughout New Jersey,<br/>2 eventually went to National Jewish, and then I<br/>3 traveled throughout the Tri-State area looking for<br/>4 answers because I wasn't going to give up; I<br/>5 wanted a cure. I did not want to deal with this.<br/>6       I was too young, had too many things to<br/>7 do, and I had a young daughter. So I kept on<br/>8 looking, and eventually I found a support group,<br/>9 and history has gone on.<br/>10       It is an invisible disorder. I look<br/>11 healthy. And all of us in the group, when we have<br/>12 our support groups, people say to us, "Oh, you<br/>13 look good." And we're like ready to (laughter)<br/>14 shoot them because they don't know how we feel.<br/>15       People complain if they have a cold, and<br/>16 it wears them down for two or three days, but just<br/>17 imagine having a life that you feel like you're<br/>18 sick half the time. I also compare it to like the<br/>19 manic depressive lung disease. You feel good a<br/>20 few days, and then, all of a sudden you are wiped.<br/>21 It's very hard to live this type of life because<br/>22 you're on an emotional rollercoaster. So again,</p> |
| 43 | <p>1 patients who, unfortunately, cannot be here, or on<br/>2 the webinar, or just are too sick to join us<br/>3 today, and also many other friends who were in our<br/>4 original New York City Area support group who have<br/>5 passed away, and others who have passed away<br/>6 throughout the country who we had befriended over<br/>7 the years. The support we have given each other<br/>8 was enormous.<br/>9       I am just really -- I have hope now that<br/>10 something is going to happen. I am a nurse and<br/>11 long-term care administrator by background, and<br/>12 when I was diagnosed, I researched online, and<br/>13 there were very few articles. Very few. I even<br/>14 went to New York City library and MEDLINE and<br/>15 tried to get everything I possibly could, and<br/>16 there was hardly anything there.<br/>17       NIH had been studying NTM for 37 years.<br/>18 Mycobacteria was first identified over a hundred<br/>19 years ago. But I felt so alone as a nurse, and I<br/>20 had nowhere to turn to; it took me a period of<br/>21 time, a year searching.<br/>22       I started looking for a diagnosis, many</p> | 45 | <p>1 I'm really, really happy to be here.<br/>2       I know we have limited time, so I'll<br/>3 continue. The three symptoms that I experience<br/>4 that have the most impact on my life are fatigue<br/>5 and stamina. My day is based on personal energy.<br/>6 I plan out what I am going to do based on how I<br/>7 feel. When the weather changes, it greatly impacts<br/>8 my energy, humidity, the rain, et cetera; it<br/>9 really impacts what I'm able to do.<br/>10       I prioritize, of course, on activities<br/>11 of daily living, what I must do, and then add on<br/>12 other. There are some days I could function more<br/>13 than others, and on those days, I get a lot more<br/>14 done because I know that it has this up and down<br/>15 curve.<br/>16       My stamina is just not what I was. I<br/>17 used to run 7 or 8 miles. When I first was sick<br/>18 with my first NTM infection, I had to take a taxi<br/>19 cab in New York one city block. My sister looked<br/>20 at me like, are you crazy spending money on a cab<br/>21 to go a block? But you get so beat.<br/>22       Again, it's an invisible disorder. We</p>   |

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| 46 | <p>1 don't have, unless you're losing weight, the<br/>2 apparent look that other diseases have.<br/>3       The lack of stamina has affected my<br/>4 ability to work full time. I was at the height of<br/>5 my career, in charge of quality assurance for the<br/>6 state. I could've really done really well in my<br/>7 career, but had to give that up due to this. When<br/>8 you can't plan that you can commit to projects,<br/>9 you are not going to really be productive. I do<br/>10 some per diem work, but there is not -- you're<br/>11 unable to work full time.<br/>12       I envy people who can get up in the<br/>13 morning, take a shower. Since this is based in<br/>14 water, we don't take showers. We have to watch<br/>15 the water we drink. We only drink certain bottled<br/>16 water. We can't have water in restaurants. Every<br/>17 day, I have to be cognizant of what I can do to<br/>18 avoid an infection.<br/>19       Not being able to work, of course, takes<br/>20 a toll on your life. It leads to social<br/>21 isolation. We have a support group, which helps<br/>22 us, but it really affects every aspect of your</p>              | 48 |
| 47 | <p>1 life when you're not able to work full time. And<br/>2 I was 39, so I had financial goals, which<br/>3 unfortunately cannot be met.<br/>4       Nobody thinks things are going to happen<br/>5 to them. We're like the 21-year-old, you know,<br/>6 guy; nothing is going to happen to us. I didn't<br/>7 think at 39, my life would change overnight. And<br/>8 being at this meeting, I have hope that in my<br/>9 lifetime -- because when I found out it was being<br/>10 studied for 37 years, I thought never in my<br/>11 lifetime, since it was so long, that something<br/>12 would happen. But now, there is hope.<br/>13       Being a patient, daily, we do airway<br/>14 clearance. We do nasal washes, nebulizers as<br/>15 needed; we go to the lab; we watch our diet. We<br/>16 are constantly in and out of remission.<br/>17       February and in August are my two<br/>18 critical months because February, flu season, I<br/>19 often get pneumonia; and in August, with the<br/>20 humidity. August, I don't go out. Most people go<br/>21 to barbecues and outdoor events. I have a young<br/>22 daughter. I stay in a lot because I don't want to</p> | 49 |
| 46 | <p>1 take the risk of getting sick.<br/>2       Many of us feel like we should live in a<br/>3 bubble, but then we won't live a quality life.<br/>4 Sometimes we push, and I do go out to places that<br/>5 I'm not -- and then I end up sick. Everybody says<br/>6 to me, "What the heck did you do that for?" But<br/>7 after a while, with every kind of illness, it's<br/>8 easy to get noncompliant. It takes a toll on you<br/>9 over time.<br/>10       The third symptom is coughing,<br/>11 constantly coughing up into a tissue. Years ago,<br/>12 when I first had this condition, I'd walk to the<br/>13 restroom, but over time, it's gotten worse and you<br/>14 just can't help it. I'm not going to walk to the<br/>15 restroom; you just cough up because the<br/>16 bronchiectasis has gotten worse. You do cough up<br/>17 in tissues, and it's repulsive to some. But I'm<br/>18 just like blinded now because overtime, it just<br/>19 has increased.<br/>20       Question number 2, specific activities<br/>21 that are important to you that I can't do, I used<br/>22 to run. I can't run; I walk. I watch every</p>                                       | 49 |
| 47 | <p>1 water. We can't do planting. We can't wear<br/>2 perfumes, terrified of mold, no hot tubs, no<br/>3 indoor pools. I had to move to a home with<br/>4 hardwood floors, no rugs. Radiator heat is the<br/>5 best because forced air is really bad for people<br/>6 with lung problems. No humidifiers, no<br/>7 fireplaces, no barbecue pits.<br/>8       I had to leave church recently because<br/>9 the incense, all these respiratory irritants that<br/>10 bother you. We don't go to crowded places, movies<br/>11 in fear of getting a respiratory infection. I<br/>12 travel less frequently.<br/>13       Again, I was a nurse, but I won't go<br/>14 into a hospital, or a nursing home, or other<br/>15 healthcare facility because I'm fearful of getting<br/>16 sick. I get sick like that, and it doesn't last<br/>17 for two days; it goes often to a pneumonia.<br/>18       Examples of severe fatigue, it just<br/>19 comes upon you at times. I've been in the grocery<br/>20 store with the shopping cart, but I didn't have<br/>21 the energy to wait in line to check out. That's<br/>22 how severe the fatigue becomes at times. We laugh</p>             | 49 |

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| 50 | <p>1 in our support groups on how it suddenly creeps up<br/>2 on you.<br/>3       Other things I can't do, exercise. I<br/>4 try to exercise and push, but there are some days<br/>5 I just can't. I know it helps but I just can't.<br/>6       How does your condition change over<br/>7 time? It has taken a toll, and I try to deal with<br/>8 the new normal, but it has gotten worse, and the<br/>9 duration for recovering is a lot longer.<br/>10       What makes your symptoms better? Doing<br/>11 everything, all the suggestions that they have on<br/>12 the website to prevent infections makes it better.<br/>13 But at times, after 14 years, you get tired of<br/>14 getting up every morning and doing chest airway<br/>15 clearance. Every patient has a patient burnout<br/>16 after a while.<br/>17       What worries me most about the<br/>18 condition? When I first researched, there was no<br/>19 new antibiotics on the market. All the money was<br/>20 going into all the psychotropics and all the<br/>21 sexual drugs at that time. Now, there is -- we<br/>22 are being paid attention to, which makes me really</p> | 52 | <p>1 health service. Though I didn't interface a lot<br/>2 with FDA, I do recognize some names still. So<br/>3 it's a lot like coming home for me.<br/>4       You know, there's a commercial on TV --<br/>5 I don't watch a lot of TV, but I see this<br/>6 commercial from time-to-time. A woman is walking<br/>7 through the woods, and she begins something like,<br/>8 "I'm only in my 60s," nice long life ahead, big<br/>9 plans.<br/>10       When I see that commercial, it kind of<br/>11 irks me a little bit because I thought, well,<br/>12 that's me. I'm in my 60s; I love to hike, walking<br/>13 through the woods, big plans, and then<br/>14 unexpectedly, NTM changed some of those plans.<br/>15       Two years ago, after I retired from this<br/>16 department, I had retina eye surgery, and I had to<br/>17 be face down for two weeks on kind of a cot, and I<br/>18 was about yay off the floor. Well, that's kind of<br/>19 hard. You know, I'm going to sleep face down for<br/>20 two weeks. And at the end of the two weeks, I<br/>21 thought, "Whew, I'm glad that's over with." And I<br/>22 stood up and I coughed. And I haven't stopped</p> |
| 51 | <p>1 happy because years ago, I was worried that I was<br/>2 going to have the infection and there was nothing<br/>3 going to be available. Other worries are --<br/>4       MS. GIAMBONE: Any final remarks, Katie?<br/>5       MS. KEATING: Excuse me?<br/>6       MS. GIAMBONE: Any final remarks?<br/>7       MS. KEATING: I'm just really, really<br/>8 happy that we are here and that I hope that we can<br/>9 just go forward getting the antibiotics and the<br/>10 research that we really need to improve the<br/>11 quality of life for all of those out there.<br/>12       MS. GIAMBONE: Thank you, Katie. Thank<br/>13 you so much. Next, we have Barbara.<br/>14       MS. HUDSON: Good morning. I echo<br/>15 Kathleen's comments about just the gratefulness<br/>16 for everybody that's here, especially those of you<br/>17 at FDA.<br/>18       Being here for me, although I live in<br/>19 Indiana now, it's a lot like coming home. I spent<br/>20 my whole working career with the Department of<br/>21 Health in Human Services, specifically with the<br/>22 Office of General Counsel advising the public</p>              | 53 | <p>1 coughing since I came from eye surgery.<br/>2       I met with lots of specialists,<br/>3 pulmonologists, ENT, allergists, internal med, a<br/>4 lot of famous docs even here in the Washington, DC<br/>5 area. Nobody could figure out why I was coughing.<br/>6 Finally, I have a wonderful physician here in<br/>7 Bethesda, and he said, "Barb, let's go to National<br/>8 Jewish." So that was really key.<br/>9       In 2004, I went to National Jewish.<br/>10 They performed a whole lot of tests, and they<br/>11 diagnosed me with NTM, along with several other<br/>12 diseases:<br/>13       bronchiectasis; I'm alpha-1 deficient.<br/>14 So we at least knew what we were dealing with.<br/>15       Physically, I'd say I'm just tired.<br/>16 Last night, I was at the meet and greet, and I was<br/>17 telling the woman and gentleman I was talking<br/>18 with, "Hey, I'm going to faint here in a minute."<br/>19 I had to sit down. I was just so tired, and<br/>20 that's so unusual for me.<br/>21       I saw both my parents active in their<br/>22 70s and 80s. Before I got NTM, I was very active.</p>   |

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| 54 | <p>1 I held a very demanding job in the Office of<br/>2 General Counsel. A couple years after retirement,<br/>3 I was walking, hiking, biking, caring for parents.<br/>4 I'm now very careful about my energy<br/>5 level as Kathleen said. I may wash windows, but<br/>6 it may take me all day, wash a window, sit down<br/>7 and rest; wash another window, sit down and rest.<br/>8 Things that once took a few minutes may take the<br/>9 whole day.<br/>10 I wear a mask when I'm in the garage or<br/>11 cleaning to prevent further infection. I no<br/>12 longer fix really large meals. If I want to do<br/>13 anything else during the day, I got to fix a meal<br/>14 that doesn't zap my energy level. Instead of<br/>15 having this much energy, I feel like I've got this<br/>16 much energy, and I'm careful how I allocate it.<br/>17 I joined exercise classes at the Y. I<br/>18 thought, well, kind of a new city, a good way to<br/>19 know people. I dropped two of those classes just<br/>20 because I couldn't keep up, and those classes were<br/>21 for seniors. There are people in those classes in<br/>22 their 70s and 80s, and I thought, "Good grief."</p> | 56 | <p>1 neighbor came rushing over. I had no idea she<br/>2 could hear me, but she came rushing over. "Should<br/>3 I call 911?" I said, "No, go back. I'll go in<br/>4 the house and finish coughing." It's just an<br/>5 embarrassment a lot of times.<br/>6 I guess I have some fear of the future.<br/>7 I'm single. I thought, well, gee, I could take<br/>8 good care of myself. I'm physically active. But<br/>9 now, I don't know. I've declined a lot in the<br/>10 last couple of years. What's the next couple of<br/>11 years going to be like?<br/>12 The next panel will talk a little bit<br/>13 more about treatment. I began treatment in<br/>14 August, late August, and three weeks later, I was<br/>15 so sick. In fact, last week, I was in bed three<br/>16 days, just shaking and thinking, well, am I going<br/>17 to be able to be here or not?<br/>18 So I came off the drugs, but I don't<br/>19 know what the future holds for me who can't take<br/>20 the three-drug cocktail. What are you going to<br/>21 look two years from now or four years from now?<br/>22 I guess my goal is to push myself as</p> |
| 55 | <p>1 You know, I've always been kind of the leader in<br/>2 the exercise, and now, I can't keep up with people<br/>3 who are much older than I am.<br/>4 I still exercise a lot. I go to the Y<br/>5 on a daily basis, but it's more individualized.<br/>6 In fact, I'm in a class for cardiac rehab, but I'm<br/>7 getting the exercise, whatever it takes.<br/>8 My big plans for the 60s have changed.<br/>9 I'm 67 now. I've had NTM for at least two years.<br/>10 But it's affecting not just my physical life. I'm<br/>11 certainly fatigued. I'm certainly coughing. I<br/>12 have a lot of shortness of breath, but it's<br/>13 affecting social life, which I don't like either.<br/>14 I'm often embarrassed because I've got<br/>15 to excuse myself and go cough up my lungs for an<br/>16 hour. Or I'm going out to lunch with a friend, and<br/>17 I have to call and say, "You know, I've got to<br/>18 cough up for another 45 minutes or so, and then<br/>19 we'll have lunch."<br/>20 Recently, I was trying to clear my<br/>21 lungs. I was, I guess, sitting on the front stoop<br/>22 or whatever, cough-spit, cough-spit, you know. My</p>                          | 57 | <p>1 much as I can to remain active, notwithstanding<br/>2 the fatigue, the shortness of breath, the<br/>3 coughing, but to remain positive as I go through<br/>4 the future.<br/>5 As with Kathleen, I remain hopeful that<br/>6 together, we can work together to find some<br/>7 answers, maybe not the final answer but at least<br/>8 the next step forward. How do we get this before<br/>9 the people -- even in the department, how do we<br/>10 get it before the Commissioner of FDA? How do we<br/>11 get this issue before the secretary of HHS?<br/>12 Those are the things, and I look forward<br/>13 to any questions you have later.<br/>14 MS. GIAMBONE: Thank you so much,<br/>15 Barbara.<br/>16 Philip?<br/>17 MR. LEITMAN: I'm delighted to be here.<br/>18 Those of you who have met me before know that I<br/>19 usually have some notes, and then usually, I<br/>20 listen to what people have to say and go in a<br/>21 different direction. Today is no exception.<br/>22 I'm here because Fern is not, because</p>  |

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| 58 | <p>1 she cannot speak for the illness that she battled<br/>2 from the time she was in her 40s. I'm not going<br/>3 to into defining what NTM is or any of that<br/>4 because that's been done.<br/>5       What I'd like to talk about is what it<br/>6 does. Frankly, you can't separate symptoms and<br/>7 impacts on daily life of the disease from the<br/>8 treatment because they really do go hand in hand.<br/>9 Both affect the ability to live and the quality of<br/>10 life.<br/>11       In Fern's case, she was on multiple<br/>12 drugs for 18 years. She had -- and this is not a<br/>13 misquote -- over 26,000 IV infusions during the<br/>14 period of her treatment. They were difficult to<br/>15 tolerate. I'm delighted so many patients are<br/>16 here, doctors, scientists, and FDA.<br/>17       In her case, we knew that the treatments<br/>18 extended her life. From the time she was<br/>19 diagnosed until the very last day, there was this<br/>20 smile on her face and optimism, but it did have an<br/>21 impact. What we're hearing from Katie, Barbara,<br/>22 what I'm sure you're going to say, Marilynn and</p>                    | 60 |
| 59 | <p>1 others, is fatigue, the inability to be<br/>2 spontaneous, get up, take a quick shower, go out<br/>3 and live your life.<br/>4       Your life changes because your life is<br/>5 planned around the treatments and the impacts of<br/>6 the disease. From the treatments, Fern had loss<br/>7 of hearing, not complete, but she could read lips.<br/>8 Her eyesight was affected. She was still able to<br/>9 drive until she didn't have enough energy to do<br/>10 that. Part of that was from the disease, the long<br/>11 term inflammation. Part of it was from the drugs.<br/>12 We know that.<br/>13       So while treatments help, they extend<br/>14 life, at times, improve life, those treatments are<br/>15 not a cure. In fact, I would challenge anybody to<br/>16 define a cure for NTM because we really don't know<br/>17 what a cure means because even if you're culture<br/>18 negative, it comes back.<br/>19       So we need to start by defining what are<br/>20 the goals. In my mind, the goals are to extend<br/>21 life and improve quality of life, reduce the<br/>22 amount of fatigue, increase stamina, decrease the</p>              | 61 |
| 60 | <p>1 number of exacerbations because everybody with<br/>2 this disease has an exacerbation.<br/>3       We need to have treatments that will be<br/>4 less toxic and more effective. And I'm thrilled<br/>5 because you all are listening. So many patients<br/>6 are here whereas years ago, we would've come to an<br/>7 empty room. So many doctors are looking at it,<br/>8 and industry is here. They were here with us last<br/>9 night; they're here now.<br/>10       While we heard earlier that the<br/>11 treatments are off label, one of the things needed<br/>12 is to really have some trials to understand the<br/>13 existing treatments that are used off label, what<br/>14 do they really do? What's the role of the new<br/>15 drugs because we know that they're needed, but we<br/>16 need to better understand the current treatments<br/>17 and what that means.<br/>18       There is a history of drug resistance<br/>19 that's acquired over time. We now know from more<br/>20 sophisticated testing over the last few years that<br/>21 if you have a certain gene, certain strains,<br/>22 they're going to be more inherently resistant.</p> | 62 |
| 61 | <p>1       But with the newer technology, those<br/>2 treatments can be refined. But we know this is<br/>3 very different than typical drug approval because<br/>4 many patients are on treatment for a very, very<br/>5 long time, many months to many years, and that has<br/>6 a different impact.<br/>7       I think that many of the patients,<br/>8 including my wife, took the approach that there<br/>9 were some calculated risks in order to extend life<br/>10 and try to improve quality. Those are individual<br/>11 decisions made with their physicians.<br/>12       I will tell you from a personal point of<br/>13 view, in 2009, with the help of a physician, a<br/>14 drug company, and approvals, Fern was given a drug<br/>15 on a compassionate use basis before it got on the<br/>16 market.<br/>17       It extended her life for five years.<br/>18 She saw our grandchildren grow. Everybody in this<br/>19 room who has the disease, every family member<br/>20 wants that same opportunity. That's why we're<br/>21 here. This is different than something that is a<br/>22 short term treatment.</p>   | 63 |



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| 62 | <p>1 I echo what all the patients are saying,<br/>2 and thank you.<br/>3 MS. GIAMBONE: Thank you so much,<br/>4 Philip.<br/>5 Now, we have Marilyn.<br/>6 MS. LUNDY: Well, I'm thankful to be<br/>7 here, and I'm fortunate to be here. I think I can<br/>8 come from a little bit of a different viewpoint<br/>9 than the people that have spoken. So I'm not<br/>10 going to repeat a lot of the symptoms that caused<br/>11 me to be diagnosed, finally after five years, took<br/>12 me to be diagnosed.<br/>13 I began to feel tired and so forth.<br/>14 This was about 15 years ago. I probably would've<br/>15 contributed a lot of the symptoms that we have to<br/>16 maybe aging, because at one time or another, I had<br/>17 every one of those symptoms that was up there on<br/>18 the board this morning, except I never lost much<br/>19 weight.<br/>20 But the one symptom for me that actually<br/>21 got me through those five years to finally get a<br/>22 diagnosis was every morning, getting up and</p>   | 64 | <p>1 now -- and I have been feeling pretty well most of<br/>2 the time. However, the symptoms of that nature,<br/>3 who knows --<br/>4 I mean it feels as though we don't even<br/>5 know why suddenly those days happen.<br/>6 Unfortunately, a lot of times, it's on the<br/>7 weekend. That's the first thing for me as a<br/>8 patient that went, because I worked full time<br/>9 through all the medication, had to work. I live<br/>10 alone. I've never been married, don't have -- I'm<br/>11 not independently wealthy or anything, so I have<br/>12 to make a living. And through all this, I have<br/>13 worked five days a week at least.<br/>14 However, I'm an interior designer, and I<br/>15 had to change my career totally because there's<br/>16 nothing that can get me coughing faster than being<br/>17 on a construction site with a lot of dust and, you<br/>18 know, the nature of a construction site.<br/>19 I used to be there at 7:00 in the<br/>20 morning, going over things with the contractors<br/>21 and being sure that it was done the way I planned<br/>22 it to be done, and I can't do that anymore. I</p> |
| 63 | <p>1 coughing up green sputum. For me, that has been<br/>2 the biggest thing that I've had to deal with. And<br/>3 it has affected everything in my life, and still<br/>4 does.<br/>5 After I was diagnosed, I was on<br/>6 antibiotics for five years, and I have been off of<br/>7 any medications for about two and a half years. I<br/>8 guess I maybe represent life after drugs or life<br/>9 after medication. I can tell you that I still<br/>10 have symptoms. I still get up every morning and<br/>11 cough up sputum, which my sister, who's been<br/>12 staying with me the last couple of days, can<br/>13 attest to.<br/>14 I still have those days when I get up,<br/>15 and it doesn't seem like there's any known reason,<br/>16 but I cannot function very well. I can't think<br/>17 straight. I ache all over. Those days, if I can,<br/>18 I cancel everything and try to lay low.<br/>19 In spite of the fact that I'm<br/>20 stabilized, my lung scans don't show that there's<br/>21 much more deterioration going on -- and that's one<br/>22 of the reasons why I'm not on medications right</p> | 65 | <p>1 still do a little decorating, but I can't make the<br/>2 kind of money that I used to make.<br/>3 Another thing that I did, I did a lot of<br/>4 presentations. I traveled around the country on<br/>5 media tours for some corporations as an interior<br/>6 designer. I even wrote a book on public speaking<br/>7 just about 15 years ago when I started to feel so<br/>8 poorly.<br/>9 I have not been able to do that. A lot<br/>10 of my clients came from those presentations and so<br/>11 forth, but to stand up and give a presentation<br/>12 without coughing or without being totally<br/>13 fatigued, it was pretty impossible.<br/>14 The good news is that I was just at NIH<br/>15 yesterday, and as I said, things are looking good.<br/>16 My scans are -- everything is stabilized and so<br/>17 forth. And I won't have to come back again for a<br/>18 couple of years.<br/>19 But that doesn't mean that the symptoms<br/>20 are gone. As long as there's bronchiectasis --<br/>21 and we don't even have a clue about, it seems to<br/>22 me, about bronchiectasis and how to deal with it,</p>                        |

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| 66 | <p>1 that's the underlying disease that I have, and<br/> 2 that's there. The airways are already ruptured,<br/> 3 and they are just sitting there waiting for MAI or<br/> 4 some other bacteria to come and move in.<br/> 5 I do a lot, of course, to prevent it. I<br/> 6 was part of the Falkenheim's water research and<br/> 7 found that in my building, 600 apartments in New<br/> 8 York City, that the water in the pipes in my<br/> 9 building, everything in my building has the exact<br/> 10 strain of MAI that I was diagnosed with initially.<br/> 11 I talked to Dr. Falkenheim about what<br/> 12 can I do about this? At that time -- I understand<br/> 13 there's now some filters that we may be able to<br/> 14 get for our homes. But there was nothing at that<br/> 15 time. And he said the only thing to do was to boil<br/> 16 my water. So I do that every day. I boil all my<br/> 17 drinking water, all the water that I cook with.<br/> 18 There are so many things that I do now<br/> 19 to prevent and to take care of myself, and as<br/> 20 Katie was saying, to prevent myself from being<br/> 21 exposed so that I don't have as many<br/> 22 exacerbations. I had one a month ago, and I had</p> | 68 |
| 67 | <p>1 one two months before that.<br/> 2 It's not like a normal cold. You're out<br/> 3 for at least a week with a fever and flu-like<br/> 4 symptoms, I ache all over kind of thing. If you<br/> 5 want to live your life, you're going to be exposed<br/> 6 to these things.<br/> 7 I'll end on the high notes for me. When<br/> 8 Dr. Oliviaz [ph] asked me yesterday what was new,<br/> 9 I said, "Well, what do you mean?" What category<br/> 10 are we talking about? And so suddenly I realized,<br/> 11 well, what's really new with me is that for the<br/> 12 first time, in a long time, I was able to -- I've<br/> 13 always been singing all my life. There was a<br/> 14 period of time when I was on the meds when I<br/> 15 couldn't sing at all. I had no voice.<br/> 16 I don't know if you can tell what's<br/> 17 happening in my voice right now. This stuff is<br/> 18 hanging down there, et cetera. Well, I wasn't<br/> 19 even able to sing at all. Sometimes I couldn't<br/> 20 speak very much either.<br/> 21 So for the first time in many years, in<br/> 22 June, I gave a performance on stage, off Broadway,</p>   | 69 |
| 66 | <p>1 so to speak, and sang. That's been very exciting<br/> 2 to me, to be able to sing again.<br/> 3 I also was able to give an hour's<br/> 4 presentation, standing, with 15 minutes questions<br/> 5 afterwards for the first time again in about 15<br/> 6 years.<br/> 7 So I'm one of the very fortunate people<br/> 8 that has really benefited from all the research<br/> 9 and everything that's happened in recent years,<br/> 10 and I mean recent. I mean, when I -- you know, in<br/> 11 New York City, it took five years to be diagnosed.<br/> 12 That tells you how few people, even the medical<br/> 13 profession, understood very little at that point.<br/> 14 Today, through all the research and<br/> 15 because of my experience, every research project<br/> 16 that comes my way, I participate in because I want<br/> 17 to be able to educate and have everybody know and<br/> 18 understand this disease.<br/> 19 This is great to be here today, and this<br/> 20 is so different than it was before all this<br/> 21 happened. When I was first diagnosed, the only<br/> 22 thing that was online was people that had HIV or</p>  | 68 |
| 67 | <p>1 AIDS, and I was terrified. I thought, well, it<br/> 2 won't be long before I'm dead, you know?<br/> 3 Then I found the support group -- I'm in<br/> 4 the same support group as Katie -- and found out<br/> 5 that it didn't necessarily mean you're going to<br/> 6 die of this disease, but it looks like I'm going<br/> 7 to have it the rest of my life.<br/> 8 MS. GIAMBONE: Thank you. Thank you so<br/> 9 much, Marilyn. Thank you for sharing that really<br/> 10 positive story about being able to sing recently.<br/> 11 That's really very nice to hear.<br/> 12 I would like to ask everyone to give our<br/> 13 panelists a round of applause.<br/> 14 (Applause.) Large Group Facilitated<br/> 15 Discussion on Topic 1<br/> 16 MS. GIAMBONE: Thank you for working so<br/> 17 hard to prepare your comments and for being so<br/> 18 courageous and sharing them with us.<br/> 19 What I'd like to do is a few show-of-<br/> 20 hands exercise now. How many of you felt that you<br/> 21 heard -- that what our panelists said that some of<br/> 22 it resonated with you?</p>  | 69 |

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| 70 | <p>1 (Show of hands.)</p> <p>2 Many, many hands. Okay, I see at least a dozen</p> <p>3 hands that have been raised. That's great to hear</p> <p>4 that there's a lot of similar experiences, and I</p> <p>5 know there must be some that are not similar, too,</p> <p>6 so we look forward to hearing them.</p> <p>7 But I also want to ask, we heard some</p> <p>8 very interesting concepts, and I want to see by a</p> <p>9 show of hands if these also resonate with you.</p> <p>10 Katie mentioned weather changes are -- that's a</p> <p>11 trigger for some of the symptoms. How many of you</p> <p>12 feel the same way?</p> <p>13 (Show of hands.)</p> <p>14 MS. GIAMBONE: I see about 16 hands or</p> <p>15 so, 16 or 17 hands.</p> <p>16 We also heard about having to pace</p> <p>17 yourself for activities during the day. How about</p> <p>18 that? How many does that resonate with?</p> <p>19 (Show of hands.)</p> <p>20 MS. GIAMBONE: Again, another 16, 18</p> <p>21 hands I think I see.</p> <p>22 Marilynn brought up this difficulty in</p>  | 72 | <p>1 symptoms not mentioned.</p> <p>2 Again, for those of you on the Web, you</p> <p>3 can answer through the webcast.</p> <p>4 (Polling audience.)</p> <p>5 It looks like 80 percent of you voted for G,</p> <p>6 fatigue or lack of energy, so we'll definitely</p> <p>7 hear more on that. Then we see almost 40 percent</p> <p>8 or so cough; coughing up blood, phlegm and mucous;</p> <p>9 and shortness of breath, so we'll touch on those</p> <p>10 as well.</p> <p>11 We have several people that identified</p> <p>12 fever and night sweats, pain. We also have people</p> <p>13 that identified other symptoms not mentioned, so</p> <p>14 we'll be sure to get to those as well to hear from</p> <p>15 you.</p> <p>16 How about on the Web, what do we see?</p> <p>17 MR. THOMPSON: Pretty similar. We have</p> <p>18 45 percent for chronic cough, 48 for coughing up</p> <p>19 blood or mucous, 45 for shortness of breath, 21</p> <p>20 for fever and night sweats, 12 for loss of</p> <p>21 appetite, 9 for weight loss, 75 percent for</p> <p>22 fatigue or lack of energy, 15 percent for pain,</p>   |
| 71 | <p>1 thinking. How about that? How about that</p> <p>2 concept, which again we'll dive into in just a</p> <p>3 little bit? But I just want to see how many of</p> <p>4 you.</p> <p>5 (Show of hands.)</p> <p>6 MS. GIAMBONE: So I'm seeing about 10</p> <p>7 hands or so raised on that.</p> <p>8 All right. Great. Why don't we get our</p> <p>9 clickers out? I want to do a polling question,</p> <p>10 which is going to help kick off this discussion.</p> <p>11 So again, patients and caregivers, if you can grab</p> <p>12 your clicker.</p> <p>13 Of all the symptoms you have experienced</p> <p>14 because of your NTM lung infection, which do you</p> <p>15 consider to have the most significant impact on</p> <p>16 your daily life? You can choose up to three</p> <p>17 symptoms: A, chronic cough; B, coughing up blood,</p> <p>18 phlegm or mucous, and mucous; C, shortness of</p> <p>19 breath or other breathing difficulties; D, fever</p> <p>20 or night sweats; E, loss of appetite; F, weight</p> <p>21 loss; G, fatigue or lack of energy; H, pain such</p> <p>22 as chest pain or shoulder pain; or I, other</p> | 73 | <p>1 and 6 percent for other symptoms not mentioned.</p> <p>2 MS. GIAMBONE: Great. Thank you. Let's</p> <p>3 start with fatigue. Many of you voted for that,</p> <p>4 and we heard it on the panel, too. What I'd like</p> <p>5 to ask is if you can describe to us, how do you</p> <p>6 experience the fatigue? And as Philip mentioned,</p> <p>7 can you talk about maybe what exacerbates it or</p> <p>8 what triggers it? How do you cope with that?</p> <p>9 One sec, we have a microphone coming to</p> <p>10 you.</p> <p>11 MS. WEINER: Thank you. My name is</p> <p>12 Marcy Weiner. I was diagnosed about eight and a</p> <p>13 half years ago. The fatigue, as one of our</p> <p>14 panelists stated, can come on very suddenly. If I</p> <p>15 lie down, instead of taking maybe a doze for 10 or</p> <p>16 20 minutes, which would've been normal, it might</p> <p>17 be three and a half or four hours later I wake up,</p> <p>18 and you're not refreshed. I could maybe not find</p> <p>19 that I could move.</p> <p>20 Now, I'm fortunate so far to have a</p> <p>21 lighter case. But this still can happen. It's</p> <p>22 totally unpredictable. And you may not have any</p> |

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| 74 | <p>1 other symptoms along with it. There may be, at<br/>2 the time, no necessarily increase in sputum or no<br/>3 night sweats or fevers, which you could put<br/>4 towards TB, et cetera, like that.<br/>5 I think this is the one thing. You<br/>6 heard this from the panelists, but it's very<br/>7 dramatic at times. You could be driving along in<br/>8 the car between Massachusetts and Connecticut and<br/>9 all of sudden have to pull off to the side of the<br/>10 road, literally, and take that -- and know because<br/>11 you know your eyes are closing, and you're going<br/>12 to just bottom out.<br/>13 MS. GIAMBONE: Okay. So fatigue that<br/>14 comes on very abruptly. Marcy, as you mentioned,<br/>15 sometimes sleep is not even help -- it doesn't<br/>16 help refresh you. Okay. Thank you, Marcy.<br/>17 FEMALE SPEAKER: With the fatigue, as I<br/>18 -- it actually is brought on even more so with the<br/>19 constant coughing, as you can tell, that it wears<br/>20 you down. Constant coughing all the time creates<br/>21 more fatigue, so it's kind of a vicious circle.<br/>22 In addition to that, I cannot sleep</p> | 76 | <p>1 my stepdaughter, that I homeschool.<br/>2 But obviously, this is bad because who<br/>3 wants to operate under the influence almost every<br/>4 day of their life and not be able to drive? My<br/>5 daughter goes to the NIH out here, and my husband<br/>6 cannot even let me drive her because what if I get<br/>7 tired? Either that or I'm under the influence,<br/>8 and it's just got a good idea. It folds into<br/>9 everything.<br/>10 MS. GIAMBONE: Thank you. Thank you.<br/>11 Katie, did you want to say something?<br/>12 MS. KEATING: I'd like to say something<br/>13 also on that note. Since fatigue is so<br/>14 unpredictable, I also was driving. I tried to go<br/>15 back to work a couple of years ago. I have a very<br/>16 good driving record that I just -- suddenly, it<br/>17 came on me. It went through the stop sign, got<br/>18 pulled over.<br/>19 Then a few weeks later, I went to pick<br/>20 up my daughter at school, and I was speeding. I<br/>21 never had a speeding ticket in my life. But<br/>22 again, it came on suddenly. I didn't feel well.</p>       |
| 75 | <p>1 through the night, so I don't get a lot of rest at<br/>2 nighttime, and that unfortunately also contributes<br/>3 to fatigue as well.<br/>4 MS. GIAMBONE: Thank you. Is it the<br/>5 cough -- what is it that you're not able to --<br/>6 what's impacting you not being able to sleep? Is<br/>7 it the cough keeping you up?<br/>8 FEMALE SPEAKER: My coughing.<br/>9 MS. GIAMBONE: Okay.<br/>10 FEMALE SPEAKER: Yes.<br/>11 MS. GIAMBONE: All right. Thank you so<br/>12 much. We have a hand over here.<br/>13 JACQUELINE: Hi. My name is Jacqueline.<br/>14 I'm 53 years old, and I've been battling this for<br/>15 40 years. The fatigue is just the tip of the<br/>16 iceberg because with the fatigue comes confusion.<br/>17 It comes with just so much you cannot even<br/>18 believe.<br/>19 My way of dealing with this after 30<br/>20 years was I will just take -- I am blessed because<br/>21 hydrocodone makes me awake, not fall asleep, so I<br/>22 can do my housework and take care of my daughter,</p>  | 77 | <p>1 I was trying to go back to work and doing<br/>2 everything I wanted to do.<br/>3 It's just hard to accept, to surrender,<br/>4 to give in, but that's how suddenly it comes upon<br/>5 you. When you have a young child -- I didn't get<br/>6 into [indiscernible]. But when I first had my<br/>7 first MAC infections, the first few in the early<br/>8 years, I couldn't even do my daughter's homework,<br/>9 check it.<br/>10 Big thing was rest up just so I could<br/>11 sign her papers. You know, in the beginning of<br/>12 the year, they give you a ton of papers. That was<br/>13 like a big accomplishment. That's how minimal<br/>14 energy.<br/>15 When you go through chemo -- I have<br/>16 friends that went through chemo recently, and you<br/>17 feel beat for a period of time; you take off the<br/>18 weekend. Six months later, you go back to work.<br/>19 This is no getting-better-and-go-back-<br/>20 to- work. You just go through ups and downs.<br/>21 It's just -- I often call it like microbial prison<br/>22 because you're never out of the sentence of -- you</p> |

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| 78 | <p>1 know, we innocently got this disease. We took a<br/>2 shower one day, and it totally changed your life.<br/>3 MS. GIAMBONE: Thank you, Katie.<br/>4 MS. KEATING: You're welcome.<br/>5 MS. GIAMBONE: We can hear you, Donna.<br/>6 DONNA: My name is Donna. I think my<br/>7 fatigue comes from lack of sleep, finding a good<br/>8 position, so I'm not wheezing; not so much<br/>9 coughing but the wheezing is terrible and mostly<br/>10 in a prone position.<br/>11 What also keeps me up at night is the<br/>12 fear of the future, which Barbara had touched on,<br/>13 and being a pulmonary cripple, which I've been<br/>14 told I might be someday as a result of -- they<br/>15 can't even operate on my lung. That's how bad it<br/>16 is. And they said if I do have a pneumonectomy,<br/>17 I'd become a pulmonary cripple. So the fear and<br/>18 the anxiety is what keeps me up at night.<br/>19 MS. GIAMBONE: Okay. I'd like to ask,<br/>20 is there a sort of -- I know that we heard that<br/>21 fatigue is abrupt, but we're also hearing -- I'm<br/>22 hearing sort of a daily battle with it, too, a</p> | 80 | <p>1 for a long time.<br/>2 I stayed on the cocktail, the three for<br/>3 two and a half years. And by then, I saw an<br/>4 infectious disease doctor. He said, let's give<br/>5 your body a holiday from the drugs. Of course, I<br/>6 felt fine, but I never had a negative sputum. By<br/>7 then, I was diagnosed with MAC.<br/>8 While I walked out of the office, I<br/>9 think two minutes later, I start coughing. My<br/>10 husband said to me, Oh, my God, they just turned<br/>11 on the cough. So I coughed enough that I started<br/>12 bleeding a little and scared me half to death,<br/>13 still never fatigued to this day.<br/>14 I went to Denver. I saw Dr. Eisman. I<br/>15 saw Dr. Daley. They said because I'm so healthy,<br/>16 I should have -- I had millions of tests, and I<br/>17 did have -- Dr. Mitchell did a lung resection in<br/>18 my upper right and my middle lobe. I did very<br/>19 well with that and stayed with medicine another<br/>20 year or so.<br/>21 I was negative for about three and a<br/>22 half years, and this February, I had one positive</p>  |
| 79 | <p>1 daily sense of fatigue, tiredness.<br/>2 Is that accurate that you're also having<br/>3 a daily battle with fatigue? No? I'm seeing many<br/>4 head nods, but I'm also seeing a no here. One<br/>5 second.<br/>6 DEBORAH: I didn't know I would be<br/>7 talking. Mine is a little different. I always<br/>8 have bronchitis. Seasonal change, I went to my<br/>9 doctor, he gave me my typical antibiotic. And<br/>10 then as I was walking out, he said, you know what,<br/>11 let's take an X-ray of your chest, make sure you<br/>12 don't have pneumonia, which I did not have.<br/>13 But they found little nodules here and<br/>14 there, and the radiologist said since he had<br/>15 nothing to compare it to, he wanted CAT scan every<br/>16 six months for two years, which I did. Never<br/>17 coughed, never sick.<br/>18 Eighteen months later, a cavity formed<br/>19 in the upper right. I saw a pulmonary specialist.<br/>20 He said, I'm doing a full PET scan to make sure<br/>21 it's nothing cancerous, but I think I know what<br/>22 you have, and you'll be in a lot of antibiotics</p>                | 81 | <p>1 sputum, again, not sick really, but they have me<br/>2 back on my medicine. I've had now 7 negatives,<br/>3 but I have to stay on the meds. I'm assuming I'll<br/>4 be on meds off on the rest of my life.<br/>5 MS. GIAMBONE: Thank you, Deborah.<br/>6 DEBORAH: That's my story.<br/>7 MS. GIAMBONE: Thank you, Deborah. And<br/>8 we'll definitely be hearing more about treatment<br/>9 regimens in topic 2. But you bring up cough, and<br/>10 that's a good lead in to the other symptoms that<br/>11 you've all identified: chronic cough; coughing up<br/>12 blood, phlegm and mucous; and then also breathing<br/>13 difficulties, which I know you had mentioned.<br/>14 Can we hear some perspectives on the<br/>15 cough? Tell us about how you're experiencing that<br/>16 cough? Is there a good day? What triggers the<br/>17 bad day? Would anybody like to share? I thought<br/>18 I saw a hand here. Okay.<br/>19 JAQUELINE: Hi. The cough is something.<br/>20 I've had an AVI vest since 1999 that I had to wear<br/>21 for 3 to 5 hours a day to clear my lungs. I've<br/>22 had the first flutter valve. I now have a brand</p> |

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| 82 | <p>1 new AFLOW VASP that you can actually walk around<br/>2 with and not sit at a corner two feet away from a<br/>3 wall for 3 to 5 hours a day. That brings on<br/>4 depression. I mean, who wants to sit in a corner<br/>5 for 4 hours a day?<br/>6 So now, I have a new vest, but the cough<br/>7 causes so much pain. You're always pulling<br/>8 muscles, and it makes you so tired. It leads<br/>9 right into the fatigue when you cough. It just<br/>10 creates like a horrible syndrome.<br/>11 MS. GIAMBONE: So the cough is bringing<br/>12 on pain, and it's also impacting -- it's also<br/>13 triggering the fatigue.<br/>14 JAQUELINE: Yes. If one of you put on a<br/>15 vest, one of the precaution types of vest, and you<br/>16 wore it for a half hour, it would do you all in.<br/>17 I mean, it would just do you in. Everybody would<br/>18 have to take a nap. And then to cough on top of<br/>19 it, each one of you at that table would need to<br/>20 take a nap and take some Tylenol.<br/>21 MS. GIAMBONE: Thank you. And your<br/>22 name?</p>                | 84 |
| 83 | <p>1 JAQUELINE: My name is Jaqueline.<br/>2 MS. GIAMBONE: Jaqueline. Thank you,<br/>3 Jaqueline. We have a comment here.<br/>4 DOROTHY: I'm Dorothy. Two years ago, I<br/>5 started using the sodium chloride 7 percent<br/>6 solution twice a day, and I haven't had pneumonia<br/>7 since. But I cough a great deal, and the only<br/>8 thing that will stop it is a cough drop.<br/>9 Yesterday in the afternoon, I coughed<br/>10 three times; twice, I was on the phone, had to<br/>11 hang up and wait until I could it under control<br/>12 before I called back. Twice this morning, I've<br/>13 been doing it, too.<br/>14 MS. GIAMBONE: Thank you, Dorothy. We<br/>15 have a comment here.<br/>16 BETSY: Hi, I'm Betsy. When I start<br/>17 trying to talk, I start coughing. I cough like<br/>18 episodes. Well, it will go on for 5 or 10 minutes<br/>19 just coughing. I mean I walk up the street and<br/>20 suddenly I'm seized with this huge coughing<br/>21 episode. I just have to stop. People think I'm<br/>22 dying or something awful. They keep offering</p>       | 85 |
| 82 | <p>1 lozenges, which really don't help much. Water, I<br/>2 carry water with me everywhere. It just doesn't<br/>3 stop. It doesn't stop the cough.<br/>4 It's really affected my life in a<br/>5 horrible way in terms of socializing and even<br/>6 volunteering. Nobody even wants me around because<br/>7 you may say you're not contagious but people don't<br/>8 believe that. Most people say, oh, yeah, and I can<br/>9 clear a subway car, or a bus.<br/>10 (Laughter)<br/>11 So if you want a seat, just watch me.<br/>12 Anyway, it's exhausting as everybody has<br/>13 been saying. It's really exhausting. I'm quiet<br/>14 until I start trying to talk or eat. Even when<br/>15 eating, it seems to trigger a lot of coughing.<br/>16 So I don't know. I'm working on it from<br/>17 a lot of different angles: swallowing therapy,<br/>18 acid reflux. I'm looking everywhere to try to<br/>19 deal with it, but so far, not much luck.<br/>20 MS. GIAMBONE: Thank you, Betsy. Can I<br/>21 ask you, how many episodes of coughing do you<br/>22 typically experience?</p> | 84 |
| 83 | <p>1 BETSY: A day?<br/>2 MS. GIAMBONE: In a day.<br/>3 BETSY: Average day, maybe four.<br/>4 MS. GIAMBONE: Four episodes.<br/>5 BETSY: At least. I mean it could be<br/>6 more, but four, yeah. Yeah.<br/>7 MS. GIAMBONE: Okay. Does that resonate<br/>8 with others about four or so -- just sounds like<br/>9 about 10, 15 minutes of coughing episodes a day?<br/>10 Does that sound similar to your experience? So<br/>11 I'm hearing some, it depends, but I'm seeing head<br/>12 nods also. Okay.<br/>13 We're hearing that talking, eating can<br/>14 trigger cough, weather changes, it sounds like.<br/>15 What other triggers the cough? I see some hands<br/>16 here.<br/>17 MS. WEINER: Yes, mold, and I think that<br/>18 is the tie-in with the rainy weather. I've<br/>19 noticed if I'm in the Caribbean -- or I went to<br/>20 Hawaii for our 50th wedding anniversary, rained<br/>21 the whole week, huge reaction. It was very<br/>22 dramatic, and I was really upset that the place we</p>  | 85 |

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| 86 | <p>1 were staying at, which had dehumidifiers, never<br/>2 offered them.<br/>3 But I think the mold -- I've talked with<br/>4 Joe about this before, I think they're doing some<br/>5 research in France, perhaps in Paris, one of the<br/>6 institutes on this tie-in. And I'd like to see a<br/>7 little bit more of that.<br/>8 MS. GIAMBONE: Thank you. Marcy, right?<br/>9 Okay, thank you, Marcy.<br/>10 Continuing -- yes, Marilyn?<br/>11 MS. LUNDY: I have an extreme coughing<br/>12 story, again a travel story. Traveling changes<br/>13 dramatically when you have this disease. I was in<br/>14 treatment early on, and towards the end of a trip,<br/>15 and I got an exacerbation and was really sick and<br/>16 coughing very, very badly.<br/>17 It was the end of the trip, and I got<br/>18 home and realized that I wasn't cognitive like I<br/>19 usually am. My mind was working properly but --<br/>20 and I went to a meeting, and people said, you need<br/>21 to see a neurologist. And it turned out that I<br/>22 had a broken blood vessel in my brain.</p> | 88 | <p>1 could go on for a good 90 minutes, and I'm just<br/>2 down on the floor, on my knees, grabbing my ribs,<br/>3 hacking. So it's not your standard little cough.<br/>4 MS. GIAMBONE: Barbara, that severe<br/>5 cough that you just mentioned that can last 90<br/>6 minutes, is that something you experience on a<br/>7 daily basis or how frequently --<br/>8 MS. HUDSON: It is.<br/>9 MS. GIAMBONE: Okay.<br/>10 MS. HUDSON: And I even got a little<br/>11 fearful of coming up here. Usually, I can delay<br/>12 it if I chew gum or something. But I would say 2<br/>13 to 3 hours a day, I'm coughing a lot, a heavy<br/>14 cough, trying to clear my lungs.<br/>15 MS. GIAMBONE: Is there a time of day<br/>16 that you experience it?<br/>17 MS. HUDSON: It doesn't matter.<br/>18 Sometimes using the Aerobika, which is to shake<br/>19 your airways and clear your lungs -- and I can<br/>20 start clearing my lungs, but then it never ends.<br/>21 You know, it's like an eternal fountain there that<br/>22 I'm coughing for 1 to 2 hours, and sometimes I</p> |
| 87 | <p>1 They did everything to try to diagnose<br/>2 where that came from. They were down behind the<br/>3 heart too see if there were any holes there and so<br/>4 forth and so on. And in the end, they said it's<br/>5 conceivable that it could've been from the<br/>6 coughing.<br/>7 Luckily for me, it went away in a week.<br/>8 I understand that that's called a mini-stroke.<br/>9 They didn't call it that. They said a broken<br/>10 blood vessel. But the coughing can be really,<br/>11 really unbelievably extreme, especially during an<br/>12 exacerbation.<br/>13 MS. GIAMBONE: Thank you, Marilyn.<br/>14 We'll take one comment from Barbara, and<br/>15 then I'm going to check in with the Web.<br/>16 MS. HUDSON: Well, I was just going to<br/>17 say, the first year I was coughing, I broke two<br/>18 ribs and a vertebrae in my back.<br/>19 MS. KEATING: I was going to say the<br/>20 same.<br/>21 MS. HUDSON: The coughing for me may<br/>22 start 10 minutes of trying to clear it. But it</p>  | 89 | <p>1 just say to myself, "Well, enough," you know. I<br/>2 just start chewing gum and say, "Let's end this."<br/>3 MS. GIAMBONE: Okay. Thank you,<br/>4 Barbara. When you mentioned about coughing so hard<br/>5 that you've broken some ribs, I saw a lot of head<br/>6 nods. But I just wanted to turn back to the<br/>7 audience. By a show of hands, how many of you<br/>8 have experienced that sort of severe cough and<br/>9 you've broken ribs?<br/>10 (Show of hands.)<br/>11 MS. GIAMBONE: One, two, three, four,<br/>12 five, six, seven -- about seven hands -- eight<br/>13 hands, okay. Thank you.<br/>14 Let me check in with the Web quickly to<br/>15 see what's coming in, what our Web participants<br/>16 saying.<br/>17 MS. CHALASANI: So we have 115<br/>18 participants on the Web with us today, and many of<br/>19 them are echoing what we've been hearing in the<br/>20 room so far. They also say difficulty thinking is<br/>21 a problem. They discuss fatigue. One participant<br/>22 commented on sudden fatigue, which is when she</p>            |

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| <p style="text-align: right;">90</p> <p>1 just wants to put her head down on a steering<br/>2 wheel when she's driving. Another participant<br/>3 commented that it's like walking through molasses<br/>4 throughout the day.<br/>5 As far as triggers, we've heard weather<br/>6 again. Scents are a huge trigger that make them<br/>7 cough and give them shortness of breath. One<br/>8 participant noted that lying down just flat is a<br/>9 trigger as well for them, and so she's afraid to<br/>10 lay down.<br/>11 Another participant noted that it's just<br/>12 a full time job trying to stay well, especially<br/>13 participants with reflux. This participant has to<br/>14 set an alarm clock after each time he drinks 5<br/>15 ounces just to make sure that he's able to take<br/>16 care of himself well.<br/>17 MS. GIAMBONE: Thank you. Thank you for<br/>18 that.<br/>19 FDA panel, any questions?<br/>20 (No response.)<br/>21 Okay. Yes?<br/>22 FEMALE SPEAKER: Nobody mentioned the</p>                                   | <p style="text-align: right;">92</p> <p>1 you also mentioned other symptoms not mentioned.<br/>2 I'd like to open it up to see if you'd like to<br/>3 share with you some of the breathing difficulties<br/>4 that you mentioned here. What do you experience<br/>5 and how do you experience it?<br/>6 ANDREA: Thank you. Shortness of breath<br/>7 impacts everything. I have to walk at my pace<br/>8 going down the street, or I end up very winded.<br/>9 Even when I do the suggested breathing, I cannot<br/>10 talk and walk because I don't have enough air or<br/>11 talk on the phone.<br/>12 I have grandchildren. The fatigue, the<br/>13 chronic fatigue, shortness of breath impacts my<br/>14 interactions with them. I didn't know if you're<br/>15 going to get to loss of -- not loss of appetite,<br/>16 but weight loss, which since I'm on a diabetic<br/>17 diet is impossible.<br/>18 You can say things that I would eat,<br/>19 that I enjoy, I cannot eat. So protein drinks and<br/>20 this and that. And I manage to just barely keep<br/>21 my weight at -- but I eat all day long. I'll have<br/>22 to work at it constantly. And since I'm watching</p> |
| <p style="text-align: right;">91</p> <p>1 coughing, which leads me sometimes to vomit, which<br/>2 is a vicious cycle because I lose my appetite, I<br/>3 don't eat. And I can go for two, three days<br/>4 without eating anything. So it's like a vicious<br/>5 cycle. You know, I could cough so badly that I<br/>6 end up throwing up my guts.<br/>7 MS. GIAMBONE: And you're losing the<br/>8 appetite because you're just not able to keep it<br/>9 down with the cough, and you just don't feel like<br/>10 eating?<br/>11 FEMALE SPEAKER: You just don't want to<br/>12 eat.<br/>13 MS. GIAMBONE: Okay.<br/>14 FEMALE SPEAKER: You just have that<br/>15 total loss of appetite. Like I said, I can go for<br/>16 two days without eating. I'll drink a protein<br/>17 drink, cough, and it comes right up.<br/>18 MS. GIAMBONE: Okay. Thank you for<br/>19 sharing that.<br/>20 Let's look at some of -- a few of you<br/>21 mentioned from other symptoms here, shortness of<br/>22 breath, breathing difficulties, and then a few of</p> | <p style="text-align: right;">93</p> <p>1 how much sugar, it's turned into -- I mean all the<br/>2 other things, you pace yourself. You pick the<br/>3 primary thing you have to do that day.<br/>4 Every once in a while, I have a day<br/>5 where I go through things and get a bunch of<br/>6 things done. But mostly, I do one thing, and then<br/>7 I have to take a nap. I mean, I pretty much go<br/>8 about my business, but it certainly dominates<br/>9 everything I do.<br/>10 MS. GIAMBONE: Okay. And your name?<br/>11 ANDREA: I'm Andrea.<br/>12 MS. GIAMBONE: Andrea, let me ask. You<br/>13 mentioned that you're not able to eat. Again, is<br/>14 it the coughing? We heard earlier that coughing<br/>15 leads to vomiting and that's leading to loss of<br/>16 appetite. What's leading to your loss of appetite?<br/>17 ANDREA: I don't have a loss of<br/>18 appetite; I eat all the time, but it doesn't --<br/>19 MS. GIAMBONE: Oh, but the weight --<br/>20 okay, the weight loss, right.<br/>21 ANDREA: I mean it's affected by this<br/>22 diabetic diet. Before I was on it, I've been --</p>  |



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| 94 | <p>1 I've been sick for 18 years. I've been on<br/>2 antibiotics constantly for 9 years, 8 years,<br/>3 whatever. And my sputum is negative, but when I<br/>4 go off it, within two or three weeks, the MAI is<br/>5 back. Plus, Nocardia and Aspergillus, so it's<br/>6 really a constant battle.<br/>7 MS. GIAMBONE: Thank you. Graham,<br/>8 Meghana, do we have anybody that's waiting on the<br/>9 phone? Okay. So we'll take two callers on the<br/>10 phone. But before we go there, I'd like to ask if<br/>11 there's other symptoms that have not been<br/>12 mentioned through this polling? Is there<br/>13 something that you'd like to share?<br/>14 Philip, I saw you -- let's hear --<br/>15 Marilynn?<br/>16 MS. LUNDY: One of the symptoms that I<br/>17 still am dealing with, often in the support group,<br/>18 a lot of the people seem to have GERD and have<br/>19 been diagnosed with GERD. I'm not sure that I<br/>20 really have GERD, but I belch a lot.<br/>21 There seems to be air pockets in my<br/>22 system, and I'm not sure what causes it. But it</p> | 96 | <p>1 bad. And it comes and goes. So I just throw in<br/>2 joint pain, and I don't know if other people have<br/>3 that --<br/>4 MS. GIAMBONE: Okay.<br/>5 MS. PEFFERS: -- as well as muscle,<br/>6 fatigue and aches. Thanks.<br/>7 MS. GIAMBONE: Okay. Let's do another<br/>8 show of hands, joint pain?<br/>9 (Show of hands.)<br/>10 MS. GIAMBONE: Okay. I'm seeing about<br/>11 eight hands. And we saw others also identify --<br/>12 we have fever and night sweats, okay. So it looks<br/>13 like others also experience that.<br/>14 I know we're getting close to the break<br/>15 time here, so I'd like to see from our phone<br/>16 panelists if I have somebody lined up. So go<br/>17 ahead, Graham.<br/>18 MR. THOMPSON: Operator, can you open<br/>19 the first line?<br/>20 OPERATOR: Yes, your line is now open.<br/>21 MS. STEINBERG: Hello?<br/>22 MS. GIAMBONE: Yes, hello?</p>  |
| 95 | <p>1 does seem to be a symptom with most of us to have<br/>2 to deal with. And it's not acid reflux or<br/>3 anything like that. It's just like trapped air in<br/>4 parts of the body. I don't know how to explain it<br/>5 other than that.<br/>6 MS. GIAMBONE: Okay. Okay.<br/>7 MS. LUNDY: And I'm still dealing with<br/>8 that. Again, my sister can attest to that.<br/>9 MS. GIAMBONE: Do others experience that<br/>10 by a show of hands?<br/>11 (Show of hands.)<br/>12 MS. GIAMBONE: Okay. Gastric issues,<br/>13 I'm hearing. I'm seeing a lot of -- oh, okay,<br/>14 let's see. Keep your hands up real quick. One,<br/>15 two, three, four -- 14 hands, 15 hands raised for<br/>16 that, okay. Other issues not mentioned? We have<br/>17 a hand back there, back there, Sarah, with the<br/>18 black dress. Right there.<br/>19 MS. PEFFERS: Hi. I'm Mel Peffers. It<br/>20 was bronchiectasis, and then NTM diagnosis, like<br/>21 10 years apart each. I get joint pain with the<br/>22 night sweats and the fever, and it's like really</p>                            | 97 | <p>1 MS. STEINBERG: How are you?<br/>2 MS. GIAMBONE: Very good. How are you?<br/>3 MS. STEINBERG: Okay. So I'm Esther<br/>4 Steinberg. I'm the coordinator and support group<br/>5 leader in Canada. I want to thank you very much<br/>6 for this webcast because it allows many of us to<br/>7 have the access to information sharing that we<br/>8 would otherwise not have.<br/>9 In Toronto and across Canada where the<br/>10 temperature is changed, I can see from all the<br/>11 patients that everybody is now getting sicker than<br/>12 they were two weeks ago and developing all the<br/>13 symptoms. Right now, I'm watching you from my<br/>14 bed. I can't stop coughing. For a while, I was<br/>15 able to come off the meds, but now I'm going to<br/>16 have to go on.<br/>17 Listening to everyone at the meeting, we<br/>18 all share the same symptoms, the same pain, the<br/>19 same concerns. We're appreciative.<br/>20 The one thing I have to say, I know that<br/>21 Philip is there, and I have to add how grateful<br/>22 that we all are to Philip and his late wife, Fern,</p> |

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| 98 | <p>1 for all that they have done to bring this disease<br/>2 to the forefront, give us a voice that would not<br/>3 otherwise have been heard.<br/>4 Philip, if you can hear me, thank you<br/>5 very much.<br/>6 (Applause.)<br/>7 MS. GIAMBONE: Thank you so much for<br/>8 your comment.<br/>9 MS. STEINBERG: There isn't a lot that I<br/>10 can add. It's repeated, it's so common to all of<br/>11 us to watch all this going on and hoping that one<br/>12 day that someone will develop a drug, something<br/>13 that would make our life easier.<br/>14 I would say that from people that I<br/>15 know, 90 percent of the people push forward<br/>16 through all the symptoms and do whatever they can<br/>17 to give themselves what we now call a new normal<br/>18 life and to keep up the good fight.<br/>19 MS. GIAMBONE: Thank you so much. There<br/>20 were a lot of people that were nodding along with<br/>21 you, so thank you for sharing that. And we have<br/>22 time for one more caller.</p>   | 100 |
| 99 | <p>1 Operator, could you open up the line?<br/>2 OPERATOR: Yes. Cynthia, your line is<br/>3 now open.<br/>4 CYNTHIA: Thank you.<br/>5 MS. GIAMBONE: Yes, we can hear you.<br/>6 CYNTHIA: Hi. I wanted to comment that<br/>7 many of us have what doctors refer to as asthmatic<br/>8 component to the illness. That's why one of the<br/>9 things that would bring on my coughing is exposure<br/>10 to a vast array of lung irritants from diesel<br/>11 fumes to perfumes, anything sprayed that has scent<br/>12 in it, also VOCS or volatile organic compounds<br/>13 from glue, paint, et cetera, air conditioning,<br/>14 sprayed sunscreens. [Indiscernible] used to set<br/>15 off quite a hacking episode.<br/>16 I don't think that's true of everyone,<br/>17 but it was certainly true for me. I was lucky<br/>18 enough to be a candidate and had a successful<br/>19 middle lobectomy, which greatly improved my<br/>20 condition and reduced that sensitivity. But it's<br/>21 still there.<br/>22 I fear in the future it may come back.</p>                   | 101 |
|    | <p>1 And even now when I'm not as sensitive, I'm aware<br/>2 that those things do irritate my lungs, so I'm<br/>3 kind of scared of being in situations where those<br/>4 thing are present.<br/>5 Cigarette smoke and campfire smoke are<br/>6 some of the worst. Unfortunately, I can't camp<br/>7 anymore because of that. It's almost impossible<br/>8 to go camping in America without campfires around<br/>9 you.<br/>10 Anyway, thanks for letting me comment<br/>11 and thank you for doing this.<br/>12 MS. GIAMBONE: Thank you so much for<br/>13 your comment. Yes, and I believe what you said on<br/>14 the phone, I know others have also mention that<br/>15 smells, different scents can trigger this. So<br/>16 thank you for sharing that.<br/>17 We are now at break time, but thank you<br/>18 for an incredibly rich discussion on topic 1. And<br/>19 we'll see you back in 15 minutes for our topic 2<br/>20 discussion.<br/>21 (Applause.)<br/>22 (Whereupon, at 10:49 a.m., a recess was</p>  |     |
|    | <p>1 taken.)<br/>2 MS. GIAMBONE: So we're going to go<br/>3 ahead and get started. We had a really great<br/>4 discussion in topic 1. We couldn't get to<br/>5 everything because there was so much to share, and<br/>6 there are so many aspects to it as we talked<br/>7 about.<br/>8 Again, I'm going to really encourage you<br/>9 to go that public docket. Please, please submit<br/>10 your comments there. They're so important to us,<br/>11 and we will read through every one of them. So if<br/>12 we didn't get to something in topic 1, or if you<br/>13 didn't get share something in topic 1, please do<br/>14 go there, go to the public docket and submit it<br/>15 there.<br/>16 We also heard some very interesting<br/>17 things that came up during break, which I want to<br/>18 just mention. We heard a symptom that was<br/>19 mentioned. She said, "You know, I'm a little<br/>20 embarrassed to tell you this, but one of the<br/>21 symptoms that many patients experience is, because<br/>22 of the chronic cough, hemorrhoids and leaking."</p> |     |

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| 102 | <p>1 So by a show of hands, can we see if</p> <p>2 others also experience that because of the cough?</p> <p>3 (Show of hands.)</p> <p>4 MS. GIAMBONE: Okay. So I see 11 hands</p> <p>5 raised, but I'm also hearing that a lot of people</p> <p>6 may not feel comfortable to raise their hand with</p> <p>7 that. It's noted that it is a significant -- it's</p> <p>8 something that definitely does impact you very</p> <p>9 much.</p> <p>10 There were two other questions that came</p> <p>11 up. Again, we'll do a show of hands for this one.</p> <p>12 If you were working at the time of your diagnosis,</p> <p>13 how many of you either had to stop working or you</p> <p>14 had to significantly alter your work schedule</p> <p>15 because of your diagnosis? Okay, let's see.</p> <p>16 (Show of hands.)</p> <p>17 MS. GIAMBONE: Let's see. I'm seeing 17</p> <p>18 hands raised, but it definitely sounds like it's a</p> <p>19 very, very important aspect of this. Okay.</p> <p>20 Then last but not the least, and I think</p> <p>21 this is really a place for the public docket</p> <p>22 again, one question that we did have raised from</p> | 104 |
| 103 | <p>1 the FDA panel was with the fatigue. If you</p> <p>2 experience it even at rest, or if you experience</p> <p>3 it only during activity.</p> <p>4 So keep that in mind, and if you can</p> <p>5 take that and answer that in the docket, it's</p> <p>6 going to be very helpful for us to read through.</p> <p>7 You can see so many really important</p> <p>8 considerations that came up in topic 1. Panel 2</p> <p>9 Comments on Topic 2</p> <p>10 MS. GIAMBONE: Now, we're ready to start</p> <p>11 topic 2. Again, we have five panelists here, and</p> <p>12 they've worked very, very hard to put these</p> <p>13 comments together, so thank you for that.</p> <p>14 Topic 2 is on patient perspectives to</p> <p>15 treating their NTM lung infections. What's</p> <p>16 working, what's not working, what are the</p> <p>17 downsides, and what do you look for in an ideal</p> <p>18 treatment. So that's what we're focused on for</p> <p>19 this segment.</p> <p>20 On that, I'd like to get started.</p> <p>21 Betsy, we have you going first.</p> <p>22 MS. GLAESER: Well, I'm 76, and I've had</p>  | 105 |

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| 106 | <p>1 were stopped because of toxic, sometimes life-<br/> 2 threatening side effects. Initial treatment<br/> 3 involved IV, EMI, and then meropenem, followed by<br/> 4 IV cefoxitin. Desensitization bought only limited<br/> 5 time. All three drugs were effective, but they<br/> 6 produced, for me, anaphylactic type reactions, and<br/> 7 they sent me to the emergency room.</p> <p>8 In 2006, still searching for something<br/> 9 to combat abscessus, I was started on linezolid.<br/> 10 I took it for a full year. I felt great, but I<br/> 11 had to stop because I developed neuropathy, numb<br/> 12 toes in both feet, which never improved. But it<br/> 13 was the most effective drug for my NTM that I'd<br/> 14 ever taken, and it was an oral, not an IV.</p> <p>15 I inhaled generic amikacin for 8 months<br/> 16 in 2009. While improving energy, reducing cough,<br/> 17 and hitting two infections, amikacin left me with<br/> 18 serious life-limiting, not threatening but<br/> 19 limiting, side effects, which appeared quite<br/> 20 suddenly.</p> <p>21 I now have two hearing aids, I suffered<br/> 22 severe vertigo initially, and I'm still sensitive</p> | 108 |
| 107 | <p>1 to certain stimuli. I made the mistake of riding<br/> 2 backwards coming to Washington on the train<br/> 3 yesterday; that was a terrible mistake. The<br/> 4 damage to my vestibular, which is your inner ear,<br/> 5 produces frequent dizziness and poor balance. I'm<br/> 6 a fall risk three times this year.</p> <p>7 Now, beginning about five years after<br/> 8 diagnosis, half of my meds were targeting gram<br/> 9 positive and negative infections, which then<br/> 10 became more active. Pseudomonas is recurrent and<br/> 11 common in NTM and CF patients. Effective drugs<br/> 12 for me were the IV aztreonam, taken for six months<br/> 13 in '04, and the inhaled generic amikacin that I<br/> 14 mentioned.</p> <p>15 Klebsiella pneumoniae is my most<br/> 16 stubborn recurring drug. Of no use was IV<br/> 17 tigecycline for 11 months in '07 despite high<br/> 18 sensitivity in the lab. Augmentin was ineffective.<br/> 19 But the inhaled generic amikacin, I mentioned, hit<br/> 20 both the Pseudomonas and the Klebsiella. It was<br/> 21 an enormous surprise that it hit the Klebsiella,<br/> 22 and perhaps it was due to synergies with other</p>   | 109 |
| 106 | <p>1 drugs.</p> <p>2 Recently, after two and a half years on<br/> 3 nebulized aztreonam called Cayston, neither my<br/> 4 Klebsiella nor Pseudomonas shows up in cultures.<br/> 5 It's unclear why, but Cayston has been a fantastic<br/> 6 drug for me. I have more treadmill stamina --<br/> 7 yes, I do treadmill and I do weights and so on --<br/> 8 higher saturation, energy, mental acuity, and I'm<br/> 9 clearly stronger than three years ago. I no<br/> 10 longer take the portable oxygen concentrator to<br/> 11 the gym.</p> <p>12 Serratia was treated by Bactrim from<br/> 13 '05, and I still take it. I do wonder if the NTM<br/> 14 patient is producing something particular, which<br/> 15 is very appealing to all these bugs. Fungal<br/> 16 infections have been with me for all 16 years in<br/> 17 different forms and locations treated by<br/> 18 posaconazole and fluconazole.</p> <p>19 Statistics in '99 predicted I should<br/> 20 have died years ago. My lungs deteriorate slowly<br/> 21 but steadily, but I'm not on any drugs right now,<br/> 22 specifically for abscessus, and there are now no</p>   | 108 |
| 107 | <p>1 new NTM-focused drugs which would work for me that<br/> 2 I'm aware of.</p> <p>3 I know I'm out of time or close. I'd<br/> 4 just like another minute to list some ideas for<br/> 5 new or improved treatments: a fast approval of<br/> 6 inhaled drugs, especially liposomal whose higher<br/> 7 concentration in even my damaged lungs penetrates<br/> 8 more than IV. Look at longer-term drug side<br/> 9 effects.</p> <p>10 I mean I'm on drugs for 16 years, but my<br/> 11 amikacin damage occurred after 8 months, 5 days a<br/> 12 week. Study of breakpoints and risk would be<br/> 13 helpful. Drugs to combat resistance, common NTM<br/> 14 infections like Klebsiella, an ESBL producer, or<br/> 15 certain abscessus species like mine are resistant.</p> <p>16 Faster NTM species identification by<br/> 17 more labs would permit drugs to target specific<br/> 18 species. Then FDA approvals should support the<br/> 19 resulting new drugs, which will become available<br/> 20 from this species identification.</p> <p>21 Encouragement of treatments based on<br/> 22 genetic research, identifying NTM and diseases</p>  | 109 |

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| 110 | <p>1 with relevant profiles and genetic mutation. Is<br/>2 there anything to increase energy without<br/>3 undesirable side effects? How about Ritalin for<br/>4 NTM?<br/>5 (Laughter.)<br/>6 MS. GLAESER: Two studies I participated<br/>7 in could lead to effective treatment. One was a<br/>8 proof of concept, testing whether sildenafil,<br/>9 Viagra, increased ciliary beat frequency, which is<br/>10 too slow in NTM and CF patients, thus increasing<br/>11 lung protective performance.<br/>12 The test was would the Viagra increase<br/>13 the ciliary beat? It did. Incidentally, Viagra<br/>14 did nothing for me except it gave me a headache,<br/>15 for two days. Disappointing.<br/>16 This work could lead to strategies to<br/>17 reduce NTM vulnerability initially and as part of<br/>18 treatment. Second, I participated in a research<br/>19 effort testing interferon gamma against NTM.<br/>20 Immunology could be a very fruitful route.<br/>21 In conclusion, my present level of<br/>22 functioning owes everything to great doctors and</p>              | 112 | <p>1 and producing positive sputum results, I have<br/>2 never had a negative sputum culture.<br/>3 My medicine treatment for that past 20<br/>4 years has included many different drugs taken<br/>5 every day and administered orally, intravenously,<br/>6 nebulized, and inhaled in the attempt to slow the<br/>7 growth of the bacteria, as well as to minimize the<br/>8 damaging effects to my lungs.<br/>9 Currently, I take clarithromycin,<br/>10 Biaxin, and rifampin to slow the growth of the<br/>11 disease; ipratropium bromide and albuterol to help<br/>12 bring up more mucous and sputum to try to avoid<br/>13 yet another bout with pneumonia; decongestants to<br/>14 help dry up excess mucous; Prilosec for my acid<br/>15 reflux; Prozac for the negative emotional effects<br/>16 of dealing with a chronic disease; and vitamins<br/>17 and probiotics to balance the negative effects of<br/>18 the medications on my digestive system and the<br/>19 many yeast infections including thrush.<br/>20 Additionally, I was recently accepted<br/>21 and admitted to the current clinical trial at the<br/>22 University of Pennsylvania for the inhaled</p> |
| 111 | <p>1 the aggressive use of our present multiple long-<br/>2 term meds mainly adapted from other diseases like<br/>3 TB, also, my own competitive drive not to let NTM<br/>4 beat me, initially, not before I saw my first<br/>5 grandchild. But he's 10 now, so now I'm going for<br/>6 a high school graduation.<br/>7 Still, my personal NTM future is not<br/>8 reassuring without new approaches to NTM drugs,<br/>9 which I trust this important FDA conference will<br/>10 encourage. Thank you for letting me speak.<br/>11 MS. GIAMBONE: Thank you, Betsy.<br/>12 (Applause.)<br/>13 Next, we have Patricia.<br/>14 MS. YOST: Good morning. My name is<br/>15 Patricia Yost, and I am from Bucks County,<br/>16 Pennsylvania. I'm a retired middle school and<br/>17 high school English and theater teacher of 33<br/>18 years. I was diagnosed with mycobacterium avium<br/>19 and bronchiectasis in 1995 at age 38.<br/>20 I have been under treatment, in other<br/>21 words, taking medicines and dealing with my<br/>22 disease since 1995. As it has always been active</p> | 113 | <p>1 liposomal, amikacin; so I am also taking the<br/>2 inhaled liposomal amikacin through a nebulizer<br/>3 every day as well.<br/>4 In the past, I have taken ethambutol and<br/>5 voriconazole. However, these medications were<br/>6 discontinued because of their damaging effects to<br/>7 my optic nerve. I had taken Levaquin after a<br/>8 severe pneumonia requiring a chest tube for<br/>9 drainage back in 2008, but that was stopped so<br/>10 that I would not build resistance to that drug in<br/>11 case I needed it again for something.<br/>12 The non-drug therapies for my disease<br/>13 include the daily use of the percussion vest<br/>14 therapy, the use of the Acapella device, exercise,<br/>15 meditation and prayer, and my very supportive<br/>16 family, especially my wonderful husband who is<br/>17 very understanding and helps.<br/>18 All of my treatments have helped in<br/>19 slowing down the growth of the disease and<br/>20 clearing the increased mucous from my lungs over<br/>21 the years, but the disease continues to grow and<br/>22 damage my lungs and diminish my lung capacity.</p>   |

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| 114 | <p>1 I retired early from teaching and no<br/>2 longer can participate in my theater or music<br/>3 activities because the constant coughing from<br/>4 bringing up the sputum has affected my vocal<br/>5 chords, which is obvious, and the medications<br/>6 cause nausea and increased acid reflux, fatigue,<br/>7 itchy skin, lingering hearing and eyesight<br/>8 problems, restless sleep, and numbness in my toes.<br/>9 Additionally, it is inconvenient to<br/>10 travel as I must bring my vest and nebulizer<br/>11 machines with me, as well as administer my other<br/>12 treatments twice a day.<br/>13 In conclusion, having NTM and treating<br/>14 NTM is a daily struggle and has been for me for<br/>15 the past 20 years. As there is no cure, I will<br/>16 continue to deal with its impact and the impact of<br/>17 the treatments for years to come. I hope and pray<br/>18 that something will work to minimize the negative<br/>19 effects and perhaps grant me the possibility of<br/>20 finally getting a negative sputum culture and a<br/>21 reprieve from taking medicines every day.<br/>22 Thank you for your time and considerate</p> | 116 | <p>1 I'm here today to personally highlight<br/>2 the devastating effect of M. abscessus and to<br/>3 implore the FDA to take steps immediately to<br/>4 advance treatment that's existing today, yet are<br/>5 not made available to those who suffer from NTM<br/>6 and are short on time like me. My full commitment<br/>7 has been submitted for the record, so I will get<br/>8 to the heart of it.<br/>9 Diagnosis in 2010. I have undergone<br/>10 various treatment approaches. I have taken at<br/>11 least 10 and different kinds of antibiotics from<br/>12 [indiscernible] to pills to inhale. Those include<br/>13 cefoxitin, tigecycline, Flovent, cipro, to name a<br/>14 few.<br/>15 With little known about M. abscessus, I<br/>16 was like a human experiment. My reaction was<br/>17 invariable from loss, my balance, and the rashes<br/>18 from across my body from the leg, itch, red,<br/>19 swollen, through the arms and the face.<br/>20 I have a blurred vision and I paint.<br/>21 Fatigue, shortness of breath, sweat and a loss of<br/>22 hearing and the loss of sensation on my lips and</p>  |
| 115 | <p>1 compassion to learn the patients' perspectives<br/>2 concerning the effects and impact of the disease<br/>3 and its treatments. Also, thank you for<br/>4 encouraging the research and clinical trials from<br/>5 new medications and treatments to help in our<br/>6 daily struggle for a normal and healthy life free<br/>7 from this insidious disease. Thank you.<br/>8 MS. GIAMBONE: Thank you so much,<br/>9 Patricia.<br/>10 (Applause.)<br/>11 Next, we have Gaby and her son, Arthur.<br/>12 MS. CHIEN: Good morning, gentlemen,<br/>13 ladies. Thank you for allowing me to speak today.<br/>14 My name is Gaby Chien. I'm retired after running<br/>15 an international business for 30 years. I'm 77<br/>16 years old and a proud mother of my three children.<br/>17 This is my son, Arthur, who encouraged<br/>18 me to come over today to have my voice to speak<br/>19 out for the NTM patients.<br/>20 Thank you, Arthur. He says, "Mom, in<br/>21 case you're short of breath, I will continue your<br/>22 testimony today."</p>   | 117 | <p>1 my tongue are a few of the side effects I record.<br/>2 This was the only known approach, one<br/>3 that has required me to eliminate trouble,<br/>4 restrict all physical activities including<br/>5 exercise, remain indoors. At times, I can barely<br/>6 hold conversation with my children, with my<br/>7 friends, with my grandchildren, and so on.<br/>8 I beg the FDA a fast track treatment<br/>9 where they be promising drugs that should be given<br/>10 priority to become clinical trials to support<br/>11 other drugs already in that process.<br/>12 I am also here to tell you we need<br/>13 accessibility of this treatment, that healthcare<br/>14 system is taking a toll on us. I'm currently on<br/>15 triple therapy of antibiotics. Those are macin<br/>16 [ph], amikacin, and linezolid, Zyvox; the project<br/>17 treatment duration, 18 months.<br/>18 The cost of linezolid, a month's supply,<br/>19 is \$6,000. Because my insurance company, United<br/>20 Healthcare has denied the coverage saying NTM is<br/>21 an off label use, it cannot approve. My Medicare<br/>22 Part D benefits refuse to cover as well as the</p> |

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| 118 | <p>1 AARP Medicare Complete.<br/> 2 Tens of thousands of dollars in cash for<br/> 3 this one medication that has benefited fully from<br/> 4 its patent period is not what our government would<br/> 5 tell me and my fellow NTM patients is the best we<br/> 6 can do, when in other countries, linezolid is sold<br/> 7 for under \$600 a month without insurance.<br/> 8 I have been a taxpayer, law-abiding<br/> 9 citizen my entire life. I beg this panel, for we<br/> 10 want to live to use the retirement years I have<br/> 11 earned to be with my family, my children, and my<br/> 12 grandchildren.<br/> 13 Please, urgently help me and my fellow<br/> 14 sufferers by making the currently available<br/> 15 options like linezolid obtainable and to be a<br/> 16 force in urgently supporting present research to<br/> 17 help us overcome NTM.<br/> 18 Thank you with all my heart. I pray the<br/> 19 next time we meet, we'll be celebrating progress.<br/> 20 Thank you.<br/> 21 (Applause.)<br/> 22 MS. GIAMBONE: Thank you, Gaby. Thank</p>                                       | 120 |
| 119 | <p>1 you so much, Gaby. Next, we have Jennifer.<br/> 2 MS. BOGENRIEF: Hi. My name is<br/> 3 Jennifer. I was 35 years old when doctors found a<br/> 4 spot in my lung, and I was diagnosed with M.<br/> 5 xenopi in December of 2011, and I completed<br/> 6 treatment in December of<br/> 7 2013.<br/> 8 I went through intense treatment, and<br/> 9 I'll tell you about that. I'm currently clear of<br/> 10 infection although the stories that I'm hearing<br/> 11 today are terrifying because I have been told by<br/> 12 my doctor that there's a very high likelihood that<br/> 13 I will have recurrence, if not of M. xenopi, of<br/> 14 some other strain.<br/> 15 After having a lung wedge resection<br/> 16 surgery to remove the nodule in my right lung in<br/> 17 November of 2011, I was diagnosed with M. xenopi,<br/> 18 which is considered rare in the United States so<br/> 19 treatment was very unknown.<br/> 20 My physicians at Johns Hopkins, which I<br/> 21 was lucky enough to go to -- that was the first<br/> 22 place that I went for treatment -- they were able</p> | 121 |

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| 122 | <p>1 could do to go to work and then come home at the<br/>2 end of the day, which was a shorter day than it<br/>3 had been previously because of the fatigue.<br/>4 Thank goodness my husband is a good cook<br/>5 and he doesn't mind cooking because I did not have<br/>6 the energy to cook, and he was a lifesaver for me.<br/>7 He was very supportive.<br/>8 The symptoms that my treatments<br/>9 addressed were I had a very painful cough. It<br/>10 almost sounded like barking that often left me<br/>11 doubled-over. And it was infrequent, so at first,<br/>12 I didn't realize that there was something that<br/>13 should be addressed necessarily.<br/>14 I know with asthma and allergies, I have<br/>15 a history of bronchitis and pneumonia, and so you<br/>16 never really know at first, before a diagnosis<br/>17 that something is more seriously wrong. The cough<br/>18 went away right after surgery, and I had shortness<br/>19 of breath also that actually was the first thing<br/>20 that I noticed back in 2009. That gradually went<br/>21 away as I recovered from the surgery.<br/>22 The prescription medications,</p>                       | 124 |
| 123 | <p>1 antibiotics seem to have gotten rid of the<br/>2 infection for me. My CT scans have improved, and<br/>3 they continue to improve after the treatment<br/>4 ended, which was sort of surprising to me that<br/>5 even a year later, my scans were still improving<br/>6 after I ended the antibiotics.<br/>7 The Vitamin B6 helped with the<br/>8 neuropathy as well as the acupuncture, which I've<br/>9 mentioned. My acupuncturist was addressing lungs,<br/>10 liver, and kidney function, which suffered because<br/>11 of the antibiotics. I was doing weekly blood<br/>12 draws to monitor liver and kidney function. And<br/>13 at one point, I was told by my doctor that if<br/>14 things didn't improve the next time, I would have<br/>15 to discontinue -- I believe it was the rifampin.<br/>16 I can't remember for sure but --<br/>17 I started acupuncture actually right<br/>18 after that. And within a week, my liver and<br/>19 kidney function was better. So I very firmly<br/>20 believe in acupuncture, and I really wish that it<br/>21 was something that was covered by insurance across<br/>22 the board because I think it is very helpful.</p> | 125 |
| 124 | <p>1 There weren't any changes to my<br/>2 treatment regimen until my treatment ended, and it<br/>3 was determined to be effective. I stopped the<br/>4 amikacin after 8 months on advice from National<br/>5 Jewish Health, and I ended all of the other<br/>6 antibiotics after 22 months. That decision was<br/>7 made after my CT scans showed improvement, and I<br/>8 had a negative sputum culture, which actually,<br/>9 I've never had a positive sputum culture.<br/>10 Unlike what sounds like most people<br/>11 here, I have not had a problem with excessive --<br/>12 with coughing up sputum. I had a cough, but it<br/>13 was a non-productive cough that was sort of<br/>14 frustrating because they couldn't test anything to<br/>15 find out what I had, which was part of why I<br/>16 needed to have the surgery, that, and to get rid<br/>17 of the nodule.<br/>18 Like I said, I currently don't really<br/>19 have symptoms. I do still have asthma, and I<br/>20 always kind of wonder when I'm feeling a little<br/>21 bit worse, is it coming back. The treatment seems<br/>22 to have reversed my disease. Talking about how</p>                     | 125 |
| 125 | <p>1 the therapy improved my ability to do activities<br/>2 that were important to me, I was able to do<br/>3 infusions at home because of my port and a weekly<br/>4 home nurse visit, which allowed me to continue<br/>5 working full time, which was really important to<br/>6 me.<br/>7 I barely had any savings at the time<br/>8 that this started. I was pretty young, and I<br/>9 needed to work. And my husband, he works too. We<br/>10 both needed to be working. Washington, DC is<br/>11 where we live, and it's an expensive place to<br/>12 live, and working was critical to me. In addition<br/>13 to the fact that I think that if I hadn't been<br/>14 able to work, I would've slept my life away on the<br/>15 couch and in bed because really, getting up and<br/>16 going to work every day was what kept me going.<br/>17 MS. GIAMBONE: Jennifer, any final<br/>18 remarks on what you look for in an ideal<br/>19 treatment?<br/>20 MS. BOGENRIEF: Sure. Let's see. One<br/>21 of the things I wanted to mention was the<br/>22 antibiotic schedule was complicated. Some of the</p>   | 125 |



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| 126 | <p>1 foods have to be taken with -- some of the<br/> 2 medication has to be taken with food; some has to<br/> 3 be taken on an empty stomach. That's difficult<br/> 4 especially when you're trying to travel. And I<br/> 5 used to travel; didn't travel as much going<br/> 6 through the treatment.<br/> 7 I think I've talked about a lot of<br/> 8 things. Some of the things about ideal treatment,<br/> 9 better upfront communication from the physician<br/> 10 about what the treatment entails. And I think<br/> 11 that as we hear stories from other patients, it<br/> 12 becomes more clear what maybe works for some<br/> 13 people and what doesn't. And it's difficult<br/> 14 because different drugs work for different people.<br/> 15 But in the beginning, it was very<br/> 16 unclear to me what the treatment would be like,<br/> 17 and I was originally told that it would be up to 6<br/> 18 months, and then it ended up being 22 months.<br/> 19 In the middle of all of this, my husband<br/> 20 I wanted to start a family, and that is something<br/> 21 that you cannot do when you're taking five<br/> 22 antibiotics, including amikacin infusions. And we</p> | 128 | <p>1 to be a granuloma, which nobody bothered to<br/> 2 culture. And 10 months later, I was sick again.<br/> 3 I was finally diagnosed with NTM<br/> 4 abscessus in 2008. At that time, they put me on<br/> 5 IV amikacin, IV cefoxitin, and oral azithromycin.<br/> 6 After three months, they removed the amikacin and<br/> 7 the cefoxitin due to increased kidney function<br/> 8 tests.<br/> 9 For the past seven years, with a few<br/> 10 drug holidays here and there, I have remained on<br/> 11 inhaled amikacin and oral azithromycin. In 2011,<br/> 12 the investigational drug clofazimine was added to<br/> 13 the regimen as research showed that it had a<br/> 14 synergistic effect with amikacin.<br/> 15 Over the course of my illness, I've had<br/> 16 five cycles of IV cefoxitin, one round of IV<br/> 17 imipenem, and two rounds of tigecycline. Even<br/> 18 though my sputum cultures indicated sensitivity to<br/> 19 these medications, I rarely converted to a<br/> 20 negative.<br/> 21 To my knowledge at that this point for<br/> 22 my particular abscessus, there are no other</p>                                     |
| 127 | <p>1 weren't able to do that, and we have not yet been<br/> 2 able to do that. And that is something that is a<br/> 3 big impact on a person's life when a disease<br/> 4 impacts that ability to have a family.<br/> 5 One other important thing was<br/> 6 coordination between the infectious disease doctor<br/> 7 and the primary care physician was very important<br/> 8 for me because they were great about talking to<br/> 9 each other and being very responsive to me. Thank<br/> 10 you for this opportunity.<br/> 11 MS. GIAMBONE: Thank you so much,<br/> 12 Jennifer.<br/> 13 (Applause.)<br/> 14 MS. GIAMBONE: And finally, we have<br/> 15 Mary.<br/> 16 MS. FISHER: Hi. I'm Mary Fisher, and<br/> 17 I'm from Northern Michigan. I originally started<br/> 18 getting sick in 2006 with a cough and fatigue. To<br/> 19 make a long story short, living in rural Michigan,<br/> 20 there was nobody that had a clue what was going<br/> 21 on, and I ended up with a right middle lobe<br/> 22 resection thinking I had cancer, which turned out</p>  | 129 | <p>1 antibiotics that are available for me to try.<br/> 2 I've also developed neuropathy, nerve<br/> 3 pain and muscle spasms due to the two chest<br/> 4 surgeries that I had. After the second surgery is<br/> 5 when they started me on Lyrica, which had minimal<br/> 6 effect. I've had better results with a heating pad<br/> 7 and massage therapy.<br/> 8 During the time I had only three<br/> 9 negative cultures, prior to my second surgery,<br/> 10 they started IV tigecycline. When the damaged<br/> 11 lung was cultured, it was negative. However,<br/> 12 tigecycline was discontinued due to the low<br/> 13 protein and albumin levels along with decreased<br/> 14 blood sugars. Two months after it was withdrawn,<br/> 15 the sputum returned positive.<br/> 16 Prior to my diagnosis, I was very active<br/> 17 and extremely independent. I cleaned my own home,<br/> 18 planted my flower gardens, traveled quite a bit,<br/> 19 and took care of my horses. After years of<br/> 20 antibiotics, my disease only progressed, and I no<br/> 21 longer could do those activities due to decreased<br/> 22 energy and stamina.</p> |

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| 130 | <p>1 I had to hire somebody to help clean the</p> <p>2 house, help with my flower gardens. But when I</p> <p>3 was told to find someone to take care of my horse,</p> <p>4 that's when I drew the line. I said, you cannot</p> <p>5 take away the only activity that brings me the</p> <p>6 most pleasure.</p> <p>7 When I feel down or depressed, I will go</p> <p>8 to the barn or pasture and just seeing her</p> <p>9 brightens my day. Spending time with her allows</p> <p>10 me to forget about my illness for a while.</p> <p>11 The most significant downsides for me</p> <p>12 are the timing of multiple medications. I take</p> <p>13 azithromycin, which can be taken with or without</p> <p>14 food, but they recommend without food for better</p> <p>15 absorption.</p> <p>16 The clofazimine needs to be taken with</p> <p>17 food. Omeprazole needs to be taken 30 minutes</p> <p>18 before you eat. Calcium should not be taken two</p> <p>19 hours before your antibiotics because it has</p> <p>20 neutralizing effect. Probiotics should not be</p> <p>21 taken 3 to 4 hours next to the antibiotics because</p> <p>22 it will render them useless.</p>             | 132 |
| 131 | <p>1 I also take another medication that has</p> <p>2 to be taken four times a day. Three times a week,</p> <p>3 I need an hour or two to take my inhaled amikacin.</p> <p>4 When IV antibiotics enter the regimen, they are</p> <p>5 usually 2 to 3 times a day.</p> <p>6 Finally, I need to incorporate one hour</p> <p>7 of exercise four times a week. I echo what Betsy</p> <p>8 says. My pulmonary rehab and exercise have been my</p> <p>9 lifesavers. It's very hard to work, plan any</p> <p>10 social activities or get projects done around the</p> <p>11 house when my days are dictated by all these</p> <p>12 treatments.</p> <p>13 The whole process is very difficult and</p> <p>14 frustrating. I would like to see medications that</p> <p>15 are developed that do not have so many</p> <p>16 interactions that require so much time and effort</p> <p>17 to take, that you can have simplelize [ph] the</p> <p>18 process.</p> <p>19 I would also like to see a medication if</p> <p>20 we cannot find a cure that would at least suppress</p> <p>21 or put the infection into remission for more than</p> <p>22 a few months while decreasing the further damage</p> | 133 |

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| 134 | <p>1 D, inhaled therapies; E, other prescription<br/>2 medication such as pain medication; F, other drugs<br/>3 not mentioned; or G, I'm not sure?<br/>4 AUDIENCE: (Inaudible).<br/>5 MS. GIAMBONE: Sorry? Yes, you can<br/>6 check all that apply.<br/>7 (Polling audience.)<br/>8 MS. GIAMBONE: Okay. So it looks like<br/>9 actually nearly all of you that are responding are<br/>10 taking or have taken oral antibacterials, followed<br/>11 by B and D, so IV antibacterials and D, inhaled<br/>12 therapies. And then it looks like we also have a<br/>13 nice range of other ones, too, including some drug<br/>14 therapies not mentioned here.<br/>15 What are we seeing on the Web?<br/>16 MR. THOMPSON: Similar for the oral<br/>17 antibacterial, about 85 percent; only 21 percent<br/>18 for intravenous antibacterial; 46 percent for<br/>19 steroids, which is more than in the room, 40<br/>20 percent for inhaled therapies; and then around 20<br/>21 percent for the rest.<br/>22 MS. GIAMBONE: Okay. Thank you.</p>  | 136 |
| 135 | <p>1 So what I'd like to do is kind of open<br/>2 this up to any of what you've answered here. But<br/>3 the question that I'd like to ask you is, what<br/>4 symptom is your medication -- what is it for and<br/>5 how do you know that it's working? How do you<br/>6 know that the medication that you're taking is<br/>7 actually making a positive difference? And then<br/>8 we're going to spend some time hearing about the<br/>9 downsides.<br/>10 But how do you know that a medication is<br/>11 working for you? What symptom is improving?<br/>12 Let's see. Why don't we go to --<br/>13 JEANNE: Hello, my name is Jeanne, and<br/>14 I'm from around Dayton. I was diagnosed two years<br/>15 ago with MAC and about a year later with<br/>16 abscessus. I also have Staph, which has been my<br/>17 biggest problem.<br/>18 My treatment, they have not put me on<br/>19 treatment for either the MAC or the abscessus<br/>20 because the Staph has been the biggest problem. I<br/>21 was on Duricef for a while; that did not work.<br/>22 Currently, I'm on cephalexin. I took it</p>               | 137 |
| 136 | <p>1 for 10 days, and now they have me on a daily<br/>2 regimen with it. And I tell you what, I feel so<br/>3 much better. I can work better now.<br/>4 I'm a retired nurse, but I go back now<br/>5 and help them in cardiology once a week for sure<br/>6 and then vacations, then whenever they can use me,<br/>7 and I'm agreeing to come in. But this is the<br/>8 first time in a year that I can say that I feel<br/>9 better.<br/>10 My energy is better. My appetite is<br/>11 better. I'm now maintaining my weight. I have<br/>12 lost 16 pounds in the last year, unavoidable<br/>13 because there was no appetite. This wonderful man<br/>14 here made a special trip out for ice cream one<br/>15 night because that's the only thing I felt like I<br/>16 could eat. I call it swallow food. You don't<br/>17 have to use any energy. You just put it in and it<br/>18 goes down.<br/>19 So this is helping me right now.<br/>20 They're not sure if and when -- my two doctors, ID<br/>21 doctors -- I have one in Florida that I see during<br/>22 the winter when I'm there, and one in Ohio when</p> | 137 |

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| 138 | <p>1 was there, I discovered I was also ZZ alpha 1<br/>2 antitrypsin deficient patient. So I started on<br/>3 the cocktail of three oral antibiotics, every one<br/>4 which has been mentioned up here, linezolid,<br/>5 ethambutol, rifampin, azithromycin.<br/>6 After five years, they added<br/>7 clofazimine. I never had any serious side effects,<br/>8 upset stomach. I was very fortunate. I tolerated<br/>9 them. But after six years and I'm up to four oral<br/>10 antibiotics, I had peripheral neuropathy. I have<br/>11 hearing loss. I have ringing in my ears.<br/>12 What else? My FEV1, when I was first<br/>13 entered in the study, was 92 percent, and I'm now<br/>14 down to the mid-70 percent, so the drugs just<br/>15 weren't working. But then in 2013, I entered the<br/>16 clinical trial for the inhaled form of liposomal<br/>17 form of amikacin, and 60 days later, I cultured<br/>18 negative, and I've cultured negative ever since.<br/>19 That's kind of the negative and the<br/>20 positive of what the oral antibiotics were doing<br/>21 for me and then how positive the inhaled therapy<br/>22 has worked for me. I actually have a sputum</p> | 140 | <p>1 there was a nebulizer you had to keep clean. And<br/>2 I travel for my job, so I had to take it with me<br/>3 on an airplane and do it in a hotel room, and then<br/>4 sterilize the equipment. But it was very<br/>5 effective. I mean within 60 days, I was culturing<br/>6 negative.<br/>7 MS. GIAMBONE: Okay, great. Thank you<br/>8 for that.<br/>9 But I did want to do a show of hands for<br/>10 is that we've heard a range of downsides. We've<br/>11 heard neuropathy from several people, and I just<br/>12 want to do a show of hands if others also<br/>13 experience that as a significant downside to the<br/>14 treatments.<br/>15 (Show of hands.)<br/>16 MS. GIAMBONE: I see about 8 hands<br/>17 raised -- or 9 hands raised for that.<br/>18 I've also heard mentioned vision loss,<br/>19 hearing loss. Again, others with that also?<br/>20 (Show of hands.)<br/>21 MS. GIAMBONE: I see 11 hands there.<br/>22 Okay. So let me check in with the Web</p>   |
| 139 | <p>1 sample up in NIH this week, and I'm keeping my<br/>2 fingers crossed I'm still negative.<br/>3 MS. GIAMBONE: Great to hear. Thank you<br/>4 so much. And your name, sorry?<br/>5 LAURA: Laura.<br/>6 MS. GIAMBONE: Laura. Thank you, Laura,<br/>7 for your comments.<br/>8 LAURA: Yes, thank you. Thank you for<br/>9 this meeting here.<br/>10 MS. GIAMBONE: So I do want to do a show<br/>11 of hands here. Laura, you mentioned that the<br/>12 inhaled therapies are working. Is it that the<br/>13 inhaled therapy is working better for you, and is<br/>14 it easier for you, too, also to take inhaled<br/>15 therapy?<br/>16 LAURA: I tried<br/>17 malfunction.]<br/>18 FEMALE SPEAKER: We can't hear her.<br/>19 MS. GIAMBONE: Still can't hear? Okay.<br/>20 Go ahead.<br/>21 LAURA: So the inhaled therapy was not<br/>22 that difficult. It was a little tedious because</p>  | 141 | <p>1 quickly and see what we're hearing there.<br/>2 MS. CHALASANI: Sure. We have 130<br/>3 participants now on the Web and a very active<br/>4 conversation, much echoing what we've heard in the<br/>5 room that some people say that they know when the<br/>6 meds are working because their cough is not as<br/>7 deep or the choking mucous sort of eases up.<br/>8 But just as many participants are saying<br/>9 that they have no idea that the drug is helping<br/>10 them. They only know when they go into to go<br/>11 their lab results, and that's when they know that<br/>12 it's actually helping them.<br/>13 Lots of talk about vision and hearing<br/>14 loss, and then some non-drug therapies mentioned,<br/>15 include behavioral changes, adding postural and<br/>16 nutritional behavior modifications. And there's<br/>17 some talk about a hypertonic saline solution as<br/>18 well.<br/>19 MS. GIAMBONE: Okay, great. Any other<br/>20 comments on either the therapies that are up here<br/>21 or a drug therapy not mentioned, what was that<br/>22 therapy; how did you experience it, what was the</p> |

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| 142 | <p>1 down side of it?</p> <p>2 MS. BRESLAWSKY: Hi. My name is Debbie</p> <p>3 Breslawsky. I would like to say a couple of</p> <p>4 things. I'll keep it short.</p> <p>5 One is I was on inhaled amikacin as well</p> <p>6 as IV, and I found that I was able to tolerate the</p> <p>7 inhaled much better than the IV. In fact, I had</p> <p>8 to be taken off the IV because of tinnitus, a</p> <p>9 ringing in the ears.</p> <p>10 Perhaps maybe there should be a focus,</p> <p>11 if there has to be, on inhaled, which goes</p> <p>12 straight into the lungs rather than any other</p> <p>13 type, not to say we want to discord anything else.</p> <p>14 But the other thing I would to bring up</p> <p>15 is that I know that we have some really tough side</p> <p>16 effects from some of these meds. I'm probably</p> <p>17 speaking for many people in this room, but</p> <p>18 probably not everybody, depending on what the side</p> <p>19 effects are.</p> <p>20 We're in a situation right now that we</p> <p>21 have limited options. I, for one, would take the</p> <p>22 side effects of these drugs or of any other new</p>                        | 144 | <p>1 with the fatigue, even though I still have</p> <p>2 fatigue. Seven percent saline and the Aerobika</p> <p>3 that I was told about at National Jewish were</p> <p>4 extremely helpful for immediately bringing up</p> <p>5 mucous, and just amazing for me.</p> <p>6 Then weight training reversed my</p> <p>7 osteoporosis, and food. I avoid dairy. I don't</p> <p>8 know if it's the lactose. I really would like a</p> <p>9 study on dairy, inflammation for the GI and lungs.</p> <p>10 MS. GIAMBONE: Thank you so much. Any</p> <p>11 other -- yes, we had one.</p> <p>12 FEMALE SPEAKER: Sorry. It's me again.</p> <p>13 I'll make it quick. I did probably the three that</p> <p>14 we all start with, rifampin, azithromycin. By the</p> <p>15 way, that may have orange -- it's totally orange.</p> <p>16 I mean, there's no way around that. There's weird</p> <p>17 side effects. But you do that.</p> <p>18 I then keep getting the sputum samples,</p> <p>19 and then went on an inhaled amikacin. For me, it</p> <p>20 was it was awesome in the clinical trial. I had a</p> <p>21 little nebulizer I could travel with. I just put</p> <p>22 that thing -- you could go through TSA. You bring</p> |
| 143 | <p>1 drugs knowing that there are no other options and</p> <p>2 knowing that the progression won't go any further</p> <p>3 than what it is or progress slowly.</p> <p>4 I just wanted to mention that because</p> <p>5 these side effects are tough, and I have to say</p> <p>6 I've had many myself, but I've just stuck with it.</p> <p>7 Probably they weren't as bad as some other</p> <p>8 people's descriptions, but I just rather have the</p> <p>9 drugs and not have the drugs, and not fear that</p> <p>10 I'm going to get really bad in the future. I</p> <p>11 wanted to make that point.</p> <p>12 MS. GIAMBONE: Thank you for sharing</p> <p>13 that. In just a few moments, we will talk on a</p> <p>14 similar issue. We're going to have a scenario</p> <p>15 that goes right into that, what you just brought</p> <p>16 up.</p> <p>17 Yes, we have one comment here.</p> <p>18 FEMALE SPEAKER: I just like to say</p> <p>19 there are two fairly non-invasive medical</p> <p>20 therapies that really helped me. I was told if I</p> <p>21 had bronchiectasis to get a test for a sleep</p> <p>22 study, sleep apnea. And so CPAP really helped</p> | 145 | <p>1 your drug stuff. You can travel with that puppy;</p> <p>2 it was great.</p> <p>3 For me, the inhaled amikacin, way to go.</p> <p>4 The better symptoms were -- yeah, I produced a lot</p> <p>5 of phlegm, but then afterwards, I got the clean</p> <p>6 sputum sample results. Yay! I got a negative,</p> <p>7 and gained 10 pounds. Boom! It was like the</p> <p>8 weight came right back on. So that was great, and</p> <p>9 it wasn't like I changed my diet or started eating</p> <p>10 more. The NTM was obviously yummy eating that.</p> <p>11 But one other thing I'd like to bring up</p> <p>12 is I love the goals Phil put out, which he had</p> <p>13 three, which was really nice. He was like</p> <p>14 extended life, quality of life, and less toxic</p> <p>15 drugs. But one other one I'd like to add --</p> <p>16 because it's not even on the agenda -- early</p> <p>17 diagnosis.</p> <p>18 Every single one of us will have</p> <p>19 stories. I went 10 years before -- well, I went 10</p> <p>20 years before bronchiectasis diagnosis; then I had</p> <p>21 10 years before the NTM. People send sputum</p> <p>22 samples out. They don't have the right paperwork.</p>                   |

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| 146 | <p>1 You don't know where to send the sputum samples<br/>2 out. Earlier diagnosis I think will definitely<br/>3 help because everybody is like, Oh, you're so<br/>4 young.<br/>5 I think I'm going to check white<br/>6 privilege here. I have good health insurance. I<br/>7 kept going to doctors. People saying, oh, it's<br/>8 TB; oh, it's cystic fibrosis; oh, it's this. I<br/>9 kept going.<br/>10 I think there's a lot of other people<br/>11 outside of my demographic that have these sorts of<br/>12 diseases. Earlier diagnosis and better diagnosis<br/>13 I think could really help. So there.<br/>14 MS. GIAMBONE: Thank you for sharing<br/>15 that.<br/>16 I'm hearing a lot of people say that<br/>17 inhaled therapies have worked a little bit better<br/>18 for them than the oral therapies. Okay. Let's<br/>19 take one more comment.<br/>20 DEBBIE: I'd just like to echo what Gaby<br/>21 was saying about linezolid. I am fortunate to be<br/>22 a nuisance to my insurance company and my</p> | 148 | <p>1 question. We've heard a lot of other therapies<br/>2 that you're also using such as acupuncture. I do<br/>3 want to make sure we get to the next polling<br/>4 question. Then we won't spend too much time on<br/>5 it. We'll go into the scenario question, where<br/>6 we're going to hear your thoughts on if you would<br/>7 participate in a hypothetical trial given some<br/>8 data.<br/>9 So let's answer this question so we have<br/>10 the results recorded, and then we'll go forward.<br/>11 Besides your drug therapies, what else<br/>12 are you doing to manage any symptoms you have<br/>13 experienced because of your NTM lung infection? A,<br/>14 cough medicines; B, supplemental oxygen; C,<br/>15 pulmonary rehab; D, breathing exercises; E,<br/>16 dietary supplements; F, diet modifications; G,<br/>17 complimentary or alternative therapies; H, other<br/>18 therapies not mentioned; or I, I'm not doing or<br/>19 taking any therapies to treat symptoms?<br/>20 While we're answering that, I'm just<br/>21 going to put a plug-in for those on the webcast.<br/>22 If you're interested in sharing some comments on</p> |
| 147 | <p>1 employer, who provides lifetime health insurance<br/>2 for which I am very grateful. But I did not get<br/>3 my linezolid covered without a major, major<br/>4 battle.<br/>5 I am also fortunate not to be on<br/>6 Medicare yet, and yet linezolid was the only drug<br/>7 that my sputum sample showed was going to be<br/>8 effective. I think it's crazy that those sorts of<br/>9 medications, because they're off label, won't be<br/>10 covered.<br/>11 I fought a battle, and it cost me \$300 a<br/>12 month as opposed to \$2500. And I would've paid<br/>13 out of pocket, but not everyone is in that<br/>14 position. And you shouldn't have to fight for a<br/>15 medicine that medical tests show should help your<br/>16 disease.<br/>17 MS. GIAMBONE: Thank you for sharing<br/>18 that. And your name?<br/>19 DEBBIE: Debbie.<br/>20 MS. GIAMBONE: Debbie. Thank you,<br/>21 Debbie.<br/>22 Okay. Let's do a quick polling</p>  | 149 | <p>1 ideal treatments by phone, we'll check in, in just<br/>2 a little bit.<br/>3 So it looks like over half of you in the<br/>4 room are doing some breathing exercises or<br/>5 relaxation techniques, dietary supplements, and<br/>6 then it looks we have a good range of everything<br/>7 else to pulmonary rehab, diet modifications.<br/>8 Okay, great.<br/>9 What did we see on the Web for this?<br/>10 MR. THOMPSON: For cough medicine,<br/>11 supplemental oxygen and pulmonary rehabilitation,<br/>12 around 15 percent for each; 53 percent, breathing<br/>13 exercise/relaxation techniques; 56 percent,<br/>14 dietary supplements; 40 percent, diet<br/>15 modifications and alternative oral therapies; and<br/>16 then 20 percent, therapies not mentioned.<br/>17 MS. GIAMBONE: Thank you. Okay. Let's<br/>18 go to our scenario question. I'm going to read<br/>19 this out loud in just a second, but the scenario<br/>20 question is we're going to present you with this<br/>21 scenario regarding a clinical study. We're not<br/>22 giving you a lot of data here. This is just the</p>  |

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| 150 | <p>1 hypothetical. But what's important to us is some<br/>2 of the first considerations or questions that come<br/>3 to mind. We want to hear what those are.<br/>4       Then like I said, in the afternoon,<br/>5 we're going to have a discussion on clinical trial<br/>6 design. But for now, we want to hear your<br/>7 immediate thoughts when you imagine that you've<br/>8 been invited to participate in a clinical trial to<br/>9 study an experimental antibiotic treatment for NTM<br/>10 lung infections.<br/>11       The purpose of the study is to better<br/>12 understand how well this treatment works and its<br/>13 safety. The clinical trial lasts two years and<br/>14 clinical visits will occur every month for two<br/>15 years in addition to your regular doctor's visits.<br/>16       These visits will involve monthly sputum<br/>17 collections, lab tests, lung function tests, and<br/>18 other lab tests as needed. Treatments may involve<br/>19 either IV medication or inhaled therapy, and<br/>20 treatment will be given in addition to your<br/>21 standard of care.<br/>22       Given just this amount of information,</p> | 152 | <p>1       FEMALE SPEAKER: Do I have to stop the<br/>2 meds I'm currently on to participate?<br/>3       MS. GIAMBONE: Okay. Do you have to<br/>4 stop the meds that you're currently on to<br/>5 participate? I saw a lot of heads nodding for<br/>6 that. But it's in addition to your -- FDA panel,<br/>7 you'll have to chime in here. This is in addition<br/>8 to the standard of care.<br/>9       So you wouldn't be stopping, right? Is<br/>10 that what I'm understanding? Okay. Good<br/>11 question. Thank you for asking.<br/>12       We have another -- sorry. Yes,<br/>13 Patricia?<br/>14       MS. YOST: Sign me up.<br/>15       (Laughter)<br/>16       MS. GIAMBONE: Sign you up. Got it. So<br/>17 regardless of the risks that have been identified,<br/>18 you want to go ahead and take -- okay. We'll take<br/>19 one more comment.<br/>20       DR. WALLACE: I'm going to say this from<br/>21 a practical standpoint because I try to recruit<br/>22 patients. Having patients come who live 50, 100,</p>  |
| 151 | <p>1 what thoughts or questions come to your mind when<br/>2 you hear this scenario? It can be anything.<br/>3 What's the first thing that comes to your mind<br/>4 when you see this and how you would consider<br/>5 participating?<br/>6       DEBORAH: Probably, the first question<br/>7 comes to my mind since I'd been on IVs and I've<br/>8 gone on inhaled, why 1 to 2 hours?<br/>9       MS. GIAMBONE: So why is the IV --<br/>10       DEBORAH: Why the length of time.<br/>11       MS. GIAMBONE: Okay. Why that length of<br/>12 time.<br/>13       DEBORAH: I'm not saying I wouldn't do<br/>14 it, but that's the first thing that I thought.<br/>15       MS. GIAMBONE: Sure. Okay, thank you,<br/>16 Deborah. Philip?<br/>17       MR. LEITMAN: If the patient is not<br/>18 already on IV, in order to participate in IV,<br/>19 they're going to have to have something inserted.<br/>20 That seems very, very challenging to me.<br/>21       MS. GIAMBONE: Okay. Thank you, Philip.<br/>22       Other thoughts?</p>  | 153 | <p>1 150 miles away every month is almost impossible.<br/>2 Many of these people can't drive by themselves;<br/>3 they have to have someone come with them.<br/>4       That one marker, which is often required<br/>5 for these studies, often will take out at least<br/>6 two-thirds of the potential patients because it's<br/>7 not a practical possibility just because of the<br/>8 complexity of their disease and how far they live<br/>9 away. This is an issue for every orphan disease<br/>10 where everybody doesn't live in the same town<br/>11 where the study is being done.<br/>12       MS. GIAMBONE: Thank you. So the burden<br/>13 of how frequently you'll need to go in. Okay. I<br/>14 see several more hands raised.<br/>15       FEMALE SPEAKER: The visits are monthly.<br/>16 How often are the treatments administered?<br/>17       MS. GIAMBONE: Okay. How often are the<br/>18 treatments administered? Okay. And then let's<br/>19 just take one more comment, and then we'll dive<br/>20 into ideal treatments.<br/>21       FEMALE SPEAKER: Yes, addressing this<br/>22 gentleman's comments, if various centers were --</p> |

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| 154 | <p>1 most of my clinical trials have been at NIH. I<br/> 2 live in New York. It would be a major hassle. I<br/> 3 go regularly but not once a month. But if my New<br/> 4 York doctor could administer whatever, it would<br/> 5 make a huge difference.<br/> 6 MS. GIAMBONE: Okay. So if your current<br/> 7 doctor-- or the one that you go to, if you could<br/> 8 get --<br/> 9 FEMALE SPEAKER: My New York doctor<br/> 10 rather than my NIH doctor.<br/> 11 MS. GIAMBONE: Got it.<br/> 12 FEMALE SPEAKER: They talk to each other<br/> 13 all the time anyway.<br/> 14 MS. GIAMBONE: Thank you. It looks like<br/> 15 there's definitely a lot of considerations here,<br/> 16 and I'm going to ask that you please submit those<br/> 17 considerations to the docket just so we can move<br/> 18 on --<br/> 19 FEMALE SPEAKER: May I say one more<br/> 20 quick thing?<br/> 21 MS. GIAMBONE: Yes.<br/> 22 FEMALE SPEAKER: I was wondering -- and</p>  | 156 | <p>1 harm. I kind of think of antibiotics as a shock<br/> 2 and awe for us, and they're absolutely essential,<br/> 3 and thank God we have them.<br/> 4 But I know many of us suffer from other<br/> 5 health issues. I myself have osteoporosis and<br/> 6 children [indiscernible]. And some of my meds,<br/> 7 the Symbicort and corticosteroids that we take<br/> 8 lessen the bone density. And I'm kind of really<br/> 9 worried about getting frail bones, and exercise<br/> 10 seems to be key to staying well. And I think it's<br/> 11 poorly understood the long-term effects of the use<br/> 12 of these toxic antibiotics on our overall health.<br/> 13 I'm hopeful that in the future, they can<br/> 14 look to biologics and cellular mechanisms to<br/> 15 weaken the tough cell walls that keep meds from<br/> 16 getting at the bug, so that we could perhaps<br/> 17 really make that shock and awe much more<br/> 18 effective, so we have to take it for a shorter<br/> 19 periods of time and less toxic drugs.<br/> 20 MS. GIAMBONE: Thank you, Cynthia.<br/> 21 CYNTHIA: Thank you.<br/> 22 MS. GIAMBONE: Thank you, Cynthia. So</p> |
| 155 | <p>1 there were times I'd like to participate in a<br/> 2 clinical trial -- and there's many of us that live<br/> 3 in the Northeast, let's say, for part of the year,<br/> 4 and then they go to Florida or California.<br/> 5 I was wondering if the clinical trials<br/> 6 could be set up where you can switch locations and<br/> 7 the centers could share information or pass it on.<br/> 8 MS. GIAMBONE: Okay. So it definitely<br/> 9 appears that the travel to this and the burden of<br/> 10 getting to the doctor is a major issue.<br/> 11 I know we're approaching lunchtime, so I<br/> 12 do not want to keep you very long. But do we have<br/> 13 anybody on the phone, Graham and Meghana?<br/> 14 MR. THOMPSON: Operator, can you open up<br/> 15 Cynthia's line?<br/> 16 MS. GIAMBONE: We'll take one comment on<br/> 17 what you look for in an ideal treatment.<br/> 18 OPERATOR: Cynthia, your line is now<br/> 19 open.<br/> 20 MS. GIAMBONE: Hi. Cynthia?<br/> 21 CYNTHIA: Thank you. Hi. An ideal<br/> 22 treatment for me would be one that does little</p> | 157 | <p>1 drugs with minimal side effects, I heard, and<br/> 2 exploring biologics.<br/> 3 Other thoughts on ideal treatment, what<br/> 4 you look for? Yes?<br/> 5 MS. BUONVIRI: Hi. I've been a patient<br/> 6 for 10 years, and I've been treated for MAC. I've<br/> 7 been treated for abscessus twice with IVs and<br/> 8 orals. Just for the record, I went to National<br/> 9 Jewish in February after 8 years of being urged to<br/> 10 do so by my doctors at Johns Hopkins. And I was<br/> 11 treated by Dr. Drummond with lifestyle changes and<br/> 12 exercise and a nebulizer. I just got back two<br/> 13 weeks ago, and the first time I had a CT scan<br/> 14 improvement without drugs. And I am eternally<br/> 15 grateful to Dr. Drummond for that.<br/> 16 But my ideal treatment has to do with<br/> 17 something that's being advertised in magazines as<br/> 18 a lung treatment, and that is stem cells. I've<br/> 19 heard no one mention that. I've taken it to my<br/> 20 doctors. They don't know that much about it.<br/> 21 I would like to know what the status of<br/> 22 it is. It's being practiced throughout the</p>          |



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| 158 | <p>1 country at multiple locations by a group called<br/>2 The Lung Institute. I have spoken with them. It<br/>3 sounds like the greatest thing since sliced bread.<br/>4 They take your own stem cells and they transplant<br/>5 them, and supposedly, it helps your lung function<br/>6 and a repair of your lungs.<br/>7 I'd like to submit that for<br/>8 consideration. I'd like to know any comments or<br/>9 responses about what it is, and how it fits in the<br/>10 FDA plans, and what's known about it.<br/>11 MS. GIAMBONE: Thank you so much. And<br/>12 your name?<br/>13 MS. BUONVIRI: Lynn Buonviri.<br/>14 MS. GIAMBONE: Thank you so much, Lynn.<br/>15 Okay. Another comment on ideal<br/>16 treatment? Yes, Marilynn, the mic is coming to<br/>17 you.<br/>18 MS. LUNDY: Thank you. Dealing with the<br/>19 sleep issues when you're on medications, I think,<br/>20 is underrated. It's one of the most important<br/>21 things for me, and I've realized as time has gone<br/>22 on, that those five years, I hardly ever got a</p>   | 160 |
| 159 | <p>1 good night's sleep.<br/>2 Part of the reason is because there does<br/>3 seem to be some diuretic action -- I'm not sure<br/>4 which one it comes from or whatever, but I was up<br/>5 peeing at least five times a night. It's really<br/>6 difficult to get back to sleep. So you are sleep<br/>7 deprived, at least most people that I know, and<br/>8 myself.<br/>9 If they could come up with some kind of<br/>10 medications that were effective and that you could<br/>11 still get some sleep -- and you're supposed to get<br/>12 so much more sleep when you have this disease<br/>13 because you're weary all the time, and that's part<br/>14 of the fatigue, is you never got a good night's<br/>15 sleep. Five years on no sleep is pretty difficult<br/>16 and psychologically a huge problem.<br/>17 MS. GIAMBONE: Thank you, Marilynn.<br/>18 So we are approaching closing, but I do<br/>19 have a question for you as a show of hands that I<br/>20 know the FDA panel identified would be helpful for<br/>21 them to know.<br/>22 How many of you have had to take a 6-</p> | 161 |
|     | <p>1 minute walk test as a way to measure the<br/>2 progression? Let's see. How many of you have<br/>3 taken a 6-minute walk test? Is there a different<br/>4 name for it or is that the name? Okay, that's the<br/>5 name.<br/>6 (Show of hands.)<br/>7 MS. GIAMBONE: All right. So just keep<br/>8 your hands up for a second while we do a quick<br/>9 count. I'm seeing 19 hands raised on that one, so<br/>10 it does seem that way.<br/>11 Just very quickly, which symptom gets in<br/>12 the way of you not being able to maybe do your 6-<br/>13 minute walk test as well as you would like? Is it<br/>14 like the shortness of breath? Is it -- the<br/>15 stamina? Okay.<br/>16 MS. KEATING: [Inaudible - off mic.] --<br/>17 tomorrow it rains, and your 6-minute will be off.<br/>18 So it's really not a valid test. In my eyes, I<br/>19 don't --<br/>20 MS. GIAMBONE: Okay.<br/>21 MS. KEATING: Some days I can walk<br/>22 forever and some days I can't walk a block.</p>  |     |

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| 162 | <p>1 recess was taken.)</p> <p>2 AFTERNOON SESSION</p> <p>3 (1:13 p.m.)</p> <p>4 DR. FARLEY: I want to thank everybody</p> <p>5 for their input this morning, which was extremely</p> <p>6 valuable. We have an afternoon agenda focused on</p> <p>7 helping us, first of all, kind of have the same</p> <p>8 background information and also talk about the way</p> <p>9 forward.</p> <p>10 We have Ken Olivier from NIH who many of</p> <p>11 you know, who's going to talk about the</p> <p>12 epidemiology and natural history of the disease.</p> <p>13 Dave Griffith is going to talk about treatment</p> <p>14 guidelines and what the current standard of care</p> <p>15 is.</p> <p>16 Hala is going to share with you the</p> <p>17 review considerations for new drugs in the United</p> <p>18 States, what authority the FDA has from Congress,</p> <p>19 and we'll talk a little bit about kind of what</p> <p>20 authorities we don't actually have. That's also</p> <p>21 very helpful, I think, for folks to understand.</p> <p>22 Selena Daniels and Alexandra Quittner</p> | 164 | <p>1 DR. FARLEY: Give us a chance to fix the</p> <p>2 mics. While we're working on that, just to remind</p> <p>3 the panelists that our patients told you very loud</p> <p>4 and clear that some of them struggle with hearing</p> <p>5 issues. There'll be no mumbling into the</p> <p>6 microphone, so speak loudly and make sure your mic</p> <p>7 is on. And this is a crisis; we will fix it.</p> <p>8 DR. SHAMSUDDIN: Hala Shamsuddin,</p> <p>9 Division of Anti-Infective Products, FDA.</p> <p>10 DR. WINTHROP: Hi. Kevin Winthrop from</p> <p>11 Oregon Health Science University in Portland,</p> <p>12 Oregon.</p> <p>13 DR. NAMBIAR: Sumathi Nambiar, director</p> <p>14 of Division Anti-Infective Products.</p> <p>15 DR. FARLEY: John Farley from FDA, and</p> <p>16 this isn't working either. This is bad. John</p> <p>17 Farley from FDA.</p> <p>18 (Laughter.)</p> <p>19 DR. TOERNER: I'm Joe Toerner from FDA.</p> <p>20 DR. OLIVIER: Ken Olivier from the</p> <p>21 National Heart, Lung, and Blood Institute.</p> <p>22 DR. HUGHES: David Hughes, global</p> |
| 163 | <p>1 are going to tag team around taking input from</p> <p>2 patients and translating that into clinical trial</p> <p>3 endpoints. Then lastly, Dr. O'Donnell, who has</p> <p>4 really been in the trenches working on clinical</p> <p>5 trials, is going to talk about the challenges that</p> <p>6 we face to-date, and then we're going to move on</p> <p>7 to a panel discussion.</p> <p>8 I want to thank particularly all of our</p> <p>9 panelists for taking time out of their schedules</p> <p>10 to be with us. I'm going to give them a chance to</p> <p>11 introduce themselves starting with Chuck Daley on</p> <p>12 my left.</p> <p>13 DR. DALEY: Hi. I'm Chuck Daley from</p> <p>14 National Jewish.</p> <p>15 DR. GRIFFITH: Dave Griffith from</p> <p>16 University of Texas Health Science Center in</p> <p>17 Tyler, Texas.</p> <p>18 DR. QUITTNER: I'm Alexandra Quittner</p> <p>19 from the University of Miami.</p> <p>20 DR. DANIELS: Selena Daniels. I'm a</p> <p>21 reviewer on the clinical outcome assessment staff</p> <p>22 here at FDA.</p>                   | 165 | <p>1 program head, clinical development from Novartis</p> <p>2 Pharma.</p> <p>3 DR. O'DONNELL: Anne O'Donnell from</p> <p>4 Georgetown University here in DC.</p> <p>5 DR. HIGGINS: Karen Higgins. I'm a</p> <p>6 statistician supporting the Division of Anti-</p> <p>7 Infective Products.</p> <p>8 DR. WALLACE: I'm Richard Wallace. I'm</p> <p>9 from the University of Texas Health Center in</p> <p>10 Tyler.</p> <p>11 DR. EAGLE: Hi. I'm Gina Eagle. I'm</p> <p>12 working on the clinical development of Arikace at</p> <p>13 Insmmed Incorporated.</p> <p>14 DR. FARLEY: Thanks. I think this one</p> <p>15 is still working, which is great. I'm going to</p> <p>16 invite Ken Olivier to the podium. He's senior</p> <p>17 clinician and chief of the Pulmonary Clinical</p> <p>18 Medicine Section at the National Heart, Lung, and</p> <p>19 Blood Institute, which is part of the National</p> <p>20 Institutes of Health. Presentation - Kenneth</p> <p>21 Olivier</p> <p>22 DR. OLIVIER: Thank you very much, John.</p>   |

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| 166 | <p>1 It's a pleasure to be here. I just want to start<br/>2 with a brief story.<br/>3       When I got to the NIH a little more than<br/>4 10 years ago, I was all excited and ready to get<br/>5 started, and I did a lot of cold calls to members<br/>6 of the pharmaceutical industry saying I have this<br/>7 terrible disease, NTM, and would you be interested<br/>8 in taking your drug and studying it in NTM<br/>9 patients?<br/>10       Most of those calls weren't returned,<br/>11 but one of the companies that did return it asked<br/>12 me, well, how many people have this disease; what<br/>13 do they look like; what are their comorbidities;<br/>14 where do they live; what's the natural history of<br/>15 the disease?<br/>16       I was armed with the data in the first<br/>17 two slides that I'll show you, and it became<br/>18 quickly apparent that we needed to do some<br/>19 updating of that data. I was very fortunate, at<br/>20 that time, to meet Becky Prevots, who's sitting in<br/>21 the front here, who is a phenomenal<br/>22 epidemiologist. And for the last 10 years, we've</p> | 168 | <p>1 so they did this series of skins tests. They<br/>2 asked them where they had lived all their life,<br/>3 and they generated this map of the U.S. to kind of<br/>4 give you an idea of where exposure was most<br/>5 prevalent. And it showed this concentration along<br/>6 the Southeastern U.S., up along the West Coast,<br/>7 and in the Hawaiian Islands.<br/>8       It told us very little about who was<br/>9 actually infected, actually told us nothing about<br/>10 who was infected with these organisms. We had to<br/>11 wait a bit for that data. It came from a study<br/>12 that was conducted by folks at the CDC.<br/>13       At that time, all positive mycobacterial<br/>14 islets were referred to state epidemiology labs<br/>15 for identification of the mycobacteria. So this<br/>16 was a study that surveyed those state labs to<br/>17 identify positive islets.<br/>18       They had a limited amount of metadata<br/>19 associated with that, that they knew something<br/>20 about things like the gender of the patient, but<br/>21 nothing enough to establish a case definition.<br/>22 But it generated a very similar map of where the</p> |
| 167 | <p>1 sought to address a number of these issues.<br/>2       I'm very happy to also have Jen Adjemian<br/>3 and Sara Strollo from our epidemiology group here.<br/>4 A lot of the data that I'll show has been<br/>5 collected primarily from them with the hopes of<br/>6 trying to shed some light on these areas as a<br/>7 place to start for drug development.<br/>8       The current status of what we knew about<br/>9 the epidemiology of this disease sort of began<br/>10 with studies that were done in the late 1950s and<br/>11 1960s. These were fairly elegant studies where<br/>12 they did a series of skin tests with antigens that<br/>13 were prepared from the Mycobacterium, looking to<br/>14 try assess where exposure was occurring in the<br/>15 U.S.<br/>16       They were using the model of the<br/>17 standard PPD reflecting exposure infection from<br/>18 tuberculosis. And this was done in lifetime,<br/>19 single-county naval recruits. These were<br/>20 essentially all white males between the age of 17<br/>21 and 21 years.<br/>22       They were aggregated in basic training,</p>  | 169 | <p>1 concentration of disease was. And again, if you<br/>2 look at this map, the Southeastern U.S. stood out<br/>3 prominently, the West Coast, and the Hawaiian<br/>4 Islands.<br/>5       After that time, and especially in<br/>6 recent years with the advent of DNA probes and the<br/>7 ability for basically any lab that was culturing<br/>8 mycobacteria to tell whether it was TB or not, a<br/>9 variety of other factors led to sort of a drying<br/>10 up of that pipeline of islets to the state<br/>11 mycobacterial lab, making this study design no<br/>12 longer feasible.<br/>13       So when Becky and I got together and<br/>14 started talking about this problem, we tossed<br/>15 around several ideas of how to get at it. One of<br/>16 the things that was very attractive was putting<br/>17 together a consortium of integrated healthcare<br/>18 systems. The model of this was Kaiser Permanente<br/>19 on the West Coast where you have a fairly stable<br/>20 beneficiary population.<br/>21       You have years, at that time, of<br/>22 electronic medical records where we could go in</p>   |

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| <p style="text-align: right;">170</p> <p>1 and search for positive islets and then link those<br/> 2 islets within the system to get demographics of<br/> 3 the patients, to link into billing records, to<br/> 4 establish how often the correct diagnosis was made<br/> 5 once we had established an islet case definition,<br/> 6 and to link into radiographic records and other<br/> 7 areas of the system to tell more about the<br/> 8 patients.</p> <p>9 This study was done in collaboration<br/> 10 with four of these large centers, the two West<br/> 11 Coast, Kaiser Permanente, a health group in<br/> 12 Seattle, one in Colorado, and the Geisinger System<br/> 13 on the East Coast. This study had a beneficiary<br/> 14 population of about 4 million people, and it gave<br/> 15 us at least a snapshot of people that were in<br/> 16 those types of healthcare systems to look at<br/> 17 overall prevalence.</p> <p>18 In the study, we looked at a period from<br/> 19 1997 to 2007, and the average age adjusted period<br/> 20 prevalence between the years of 2004 and 2006 was<br/> 21 around 5.5 per 100,000. So this was a bit higher<br/> 22 than the study that had been done in the '70s by</p> | <p style="text-align: right;">172</p> <p>1 predominated in the prevalence of TB, whereas in<br/> 2 the older population, women very much<br/> 3 predominated. In that over 60 group, as you went<br/> 4 up in age by decade, the relative proportion of<br/> 5 men to women increased even more dramatically.</p> <p>6 There were other similar studies that<br/> 7 were done, and I should acknowledge people in the<br/> 8 room like Kevin Winthrop who has done quite a bit<br/> 9 of work at this, and Ted Marras, who is not here,<br/> 10 from Ontario and did similar types of studies that<br/> 11 sort of corroborated these studies together to<br/> 12 give us a clearer picture of this.</p> <p>13 This also was an islet-based study done<br/> 14 in the Province of Ontario in Canada, where they<br/> 15 did a similar type study of identifying a case<br/> 16 definition, in this case greater than or equal to<br/> 17 two positive sputum or one bronchoscopy or biopsy<br/> 18 specimen as equating to a positive case and then<br/> 19 looked at how that changed over a period of time.</p> <p>20 They also looked at the differences in<br/> 21 species with MAC being most prominent similar to<br/> 22 the study that we had done in the HMOs, M. xenopi</p> |
| <p style="text-align: right;">171</p> <p>1 the CDC where the estimated case prevalence was<br/> 2 around 2.8 per 100,000. If you use average census<br/> 3 data from 2005, that equates to about 16,000<br/> 4 people in the U.S.</p> <p>5 Some important things that we noticed<br/> 6 from the study was that the prevalence was<br/> 7 increasing at rate of about 3 percent per year,<br/> 8 and we were able to do things like compare the<br/> 9 prevalence of tuberculosis to that of non-<br/> 10 tuberculous mycobacterium and look at the<br/> 11 differences in the patient population between the<br/> 12 two.</p> <p>13 One of the striking things that you can<br/> 14 see from this slide is that there's definitely an<br/> 15 age correlation with the prevalence of both<br/> 16 mycobacterial islets, but it's even more dramatic<br/> 17 for non-tuberculous mycobacteria that are showing<br/> 18 up as the sort of greenish-blue and fuchsia bars<br/> 19 there as opposed to TB in the brown and green.</p> <p>20 The other striking difference was the<br/> 21 gender mix, which was almost exactly the opposite<br/> 22 of TB. In this older age range population, men</p>                               | <p style="text-align: right;">173</p> <p>1 being very prominent and M. abscessus as well.</p> <p>2 On the graph, the bottom line on that<br/> 3 depicts the case prevalence change over that<br/> 4 period of time and, or disease prevalence, and the<br/> 5 top is the isolation prevalence, finding at least<br/> 6 one positive culture.</p> <p>7 You can see that they're both increasing<br/> 8 at about the same rate, about 6 and a half percent<br/> 9 per year and that the case definition was met by<br/> 10 somewhat less than a half of the total people<br/> 11 having a single positive islet.</p> <p>12 When we looked in the HMO study, kind of<br/> 13 further looking at how people diagnosed the<br/> 14 disease once they met the case definition based on<br/> 15 the number of positive cultures, we found that<br/> 16 about a third or less of people correctly<br/> 17 identified them and assigned the correct billing<br/> 18 code to them.</p> <p>19 That's an important note. When we<br/> 20 looked in that HMO study and saw that the<br/> 21 predominance of patients was in the over 60 age<br/> 22 group, that gave us the opportunity to look at</p>   |

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| 174 | <p>1 another very important database in the U.S., the<br/>                 2 U.S. Medicare database, which over 95 percent of<br/>                 3 the U.S. population age 65 or older has that as a<br/>                 4 billing source. So it actually serves as a<br/>                 5 potentially very useful source of epidemiologic<br/>                 6 data in that age group.<br/>                 7       However, the definitions there are based<br/>                 8 entirely on billing codes as opposed to the prior<br/>                 9 two studies that were based on detecting positive<br/>                 10 islets. So we know that these data likely<br/>                 11 underestimate to a significant a degree the number<br/>                 12 of patients that have the disease in this age<br/>                 13 group.<br/>                 14       However, it allowed us to do several<br/>                 15 things, and one of them was to compare the<br/>                 16 prevalence or the change in prevalence of disease-<br/>                 17 related NTM to the prevalence of bronchiectasis,<br/>                 18 the setting that we most commonly find the<br/>                 19 organisms in the U.S.<br/>                 20       The top two lines in the graph represent<br/>                 21 the increase in prevalence in women in the red<br/>                 22 versus men in the blue of bronchiectasis in</p>   | 176 |
| 175 | <p>1 general. You can see that that's increasing at a<br/>                 2 steady rate over the 7 years of the data that we<br/>                 3 analyzed.<br/>                 4       In the bottom graph, it's a similarly<br/>                 5 constructed graph looking at the increase in<br/>                 6 prevalence of NTM over that period of time, where<br/>                 7 you can really see that the pace of increase in<br/>                 8 women is sort of exceeding that in men and that<br/>                 9 the overall prevalence of NTM disease was, on<br/>                 10 average, about 10 percent of the prevalence of<br/>                 11 bronchiectasis.<br/>                 12       This is a recent study that was done by<br/>                 13 Sara Stollo and others in Becky's group, looking<br/>                 14 at the burden of organisms or burden of having NTM<br/>                 15 disease in the U.S. in terms of cost in medical<br/>                 16 care utilization. This study actually built upon<br/>                 17 prior studies that were done. It looked at the<br/>                 18 Medicare data, and it made several assumptions<br/>                 19 based on that. It looked at the HMO data that had<br/>                 20 been collected, and it used a relatively large<br/>                 21 survey of physician practices to determine things<br/>                 22 like often patients were treated when they had the</p> | 177 |

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| 178 | <p>1 skin tests, very similar to the distribution in<br/>2 the CDC survey study with a predominance in the<br/>3 Southeastern U.S., up along the West Coast and the<br/>4 state of Hawaii.<br/>5 If you look at where many of these<br/>6 patients may come from in the broader picture,<br/>7 looking at bronchiectasis in the top, there's a<br/>8 relatively similar distribution of disease as<br/>9 well.<br/>10 This allowed us to sort of link where<br/>11 these patients are with certain conditions that<br/>12 may be prevalent in the environment to look at<br/>13 potential risk. And using a technique called<br/>14 spatial cluster analysis, which Jen Adjemian knows<br/>15 quite well and led these studies, if you take<br/>16 counties where there's a high prevalence of NTM<br/>17 disease and you compare that to clusters of<br/>18 counties where there's a very low prevalence of<br/>19 disease, you can then link those geographic areas<br/>20 into large databases such as the National<br/>21 Oceanographic and Atmospheric Association<br/>22 Database, and then derive certain environmental</p>                    | 180 |
| 179 | <p>1 risks.<br/>2 From looking at this, things like the<br/>3 amount of surface water in the area and<br/>4 particularly atmospheric qualities like the<br/>5 ability for a droplet to remain suspended that's<br/>6 large enough for mycobacteria to remain viable and<br/>7 then be inhaled to cause disease, a quality that's<br/>8 called evapotranspiration, which relates in a bit<br/>9 to relative humidity -- if you look at those odds<br/>10 ratios, that factor actually turns out to be quite<br/>11 significant.<br/>12 We've also looked at this in a known<br/>13 high risk population. The excellent introductory<br/>14 talk that was given this morning noted CF as being<br/>15 one of the high risk groups. If we break down<br/>16 data from CF patient registry, which collects data<br/>17 on essentially over 90 percent of CF patients<br/>18 throughout the U.S.<br/>19 and has been doing this over a number of<br/>20 years, we can get some very useful pictures of<br/>21 risk factors and distribution of disease from this<br/>22 as well.</p>   | 181 |
| 180 | <p>1 In 2010, the registry started collecting<br/>2 very specific data with regard to NTM culturing,<br/>3 NTM positivity, and the species associated with<br/>4 that as well. During the time period listed,<br/>5 there were about 18,000 patients over the age of<br/>6 12 in the registry. And of those who had cultures<br/>7 done, about 14 percent of these patients were<br/>8 positive either for M. avium complex or M.<br/>9 abscessus.<br/>10 So this is an exceedingly high<br/>11 prevalence in this disease relative to what we've<br/>12 seen in the general population. There were four<br/>13 significant geospatial clusters, which are shown<br/>14 in the red circles on this map, that turned out to<br/>15 be very high prevalent areas, based on the<br/>16 registry data.<br/>17 Again, when we link that in to<br/>18 atmospheric conditions, the saturated vapor<br/>19 pressure or evapotranspiration comes out as being<br/>20 a very significant climatic risk.<br/>21 In terms of the significance of the<br/>22 disease and sort of what the natural history is</p>   | 181 |
| 181 | <p>1 like, in cystic fibrosis, lung function parameters<br/>2 such as the FEV1 have been used in a number of<br/>3 drug trials. And many people equate the<br/>4 progression of disease in CF or the definitions of<br/>5 exacerbations in CF to changes in lung function.<br/>6 This is from a study that was done at<br/>7 the University of North Carolina where they looked<br/>8 at about 800 patients. They looked at the change<br/>9 in lung function over time by age, which is along<br/>10 the bottom axis, and they compared those patients<br/>11 that had no NTM to those that had Mycobacterium<br/>12 abscessus.<br/>13 As many of you in the room know,<br/>14 Mycobacterium abscessus can be a particularly<br/>15 virulent organism particularly in the setting of<br/>16 cystic fibrosis. They were able to show a<br/>17 significant change in decline in FEV1 over time.<br/>18 If you look at where the other<br/>19 mycobacteria fall on this graph such as<br/>20 Mycobacterium avium complex, they were almost<br/>21 exactly in the middle of these two lines. So the<br/>22 data were most striking for Mycobacterium</p> | 181 |

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| 182 | <p>1 abscessus.</p> <p>2 I'm not sure that these lines would</p> <p>3 necessarily look the same in non-cystic fibrosis</p> <p>4 patients or that FEV1 necessarily shows the same</p> <p>5 responsiveness, but we don't have this type of</p> <p>6 detailed data in those patients to indicate that.</p> <p>7 Unfortunately, there have been several</p> <p>8 studies that have looked at mortality in this</p> <p>9 disease, and I think it's worth discussing these a</p> <p>10 little bit to kind of give an idea of the</p> <p>11 significance of this disease. This is not just a</p> <p>12 bothersome disease, but it can be a disease that's</p> <p>13 quite severe in some patients that they do die</p> <p>14 from.</p> <p>15 This is a study done in Japan that</p> <p>16 looked at a couple of things. It coupled islet-</p> <p>17 based definitions with known death rates in the</p> <p>18 country to look at mortality related to NTM</p> <p>19 disease. It also derived prevalence from that as</p> <p>20 well, and it noted several interesting things.</p> <p>21 The bar graphs noted increase in</p> <p>22 mortality by gender and noticed that it was sort</p>                                | 184 | <p>1 diagnosed with MAC remain culture positive at two</p> <p>2 years, and a third of them or more were culture</p> <p>3 positive out to five years from that isolation.</p> <p>4 There have been several studies now that</p> <p>5 have reported 5-year mortality from this disease.</p> <p>6 Again, a study from Japan showed the 5-year</p> <p>7 mortality to be around 25 percent. A second study</p> <p>8 from Japan showed around 28 percent. Claire</p> <p>9 Andrejak did a study in Denmark showing a much</p> <p>10 higher prevalence of 40 percent. One thing to</p> <p>11 keep in mind with this study is it was</p> <p>12 predominantly cavitory disease.</p> <p>13 A general theme of many of these studies</p> <p>14 is that the prognosis in cavitory disease is</p> <p>15 significantly different from those in the sort of</p> <p>16 nodular bronchiectasis disease that we see in the</p> <p>17 U.S.</p> <p>18 Then finally, Finland, 28 percent and in</p> <p>19 a recent study that we've done at the NIH -- it's</p> <p>20 not yet been published -- we saw a similar</p> <p>21 mortality of 25 percent.</p> <p>22 In our data at the NIH, we were able to</p>                        |
| 183 | <p>1 of steadily increasing over that time period until</p> <p>2 the year of 2000 in both sexes. After that time,</p> <p>3 the mortality seems to be increasing</p> <p>4 preferentially in women.</p> <p>5 The map of Japan there looked at where</p> <p>6 these deaths were occurring, and again, there was</p> <p>7 a similar sort of geographic predominance. The</p> <p>8 areas in the darker colors were in the southern</p> <p>9 part of Japan, basically warmer climates, more</p> <p>10 humid areas than in the northern parts of the</p> <p>11 country. They estimated the prevalence in Japan</p> <p>12 to be between 33 and 65 per 100,000 so</p> <p>13 significantly higher than what had been seen in</p> <p>14 the U.S.</p> <p>15 Then they looked in a single center at</p> <p>16 the persistence of islets over time. This give</p> <p>17 you an idea of the marked difference between</p> <p>18 looking at the epidemiology of a disease like</p> <p>19 influenza which is present for only a small period</p> <p>20 of time, or diseases like diabetes where once you</p> <p>21 have it, it's present basically for a lifetime.</p> <p>22 And they found that over 50 percent of patients</p> | 185 | <p>1 look at specific risk factors for disease. And</p> <p>2 again, fibrocavitory disease, if you look at the</p> <p>3 difference in survival, median survival, on the</p> <p>4 left, it was around 9 years for those that had</p> <p>5 fibrocavitory disease versus 13 years for those</p> <p>6 without fibrocavitory disease.</p> <p>7 The other significant risk factor was</p> <p>8 the presence of pulmonary hypertension, raising</p> <p>9 the question about whether there may be some</p> <p>10 vascular component to the disease. But those with</p> <p>11 pulmonary hypertension had a median survival of</p> <p>12 around 7 years versus greater than 18 with no</p> <p>13 pulmonary hypertension.</p> <p>14 In summary, the U.S. prevalence is</p> <p>15 difficult to assess. It's probably somewhere</p> <p>16 between 16 and 84,000, maybe even more than that</p> <p>17 if you factor in all the patients with disease</p> <p>18 that never comes to medical attention. It appears</p> <p>19 to be increased in women in age over 60. There's</p> <p>20 considerable geographic variability to the</p> <p>21 disease, which likely reflects in part</p> <p>22 environmental influences.</p> |

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| 186 | <p>1 The disease burden in costs are quite<br/>2 substantial, and it adversely affects lung<br/>3 function. At least in cystic fibrosis, it appears<br/>4 to be associated with increased mortality. Thank<br/>5 you very much.<br/>6 (Applause.)<br/>7 DR. FARLEY: Thanks, Dr. Olivier. If<br/>8 there are any questions, we'll take some after the<br/>9 second talk.<br/>10 I'd like to invite Dr. Dave Griffith,<br/>11 Professor of Medicine at the University of Texas<br/>12 Health Science Center in Tyler, Texas.<br/>13 Presentation - David Griffith<br/>14 DR. GRIFFITH: Thank you very much.<br/>15 It's wonderful to see everybody here. I very much<br/>16 appreciate the opportunity to be here today.<br/>17 I'm going to talk about the much-<br/>18 maligned treatment guidelines for NTM disease.<br/>19 Very quickly, my conflict of interest statement.<br/>20 I am and was a co-investigator on the Insmed-<br/>21 sponsored inhaled liposomal amikacin trials.<br/>22 The 2007 NTM guidelines were not the</p>   | 188 | <p>1 know a lot about NTM and not everyone embraced<br/>2 them.<br/>3 So when they were released, again, not<br/>4 everyone knew that they needed what was published<br/>5 in the guidelines. I'd just like to say for you<br/>6 cinematic purists that if you substitute the word<br/>7 "badges" in this slide, this is the actual quote<br/>8 from the movie, not the shortened version that you<br/>9 get quite often.<br/>10 We had to think again, where did we go<br/>11 wrong; what did we do that we should've done, or<br/>12 what didn't we do that we should've done better?<br/>13 I think that's what we're going to try to tackle,<br/>14 again, with this next group of guidelines.<br/>15 Why do you have to have guidelines for<br/>16 NTM disease? Well, number one, this ain't TB.<br/>17 Number two -- let me rephrase that. This ain't<br/>18 TB.<br/>19 If I had one message that I would like<br/>20 to send to my FDA colleagues is that when you<br/>21 evaluate treatments and protocols for treating NTM<br/>22 disease, you cannot look through the lenses that</p>  |
| 187 | <p>1 first guidelines to be published. There were two,<br/>2 at least, in 1990 and 1997. I would only point<br/>3 out that my friend, mentor and colleague, Dr.<br/>4 Wallace, shepherded those two through. I think<br/>5 you had three or four co-authors on each of those,<br/>6 whereas we had a host of thousands on the 2007<br/>7 guidelines.<br/>8 I want to take you through a little bit<br/>9 of the process of those 2007 guidelines. I was<br/>10 struck by a similarity between that process and a<br/>11 famous movie. This is really the agony of the NTM<br/>12 guidelines. I'd like to apologize to John and<br/>13 Walter Huston.<br/>14 In about 2003, 2004, some of our<br/>15 colleagues were sitting around deciding that we<br/>16 weren't doing very well and we needed to update<br/>17 the guidelines. By the way, I don't need to tell<br/>18 you who old Dave is in these slides.<br/>19 A bunch of us, old guys, mostly, with<br/>20 apologies to Gwen Hewitt, got together and put<br/>21 together an update on the old guidelines. But<br/>22 unfortunately, not everybody knew that they didn't</p> | 189 | <p>1 you looked through when you evaluate protocols for<br/>2 tuberculosis. There are similarities. They are<br/>3 not identical. And I'm going to point out a few<br/>4 of those.<br/>5 The guidelines are actually sometimes<br/>6 helpful, believe it or not, for both diagnosing<br/>7 disease and for successfully treating NTM disease.<br/>8 If you follow what's recommended in the<br/>9 guidelines, at a minimum, you usually don't make<br/>10 things worse. And I think they can be instructive.<br/>11 I think that they are educational.<br/>12 As folks have mentioned, this is not an<br/>13 area where a lot of physicians have expertise. If<br/>14 you want to go to one place, I think that was one<br/>15 area where the 2007 guidelines did prove to be<br/>16 fairly successful. People could go to that<br/>17 document and at least get a little bit of<br/>18 information. I'm going to talk a little bit more<br/>19 about that as we go along.<br/>20 But let's face it, you can't have a<br/>21 single document that's adequate for 160 different<br/>22 species. They vary by virulence; the host varies</p> |



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| 190 | <p>1 in terms of susceptibility. Of course, the NTM<br/>2 can infect a number of different areas obviously<br/>3 other than the lung.</p> <p>4 The guidelines do not take the place of<br/>5 knowing something about the diseases. I mean<br/>6 theoretically, we shouldn't need this.<br/>7 Theoretically, clinicians should know what the<br/>8 significance of Mycobacterium kansasii is in a<br/>9 particular patient. They should know what the<br/>10 significance of Mycobacterium abscessus and know<br/>11 the insignificance of Mycobacterium gordonae. But<br/>12 they don't. That's why we are stuck with this<br/>13 process. It's an impossible task, but we do the<br/>14 best that we can.</p> <p>15 We know that in contrast to<br/>16 tuberculosis, getting an NTM respiratory islet<br/>17 doesn't necessarily mean that someone has NTM<br/>18 disease. We know that there are frequent<br/>19 contaminants. Mycobacterium gordonae, for<br/>20 instance, I don't know that I've seen a case of M.<br/>21 gordonae lung disease. I'm sure some of the panel<br/>22 members probably have. But it's the third most</p> | 192 | <p>1 nice lady that I followed for some time. This<br/>2 lady was 75 years old when I first saw her, not a<br/>3 terribly abnormal chest X-ray, but she had<br/>4 bronchiectasis and her sputum was consistently<br/>5 culture positive for<br/>6 MAC.</p> <p>7 I have followed her now for 12 years.<br/>8 Out of 70 sputum AFB cultures, 35 were positive<br/>9 for MAC. The lady is doing fine. She feels okay,<br/>10 no radiographic progression, and I've never put<br/>11 her on medicine.</p> <p>12 The point being just, the guidelines<br/>13 don't necessarily tell you what to do with an<br/>14 individual patient, particularly with this regard.<br/>15 But the other thing, which I hope everyone here<br/>16 appreciates, is it's important to have a very<br/>17 close relationship with your doctor.</p> <p>18 This nice lady, I think she comes sees<br/>19 me every six months or so. And she always says,<br/>20 "Why do I keep coming to see you?" Partly<br/>21 because, as Ken said, we don't necessarily know<br/>22 what the natural history of these diseases are,</p>  |
| 191 | <p>1 commonly isolated NTM in the state of Texas, but<br/>2 it almost never causes disease.</p> <p>3 We know that that NTM are in tap water<br/>4 and can contaminate specimens. And frequently,<br/>5 people who have NTM in their sputum don't get<br/>6 worse with time. I think I have an example of<br/>7 that.</p> <p>8 Making the diagnosis of NTM disease<br/>9 doesn't mean that somebody needs to start therapy,<br/>10 and that's based on careful risk and benefit<br/>11 analysis. I'm mentioning this because the<br/>12 guidelines do tell you how to diagnose the<br/>13 disease. They give you criteria for diagnosing<br/>14 disease, but it's not enough. You have to know<br/>15 something about the bug, the source, the patient.<br/>16 All of that is always, always true.</p> <p>17 If you have a positive test, that is not<br/>18 necessarily a diagnosis. And here, I've just<br/>19 listed a few of the considerations that all of us<br/>20 go through when we try to decide, what is the risk<br/>21 benefit ratio for an individual patient.<br/>22 I thought I would just show this very</p>              | 193 | <p>1 and I don't know that someday this patient won't<br/>2 need therapy for MAC disease. At any rate, just<br/>3 an example of what is necessary in addition to the<br/>4 guidelines.</p> <p>5 These are the treatment recommendations<br/>6 for MAC lung disease. I think the folks are<br/>7 pretty familiar with them. For the disease<br/>8 associated with bronchiectasis, it's macrolide-<br/>9 based, usually three times a week. For cavitary<br/>10 disease, we think it's daily, frequently with an<br/>11 injectable agent.</p> <p>12 This is a study that we published not<br/>13 too long ago of our population of patients with<br/>14 bronchiectasis and MAC lung disease receiving<br/>15 three times a week therapy. As you can see, it<br/>16 was successful in the majority of our patients.</p> <p>17 We did find kind of a disturbing, the<br/>18 finding of microbiologic recurrence of MAC, which<br/>19 frequently was due to reinfection as opposed to<br/>20 disease relapse. Nevertheless, most people had<br/>21 microbiologic improvement on therapy.<br/>22 Fortunately, essentially, none of them developed</p> |

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| 194 | <p>1 resistance to macrolides on therapy.<br/> 2 I put this slide in -- this is from<br/> 3 South Korea -- to point out that it's not just in<br/> 4 Texas where this particular approach is<br/> 5 successful, but it also happens other places.<br/> 6 This is an example of where the<br/> 7 guidelines, I think, are pretty good. We didn't<br/> 8 have this data when we made the recommendation in<br/> 9 2007, but fortunately, the data that we had has<br/> 10 borne out the success of this particular approach.<br/> 11 In terms of the recommendations of the<br/> 12 guidelines, most of the time, with bronchiectasis,<br/> 13 you do get favorable microbiologic response, and<br/> 14 these regimens do not promote the emergence of<br/> 15 resistance to macrolides.<br/> 16 I'm not going to spend much time --<br/> 17 actually, I had not seen Ken's data on cavitory<br/> 18 disease. That's very important data. As you can<br/> 19 see, I think cavitory disease is not just<br/> 20 associated with all-cause mortality, but like<br/> 21 tuberculosis is probably likely associated with<br/> 22 significant long-term respiratory impairment.</p> | 196 |
| 195 | <p>1 Now, we're a little underrepresented<br/> 2 today in terms of this aspect of NTM disease.<br/> 3 Interestingly, our European colleagues see a lot<br/> 4 more cavitory disease than we do, frequently from<br/> 5 organisms. I heard someone speaking early about<br/> 6 Mycobacterium xenopi. That is a bug associated<br/> 7 with cavitory disease frequently in Northern<br/> 8 Europe and a high mortality.<br/> 9 I think this is an area also where we<br/> 10 need a lot more information, and I think we can<br/> 11 make a significant impact on the disease with<br/> 12 appropriate therapy. I also think it will<br/> 13 probably need a little bit different approach when<br/> 14 we design studies.<br/> 15 I know there's a lot of nihilism about<br/> 16 treating these diseases and pessimism, but I just<br/> 17 wanted to show you an example of a patient that I<br/> 18 had successfully treated with medication alone.<br/> 19 Many of you also know that these<br/> 20 patients also do well with surgery, or that least<br/> 21 their disease does well with surgery. So it's<br/> 22 certainly not a hopeless process by any stretch.</p>     | 197 |

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| 198 | <p>1 amikacin.</p> <p>2 The reason I want to belabor this point</p> <p>3 is doctors are not born with this knowledge. If</p> <p>4 all you know is TB, you don't know that you have</p> <p>5 to take steps to protect macrolide and amikacin</p> <p>6 more so than you do for other drugs.</p> <p>7 This type of resistance is called</p> <p>8 mutational, or acquired mutational resistance,</p> <p>9 very familiar to people who treat TB, but not that</p> <p>10 familiar to physicians who take care of MAC</p> <p>11 patients.</p> <p>12 Again, I hope that in this next</p> <p>13 guidelines process, we preserve that aspect of it.</p> <p>14 It's not directly related to therapeutic</p> <p>15 recommendations, but physicians have to know that</p> <p>16 so that they protect their patients against the</p> <p>17 emergence of resistance to these two very, very</p> <p>18 potent drugs, very powerful drugs: amikacin and</p> <p>19 the macrolides.</p> <p>20 Just very quickly, again, there are many</p> <p>21 counterintuitive aspects of treatment of non-</p> <p>22 tuberculous mycobacterial diseases. For instance,</p>  | 200 |
| 199 | <p>1 it's not clear that the level of a drug in your</p> <p>2 blood makes a difference or correlates with how</p> <p>3 you respond to that drug.</p> <p>4 Of course, the big one is the one where</p> <p>5 it doesn't necessarily correlate -- that the</p> <p>6 finding in the laboratory on how the bug responds</p> <p>7 to the antibiotic doesn't necessarily correlate</p> <p>8 with what happens in your body.</p> <p>9 I would just like to point out, again,</p> <p>10 physicians don't know this at birth. For</p> <p>11 instance, this is a patient who had their MAC</p> <p>12 islet sent to a reference laboratory. It was</p> <p>13 reported as resistant to ethambutol.</p> <p>14 We know that whether the islet is</p> <p>15 resistant or susceptible to ethambutol doesn't</p> <p>16 matter in terms of the response of that patient to</p> <p>17 ethambutol in their treatment regimen. Ethambutol</p> <p>18 is important for protecting the macrolide, for</p> <p>19 keeping people from becoming macrolide-resistant.</p> <p>20 Well, this patient's doctor saw the</p> <p>21 resistant label next to ethambutol, and he stopped</p> <p>22 it. And instead, he substituted fluoroquinolone,</p> | 201 |
| 200 | <p>1 which is of a questionable value. At any rate,</p> <p>2 this individual ended up becoming macrolide-</p> <p>3 resistant; another example of the process of</p> <p>4 education that's necessary for physicians to</p> <p>5 adequately care for patients with NTM disease.</p> <p>6 Now, we come back to -- we don't need no</p> <p>7 stinking NTM guidelines. Becky [sic] Adjemian and</p> <p>8 the folks at NIH did a survey of physicians in the</p> <p>9 United States to see how well they complied with</p> <p>10 the NTM guidelines from 2007. And the short</p> <p>11 answer is they didn't. People treated this stuff</p> <p>12 in every possible way. It was just astounding.</p> <p>13 Almost no one in the survey treated patients</p> <p>14 according to the guidelines. You can take that</p> <p>15 for what it's worth.</p> <p>16 Just very briefly, let me close with the</p> <p>17 new guidelines committee is composed of four</p> <p>18 different societies, two from your Europe, two</p> <p>19 from the United States.</p> <p>20 This is a different document. This will</p> <p>21 be a different critter. The last document was</p> <p>22 almost a reference paper. This one will be</p>  | 201 |
| 201 | <p>1 question-focused. They're called PICO-based</p> <p>2 questions.</p> <p>3 Just to give you an example, this is a</p> <p>4 recent guideline for pulmonary fibrosis, and it</p> <p>5 basically asks seven questions. And the questions</p> <p>6 were, should patients be treated with A, or B, or</p> <p>7 C, or D, or E or F?</p> <p>8 Frankly, I don't know how we're going to</p> <p>9 do that kind of a document for NTM because I can</p> <p>10 come up with seven questions for MAC without</p> <p>11 discussing any other mycobacterial pathogen. But</p> <p>12 nevertheless, we're struggling with it.</p> <p>13 Dr. Daley is chairing this effort. It</p> <p>14 will be a different document. I hope we preserve</p> <p>15 the educational aspect to it, that a physician</p> <p>16 doesn't just go it, go to the bottom line that's</p> <p>17 in bold print and take that home to treat the</p> <p>18 patients. I hope they learn something about NTM</p> <p>19 disease.</p> <p>20 I will close with a slide that I like to</p> <p>21 use in essentially all my talks. This is from Dr.</p> <p>22 Emanuel Wolinsky who is one of the fathers of NTM</p>  | 202 |

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| 202 | <p>1 disease. Many of you know, in most instances, I'd<br/>2 rather treat a patient with multi-drug resistant<br/>3 TB than someone who has macrolide-resistant MAC,<br/>4 although they're both quite difficult. So we<br/>5 certainly still need help, and hopefully we'll get<br/>6 some from the FDA. Thank you very much.<br/>7 (Applause.)<br/>8 DR. FARLEY: I think we'll pause and see<br/>9 if there are any burning questions for Dr. Olivier<br/>10 or Dr. Griffith. Any questions that folks in the<br/>11 audience would like to ask? I see a hand over<br/>12 there.<br/>13 FEMALE SPEAKER: My question is for Dr.<br/>14 Olivier. If I understood your epidemiological<br/>15 charts, it would appear that the prevalence as we<br/>16 understand it of NTM disease in the U.S. is much<br/>17 lower than in Japan. Is that, in your opinion,<br/>18 because we measure it less well or because there's<br/>19 something in people in Japan or in the environment<br/>20 that makes it more common?<br/>21 DR. OLIVIER: It's a very good question,<br/>22 and I think when we talk about etiology of</p>                | 204   |     |
| 203 | <p>1 disease, we need to consider both the<br/>2 opportunities for exposure and other risk factors<br/>3 that might go along with that.<br/>4 In many of these studies in the U.S. and<br/>5 in Japan, many of these of patients had relatively<br/>6 few other comorbidities associated with their<br/>7 disease. But you have to think about things such<br/>8 as genetic risks. And we know from other genetic<br/>9 diseases that those genetic risks can vary<br/>10 considerably based on ethnicity and geographical<br/>11 background.<br/>12 There may be differences in methodology;<br/>13 there may be differences in sensitivity to the<br/>14 disease. If you just weigh the amount of<br/>15 literature on this disease coming out of Japan and<br/>16 South Korea, it vastly outweighs the amount of<br/>17 literature coming out of the U.S.<br/>18 Maybe people are more aware. Maybe<br/>19 they're looking for it more. But there could be a<br/>20 variety of issues why that difference in mortality<br/>21 occurs. Some may actually be attributed to just<br/>22 differences in study design and technique.</p> | <p>1 MALE SPEAKER: I had a question. I'm<br/>2 not sure who on the panel would be best to answer<br/>3 it. We heard earlier today about bronchiectasis as<br/>4 a risk factor for NTM. My question is, does<br/>5 bronchiectasis cause NTM or does NTM cause<br/>6 bronchiectasis? Or do we really know?<br/>7 DR. OLIVIER: The answer is yes.<br/>8 (Laughter.)<br/>9 This is sort of like the chicken and the egg<br/>10 argument about what comes first. Our group has<br/>11 been very interested in looking at genetic risks<br/>12 of this.<br/>13 My former boss and I used to argue about<br/>14 this all the time. If we knew what the truth was,<br/>15 if we knew what the generic risks were, would they<br/>16 be risk factors for the development of<br/>17 bronchiectasis, and then having that altered<br/>18 airway clearance predisposes you to having<br/>19 whatever you're inhaling stick in the airway and<br/>20 cause problems.<br/>21 On his side of the fence would be<br/>22 identify genetic risks that make it more likely</p> | 205 |

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| 206 | <p>1 It may be that you need a minor change<br/>2 in genes controlling for bronchiectasis, coupled<br/>3 with a minor change in genes that control<br/>4 mycobacterium, coupled with enough environmental<br/>5 risk exposure time to go by to result in this<br/>6 disease occurring in this population in the age<br/>7 range that it does.<br/>8 DR. WALLACE: John, can I make one<br/>9 comment?<br/>10 DR. FARLEY: Absolutely, Dr. Wallace.<br/>11 DR. WALLACE: David's data about follow-<br/>12 ups on patients who were treated with standard<br/>13 regimens for MAC, you'll make note that in the<br/>14 follow-up, which was only two or three years, 50<br/>15 percent of the patients developed one or more<br/>16 positive cultures for MAC, most of which were not<br/>17 of the same genetic type as the original islet.<br/>18 When you look at studies or long terms<br/>19 studies, and this especially applies to the<br/>20 Japanese studies, you have no idea if you have may<br/>21 have successfully treated those patients and they<br/>22 now have another episode. They're all assumed to</p> | 208 | <p>1 away from it. You're always exposed to it. And<br/>2 sooner or later, if you have it once, you're going<br/>3 to have positive cultures again.<br/>4 It taints a little bit the data because<br/>5 we don't have that piece of information. This is<br/>6 always an encouragement of how important that is<br/>7 to analyze this data and hopefully sometime in the<br/>8 future, we'll do this with more regularity.<br/>9 DR. FARLEY: Great. Thanks. That was<br/>10 very helpful.<br/>11 So we're going to turn our attention to<br/>12 clinical trial design. When the FDA recruits<br/>13 physicians, we actually are looking for real docs.<br/>14 And our next speaker is one of those folks. I've<br/>15 had the delight, really, over the last -- since<br/>16 I've been at the FDA working with Dr. Shamsuddin.<br/>17 She was, prior to coming to the FDA, an infectious<br/>18 disease physician caring for very sick<br/>19 immunosuppressed patients. And many of you do<br/>20 know her because she was the point person for the<br/>21 clofazimine expanded access program for quite some<br/>22 time.</p>                 |
| 207 | <p>1 have the same episode and they're all assumed to<br/>2 be treatment failures.<br/>3 We've been very slow in adopting the<br/>4 willingness to do both species identification and<br/>5 to do fingerprinting. I mean, I know it's -- I<br/>6 preach on this a lot. But it's impossible to<br/>7 analyze --<br/>8 One of you who says, gee, I've had MAC<br/>9 for 10 years; they've treated me five times. You<br/>10 could've had five episodes with five different<br/>11 organisms. I mean that means you were<br/>12 successfully treated for each of those episodes<br/>13 and then because either of your individual risk<br/>14 factors or occupational risk factors, you acquired<br/>15 it more than once.<br/>16 All of this data is kind of tainted by<br/>17 the fact that we have no knowledge about whether<br/>18 all of these people that die of MAC, did they have<br/>19 a single episode that they never got rid of or<br/>20 they couldn't stay away from MAC?<br/>21 My wife has a saying that "you're never<br/>22 cured of MAC" and by that means you never stay</p>                          | 209 | <p>1 She's going to talk about review<br/>2 considerations for new drugs, focusing on the<br/>3 standards, which were established by Congress in<br/>4 1962. The FDA was granted the authority by<br/>5 Congress to follow those standards and review<br/>6 drugs based on those standards, as well as some<br/>7 other review considerations. Thanks, Hala.<br/>8 Presentation - Hala Shamsuddin<br/>9 DR. SHAMSUDDIN: Thank you. We'll<br/>10 switch gears here and talk about review<br/>11 considerations for new drugs. Hearing this<br/>12 morning about safety, I'm going to start by saying<br/>13 that I will be discussing mostly efficacy because<br/>14 a lot of times, you cannot really interpret safety<br/>15 except in the context of efficacy. The risk<br/>16 benefit evaluation really depends on each patient<br/>17 population. If you don't hear much about adverse<br/>18 reactions, that is why.<br/>19 Before I start with how to evaluate<br/>20 clinical trials and evaluate efficacy, I'd like to<br/>21 have a shout out for our nonclinical disciplines<br/>22 because there is a lot of work that goes even</p> |

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| 210 | <p>1 before a clinical trial is started. And that<br/> 2 really includes chemistry and manufacturing<br/> 3 controls where you have to assure that the drug<br/> 4 can be safely, and reliably, and consistently<br/> 5 manufactured without a lot of impurities, and that<br/> 6 the drug is stable.<br/> 7       There's some toxicology studies that go<br/> 8 on with evaluation of safety in animals because<br/> 9 that gives us an idea of what safety signals to<br/> 10 follow in the course of a clinical trial.<br/> 11       There's some data about pharmacology,<br/> 12 how that drug is handled in the body, and in vitro<br/> 13 antimicrobial activity, how active is it and<br/> 14 against what species. And finally if there's any<br/> 15 animal model of infection in which the drug is<br/> 16 active.<br/> 17       Having said that, for any drug to obtain<br/> 18 market authorization or approval, the drug must<br/> 19 show substantial evidence of efficacy, and this is<br/> 20 according to Section 505(d) of the Food, Drug, and<br/> 21 Cosmetic Act that this is shown through adequate<br/> 22 and well-controlled investigations. We interpret</p> | 212 | <p>1 historical experience. And we generally reserve<br/> 2 these types of trials for special circumstances.<br/> 3       Another way really to think about these<br/> 4 trials is to categorize them in to two categories:<br/> 5       either a trial design to show<br/> 6 superiority or a trial design to show non-<br/> 7 inferiority.<br/> 8       For a superiority trial, the trial is<br/> 9 designed to show that the test drug is better than<br/> 10 the comparator; it's more effective than the<br/> 11 comparator whatever that comparator might be. It<br/> 12 may be designed to show it's better than placebo,<br/> 13 no treatment, one dose better than another, or<br/> 14 it's better than what is available.<br/> 15       The advantage of these trials is that<br/> 16 they are really a direct assessment of the drug<br/> 17 benefit. They also can assess any outcome of<br/> 18 interest regardless of what historical trials have<br/> 19 assessed.<br/> 20       Non-inferiority trials, on the other<br/> 21 hand, are designed to show that the test drug is<br/> 22 not worse than the active comparator by a certain</p> |
| 211 | <p>1 investigations to mean trials.<br/> 2       According to the Code of Federal<br/> 3 Regulations, an adequate and well-controlled<br/> 4 clinical trial is done to distinguish the effects<br/> 5 of a drug from other influences such as<br/> 6 spontaneous change in the course of the disease,<br/> 7 placebo effect or biased observation.<br/> 8       The Code goes on to describe the<br/> 9 different types of adequate and well-controlled<br/> 10 trials. It describes five types. The first four<br/> 11 are all randomized trials. The test drug, the<br/> 12 patient is either randomized to receive the test<br/> 13 drug or placebo, and that's the placebo concurrent<br/> 14 trial; randomized to receive the test drug or no<br/> 15 treatment at all; or is randomized to receive one<br/> 16 or more doses of the test drug.<br/> 17       We can also have a trial where the<br/> 18 control is active. It is a randomized trial in<br/> 19 which the test drug is compared to another drug<br/> 20 that is known to be effective for this condition.<br/> 21       Finally, we have historical control<br/> 22 trials where the test drug is compared to</p>    | 213 | <p>1 prespecified degree, which we refer to as the non-<br/> 2 inferiority margin.<br/> 3       These trials are done when it's really<br/> 4 not ethical to do a placebo trial, or when I don't<br/> 5 think I can be superior than what is available,<br/> 6 but I may have some other advantage.<br/> 7       The disadvantage of these trials is that<br/> 8 the active comparator should be known to be<br/> 9 effective in that population, and the magnitude of<br/> 10 that effect, we should be able to estimate that<br/> 11 compared to placebo from previous trials.<br/> 12       We also should be able to estimate the<br/> 13 magnitude of the effect in that particular<br/> 14 population of interest. A drug that may have a<br/> 15 treatment effect in one population may not have it<br/> 16 in another.<br/> 17       We also would like to know that this<br/> 18 treatment effect can be estimated for that<br/> 19 particular outcome of interest. If previous<br/> 20 trials had evaluated mortality and I know the<br/> 21 effect on survival, I may not be able to<br/> 22 extrapolate that for a trial that's evaluating a</p> |

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| 214 | <p>1 patient-reported outcome, for example.<br/>                 2 All of these disadvantages really pose<br/>                 3 challenges for us, and they pose challenges and<br/>                 4 limits as to the choice of the study population<br/>                 5 and the choice of the outcome measure that we are<br/>                 6 measuring in that trial.<br/>                 7 It is very possible that a study cannot<br/>                 8 support the efficacy if we cannot find historical<br/>                 9 evidence of the active comparator. If a trial<br/>                 10 comes in and they say, this is my active<br/>                 11 comparator and I really don't know what is the<br/>                 12 treatment effect of that active comparator, it<br/>                 13 could be very difficult to show that I'm no worse<br/>                 14 than that because I don't know what the treatment<br/>                 15 effect is.<br/>                 16 How does this apply to NTM lung<br/>                 17 infection trials? There are several designs that<br/>                 18 can be considered. The first one is an add-on<br/>                 19 trial where a test drug or test drug combination<br/>                 20 is added to a background regimen and then compared<br/>                 21 to the background regimen alone or the background<br/>                 22 regimen with placebo. This test drug plus</p>                      | 216 | <p>1 shortened duration is going to be.<br/>                 2 What complicates matters further is that<br/>                 3 combination therapy is recommended and in general,<br/>                 4 this would complicate the trial design for a new<br/>                 5 regimen because in general, we require that any<br/>                 6 new drug must be demonstrated to make a<br/>                 7 contribution to the overall regimen. If I have a<br/>                 8 regimen that's composed of three or four drugs, I<br/>                 9 will need to know that each drug makes a certain<br/>                 10 contribution.<br/>                 11 The trial designs that we talked about<br/>                 12 generally are for demonstrating the efficacy<br/>                 13 contribution of a drug. But that may be difficult<br/>                 14 unless the drug is an add-on trial.<br/>                 15 In addition, a new test drug may not<br/>                 16 offer much advantage as far as efficacy. It may<br/>                 17 be preventing emergence of resistance or<br/>                 18 mitigating toxicity.<br/>                 19 For these situations, the FDA has<br/>                 20 published a guidance for industry, which I will<br/>                 21 refer you to, and I will not go into more detail.<br/>                 22 It's about co-development of two or more</p>    |
| 215 | <p>1 background regimen versus background regimen has<br/>                 2 been used in MDR TB trials in the past.<br/>                 3 You can also compare new regimens. You<br/>                 4 can have one combination compared to another or<br/>                 5 you can have one combination compared to placebo<br/>                 6 or no-treatment if that population you are<br/>                 7 studying in whom delayed treatment may be<br/>                 8 clinically acceptable.<br/>                 9 You can also design a non-inferiority<br/>                 10 trial where you can substitute one test drug for a<br/>                 11 drug in the background regimen. This has also<br/>                 12 been used in TB to allow treatment shortening.<br/>                 13 If feasible, you can also compare one<br/>                 14 new regimen to another. You can say, I'm not<br/>                 15 inferior to this other regimen but I do offer some<br/>                 16 advantage such as mitigation of toxicity.<br/>                 17 We think that non-inferiority trials are<br/>                 18 going to be extremely challenging for NTM lung<br/>                 19 infections mainly because we don't know what the<br/>                 20 treatment effect of a single drug substitution is<br/>                 21 for efficacy. We don't know if we shorten<br/>                 22 therapy, again, what the treatment effect for that</p> | 217 | <p>1 investigational drugs for use in combination.<br/>                 2 I'm going to switch gears here and talk<br/>                 3 about trial endpoints. We talked about<br/>                 4 demonstrating efficacy, but, really, what do we<br/>                 5 mean by that?<br/>                 6 The trial should measure something.<br/>                 7 What we would like it to measure is a clinically<br/>                 8 meaningful outcome. A clinical trial should<br/>                 9 measure a clinically meaningful outcome that is a<br/>                 10 direct measure of how a patient feels, functions,<br/>                 11 or survives.<br/>                 12 This includes, obviously, improved<br/>                 13 survival, or improvement of symptoms or functional<br/>                 14 capacity, or a prevention of disease complication.<br/>                 15 A good example here would be treatment of latent<br/>                 16 tuberculosis where patients are totally<br/>                 17 asymptomatic, but the treatment is given to<br/>                 18 prevent active disease in the future.<br/>                 19 Switching a little just to introduce the<br/>                 20 concept of a biomarker and a surrogate biomarker,<br/>                 21 because we do make the distinction between the<br/>                 22 two, according to the Biomarkers Definition</p> |

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| 218 | <p>1 Working Group, a biomarker is a characteristic<br/>2 that is objectively measured and evaluated as an<br/>3 indicator of normal biologic processes, pathogenic<br/>4 process, or pharmacologic responses to an<br/>5 intervention.<br/>6       You can think of a blood pressure<br/>7 measurement as a biomarker, microbiologic culture<br/>8 as a biomarker, radiologic appearance on X-ray as<br/>9 a biomarker.<br/>10       A surrogate is a lab measurement or a<br/>11 physical sign that is used as a substitute for<br/>12 clinically meaningful outcome. According to the<br/>13 Code of Federal Regulations, this should be<br/>14 reasonably likely to predict a clinical benefit.<br/>15       Examples of that are, for example, drugs<br/>16 that are approved for hypertension. You show an<br/>17 effect on blood pressure because blood pressure<br/>18 has been demonstrated to be predictive of future<br/>19 cardiovascular outcomes. Another good example<br/>20 would be HIV viral load where that has been<br/>21 correlated with survival.<br/>22       A surrogate is a biomarker, but not</p>             | 220 | <p>1 consideration in NTM infection trials, and we are<br/>2 certainly open to suggestions for other outcomes.<br/>3       The first is survival. The trial that<br/>4 measures survival is likely to be quite lengthy<br/>5 because the treatments are lengthy. We can have a<br/>6 trial that evaluates measures of symptoms or<br/>7 function. And examples of those may be clinician-<br/>8 reported outcomes. But some of these may be<br/>9 difficult for some symptoms. One symptom you<br/>10 heard about this morning was debilitating fatigue.<br/>11 A clinician is going to have a hard time reporting<br/>12 that.<br/>13       The other one is patient-reported<br/>14 outcomes or for short, PROs. We're going to hear<br/>15 a lot more about that in the next talk, but these<br/>16 require development and they require validation.<br/>17 The validation has to be in the population under<br/>18 study. A PRO developed for patients with<br/>19 bronchiectasis may or may not apply to patients<br/>20 who have cystic fibrosis, for example.<br/>21       Another measure of function is the 6-<br/>22 minute walk test, which we heard a little about</p> |
| 219 | <p>1 every biomarker is a surrogate. For a biomarker<br/>2 to be established as a surrogate that is<br/>3 predictive of a clinical outcome, we need to have<br/>4 evidence that the changes in this biomarker will<br/>5 correlate with the changes of the clinical<br/>6 outcome. And once established, a surrogate will<br/>7 allow development.<br/>8       Again, a good example is HIV viral load<br/>9 where drugs are approved on the basis of decreased<br/>10 viral load because, again, that has been<br/>11 demonstrated to correlate with mortality.<br/>12       If a drug receives accelerated approval<br/>13 under Subpart H on the basis of a surrogate<br/>14 biomarker, at times, a confirmatory trial that<br/>15 assesses the clinical outcome is still required.<br/>16       A good example here is TB drugs.<br/>17 Although TB drugs receive accelerated approval<br/>18 based on culture conversion to negative, we still<br/>19 require a confirmatory trial that shows a relapse<br/>20 free survival.<br/>21       How does this apply to NTM lung<br/>22 infections? We have several endpoints that are</p> | 221 | <p>1 this morning, or any other functional assessment,<br/>2 FEV1, for example. However, the degree of change<br/>3 that is meaningful to a patient should be defined.<br/>4       Finally, surrogate biomarkers, one<br/>5 example of that is microbiologic evaluations.<br/>6 Sputum culture conversion to negative may be one<br/>7 biomarker that, if studies show a correlation with<br/>8 improved survival or function, may serve as<br/>9 surrogate biomarkers.<br/>10       This is similar to TB trials. However,<br/>11 in this disease, we have a lot unanswered<br/>12 questions. We don't know how many consecutive<br/>13 negative cultures we need. We don't know the<br/>14 timing. Is it at 3 months, at 6 months, at 12<br/>15 months? Should it be during therapy? Should it<br/>16 be after therapy? We don't know how this<br/>17 correlates with clinical outcomes yet.<br/>18       We're also open to suggestions for other<br/>19 surrogates, for example, radiologic evaluations.<br/>20 However, these are exactly the same considerations<br/>21 as microbiologic surrogates.<br/>22       In conclusion, a drug needs to show</p>                    |



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| 222 | <p>1 substantial evidence of efficacy for a clinically<br/>2 meaningful outcome evaluated in an adequate and<br/>3 well-controlled trials. Surrogate markers can be<br/>4 used for approval if the surrogate has been shown<br/>5 to predict and correlate with a clinically<br/>6 meaningful outcome.<br/>7 Patient-reported outcomes have to be<br/>8 validated, but once validated, they can be used as<br/>9 a basis for approval. And finally, it is feasible<br/>10 to co-develop a new test drug combination in<br/>11 certain situations. Thank you.<br/>12 (Applause.)<br/>13 DR. FARLEY: Thanks, Hala.<br/>14 You're going to be hearing a lot of<br/>15 discussion for the rest of the day, I'd say, about<br/>16 the endpoints in clinical trials because the<br/>17 design of the clinical trial itself and -- I'll<br/>18 just throw out something provocative and the panel<br/>19 can pick up on it later. But it seems in this<br/>20 disease that the most straightforward way to an<br/>21 adequate and well-controlled trial to meet the<br/>22 Congressional standard would be to show that</p>                                    | 224 | <p>1 idea of what the group does, we provide advice to<br/>2 review divisions upon request in regards to<br/>3 clinical outcome assessments, which can include<br/>4 physician questionnaires and mostly importantly<br/>5 patient questionnaires.<br/>6 We review these questionnaires to ensure<br/>7 that they're measuring the most important symptoms<br/>8 and impact to patients and that they're measuring<br/>9 these concepts in a reliable and accurate manner.<br/>10 Today, I will briefly present on how we<br/>11 utilize information from patient-focused drug<br/>12 development meetings and how we aim to incorporate<br/>13 patient input in to clinical study endpoints.<br/>14 You may be wondering how do we use the<br/>15 information from patient-focused drug development<br/>16 meetings. We have these meetings, but where do we<br/>17 go from here? How do we take this valuable<br/>18 information and generate clinically relevant<br/>19 patient-focused endpoints and place them in<br/>20 clinical studies?<br/>21 I'm hoping that I'll be able to answer<br/>22 at least some of these questions in the next few</p> |
| 223 | <p>1 you're better than a placebo or better than<br/>2 something else, and that's the superiority trial<br/>3 that Dr. Shamsuddin was talking about.<br/>4 But the endpoint and getting to an<br/>5 endpoint that means something to patients is<br/>6 challenging in this particular disease. One of<br/>7 the most straightforward ways that it would seem<br/>8 to do it would be to take the input that we got<br/>9 from you this morning and in other fora and try<br/>10 and turn that into an instrument, which we call a<br/>11 patient-reported outcome measure.<br/>12 But one of the things I've learned<br/>13 in the last six years since I've been is that<br/>14 that's a lot harder than it sounds initially.<br/>15 Drs. Daniels and Quittner are going to walk<br/>16 through that a little bit for you, as well as<br/>17 provide you an example of a work in progress.<br/>18 Presentation - Selena Daniels<br/>19 DR. DANIELS: Good afternoon. My name<br/>20 is Selena Daniels, and as I mentioned earlier, I'm<br/>21 a reviewer on the clinical outcome assessment<br/>22 staff here at FDA. And just to give you a little</p> | 225 | <p>1 slides.<br/>2 One of the main advantages in having<br/>3 patient-focused drug development meetings is that<br/>4 it gives all stakeholders the opportunity to<br/>5 listen to the patients' voice. We find it very<br/>6 useful to hear the patient experience,<br/>7 particularly to hear what's most important to the<br/>8 patient from their perspective and how they<br/>9 describe their symptoms and impacts in their own<br/>10 words.<br/>11 We hope that it helps give drug sponsors<br/>12 ideas about what important symptoms and impact to<br/>13 measure in clinical studies and later make the<br/>14 investment to select or develop questionnaires to<br/>15 include in these studies, as well as engage with<br/>16 FDA for discussion.<br/>17 The information from these meetings also<br/>18 helps informs how we review patient questionnaires<br/>19 here at FDA. It makes sure that you guys, the<br/>20 drug developers, are adequately assessing the<br/>21 patients' perspective from their medical<br/>22 condition.</p>  |

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| <p style="text-align: right;">226</p> <p>1        While the patient-focused drug<br/> 2 development meetings provide initial input, we<br/> 3 also encourage drug sponsors, as well as other<br/> 4 researchers who are developing these<br/> 5 questionnaires to engage with additional patients<br/> 6 either in one-on-one interviews or focus groups,<br/> 7 as well as physicians and other experts.<br/> 8        The goal of this is to confirm that the<br/> 9 questionnaire includes important yet relevant<br/> 10 information and that to ensure that the questions<br/> 11 and instructions of the questionnaires are clear<br/> 12 and understandable to patients.<br/> 13        Another advantage of these meetings is<br/> 14 that it helps us to think about clinical study<br/> 15 endpoints. What's an endpoint? In the case of a<br/> 16 patient questionnaire, the study endpoint could be<br/> 17 the questionnaire score, and that's how it's going<br/> 18 to be analyzed in the clinical study.<br/> 19        For example, if patients are reporting<br/> 20 that the most important treatment benefit to them<br/> 21 is symptom improvement, then we will want to<br/> 22 encourage drug sponsors to select or develop a</p> | <p style="text-align: right;">228</p> <p>1 encourage drug sponsors to consider selecting<br/> 2 important concepts that can also be impacted by<br/> 3 treatment as key study endpoints.<br/> 4        Financial well-being and other important<br/> 5 concepts that are unrelated to treatment can still<br/> 6 very well be measured but perhaps may be for<br/> 7 exploratory purposes.<br/> 8        For non-tuberculous mycobacterial lung<br/> 9 infections, study endpoints that include patient<br/> 10 questionnaires will be helpful to provide<br/> 11 additional evidence of clinical benefit. Often,<br/> 12 cultures are considered for primary endpoints in<br/> 13 these studies. However, cultures do not directly<br/> 14 tell us how patients feel and function.<br/> 15        The information generation from these<br/> 16 patient questionnaires in combination with culture<br/> 17 and other diagnostic endpoints provides a fuller<br/> 18 picture of clinical benefit.<br/> 19        At the FDA, we have to uphold laws and<br/> 20 regulations. Within these regulations, there are<br/> 21 regulatory standards for assessments, like patient<br/> 22 questionnaires, that require methods of assessment</p> |
| <p style="text-align: right;">227</p> <p>1 symptom questionnaire that measure these concepts,<br/> 2 and of course using good measurement principles,<br/> 3 which I'll describe later in a few slides, as well<br/> 4 as within regulatory standards.<br/> 5        The study endpoint could possibly be the<br/> 6 change in the questionnaire score during the<br/> 7 clinical study, which would assess the amount of<br/> 8 symptom improvement.<br/> 9        One key consideration is that there are<br/> 10 many things that are important to patients that<br/> 11 are going to be discussed in patient-focused drug<br/> 12 development meetings, as well as in one-on-one<br/> 13 interviews and focus groups.<br/> 14        However, not all of these things lend<br/> 15 themselves to be measured in clinical study<br/> 16 studies as they may not be impacted by treatment,<br/> 17 making it difficult to interpret as results.<br/> 18        Here, at the FDA, we focus on efficacy<br/> 19 and safety. For example, financial well-being may<br/> 20 be important to patients. However, it may be<br/> 21 minimally impacted or maybe not at all impacted by<br/> 22 treatment in a clinical study setting. So we</p>               | <p style="text-align: right;">229</p> <p>1 as subjects' response to be well-defined and<br/> 2 reliable.<br/> 3        Thus, when we describe findings from<br/> 4 these assessments and labeling, we can make sure<br/> 5 that the statements are not particularly false or<br/> 6 misleading.<br/> 7        Not only do we recommend drug sponsors<br/> 8 to engage with patients on developing these<br/> 9 questionnaires using qualitative research, we also<br/> 10 recommend them to perform appropriate quantitative<br/> 11 research or statistical testing to show that the<br/> 12 questionnaire is well-defined and reliable.<br/> 13        Both qualitative and quantitative<br/> 14 research can tell us whether the patients can<br/> 15 understand and report as intended on the<br/> 16 questionnaire. Additionally, these tests can<br/> 17 provide an estimate of a meaningful change or<br/> 18 improvement on the questionnaire. Patient<br/> 19 involvement is also extremely important in telling<br/> 20 us what that meaningful change means to them.<br/> 21        We do recommend that drug sponsors seek<br/> 22 input from FDA as early and often as possible in</p>  |

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| 230 | <p>1 their drug development programs. In some cases,<br/>2 if a patient questionnaire does not exist, then an<br/>3 existing questionnaire may be modified or a new<br/>4 one developed.<br/>5       It is important for drug sponsors to<br/>6 start the process of selecting or developing these<br/>7 questionnaires early and using them early and<br/>8 often in their clinical programs to gain<br/>9 experience with them before using them in phase 3<br/>10 studies to confirm clinical benefit.<br/>11       At this time, we do not know the patient<br/>12 questionnaire that is ready for use in clinical<br/>13 studies for non-tuberculous mycobacterial lung<br/>14 infections. However, you will be hearing from Dr.<br/>15 Quittner who will be presenting some preliminary<br/>16 work on a patient questionnaire, which we are very<br/>17 excited to see.<br/>18       I do want to note that the FDA is not<br/>19 endorsing any questionnaire over another at this<br/>20 time but are encouraging drug sponsors or<br/>21 questionnaire developers to start early<br/>22 discussions with us so we can help guide them to</p> | 232 | <p>1 within this program to develop and qualify<br/>2 publicly available outcome assessment tools.<br/>3       I want to leave you with a few key<br/>4 takeaways. Patient-focused drug development<br/>5 meetings are merely a starting point to the road<br/>6 for developing patient-focused outcome measures<br/>7 and endpoints. And these meetings will support<br/>8 and guide FDA risk benefit assessments and drug<br/>9 reviews.<br/>10       Ultimately, the patient's input will<br/>11 help determine what is measured to provide<br/>12 evidence of treatment benefit, how best to measure<br/>13 concepts in a clinical study, and what a<br/>14 meaningful improvement is in treatment benefit.<br/>15       That concludes my presentation, and I<br/>16 will now turn it over to Dr. Quittner.<br/>17       DR. FARLEY: It's my pleasure to<br/>18 introduce Dr. Quittner. She's a professor of<br/>19 psychology in pediatrics at the University of<br/>20 Miami. I got to know her around the review of<br/>21 Cayston for cystic fibrosis. One of her<br/>22 instruments was actually an endpoint in some of</p>  |
| 231 | <p>1 ensure that the questionnaire meets regulatory<br/>2 standards.<br/>3       There are two pathways to provide advice<br/>4 to those who are interested in developing patient<br/>5 questionnaires or any other clinical outcome<br/>6 assessments in clinical trials. The first pathway<br/>7 is within an individual drug development program.<br/>8       We encourage drug sponsors to begin<br/>9 these discussions as early as pre-IND stage so<br/>10 that if there is work that needs to be done on the<br/>11 questionnaire, they can get this done before their<br/>12 phase 3 studies.<br/>13       The second pathway is outside of the<br/>14 individual drug development program. This is<br/>15 through our Drug Development Tool or DDT<br/>16 qualification program. In this program, we work<br/>17 with questionnaire developers to develop and<br/>18 qualify questionnaires for use across multiple<br/>19 drug development programs.<br/>20       We work with many stakeholders,<br/>21 including consortia, patient groups, individual<br/>22 academic investigators, as well as drug developers</p>                      | 233 | <p>1 those clinical trials.<br/>2       She worked in this area a very long<br/>3 time, and I was very excited to learn recently<br/>4 that she's begun working in the NTM arena. So I'm<br/>5 anxious to hear how things are going. Presentation<br/>6 - Alexandra Quittner<br/>7       DR. QUITTNER: I'm really delighted and<br/>8 honored to be here today. As Dr. Farley<br/>9 mentioned, some of my research really focuses on<br/>10 developing patient-reported outcomes. Although he<br/>11 mentioned the process is very difficult to<br/>12 actually use them as an endpoint for approval, I<br/>13 have to say that the CFQ-R improvement in<br/>14 respiratory symptoms was the primary endpoint that<br/>15 led to the approval of Cayston for patients with<br/>16 cystic fibrosis. I want you to know that there's<br/>17 hope out there that this is a possible endpoint.<br/>18       I wanted to first thank some of the<br/>19 people who've really worked hard on this work.<br/>20 Insmad has funded the work that I'm going to<br/>21 present for you today. I want to acknowledge many<br/>22 of the people in this room who've helped me to get</p> |

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| 234 | <p>1 to this point, helping me collect data, serving in<br/> 2 focus groups and stakeholder expert panels: Ken<br/> 3 Olivier, Kevin Winthrop, Matthias Salathe, Dr.<br/> 4 Wallace and Anne O'Donnell, and many others here.<br/> 5 So lots of people have already put work into this<br/> 6 effort. That's my acknowledgement slide.<br/> 7 Our objectives are pretty clear today.<br/> 8 We know that NTM is a substantial cause of<br/> 9 pulmonary infections and affects those with<br/> 10 chronic respiratory diseases such as cystic<br/> 11 fibrosis and bronchiectasis. It's rare,<br/> 12 poorly understood, and difficult to treat as we<br/> 13 have been talking about today.<br/> 14 We are developing a patient-reported<br/> 15 outcome that identifies the key symptoms that can<br/> 16 track progression of disease, show symptom<br/> 17 improvement, and potentially serve as an endpoint<br/> 18 in a clinical trial of new therapies.<br/> 19 The aim of this study, I'll present to<br/> 20 you today, was to develop an instrument for NTM<br/> 21 symptoms in particular. The key thing here is it<br/> 22 would be a module attached to the very well-</p> | 236 | <p>1 psychologist, either myself or my post-doc with<br/> 2 adults with NTM and bronchiectasis at two sites,<br/> 3 and that included 31 patients. We also did a<br/> 4 consensus panel at ATS with 9 pulmonologists who<br/> 5 were all the who's who experts in NTM, many of<br/> 6 them are in this room today, talking about how<br/> 7 they see NTM impacting their patients and how<br/> 8 those treatments affect their patients.<br/> 9 We then went on to open-ended interviews<br/> 10 with 13 patients. This is the qualitative phase<br/> 11 that Selena described so well, asking them very<br/> 12 long and detailed questions: how does NTM affect<br/> 13 your life, your daily functioning, getting to<br/> 14 work, what symptoms are frequent for you,<br/> 15 difficult for you, what are your effects not just<br/> 16 on your respiratory symptom but on your physical<br/> 17 functioning, your emotional and social<br/> 18 functioning? Actually, social functioning came up<br/> 19 a lot today in the discussions.<br/> 20 Patients then completed -- these were<br/> 21 patients with bronchiectasis -- the QOL-B, and we<br/> 22 also coded all of these transcripts in Atlas.ti.</p> |
| 235 | <p>1 validated CFQ-R in cystic fibrosis, which has a<br/> 2 very good respiratory symptom scale, which, as I<br/> 3 just mentioned, was used in the approval of<br/> 4 Cayston; or it can be used with a QOL-B, which is<br/> 5 the PRO that is very well-validated and published<br/> 6 in several papers in thorax and chest for patients<br/> 7 with bronchiectasis.<br/> 8 So as I present our development of this<br/> 9 particular symptom module, you'll notice that<br/> 10 there's less of a focus on respiratory symptoms<br/> 11 because we checked all of those in our development<br/> 12 of the two other PROs.<br/> 13 We did follow the steps that are laid<br/> 14 out in the very clear and well-defined FDA<br/> 15 Guidance on patient-reported outcomes, which came<br/> 16 out 2009. As a first step, we reviewed all the<br/> 17 literature on NTM to identify relevant, critical<br/> 18 symptoms and the challenges of living with NTM.<br/> 19 I have to say, this morning, I took<br/> 20 copious notes, and much of it is reflected, I<br/> 21 hope, in some of what I'll say today.<br/> 22 We did focus groups moderated by a</p>                         | 237 | <p>1 We then did a draft instrument based on all of<br/> 2 this work of the NTM module and did cognitive<br/> 3 testing, which is also required in the FDA<br/> 4 Guidance using a standard "think aloud" procedure<br/> 5 with 53 adults.<br/> 6 Given the variety of symptoms we're<br/> 7 hearing about today, I'm really glad we<br/> 8 oversampled in many ways. We tested this in 53<br/> 9 adults, and I have to give a huge thank you to<br/> 10 Katie Keating and her support group who really<br/> 11 helped to make a lot of that process possible.<br/> 12 They gave us input on the preliminary items and<br/> 13 the rating scale options.<br/> 14 Finally, we completed our initial -- I'm<br/> 15 most excited about this -- psychometric validation<br/> 16 of the module in 148 patients. In a rare disease,<br/> 17 I think you know that that's pretty tough. Again,<br/> 18 this required help from lots of the pulmonologists<br/> 19 that are in the room today who helped me collect<br/> 20 data.<br/> 21 So this is just laying out this pathway,<br/> 22 and this really is what I think the FDA means by</p>   |

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| <p style="text-align: right;">238</p> <p>1 developing a patient-reported outcome: focus<br/> 2 groups with both stakeholders like physicians,<br/> 3 patients with the disease, the qualitative phase<br/> 4 and try to identify key symptoms and impacts,<br/> 5 interviews that are coded systematically, draft<br/> 6 instrument, cognitive testing to make sure all of<br/> 7 you are comfortable feeling out the questionnaire,<br/> 8 understand the items, can use the rating scales<br/> 9 effectively, and finally what we would say is the<br/> 10 quantitative side, the psychometric analysis of<br/> 11 the items.<br/> 12 All of these have to work. All of these<br/> 13 are sequential processes that hopefully lead to<br/> 14 psychometrically sound tool.<br/> 15 I wanted to just you the demographics of<br/> 16 the patients participating in those different<br/> 17 studies, and you can see primarily female, and I<br/> 18 think that follows the epidemiologic data, mostly<br/> 19 Caucasian although I live in Miami and Dr.<br/> 20 Matthias Salathe helped me recruit patients, so do<br/> 21 we have some Hispanic patients. And you can see<br/> 22 the range of age here. The means are in the 60s.</p>               | <p style="text-align: right;">240</p> <p>1 The alpha was 0.73, which indicates very<br/> 2 good reliability. All of these items hung<br/> 3 together as the 148 patients with NTM filled out<br/> 4 the symptom module, so there was very good<br/> 5 reliability.<br/> 6 Just a couple of sample items for you:<br/> 7 bothered by cold weather and have you<br/> 8 experienced problems with memory? These were<br/> 9 highly endorsed symptoms.<br/> 10 The really interesting part about this<br/> 11 is if you have cystic fibrosis, all of these sort<br/> 12 of body image, eating problems, digestive symptoms<br/> 13 actually go along with that disease. Separately,<br/> 14 I've already developed all of those scales that<br/> 15 are particular to patients with CF.<br/> 16 In this project with NTM and those who<br/> 17 have bronchiectasis, patients with bronchiectasis<br/> 18 did not endorse a lot of digestive symptoms,<br/> 19 eating problems, or body image. In fact, they<br/> 20 tend to be a little bit more on the overweight<br/> 21 side.<br/> 22 What was very interesting to me is if</p>   |
| <p style="text-align: right;">239</p> <p>1 So I think these data show that we collected<br/> 2 fairly representative samples of people with NTM.<br/> 3 Here are some of the main themes that<br/> 4 I've just wanted to show you from the focus<br/> 5 groups: pain, that's something I've heard today -<br/> 6 - pressure in the chest, a metal or metallic taste<br/> 7 in the mouth, fever, lack of sleep, difficulties<br/> 8 getting to sleep; some of the main themes in the<br/> 9 open-ended interviews, of course, fatigue, we've<br/> 10 heard about this overwhelming amount of fatigue;<br/> 11 sensitivity to smell; cold -- I've been cold in<br/> 12 this room myself; hot flashes and feeling sweaty<br/> 13 at night; and then some other themes coming from<br/> 14 the physicians and patients as well: memory loss<br/> 15 and body image issues; side effects of the<br/> 16 medications including GI problems, and weight loss<br/> 17 as the disease progresses.<br/> 18 The focus groups and open-ended<br/> 19 interviews also identified eating issues, sleep<br/> 20 quality, fever chills, and body image. The NTM<br/> 21 module consists of eight unique symptoms, and we<br/> 22 administered them to 148 patients.</p> | <p style="text-align: right;">241</p> <p>1 you have bronchiectasis plus NTM, you then<br/> 2 experience these kinds of issues: body image,<br/> 3 losing weight, not feeling like you have a good<br/> 4 appetite -- we actually heard that this morning<br/> 5 very beautifully confirming that -- and digestive<br/> 6 symptoms.<br/> 7 What's fascinating is that the CFQ-R got<br/> 8 all of that, and we just add the NTM module. But<br/> 9 the QOL-B will not have those, and we developed<br/> 10 then the body image, eating, and digestive<br/> 11 symptoms that go along NTM plus bronchiectasis.<br/> 12 You can see the alphas on these; these<br/> 13 are all highly internally consistent. The<br/> 14 quantitative data on these scales worked out very<br/> 15 well also.<br/> 16 I wanted to just show you this because<br/> 17 this is for patients, and there are a lot of<br/> 18 people tuning in. You can see these are just the<br/> 19 individual item loadings. The higher the loading,<br/> 20 the more that it was endorsed and linked to that<br/> 21 underlying construct of the module.<br/> 22 Look at these really high ones, bad</p> |

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| 242 | <p>1 taste in the mouth, memory problems, bothered by<br/>2 cold weather, pain, lots other things we talked --<br/>3 fevers, chills, lots of the things that have been<br/>4 mentioned today actually loaded really nicely in<br/>5 this module.<br/>6 This is the algorithm. I know it looks<br/>7 really scary and confusing but actually, I'm just<br/>8 explaining to you that if you have NTM and<br/>9 bronchiectasis, you need the QOL-B plus our<br/>10 digestive kind of eating scales and the NTM<br/>11 module. If you have CF, you need just the CFQ-R<br/>12 plus the NTM module because those were all<br/>13 covered.<br/>14 Summary and future directions, cognitive<br/>15 testing actually indicated the draft items were<br/>16 relevant, clear, easy to understand, very strong<br/>17 reliability. I've explained how you might use the<br/>18 module depending on whether you have cystic<br/>19 fibrosis or you have bronchiectasis, and next<br/>20 steps would include additional psychometric<br/>21 testing.<br/>22 Dr. Daley is kind enough to now begin to</p>                       | 244 | <p>1 We are part of the Insmed liposomal amikacin<br/>2 trial. We're also a site for the bronchiectasis<br/>3 and NTM registry that's sponsored by the COPD<br/>4 Foundation. And I've done a little consulting with<br/>5 another company regarding this.<br/>6 We all realize here that in a perfect<br/>7 world, we give an antibiotic to the patient with<br/>8 NTM and they would get better, they would feel<br/>9 better, patient would feel better, the infection<br/>10 would be cured, and the damage to the lung would<br/>11 be reversed, i.e., antibiotic for pneumonia.<br/>12 But this is not pneumonia. This is also<br/>13 not Pseudomonas bronchiectasis. This is not<br/>14 necessarily CF NTM disease. It's really its own<br/>15 disease. Just like Dave said, this is not TB.<br/>16 This is also not Pseudomonas in bronchiectasis.<br/>17 The regimens for therapy are much more<br/>18 complex. The side effects are very potentially<br/>19 troublesome. As you've already heard, we really<br/>20 don't know the best definition for defining<br/>21 response to therapy.<br/>22 Is it microbiology? Is it lung function</p>     |
| 243 | <p>1 include the QOL-B and the NTM module in his clinic<br/>2 routinely, and I know he sees lots of patients in<br/>3 Denver, and so hopefully, we'll gather additional<br/>4 data. And the other step we need to conduct --<br/>5 and Selena mentioned this -- is identifying what<br/>6 is a meaningful change on the score for patients<br/>7 like yourselves with NTM, and that piece we have<br/>8 yet to do. So with that, I thank you.<br/>9 (Applause.)<br/>10 DR. FARLEY: Great. And to just got us<br/>11 ready for panel discussion, Dr. O'Donnell, who is<br/>12 professor and chief in the Division of Pulmonary<br/>13 Critical Care and Sleep Medicine at Georgetown is<br/>14 -- I've given her the hard job of actually<br/>15 summarizing the challenges in the design of<br/>16 clinical trials particularly that we face to date.<br/>17 Presentation - Anne O'Donnell<br/>18 DR. O'DONNELL: All right. Thank you,<br/>19 John. And thank you for the invitation to be<br/>20 here. Thanks to everybody for participating in<br/>21 this.<br/>22 I just want to give my disclosures here.</p> | 245 | <p>1 improvement? Is it radiologic improvement? And<br/>2 of course, patient symptoms, which hearing<br/>3 everybody talk today, clearly, what patients want<br/>4 is to feel better, and that's what we want for the<br/>5 patients. But we have to come up with some<br/>6 scientifically rigorous endpoints in order to make<br/>7 all these assessments so that we can actually<br/>8 prove that these drugs, which as you know are<br/>9 potentially toxic, do have benefits for the<br/>10 patients.<br/>11 Like I said, I think the big four things<br/>12 that we can look at for endpoints are number one,<br/>13 microbiology; number two, imaging change; three,<br/>14 change in lung function; and four, of course,<br/>15 patient-reported outcomes.<br/>16 Let's talk about the microbiology.<br/>17 You've already heard this is difficult because we<br/>18 don't eradicate the bugs in most patients, at<br/>19 least over the long term as best we know. Things<br/>20 that we can look at, our reduction in organism<br/>21 counts, obviously eradication of the organism in<br/>22 some patients, the duration of response of that</p> |

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| 246 | <p>1 eradication, and that's already been alluded to,<br/>2 and then of course the presence or development of<br/>3 resistance.<br/>4       What is the current microbiologic "gold<br/>5 standard" in NTM lung disease? Really looking at<br/>6 the literature on this, it's basically 12 months<br/>7 of negative cultures while receiving therapy. I<br/>8 think everybody alluded to this, that the follow-<br/>9 on after therapy is much more difficult to assess.<br/>10       Other problems we have -- and this isn't<br/>11 so much for clinical trials but this is clinical<br/>12 practice. And I know many in the audience have<br/>13 experience the foibles of dealing with clinical<br/>14 microbiology labs in terms of actually even<br/>15 diagnosing NTM or speciating the organisms or<br/>16 defining resistance.<br/>17       I think for clinical trial purposes,<br/>18 we're definitely going to need standardized lab<br/>19 microbiology. The current trial is using Richard<br/>20 and David's lab in Tyler. They published on using<br/>21 semi-quantitative cultures for monitoring patients<br/>22 on therapy.</p>                                      | 248 | <p>1 73 percent were thought to be reinfection and 27<br/>2 percent true relapse, and then about half the<br/>3 patients had positive cultures after the<br/>4 conclusion of therapy.<br/>5       Obviously, this makes it difficult for<br/>6 microbiology to be the sole endpoint for these<br/>7 clinical trials.<br/>8       I think we've already heard about<br/>9 similar studies from South Korea. The South<br/>10 Koreans in this paper that was published in the<br/>11 Blue Journal this year did not tell us what<br/>12 happened post therapy.<br/>13       Again, we haven't really focused too<br/>14 much on cavitary disease today except for a couple<br/>15 of mentions this afternoon, and there are a<br/>16 substantial number of patients who have cavitary<br/>17 mycobacterial disease, and the culture conversion<br/>18 rated there is much -- it leaves much to be<br/>19 desired, I would say, and we have to factor that<br/>20 in when we're designing these trials.<br/>21       We have a couple of small papers<br/>22 published recently about salvage therapies. As</p>            |
| 247 | <p>1       We also know that they are kind of the<br/>2 leaders in looking at amikacin resistance and in<br/>3 genotyping, as Richard already alluded to. I<br/>4 think one thing is that in clinical trials and<br/>5 hopefully for better patient care ultimately, we<br/>6 need very standardized microbiology.<br/>7       One other appeal I would make to the FDA<br/>8 because you're one of the people responsible, one<br/>9 of the organizations responsible for clinical<br/>10 laboratory management in the U.S. is that we need<br/>11 to come to some clinical consensus on this<br/>12 ultimately about how mycobacteria is handled in<br/>13 clinical labs.<br/>14       Let me just talk about a couple of<br/>15 papers that you've already heard about, Richard<br/>16 and David and colleagues' paper from Tyler that<br/>17 was published last year in Chest, where patients -<br/>18 - and again these are nodular bronchiectatic<br/>19 patients which are most of you in the audience --<br/>20 who had 82 percent culture conversion to negative.<br/>21 But as was alluded to earlier, 14 percent<br/>22 recurrence of organism while on therapy of which</p> | 249 | <p>1 was discussed, this is one way to approach these<br/>2 patients, the patients who have failed standard<br/>3 therapy:<br/>4       bedaquiline, a TB drug, has some<br/>5 potential for non-tuberculous mycobacterium, and<br/>6 Julie Philley from the Tyler Group has published a<br/>7 small series on that.<br/>8       Finally, the liposomal amikacin trials,<br/>9 what's been presented in abstract form so far show<br/>10 some, but clearly not 100 percent culture<br/>11 conversion with the addition of liposomal amikacin<br/>12 to standard therapy.<br/>13       Why do we need a microbiologic endpoint?<br/>14 For one thing, it's one of the easier things to<br/>15 measure if we do it correctly in the correct<br/>16 laboratory environment. It's clearly reproducible<br/>17 again in the right hands, I would say.<br/>18       The problem is, you know, what's<br/>19 success? What's microbiologic success? Really,<br/>20 I'm going to leave that to the panel to tell us<br/>21 after I finish my talk and we have our break<br/>22 because, honestly, I don't know the answer to</p> |

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| 250 | <p>1 this, and I don't think any of us do and know how<br/>2 to really handle this.<br/>3 Three negative cultures while on<br/>4 therapy, does that constitute success? If you<br/>5 have one positive culture and all the rest are<br/>6 negative as our colleagues from Tyler put out<br/>7 there, is that still success? What about after<br/>8 the conclusion of therapy?<br/>9 In clinical trials, do we need to<br/>10 monitor the patients for three months post<br/>11 therapy, six months post therapy, 10 years post<br/>12 therapy? How are we going to handle that in the<br/>13 context of a clinical trial to get drug approval?<br/>14 I'm anxious for the panel to tell us when we're<br/>15 done.<br/>16 I'm going to briefly touch on what I<br/>17 think are a few other potential endpoints but<br/>18 probably not primary endpoints when looking at<br/>19 antibiotic treatment for this disease.<br/>20 Imaging, a couple of patients mentioned,<br/>21 hey, my CT scan got better. We all know that<br/>22 that's not the be all and end all of treating NTM</p>  | 252 | <p>1 our hallway.<br/>2 I think a lot of studies now have 6-<br/>3 minute walks as part of the protocol. I think<br/>4 it's a pretty soft endpoint. It is reproducible.<br/>5 There is data on that, but it's not, to me, in my<br/>6 mind, the best marker of disease progression or<br/>7 disease correction when you're giving an<br/>8 antibiotic in a very complex disease where the<br/>9 infection is not the whole story for the patient.<br/>10 I think we need this. I think we need<br/>11 pulmonary function tests as part of clinical<br/>12 trials but mainly to monitor for adverse effects<br/>13 from the drugs, particularly the inhaled drugs.<br/>14 But I think we all recognize that FEV1 change is<br/>15 probably not an outcome that's going to help us<br/>16 very much in these antibiotic trials complex<br/>17 disease.<br/>18 It's clear -- I mean Alexandra just did<br/>19 a great presentation. She's done so much<br/>20 fantastic work on translating what you all said<br/>21 this morning into some scientifically validated<br/>22 way for us to incorporate your symptoms into</p>                          |
| 251 | <p>1 disease. One of the major features of NTM<br/>2 radiology, if you will, is that we often see a<br/>3 waxing and waning of the findings on the CT scan.<br/>4 So I think it will be very hard to<br/>5 quantitate CT or use CT as a primary endpoint in<br/>6 this disease. I think there is a role, but we<br/>7 need more information. We need some standardized<br/>8 scores for looking at CT scans in order to use<br/>9 this, and we also have to be concerned about the<br/>10 radiation exposure with too much imaging for<br/>11 patients who have already probably had a fair<br/>12 number of scans.<br/>13 There are a couple of trials that have<br/>14 looked at serial imaging that report improvement,<br/>15 but again, I think we have a ways to go, and this<br/>16 would not be, what I would think, a primary<br/>17 endpoint in monitoring antibiotic response.<br/>18 What about lung function testing? The<br/>19 pulmonary world loves the 6-minute walk test. I<br/>20 tell you, I hate the 6-minute walk test. And<br/>21 Michelle Cooney, my research coordinator, can<br/>22 vouch for how much we love doing those tests in</p> | 253 | <p>1 clinical trial work. It's just vitally important.<br/>2 Now, Ken published a paper looking at<br/>3 basically the things that are listed here: cough,<br/>4 fatigue, hemoptysis, that can be incorporated into<br/>5 a validated tool and clearly is vitally important.<br/>6 Whether that can be the primary<br/>7 endpoint, I think we could debate, but having your<br/>8 symptoms translated into something that we can use<br/>9 in a clinical trial by monitoring it serially<br/>10 while you're on therapy is very, very important.<br/>11 I think we need to probably incorporate this<br/>12 trial, as was said about Chuck, into our clinical<br/>13 practice.<br/>14 All right. What about looking at<br/>15 patient-reported outcomes? I think Ken, in his<br/>16 paper where a small number of patients were<br/>17 reported who received inhaled amikacin off label<br/>18 for a refractory NTM treatment, there was some<br/>19 benefit in the symptom score that was administered<br/>20 during that trial. Alexandra just showed us the<br/>21 work that was presented at the ERS meeting last<br/>22 month about this.</p> |



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| 254 | <p>1 I think to kind of summarize it, you<br/>2 know, we have these four things: microbiology,<br/>3 imaging, lung function, and patient-reported<br/>4 outcomes. But I think we also, when we're<br/>5 designing clinical trials, we have to think of a<br/>6 few other things about this disease because it's<br/>7 very heterogeneous.</p> <p>8 We have to decide I think as we launch<br/>9 more trials, are we going to include all NTM<br/>10 species in these trials or should we segregate MAC<br/>11 and M. abscessus when we design these clinical<br/>12 trials? Should we separate or stratify, in some<br/>13 way, patients with nodular bronchiectasis versus<br/>14 cavitary disease?</p> <p>15 I think we heard today from what Ken is<br/>16 saying with some data forthcoming that that<br/>17 probably would be a good idea to look at that as a<br/>18 way in the trial to stratify because the outcomes<br/>19 are quite different.</p> <p>20 We really have to decide about the<br/>21 chicken and the egg issue, right? Is the NTM<br/>22 causing the bronchiectasis or is the NTM</p> | 256 | <p>1 different types of organisms because, obviously,<br/>2 there's also some overlap.</p> <p>3 For example, with inhaled amikacin. It<br/>4 takes care, to some extent, of the Pseudomonas as<br/>5 well, and so that complicates matters. And just<br/>6 to show you a few images, I mean this is a male<br/>7 patient of mine with both MAC and Pseudomonas. I<br/>8 mean he's had it for years. He really functions<br/>9 quite well, doesn't have a lot of -- he has<br/>10 symptoms but he doesn't have frequent<br/>11 exacerbations.</p> <p>12 This is a patient with cavitary MAC. As<br/>13 you can imagine from looking at these images,<br/>14 she's quite symptomatic all the time and this has<br/>15 been a very difficult disease to get under<br/>16 control. But then we have the patients who are<br/>17 positive on their sputum cultures for 10 years but<br/>18 have non- progressive disease. How do we put<br/>19 those kind of patients into clinical trials?</p> <p>20 As was said by Dave earlier, he's<br/>21 followed his 75-year-old patient for 15 years and<br/>22 she hasn't changed, but it might change at some</p>     |
| 255 | <p>1 superimposed on chronic fibrotic disease or<br/>2 emphysema?</p> <p>3 It's a different ball of wax when you<br/>4 have patients who have a lot of underlying<br/>5 structural lung disease and get this infection<br/>6 versus getting the infection and then developing<br/>7 nodular bronchiectasis.</p> <p>8 I think another thing that patients<br/>9 brought up today, which I find to be a really<br/>10 important issue in assessing patients with NTM, is<br/>11 patients with NTM who also have other bacteria.</p> <p>12 If you have Pseudomonas, if you have<br/>13 Staph, and you have NTM, it's a different<br/>14 situation. Patients have more exacerbations<br/>15 whereas pure NTM patients tend not to have<br/>16 exacerbations and hence I don't think<br/>17 exacerbations are going to be an appropriate<br/>18 endpoint to monitor here.</p> <p>19 But patients who are co-infected with<br/>20 Pseudomonas, or with Staph, or Nocardia, or<br/>21 Aspergillus, we have to somehow figure out a way<br/>22 to make the clinical trials responsive to those</p>                    | 257 | <p>1 point. So that has to be factored in as well.<br/>2 And finally, looking at the abscessus patients.</p> <p>3 Again, I think I tried to make four<br/>4 points, four potential endpoints that we've<br/>5 already heard about today. I think imaging is<br/>6 something we have to have, but it's not something<br/>7 I would consider to be a primary endpoint.</p> <p>8 I think pulmonary function testing is<br/>9 useful in inhaled antibiotic trials for monitoring<br/>10 for any adverse effects from the inhalation but<br/>11 are is not a helpful primary endpoint. And six-<br/>12 minute walk, I think is of mixed value.</p> <p>13 I think it's clear that a patient-<br/>14 reported outcome is vital here because again, we<br/>15 face, again, positive microbiologic patients who<br/>16 are symptomatically better with therapy and vice<br/>17 versa.</p> <p>18 I think we're kind of stuck right now<br/>19 with a microbiologic endpoint, but we have to<br/>20 consider stratifying patients in clinical trials<br/>21 based on their organism. I think we also need to<br/>22 know more about these organisms, avium versus</p> |

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| 258 | <p>1 intracellulare, not something our clinical labs<br/>2 differentiate, but the patients probably have<br/>3 different prognoses.<br/>4       What about the abscessus, the true<br/>5 abscessus-abscessus patients who have macrolide<br/>6 resistance versus other M. abscessus complex<br/>7 patients? We probably need to separate in<br/>8 clinical trials nodular versus cavitary patients<br/>9 and also evaluate the impact of the co-infecting<br/>10 organisms.<br/>11       Finally, I think we need to come to some<br/>12 consensus about combining a longer term<br/>13 microbiologic endpoint with patient-reported<br/>14 outcomes.<br/>15       One last thing I would throw out there -<br/>16 - and I know there's not much on this, but whether<br/>17 there's any role for serologic monitoring of these<br/>18 patients. I know there are a couple of posters<br/>19 presented on this at the ERS meeting last month.<br/>20 This is all coming from Japan.<br/>21       I know I've had some side conversations<br/>22 kind of saying, poo-pooing this, but whether this</p> | 260  |     |
| 259 | <p>1 is some as an exploratory endpoint might have some<br/>2 value to look at IgA antibodies in MAC patients<br/>3 and see if the IgA antibodies go down with<br/>4 therapy.<br/>5       Again, that's something I see as a<br/>6 primary endpoint but something that might be of<br/>7 value that we in the U.S. really have not used at<br/>8 all in either clinical trials or in clinical<br/>9 practice.<br/>10       I would conclude by saying -- we have a<br/>11 break, I guess. I'm leaving all these questions<br/>12 to this very august group here. I think we've<br/>13 heard a lot of great things about the patient-<br/>14 reported outcomes. We need to really understand<br/>15 what we're going to do with the microbiologic<br/>16 endpoints and particularly the duration of<br/>17 response.<br/>18       Again, I thank everybody for being here,<br/>19 particularly the patients, and just acknowledge<br/>20 the NTM advocacy group and our bronchiectasis<br/>21 registry, and the FDA, of course, for bringing us<br/>22 together. Thank you very much.</p>              | <p>1       (Appause.)<br/>2       DR. FARLEY: Thanks very much, Dr.<br/>3 O'Donnell.<br/>4       We will have some time for questions<br/>5 during the panel discussion. At this point, I'm<br/>6 mindful of the time, so we're going to take a 15-<br/>7 minute break. And we're going to begin again<br/>8 promptly at 3:15. Thanks.<br/>9       (Whereupon, at 3:02 p.m., a recess was<br/>10 taken.)<br/>11       DR. FARLEY: Could we ask everyone on<br/>12 the panel to please take their seats up front, and<br/>13 we'll get started? Great. I'm going to turn the<br/>14 gavel over to Dr. Nambiar who is the division<br/>15 director for the Division of Anti-Infective<br/>16 Products.<br/>17       She trained at Children's Hospital in<br/>18 Pediatric Infectious Disease, and for quite some<br/>19 time actually was part of running a joint<br/>20 fellowship program we have in Infectious Disease<br/>21 between Children's and the FDA. She took over as<br/>22 division director about two years ago now, I</p> | 261 |

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| 262 | <p>1 appropriate controls for the trials. And then the<br/> 2 fourth topic, which is just as important, is<br/> 3 regarding practical considerations in conducting<br/> 4 these trials, and as briefly mentioned this<br/> 5 morning, did not come up much in presentations<br/> 6 this afternoon, but I think it's an important<br/> 7 point to discuss as these trials are certainly of<br/> 8 long duration; treatment regimens are very<br/> 9 complicated and the frequency of visits can be<br/> 10 quite challenging.</p> <p>11 With that, I thought the first topic<br/> 12 that we can talk about would be the populations<br/> 13 and how might we streamline our trials, and who<br/> 14 would be appropriate to enroll.</p> <p>15 In terms of the populations to study --<br/> 16 and I think Dr. O'Donnell laid this all out very<br/> 17 clearly -- is it all right to limit it to only NTM<br/> 18 patients who have underlying bronchiectasis; is it<br/> 19 okay to also include patients with cystic fibrosis<br/> 20 in the same trial, if so do we stratify them?</p> <p>21 We've heard in the discussions today<br/> 22 that these two populations can be fairly different</p> | 264 |
| 263 | <p>1 in terms of the outcomes. The frequency of the<br/> 2 pathogens might be different between these two<br/> 3 sets of patients. And there might be differences<br/> 4 in other risk factors such as steroid use and<br/> 5 macrolide use as well.</p> <p>6 So that would be one question that we<br/> 7 would really appreciate the input from the panel.<br/> 8 The second key area would be differentiating<br/> 9 between those who are treatment-experienced versus<br/> 10 treatment-naïve it okay to combine them again in<br/> 11 one study or should they be studied separately?<br/> 12 Potentially, one can have different trial designs<br/> 13 depending on whether it's a naïve population or an<br/> 14 experienced population.</p> <p>15 Would we consider different endpoints?<br/> 16 Again, if their treatment-naïve versus treatment-<br/> 17 experienced, what might be the treatment benefit?<br/> 18 Would there be a difference if this a treatment-<br/> 19 experienced patient versus being a treatment-naïve<br/> 20 patient?</p> <p>21 Again, Dr. O'Donnell has addressed this;<br/> 22 whether MAC patients and non-MAC patients should</p>                          | 265 |

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| 266 | <p>1 being able to find patients to treat.<br/> 2       MAC versus non-MAC, that depends on the<br/> 3 MIC. That decision, science should drive whether<br/> 4 you include MAC and abscessus. Not all drugs that<br/> 5 work for one work for the other. I think if they<br/> 6 work for both, same argument. To me, as with the<br/> 7 CF question, they should both be included if the<br/> 8 drug works for both.<br/> 9       The most important thing -- and this<br/> 10 really wasn't, I don't think, highlighted well<br/> 11 enough, that really what matters is the precise<br/> 12 speciation of the organism.<br/> 13       Anne mentioned this issue, but really<br/> 14 it's about speciation. And that means it needs to<br/> 15 go to the right laboratory so that it can be<br/> 16 speciated, or how do you interpret the outcome of<br/> 17 someone who's treated with abscessus versus<br/> 18 massiliense, as Anne said, where one does really<br/> 19 well and the other doesn't, but most labs don't<br/> 20 distinguish the two.<br/> 21       The final thing here is there are so<br/> 22 many confounders here that I want to propose this</p> | 268 | <p>1 That is just the beginning.<br/> 2       DR. WINTHROP: Okay. That's just the<br/> 3 start. We were just in San Diego, some of us. I<br/> 4 was there last time. I'm sure I'll hear about it.<br/> 5 But we spent five hours talking about just one<br/> 6 question for the new guidelines of meeting, so<br/> 7 this -- maybe we should move to the next question.<br/> 8       But I want to echo Chuck's comments and<br/> 9 thank everyone for doing this and for putting this<br/> 10 disease on the map. I think the last few years,<br/> 11 we've gained a lot of momentum, and a lot of that<br/> 12 has to do with the patients here and the patient<br/> 13 advocacy groups, as well as the FDA, and industry<br/> 14 and the academics. We're all in this together and<br/> 15 we're all trying to accomplish the same thing.<br/> 16 I'm very happy to see movement in the last few<br/> 17 years.<br/> 18       I liked all of Chuck's answers, so I'm<br/> 19 not going to weigh in and disagree. In fact, we<br/> 20 just submitted a grant today that took the<br/> 21 approach that Chuck just mentioned. I guess we're<br/> 22 going to get to the comparison groups later.</p> |
| 267 | <p>1 idea and I want to hear from industry. They won't<br/> 2 like it. We can't tell who's going to progress on<br/> 3 day 1; it's not possible.<br/> 4       But we do have a little better idea at<br/> 5 about six months. In South Korea -- and they<br/> 6 published this approach -- when they see someone,<br/> 7 they follow them for six months, collect<br/> 8 additional sputum, re-image at six months. And<br/> 9 now, at least, they've had six months to say, this<br/> 10 is a progressor; this patient is not a progressor.<br/> 11       I think it helps you find the right<br/> 12 people to be enrolled in a trial. Otherwise at<br/> 13 six months, many of these are going to be stable.<br/> 14 Those are not the people you want to enroll in a<br/> 15 trial. You want to enroll the progressors to be<br/> 16 able to understand, did the treatment have an<br/> 17 impact on any of the outcomes which we'll<br/> 18 subsequently measure?<br/> 19       DR. WINTHROP: Are we done with that<br/> 20 question?<br/> 21       DR. NAMBIAR: No, no, no.<br/> 22       (Laughter)</p>  | 269 | <p>1       But I think the idea that everyone needs<br/> 2 to be treated right away is obviously not true.<br/> 3 And we know that. It's in our guidelines that we<br/> 4 support watching people who clinically can be<br/> 5 watched.<br/> 6       At some point, I feel that most people<br/> 7 do need to be treated or they'll want to be<br/> 8 treated. Exactly when that happens, of course, is<br/> 9 a spectrum and it's a case by case thing. It's<br/> 10 different for everyone.<br/> 11       I do think that the answers Chuck<br/> 12 provided, I would just say I'd agree with them. I<br/> 13 don't like excluding groups up front. I'm an<br/> 14 epidemiologist. I like to handle it in the<br/> 15 analysis. And as long as you can construct a big<br/> 16 enough trial -- and I know this gets challenging<br/> 17 because it becomes more costly. But it's really<br/> 18 silly to exclude people up front if you don't have<br/> 19 to. And it's better to sort out who responded<br/> 20 later in your analysis in looking at subgroups and<br/> 21 things like that. So I think as much as possible,<br/> 22 we should try to be inclusive.</p>                            |

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| <p>1 DR. WALLACE: I'd like to make a comment<br/>2 that it depends on whether the trial is primarily<br/>3 the safety -- that is the drug has never been used<br/>4 in any of these populations -- or as we are with<br/>5 Arikace, we've already been through one trial;<br/>6 now, you're probably more interested in efficacy<br/>7 and safety is much less of an issue.<br/>8 So if it's a safety issue, the more<br/>9 patients you put in the trial, the more you may be<br/>10 able to answer that question. But an efficacy<br/>11 trial, it may also be helpful to put them<br/>12 altogether if you can divide them all out.<br/>13 I talked earlier about the design trial<br/>14 of having patients come every month and dealing<br/>15 with a patient population that averages 75 years<br/>16 of age. It is not a possible trial. We lost so<br/>17 many patients.<br/>18 We did a trial just with inhaled<br/>19 amikacin and got two-thirds of the patients<br/>20 because they were unable to find a way to get<br/>21 there to do that. So if there's anything to<br/>22 emphasize, it would be that.</p> | <p>1 safety reasons, I think that was fine. Now, if<br/>2 you want to do an efficacy trial, you might not<br/>3 make them same. I don't know we've thought about<br/>4 that in terms of what -- I mean the next trial is<br/>5 going to look at just one of them, but they may<br/>6 not be treated the same. They may not respond the<br/>7 same.<br/>8 And I actually don't know that, I mean<br/>9 in the sense that you had one group that responded<br/>10 better than the other, but I don't know if it was<br/>11 study design. Should you have gone longer before<br/>12 you assessed them or not? Six months isn't very<br/>13 long for M. abscessus.<br/>14 I pretty much agree with Chuck. The one<br/>15 other thought is if the endpoint is primarily or<br/>16 exclusively microbiologic, it doesn't really<br/>17 matter to me how sick the patient is. The<br/>18 endpoint is fairly objective. You can either make<br/>19 the cultures negative or -- I mean, they need to<br/>20 be treated or you decide, but I wouldn't -- 99<br/>21 percent of our patients come to us because they're<br/>22 symptomatic.</p>   |
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| <p>1 Again, some difference based on whether<br/>2 it's safety or efficacy, and that would, I guess,<br/>3 be whether this is the first trial or the second<br/>4 trial.<br/>5 I agree with Chuck about CF. As long as<br/>6 we're going to do them, you can always split them<br/>7 out. The clinics are often together, fairly close<br/>8 together. I mean I think we could be able to do<br/>9 that.<br/>10 I think M. abscessus, as Chuck alluded<br/>11 to, the difference between the islets that are<br/>12 macrolide-susceptible and the macrolide-resistant<br/>13 on the basis of the ERM gene is enormous.<br/>14 Obviously, there's only been maybe one trial, but<br/>15 none of us were surprised by the results.<br/>16 Again, I don't know if you have to<br/>17 separate them out but you have to identify them.<br/>18 We have to know which ones are macrolide-<br/>19 susceptible, which ones are massiliense, so you<br/>20 can separate them out when you get there.<br/>21 I think with the recently completed<br/>22 Arikace trial that had both abscessus and MAC, for</p>                        | <p>1 Somebody has referred them to us,<br/>2 primary care, a pulmonologist, or why did they<br/>3 have the test done in the first place? They had<br/>4 some kind of symptom, so most of them are usually<br/>5 willing to enter the trial at that point.<br/>6 So I don't know about the six months if<br/>7 the endpoint is primarily microbiologic. Patient-<br/>8 reported outcomes, it is tougher if the patient<br/>9 doesn't have a lot of symptoms. I mean if that's<br/>10 very important, then you may want to separate them<br/>11 out so that the ones that are the sickest, you can<br/>12 really use patient-reported outcomes as an outcome<br/>13 as compared to some patients who are -- they don't<br/>14 feel well but they're not going to give you a lot<br/>15 -- they're not really sick in the way that you<br/>16 could probably measure that very objectively.<br/>17 DR. EAGLE: I would just like to add<br/>18 that like when you're actually sitting down to put<br/>19 these clinical trial designs together, you think<br/>20 you've got it, and then you pressure test it, and<br/>21 you wonder whether you are doing the right thing<br/>22 when you're going to put so many patients through</p> |

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| 274 | <p>1 the trial and resources.</p> <p>2       One of the things I want to highlight</p> <p>3 that hasn't actually been spoken about is the</p> <p>4 timing of the endpoint, not just the endpoint.</p> <p>5 Right now, we have the microbiological endpoint,</p> <p>6 which is the gold standard.</p> <p>7       Whether that is the right thing, it's</p> <p>8 clearly a biomarker, a surrogate, and we do need</p> <p>9 correlated patient endpoints, whether they're</p> <p>10 functional or whether they are patient-reported</p> <p>11 outcomes. We welcome a patient, a PRO, for these</p> <p>12 trials because it seems like if it's one that's</p> <p>13 properly validated and works, it will solve a lot</p> <p>14 of our problems. We don't have it at this moment,</p> <p>15 unfortunately.</p> <p>16       But when we looked at -- in our</p> <p>17 experience when we looked at our trial, we did</p> <p>18 have non-CF, and we had CF patients, and we had</p> <p>19 abscessus, and we had MAC. And when you look at</p> <p>20 what happened, they behaved differently.</p> <p>21       So when we're trying to put another</p> <p>22 trial together, we do want to include all the</p> | 276 |
| 275 | <p>1 patients. The question for us became, do we</p> <p>2 include them all in the one trial or do we</p> <p>3 actually have separate trials for them because we</p> <p>4 believe of these -- if you believe that all of</p> <p>5 these patients could benefit from your drug, then</p> <p>6 you have to actually do clinical trials and</p> <p>7 include all the patients.</p> <p>8       The question isn't do we need to do</p> <p>9 clinical trials in all the patients? The question</p> <p>10 is how do we design a trial so that we capture</p> <p>11 whether the drug works or not?</p> <p>12       When we looked at our trial, the non-CF</p> <p>13 MAC population appeared to respond in terms of</p> <p>14 their cultures much, much faster. The clinical</p> <p>15 trial was it wasn't long. It was three months,</p> <p>16 double-blind, then another three months, open</p> <p>17 label.</p> <p>18       In that time, if you really dig down and</p> <p>19 look at it, I can say that some of the M.</p> <p>20 abscessus patients look like if we gave them</p> <p>21 enough time, we may have seen something that we</p> <p>22 didn't. So the subpopulation that really stuck</p>      | 277 |
| 274 | <p>1 out and seem to do really well was the non-CF MAC</p> <p>2 population.</p> <p>3       When you're pioneering trials in this</p> <p>4 area like we are without -- it is a paucity of</p> <p>5 perspective controlled clinical trials. It's very</p> <p>6 difficult to draw your assumptions. And without</p> <p>7 assumptions, you're literally just stabbing in the</p> <p>8 dark.</p> <p>9       We have some assumptions, and that's why</p> <p>10 the current study that we're doing is a much</p> <p>11 narrower population. We'd love to do more studies</p> <p>12 and hopefully have the PROs ready to go when that</p> <p>13 happens.</p> <p>14       Also, we now experience with the</p> <p>15 narrower, the non-CF MAC, we didn't know what</p> <p>16 outcomes we were going to expect, that we're</p> <p>17 actually going to show something. And it happened</p> <p>18 to be that the 6-minute walk test that was in this</p> <p>19 trial, and we don't really know what that means at</p> <p>20 this moment other than we do have a separation.</p> <p>21 We did see a separation in the non-CF MAC</p> <p>22 patients. They seem to do much better.</p>                             | 277 |

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| 278 | <p>1 The tremendous successes that cystic<br/>2 fibrosis has had in terms of clinical trials, I<br/>3 think in large part, is related to the easy<br/>4 accessibility of those patients with them<br/>5 aggregated into clinical care centers and the<br/>6 willingness of the patients to participate, but<br/>7 that comes on the backs of what we see now of<br/>8 years of building excitement in that disease.<br/>9 We don't have all of the patients<br/>10 aggregated into geographically dispersed centers<br/>11 throughout the U.S. And again, we're very early<br/>12 on in development of trials. So trying to get<br/>13 that excitement to build, trying to get patients<br/>14 encouraged to participate to where we can get the<br/>15 types of timely accrual that we need, I think is<br/>16 an issue.<br/>17 When you're looking at things like MAC<br/>18 versus M. abscessus, there may be differences in<br/>19 right or wrong the perceived need of new drugs. I<br/>20 think many of us would agree that M. abscessus has<br/>21 a pressing need for something more effective to<br/>22 develop.</p>   | 280 |
| 279 | <p>1 When we actually sit down and look at<br/>2 the numbers that we have access to, if you say<br/>3 that these organisms are more important than the<br/>4 setting of cystic fibrosis, we can calculate<br/>5 fairly quickly, and I think fairly accurately, how<br/>6 many CF patients in the U.S. have these<br/>7 infections, and it's not very many.<br/>8 If you were going to try to design a<br/>9 trial of a drug to look at M. abscessus in cystic<br/>10 fibrosis, I think even in that disease where it's<br/>11 relatively easy to accrue, you're going to have<br/>12 problems, whereas MAC, I think that there may be<br/>13 more patients, especially non-CF patients, that<br/>14 have it. Finding those patients and getting them<br/>15 to participate may be a problem.<br/>16 When it comes to treatment-naïve versus<br/>17 treatment-experienced, I think it depends, again,<br/>18 the sort of stage that you're developing the drug<br/>19 in and what you're looking to show. If you're<br/>20 trying to introduce a novel drug into treatment-na<br/>21 MAC patients as part of a multidrug regimen, as<br/>22 David and Richard have discussed, the proportion</p> | 281 |

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| 282 | <p>1 trials in the wrong populations. The path to<br/>2 registration for new antibiotics now is in skin<br/>3 infections or UTI.</p> <p>4       It's not the challenge that we have, but<br/>5 because we have that path there, we're allowed to<br/>6 follow it because we know how to design the trials<br/>7 and select the populations because we've learnt<br/>8 from that. Now, we're sort of having to learn the<br/>9 difficult way of complex patients, very<br/>10 heterogeneous, heterogeneous rate of progression,<br/>11 and that really does challenge us.</p> <p>12       So I think hopefully in the next little<br/>13 while, there'll actually be some more flexibility<br/>14 in terms of design for an area where there's such<br/>15 a big need and being a little bit more flexible up<br/>16 front in terms of what has to be prespecified<br/>17 because otherwise, the number of patients and the<br/>18 overall cost, the amount of microbiology testing<br/>19 you have to do, really is a barrier for good<br/>20 studies.</p> <p>21       DR. GRIFFITH: I would like to just<br/>22 mildly dissent on a couple of points. In terms of</p> | 284 | <p>1 we've been discussing is patient accrual.<br/>2 Clearly, we're looking at multicenter trials. In<br/>3 anything that you talk about, you got to marshal<br/>4 all of the resources in the country to get the<br/>5 power to do statistical analysis. But there's no<br/>6 overlap in medicines between MAC and abscessus<br/>7 except perhaps the study medicine like Arikace.</p> <p>8       I, personally, I think the way that<br/>9 Insmed has approached the second trial makes<br/>10 sense, but I wish they would do another trial for<br/>11 abscessus. I'm all for treating them all. Why<br/>12 don't include simiae? Simiae is such a difficult<br/>13 bug to treat. Why don't we try a few simiae<br/>14 patients?</p> <p>15       Well, you're not going to lump them with<br/>16 MAC. But at any rate -- I'm sorry; that's just my<br/>17 thought on that. You know that you're going to<br/>18 separate them in your analysis regardless.</p> <p>19       DR. O'DONNELL: I just want to address<br/>20 the getting more patients into trials and<br/>21 spreading out our network because, clearly, from<br/>22 hearing from everybody today, that sort of makes</p> |
| 283 | <p>1 the 6-month waiting period, there are very clearly<br/>2 people who are symptomatic and have progressive<br/>3 disease at the time of their initial evaluation.<br/>4 And I think that there would be no benefit gained<br/>5 by asking those people to wait further for<br/>6 initiation of therapy. As a matter of fact, I<br/>7 think they'd go somewhere else.</p> <p>8       But I mean the routine for me is -- at<br/>9 least half of the people I see, I don't start on<br/>10 therapy at the initial visit, but within two or<br/>11 three months, I've got a pretty idea about whether<br/>12 or not they need therapy</p> <p>13 I just think 6 months is kind of rigid and a<br/>14 little bit long. Perhaps it could be -- I mean,<br/>15 maybe there's room to compromise in that.</p> <p>16       The point though about MAC and<br/>17 abscessus, they're totally different. If you go<br/>18 into it knowing that you're going to post hoc<br/>19 separate the analysis, why wouldn't you do it<br/>20 initially?</p> <p>21       I mean I understand that you have to<br/>22 have numbers. And that's really a lot of what</p>                   | 285 | <p>1 me feel sad for our profession that patients<br/>2 aren't getting diagnosed in a timely fashion.</p> <p>3       One thing we're trying to promote is<br/>4 this bronchiectasis research registry, which has<br/>5 an NTM component to it to try to get more patients<br/>6 involved, and actually a patient-powered network<br/>7 so patients themselves can register to potentially<br/>8 be in clinical trials.</p> <p>9       We've got to get this word out better.<br/>10 We're not doing a very good job, I would say, in<br/>11 getting patients. Patients in the room, great,<br/>12 but there's tons of other patients out there that<br/>13 we're not getting into clinical trials.</p> <p>14       The second thing I'd like to pick on a<br/>15 little bit is this treatment-naive patients<br/>16 because maybe we do need a trial in treatment-na<br/>17 patients.</p> <p>18       My clinical experience -- and I bet many<br/>19 of the patients will say rifampin is the hard drug<br/>20 for many patients in the current regimen. Maybe<br/>21 we need a trial that looks at something other than<br/>22 those three and substitute something else for</p>       |



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| 286 | <p>1 rifampin in that head-to-head trial.<br/> 2 I know Dave is giving me the evil eye<br/> 3 there, but I do think we're not -- we don't have<br/> 4 the final answer for treatment-napatients either.<br/> 5 DR. GRIFFITH: We discussed it briefly<br/> 6 at the meeting, where do you put your resources?<br/> 7 What's the priority of your questions? I mean<br/> 8 that's tough. Is that a question you want to take<br/> 9 a sizeable number of people to enroll in a trial<br/> 10 to answer when they might be in another trial?<br/> 11 It's a tough call.<br/> 12 DR. EAGLE: First of all, I want to just<br/> 13 reiterate that we actually do believe all these<br/> 14 patients need to be studied, and we're committed<br/> 15 to that.<br/> 16 Just with respect with the treatment-na<br/> 17 patients, I'm wondering if this is a time to talk<br/> 18 about separating that group into the cavitary<br/> 19 lesions versus not having cavitary lesions. And<br/> 20 the reason for that is because without cavitary<br/> 21 lesions, the current standard of care has a high<br/> 22 success rate, which makes the sample size that you</p> | 288 | <p>1 might want to consider two trials with different<br/> 2 patient populations with different timings of<br/> 3 endpoints.<br/> 4 Karen Higgins, I invited on the panel,<br/> 5 make sure I don't say something heretical.<br/> 6 (Laughter.)<br/> 7 DR. FARLEY: She's from the Office of<br/> 8 Biostatistics. But I would think that if both of<br/> 9 those trials were successful, they could support<br/> 10 each other, and you then have a package of<br/> 11 substantial efficacy.<br/> 12 I know that funding is limited, et<br/> 13 cetera, but that's something that has been<br/> 14 effective in other infectious disease areas as far<br/> 15 as getting to approval.<br/> 16 DR. HIGGINS: Just very briefly, this<br/> 17 could also be done, these two trials kind of under<br/> 18 an umbrella protocol where the two trials are<br/> 19 considered separate, but for logistical reasons,<br/> 20 it would be easier to potentially enroll patients<br/> 21 and put them in the trial that's best for them.<br/> 22 DR. DALEY: Can I just comment? We</p>  |
| 287 | <p>1 need for your trial in this disease almost<br/> 2 impossible to achieve in a reasonable period of<br/> 3 time.<br/> 4 DR. FARLEY: Just a few comments from<br/> 5 somebody who sees development in a bunch of<br/> 6 different drug areas, but doesn't know very much<br/> 7 about NTM.<br/> 8 Just to underscore what Dr. O'Donnell<br/> 9 said, it seemed to me that in the CF world that<br/> 10 having that registry data is very, very helpful to<br/> 11 trial designers in terms of understanding the<br/> 12 optimal timing of endpoints with patients with<br/> 13 certain characteristics, et cetera. Just to sort<br/> 14 of underscore that that's a very important effort,<br/> 15 I think, based on my own observation, it really<br/> 16 helped them move forward.<br/> 17 I think one of the things just to point<br/> 18 out is that if the patient population is<br/> 19 heterogeneous enough that there are groups of<br/> 20 patients where one expects the optimal timing of<br/> 21 the endpoint to be better -- this is not an FDA<br/> 22 opinion; it's just my personal opinion -- that one</p>                                  | 289 | <p>1 don't have enough patients to do that, and the<br/> 2 need is so great. You know how many examples in<br/> 3 medicine where that's what the company said they<br/> 4 were going to do, and they didn't do it. And it's<br/> 5 left to the clinician to work off label with no<br/> 6 data.<br/> 7 So when we have a chance to enroll<br/> 8 patients who have a great need, we need to rethink<br/> 9 that, I think. And it may not be perfect, but I<br/> 10 still think it's a really important issue that we<br/> 11 go and we study non-CF because there's more of<br/> 12 them, and then we just don't study CF because it's<br/> 13 approved and everyone says, now, CF Foundation,<br/> 14 you go pay for that, or academia, you pay for<br/> 15 that.<br/> 16 I think that they're all sitting in the<br/> 17 same clinic, usually in the same hospitals, so<br/> 18 there's a real strong argument mainly based on<br/> 19 need to get them studied early, not later.<br/> 20 This 6-months is an example of trying to<br/> 21 use some kind of marker of progression. It could<br/> 22 be you use the previous 6 months, too, to be able</p> |

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| 290 | <p>1 to identify progression. That's really all I was<br/>2 saying.</p> <p>3 One thing that I think is another issue<br/>4 that's really important whether you decide to do a<br/>5 separate trial for abscessus or MAC, recognize<br/>6 that in our study of abscessus, 55 percent of the<br/>7 patients also had MAC concurrently or previously.<br/>8 This is a problem in terms of trying to figure out<br/>9 how to design a study to look for efficacy when<br/>10 there's so much recurrence and reinfection.</p> <p>11 DR. WINTHROP: And also, I'll add a lot<br/>12 of them have Pseudomonas, and they have<br/>13 Aspergillus, and they have Stenotrophomonas and<br/>14 everything else growing in there, so it does get<br/>15 complicated.</p> <p>16 DR. NAMBIAR: So I think we've heard<br/>17 quite different viewpoints on this issue. It<br/>18 hasn't made our life any easier, but I can see the<br/>19 merits of doing a study, which is sort of an all-<br/>20 comer population, so you haven't really restricted<br/>21 to one subgroup versus the other. I think that<br/>22 makes a lot of sense in terms of extrapolating to</p> | 292 | <p>1 is that I think it depends on what the question is<br/>2 a bit, right? And we're all kind of talking about<br/>3 the same thing, but no one is articulating the<br/>4 question.</p> <p>5 If the question is, does the drug kill<br/>6 NTM, that's a different question than, does the<br/>7 drug make CF better; does the drug make non-CF<br/>8 bronchiectasis better? These are different<br/>9 questions, and so are going to potentially use<br/>10 different measurements of efficacy for those<br/>11 individual groups; you might study them different<br/>12 lengths. That's why we are tempted to segregate.</p> <p>13 But again, if your question is, does the<br/>14 drug kill mycobacterium, it might kill it to a<br/>15 different extent or over different time periods in<br/>16 different subgroups of people. But if your<br/>17 ultimate questions is, does the drug kill<br/>18 mycobacterium in a human body, you can lump all<br/>19 those groups together.</p> <p>20 Again, I'm just saying it depends on<br/>21 what the question is. I know we're getting to<br/>22 that next here, what is the endpoint that we're</p> |
| 291 | <p>1 the larger population. But from a practical<br/>2 standpoint, I think it does pose some challenges.</p> <p>3 Dr. Wallace, I think you had a question<br/>4 earlier about whether the study was being done for<br/>5 safety or efficacy. I think the discussion here<br/>6 primarily is about assessing the efficacy and<br/>7 really deciding if a new therapy works or not.</p> <p>8 Our focus here was more in the context<br/>9 of an efficacy trial, but I think your point is<br/>10 valid, not that it's not important but becomes<br/>11 less of an issue with safety studies.</p> <p>12 We will get some safety obviously from<br/>13 these efficacy trials, but sometimes if the<br/>14 numbers end up being small, the treatment effect<br/>15 is large and the sample size may be smaller, then<br/>16 we might ask for a separate study primarily<br/>17 focused on safety. We'll collect some efficacy<br/>18 data, but it's not powered for any kind of<br/>19 efficiency assessment.</p> <p>20 DR. WINTHROP: Can I just add one thing?<br/>21 DR. NAMBIAR: Sure.<br/>22 DR. WINTHROP: The only thing I'll add</p>                     | 293 | <p>1 actually trying to ascertain?</p> <p>2 DR. NAMBIAR: I think the basic question<br/>3 is does it make the patient feel better? I think<br/>4 that's what we're trying to get to. Along the<br/>5 way, hopefully, it's also killing the NTM and then<br/>6 making the patient better. So it's more than just<br/>7 killing the organism. I think that's what we're<br/>8 trying to find out.</p> <p>9 DR. WINTHROP: Then the next question<br/>10 is, is killing the organism a surrogate for<br/>11 actually feeling better and living longer?</p> <p>12 DR. NAMBIAR: Right. So I think you --<br/>13 DR. WINTHROP: And that's really what we<br/>14 cared about.</p> <p>15 DR. NAMBIAR: So that's sort of the next<br/>16 question. Maybe that's a good way to start the<br/>17 discussion on the endpoint, I think Dr. O'Donnell.</p> <p>18 DR. O'DONNELL: I think that's a good<br/>19 question for Alexandra, how can we correlate the<br/>20 PRO with organism-killing. Can we for the semi-<br/>21 quantitative cultures or something? Can we do<br/>22 something like --</p>  |

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| 294 | <p>1 DR. QUITTNER: You definitely can<br/>2 correlate them. In the CFQ-R studies I've worked<br/>3 on, we did that. We would correlate change in<br/>4 respiratory symptoms with changes in microbiology.<br/>5 The FDA, of course, isn't interested in the<br/>6 microbiology as the primary but it definitely<br/>7 correlated. So with greater killing, we saw<br/>8 better symptom improvement. You can also<br/>9 correlate it with the 6-minute walk. We've done<br/>10 those kinds of studies. Yes, if you have a good<br/>11 respiratory or symptom scale, you can do that.<br/>12 DR. WALLACE: You know, I can't think of<br/>13 another disease in which we briefly talked about<br/>14 in which you have two diseases active on the same<br/>15 part of the body producing the same symptoms, and<br/>16 then you're trying to do a PRO.<br/>17 I mean these are people with<br/>18 bronchiectasis. Even if they don't have another<br/>19 identified tough pathogen and you have an NTM,<br/>20 both functional, both inflammatory, both -- and<br/>21 going through the symptoms, if your bronchiectasis<br/>22 stays calm, the PRO for the NTM will probably be</p> | 296 | <p>1 raising just a really amazingly great point. One<br/>2 thing I'd been thinking about this whole day is<br/>3 one of the advantages that we actually might have<br/>4 -- and we would need to talk to our statisticians<br/>5 and things like that -- but we do have a very<br/>6 well- validated respiratory symptom scale that's<br/>7 particular to CF and has proven efficacy, as well<br/>8 as the respiratory scale on the QOL-B. They're<br/>9 different. They actually reflect the different<br/>10 respiratory symptoms of bronchiectasis versus CF.<br/>11 One thing that would be interesting and<br/>12 perhaps an answer to this problem is to be<br/>13 examining both the respiratory symptom scale,<br/>14 which differ by disease, and the NTM module, which<br/>15 focuses in much more in what Kevin is saying.<br/>16 That might enable us to see -- if the<br/>17 respiratory symptoms are going up, that might be a<br/>18 sense that they colonize with Pseudomonas. That<br/>19 might be one way we could actually get around that<br/>20 problem. And I agree with you, it's complex.<br/>21 DR. GRIFFITH: I would just add in our<br/>22 paper on the semi-quantitative sputum cultures,</p> |
| 295 | <p>1 great. But if they're having lots of trouble --<br/>2 they grow Staph several times or in the middle of<br/>3 this stuff. And if you count it negatively against<br/>4 them because they didn't show a response when, in<br/>5 fact, the problem was bronchiectasis.<br/>6 It's such an unusual circumstance. We<br/>7 just have to think about the PRO and how to make<br/>8 it work when you have two diseases that are active<br/>9 at the same time.<br/>10 DR. WINTHROP: I agree with Richard.<br/>11 That's why I think killing NTM may be a surrogate<br/>12 for better living for some of these people, but it<br/>13 may not be for other people; not that it might be<br/>14 harmful but it just may not have the same effect.<br/>15 DR. WALLACE: I mean, there are people<br/>16 who come in after you've eradicated their MAC at<br/>17 the end of the treatment course and say they feel<br/>18 worse. That's because they have another disease<br/>19 going on at the same -- now, that doesn't mean<br/>20 that if we did enough numbers or whatnot, that<br/>21 overall that they would look better.<br/>22 DR. QUITTNER: Well, I think you're</p>          | 297 | <p>1 Kevin, the people who converted within 6 months,<br/>2 half of them had a bronchiectatic exacerbation<br/>3 during that 6-month period. For the people who<br/>4 took longer than 6 months, it was almost 80 or 90<br/>5 percent.<br/>6 There's no question that the<br/>7 bronchiectatic symptoms are going to complicate<br/>8 the deal. If you can separate them out, I mean<br/>9 that would be really helpful.<br/>10 DR. WALLACE: I mean it's a cheap test.<br/>11 I mean, you know, we just have to fill out some<br/>12 forms or paperwork, and it'd be very informative.<br/>13 We haven't done it. We're assuming that it won't<br/>14 help, but I mean I'd rather do it than not do it.<br/>15 These are great patients. I mean there<br/>16 are only a few things that keep them from saying -<br/>17 - they always want to be in trials. I mean<br/>18 virtually every one of them and it's only<br/>19 characteristics of travel or a little bit of<br/>20 reservations about being in the placebo side that<br/>21 keep them from being involved. I mean, I bet<br/>22 they'd fill out those forms in a second.</p>  |

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| 298 | <p>1 DR. GRIFFITH: I think another<br/>2 complication is the toxicity of the drug and how<br/>3 that complicates how the patient feels. If you<br/>4 just take the example of an inhaled drug that<br/>5 might have airway toxicity, that if the<br/>6 mycobacteria is killed, it may eventually make<br/>7 them feel better; it may increase their functional<br/>8 status; it may make them live longer in the long<br/>9 run, but during the period that they're inhaling<br/>10 the drug, they may cough more; they may wheeze<br/>11 more; they may feel more short of breath.<br/>12 It becomes very difficult to tease out<br/>13 exactly what's causing that PRO when you throw<br/>14 that complicating factor into it as well. It can<br/>15 be any toxicity for any drug that might affect<br/>16 that particular part of the PRO.<br/>17 DR. DANIELS: I agree. It's going to be<br/>18 hard to discern disease-related symptoms versus<br/>19 treatment-related symptoms, and that might be<br/>20 another module that needs to be added into a<br/>21 questionnaire to maybe try to get to that and<br/>22 tease that out.</p>              | 300   |     |
| 299 | <p>1 DR. FARLEY: That's a good point. Just<br/>2 to bring up -- because I know you've been talking<br/>3 a lot about how these patients are complicated;<br/>4 they have a variety of risk factors; they're<br/>5 somewhat heterogeneous. But remember that<br/>6 randomization is a wonderful thing. And that if<br/>7 it works, the risk factors should be relatively<br/>8 even between the arms.<br/>9 I think one of the things related to the<br/>10 Chuck -- we'll talk about the "Chuck Approach" --<br/>11 is that it points out to me that -- if you are<br/>12 going to have a very heterogeneous trial, it might<br/>13 be important to stratify at enrollment so that you<br/>14 make sure that you've got your risk factors<br/>15 balanced between arms.<br/>16 DR. DALEY: This brings up another<br/>17 reason to follow the "Chuck Approach." One of the<br/>18 things that we have noted at National Jewish --<br/>19 and I'm sure all my colleagues have -- is that if<br/>20 someone comes in with bronchiectasis and<br/>21 mycobacterial infection, if we introduce airway<br/>22 clearance, their cough will improve within 2</p> | <p>1 weeks, 3 weeks, a month.<br/>2 If this is a multicenter study, if that<br/>3 varies across centers, how aggressive you do<br/>4 airway clearance, which approach you use, do you<br/>5 prevent reflux from occurring, then that<br/>6 randomization may get screwed up because you can't<br/>7 randomize practice.<br/>8 If you had a period where you started a<br/>9 certain protocol like a run-in airway clearance,<br/>10 check that PRO instrument to see how much better<br/>11 the symptoms got with that intervention before you<br/>12 started the antibiotics, it would clean it up.<br/>13 That's all I can tell you. It would clean up the<br/>14 ability to understand how symptoms change with<br/>15 antibiotic therapy.<br/>16 DR. WALLACE: Couldn't you just try to<br/>17 standardize the pulmonary care that you gave them<br/>18 across -- I mean it clearly means something that<br/>19 your attention should be paid to it, and should<br/>20 not be left to just each institution to do it the<br/>21 same way.<br/>22 I mean the only way it would work is if</p> | 301 |

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| 302 | <p>1 start to put your pivotal trials together and you<br/>2 need to power them up with a sizeable number of<br/>3 patients, you're reaching out to a large number of<br/>4 sites.<br/>5 We already heard today a number of times<br/>6 that once you start moving away from the experts<br/>7 in this room, it becomes very difficult to have<br/>8 the same type of care. You need to recruit your<br/>9 patients in a reasonable amount of time, and these<br/>10 are the real life challenges that we have, and<br/>11 they're very real.<br/>12 DR. O'DONNELL: I think we saw today<br/>13 that when the room was surveyed, only 57 percent<br/>14 of people were using airway clearance in this<br/>15 room. But I think what Chuck proposes is possible,<br/>16 like a 2-week run-in, just use a device, not<br/>17 anything more complicated than that. That could<br/>18 be done. I think hypertonic saline and all that<br/>19 kind of thing is more complicated.<br/>20 DR. EAGLE: I was going to bring up one<br/>21 more thing just as a difficulty because of the<br/>22 toxicities of the medications during the</p>  | 304 | <p>1 Do you do this on treatment? Do you<br/>2 take a break after treatment to make sure things<br/>3 have gotten better? We welcome your thoughts on<br/>4 that.<br/>5 DR. QUITTNER: I mean, this is a very<br/>6 important point. I can tell you for antibiotics<br/>7 in cystic fibrosis quite well because I've worked<br/>8 on so many clinical trials in that area. One of<br/>9 the really important things we did in those<br/>10 studies, which I don't think would work here --<br/>11 the run-in, I think, is a good idea and measure<br/>12 the PRO -- is that I told the various studies to<br/>13 be sure to measure, of course, baseline, but 2<br/>14 weeks into the antibiotic, because we were fairly<br/>15 certain that it would have a lot of efficacy at a<br/>16 month.<br/>17 These were shorter studies obviously.<br/>18 These are in the days when the CF studies were<br/>19 much shorter. But I told them measure at 2 weeks<br/>20 because my sense of doing other smaller studies<br/>21 was that the efficacy was really there at 2 weeks.<br/>22 So we actually did baseline 2 weeks. In</p> |
| 303 | <p>1 treatment, and right now, following the<br/>2 guidelines, while the patient has a negative<br/>3 sputum, you still need to continue treating them.<br/>4 And it's for a long time. It's 12 months after you<br/>5 have that first negative culture.<br/>6 So the best time is probably to look at<br/>7 a PRO or any other measure of function, once you<br/>8 have durability of that treatment success. But<br/>9 the challenge is, you're facing a trial that has<br/>10 an outcome like years from when you start.<br/>11 In a disease area where you need to<br/>12 maybe fast track whether you know something is<br/>13 working or not, it just becomes very challenging<br/>14 to do that. Although, in our trial, we are looking<br/>15 at these. I mean we're looking at function, and<br/>16 we're looking at the sputum 3 months out from<br/>17 treatment success for that very reason.<br/>18 DR. NAMBIAR: Dr. Quittner, would you<br/>19 have any thoughts on what might be the right time<br/>20 to use the PRO to make a final assessment if the<br/>21 patient is getting better or not? I think as Dr.<br/>22 Eagle said, usually treatment is long.</p> | 305 | <p>1 every study that was approved and successful, they<br/>2 saw the improvement at 2 weeks. And then we<br/>3 measured it again in a month. And then if they<br/>4 were going to take them off the drug, we waited a<br/>5 month later.<br/>6 This is obviously a different paradigm<br/>7 where it takes a lot longer, but what Chuck was<br/>8 suggesting was sort of a baseline run-in, 2-week<br/>9 or 1-month point. And then where is it that you<br/>10 really think these drugs -- which we haven't<br/>11 talked about which ones -- where do they have<br/>12 their maximum efficacy? Is that 6 months; is it a<br/>13 year? And you measure it at that point as well.<br/>14 And then if you're going to take them off or<br/>15 you're going to wait, you have a follow-on.<br/>16 So what would that endpoint be? Where<br/>17 would you all, the practitioners, say is what you<br/>18 believe you get efficacy at that point?<br/>19 DR. DALEY: Don't look at me.<br/>20 (Laughter.)<br/>21 DR. NAMBIAR: That takes us right into<br/>22 the timing of the endpoint. Maybe before we go</p>                  |

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| 306 | <p>1 into timing, I was wondering if there are any more<br/>2 comments on the microbiologic endpoint, any other<br/>3 thoughts from the panel on the merits, demerits,<br/>4 the timing of the endpoint, whether it's one<br/>5 culture, two cultures, three cultures, what the<br/>6 interval must be between these various sputum<br/>7 cultures and also the merits of doing a culture a<br/>8 certain time point after treatment has stopped and<br/>9 how long that might be because 3 months has been<br/>10 chosen as fairly arbitrary. Is there any science<br/>11 behind it? We welcome any discussion on that<br/>12 topic as well.<br/>13 DR. WALLACE: Let me divert a little<br/>14 bit. I mean I've listened to -- Hala and I<br/>15 discussed semi-quantitative sputum cultures and<br/>16 its dilemma. There still may be some in-between<br/>17 points that you might be able to analyze, for<br/>18 example, positive on solid in-broth media versus<br/>19 positive in broth-only. In a way, it's semi-<br/>20 quantitative, but not as we discussed.<br/>21 I mean we find it useful because we<br/>22 usually can measure what's happening to the</p> | 308 |
| 307 | <p>1 patient, although we can't tell when they're going<br/>2 to convert or whatnot. But maybe that would be<br/>3 some sort of semi-quantitative --<br/>4 It's better than broth-alone, which I<br/>5 found very distasteful because you have such a<br/>6 huge range of potential possibilities in terms of<br/>7 the number of the organisms that are growing. You<br/>8 can be 4 plus and still be 4 plus, or you can be 4<br/>9 plus down to 5 colonies, which is an enormous<br/>10 response, and the report would still be the same,<br/>11 positive in broth.<br/>12 DR. NAMBIAR: Are there any practical<br/>13 considerations in terms of all labs being able to<br/>14 do this kind of semi-quantitative testing? I<br/>15 understand that your group is very comfortable or<br/>16 has been doing it, but I don't get a sense that<br/>17 that's true across --<br/>18 DR. WALLACE: But I think they all do.<br/>19 Virtually, all of them culture in an agar median<br/>20 broth. I mean that's the recommended standard in<br/>21 the U.S. Now, for the European studies, do they<br/>22 do it in agar broth too?</p>                                       | 309 |
|     | <p>1 FEMALE SPEAKER: Yes.<br/>2 DR. WALLACE: So you couldn't get counts<br/>3 but you could at least report it. That's our main<br/>4 issue, is in Europe where they do not. I guess in<br/>5 Australia too, they don't. They don't do counts<br/>6 so --<br/>7 DR. EAGLE: They culture it in the two<br/>8 media, but they don't use the scale and define the<br/>9 steps the way that you have defined them. That's<br/>10 the only difference.<br/>11 DR. WALLACE: And actually, many labs --<br/>12 this is very interesting. Virtually, all labs do<br/>13 it, but virtually, all labs don't report it. I<br/>14 mean, it's the check for contamination; it's the<br/>15 check for mix cultures, so it has its values, but<br/>16 no one has recommended reporting it, so they don't<br/>17 do it. It's there; you just have to ask for it.<br/>18 DR. NAMBIAR: Hala, you had a comment?<br/>19 DR. SHAMSUDDIN: Other than semi-<br/>20 quantitative cultures, have you looked at time to<br/>21 positivity in broth?<br/>22 DR. WALLACE: I don't know that we've</p>  |     |

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| 310 | <p>1 I think one thing to keep in mind is sampling<br/>2 variability. There are a couple of issues on<br/>3 that. I think the confidence you can have in one<br/>4 negative culture is a lot less than you would have<br/>5 in, say, three consecutive negative cultures.<br/>6 That's why I think the sort of terminology even<br/>7 though it may not be definitively defined in terms<br/>8 of culture conversion is a bit more attractive.<br/>9 The other thing to kind of get around<br/>10 that is the collection of multiple specimens, and<br/>11 that actually ended up working quite well in the<br/>12 Insmed trial in that for each time point, we had<br/>13 at least two, and in most cases, three cultures<br/>14 that were obtained either at the clinic or from<br/>15 home collection that allowed us to sort of compare<br/>16 the consistency of whatever finding we were having<br/>17 at that time point.<br/>18 I think when we're building these<br/>19 studies, having some redundancy in that and having<br/>20 more confidence in whatever culture-based endpoint<br/>21 we're determining, I think, was very helpful.<br/>22 DR. DALEY: I was going to say at</p> | 312 | <p>1 DR. NAMBIAR: Right. That's the next --<br/>2 DR. O'DONNELL: Yes, so it's kind of<br/>3 like either we're going to have to go with the<br/>4 positive/negative and then define the number,<br/>5 because we really don't have a correlation between<br/>6 quantitative cultures and disease state, I don't<br/>7 think. Maybe Dave and Richard do --<br/>8 DR. GRIFFITH: I was going to say we did<br/>9 correlate -- they did predict sputum conversion,<br/>10 the improvement in semi-quantitative sputum<br/>11 scores. They also correlated with symptomatic<br/>12 improvement. Now, it was gross. We looked at<br/>13 better or worse, but there was a good correlation<br/>14 in semi- quantitative culture improvement and<br/>15 symptom improvement.<br/>16 DR. DALEY: And I was just going to say<br/>17 I applaud them for doing this because actually, I<br/>18 think that study was extremely important to be<br/>19 able to do that. Now, the issue is, can it be<br/>20 done across multiple laboratories? Can they all<br/>21 get the same kind of results?<br/>22 DR. OLIVIER: I think the other issue is</p>                       |
| 311 | <p>1 National Jewish, we do this same as Richard's lab<br/>2 in terms of the semi-quantitative. The issues<br/>3 here are just so basic. It's sample collection,<br/>4 but it's also processing, too, that's very<br/>5 important.<br/>6 A lot of these patients have co-<br/>7 pathogens and require significant decontamination<br/>8 of the specimen. That greatly reduces the colony-<br/>9 forming units of the NTM, and that's going to<br/>10 vary. That's why it actually is different than TB<br/>11 in this regard.<br/>12 Where in TB, we have really quite a lot<br/>13 of good data about the consistency of CFU over<br/>14 time; it's not that way in NTM. At least, it<br/>15 doesn't appear to be. Even though it sounds good,<br/>16 I think there are some really basic<br/>17 standardization that would have to occur across<br/>18 labs to get to the same place that TB is in terms<br/>19 of being able to use these cultures and try to<br/>20 quantify or semi-quantify the counts over time.<br/>21 DR. O'DONNELL: We also don't know how<br/>22 it correlates with the extent of disease or --</p>   | 313 | <p>1 the species you're dealing for reasons that you<br/>2 raised for M. abscessus and the susceptibility,<br/>3 the decontamination process, having consistency in<br/>4 that semi-quantitation may be very different than<br/>5 what you see in MAC.<br/>6 DR. WALLACE: We're just reminding<br/>7 ourselves that Australia, Europe, and the U.S.,<br/>8 for the current trial, only has a single central<br/>9 lab so you don't have the issues of smaller labs,<br/>10 all of which are very experienced, long term doing<br/>11 these. You would be doing the best you could to<br/>12 minimize those issues that might occur if you used<br/>13 smaller labs or less experienced labs.<br/>14 DR. NAMBIAR: So it totally sounds like<br/>15 there are some issues purely from a microbiology<br/>16 standpoint, some of them we could potentially<br/>17 address but some of them, we just have to live<br/>18 with and see how to work with the information<br/>19 available.<br/>20 But I think the bigger and an important<br/>21 question is I think what Dr. Winthrop had brought<br/>22 up earlier is, how does a micro endpoint translate</p> |

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| 314 | <p>1 to clinical outcome, whether it be a semi-<br/>2 quantitative -- and it's encouraging that we at<br/>3 least have data from one institution. Whether<br/>4 that may hold true in other institutions and other<br/>5 settings, it remains to be seen.<br/>6 But if we do use microbiologic endpoint<br/>7 as a surrogate, we have to be at least comfortable<br/>8 to some degree that it reliably predicts clinical<br/>9 benefit. I mean, that's the basic definition of a<br/>10 surrogate endpoint as Dr. Shamsuddin had outlined<br/>11 in her presentation.<br/>12 We welcome your thoughts on how you<br/>13 think there is correlation, whether we define it<br/>14 based on sputum culture conversion or whether it's<br/>15 a semi-quantitative measure or saying the<br/>16 bacterial load has decreased.<br/>17 But if it does translate into clinical<br/>18 benefit, what might that clinical benefit look<br/>19 like? Is it a mortality benefit? Is it<br/>20 symptomatic benefit? I think that's a big<br/>21 question we have to deal with in terms of deciding<br/>22 whether it's a primary endpoint, an exploratory</p>          | 316 | <p>1 here, have long periods of treatment.<br/>2 Amongst those patients, the majority had<br/>3 fibrocavitary disease or at least the presence of<br/>4 cavitary lesions, so we were looking at a specific<br/>5 population. So in terms of separating out the<br/>6 things that I'm talking about, we were looking at<br/>7 one end of that spectrum.<br/>8 DR. O'DONNELL: But don't you have the<br/>9 QOL-B and the cultures at the same time?<br/>10 DR. EAGLE: We did do the QOL-B, and we<br/>11 did not see anything significant. It might have<br/>12 been a function of the time in which we were<br/>13 looking at that endpoint. There was some sort of<br/>14 a trend within the patients who received OAI for<br/>15 like activities and things like that. But I<br/>16 really wouldn't draw any conclusions.<br/>17 We didn't have anything that we saw on<br/>18 these measures, so we couldn't correlate that with<br/>19 anything as a result. The study was a short study<br/>20 in terms of the double-blind phase, where you<br/>21 would like to assess the difference between active<br/>22 and placebo.</p> |
| 315 | <p>1 endpoint, or a secondary endpoint. We welcome<br/>2 your thoughts on that topic.<br/>3 DR. O'DONNELL: Insmed trial, don't you<br/>4 have culture and QOL-B?<br/>5 DR. EAGLE: Yes. One of the things that<br/>6 I would say as the first statement would be it<br/>7 depends on the population and where that<br/>8 population is in terms of the progression of the<br/>9 disease. If somebody has severely progressive<br/>10 disease with very limited functional capacity, I'm<br/>11 not sure eradication of the organism is going to<br/>12 make that much difference to that, whereas your na<br/>13 patient who's just recently treated may actually<br/>14 get the most benefit from a PRO or from a<br/>15 functional. I mean, I would put that out there to<br/>16 everybody to address that question.<br/>17 With respect to our experience in our<br/>18 trial, we actually enrolled a population of<br/>19 patients that had refractory disease in that they<br/>20 weren't responding to standard of care treatment,<br/>21 and many of those patients, up to half of them,<br/>22 had more than two years, much like the patients</p> | 317 | <p>1 DR. OLIVIER: I mean, this is an area<br/>2 where despite and just like the 6-minute walk, I<br/>3 think having some functional assessment in there,<br/>4 I think, is very important. It can be very<br/>5 difficult to tease out, especially in the short<br/>6 term how the drug may make you feel better.<br/>7 But if you can show that the drug<br/>8 increases your functional ability, that may have<br/>9 meaning that eventually, the symptoms would catch<br/>10 up from that. Again, it depends a lot on the<br/>11 toxicity of the drug.<br/>12 DR. EAGLE: Because we did see a<br/>13 difference in the 6-minute walk test, we could<br/>14 correlate it, and it did correlate with the<br/>15 microbiological outcomes.<br/>16 DR. NAMBIAR: Microbiologic endpoint<br/>17 itself might be problematic but if one could<br/>18 couple it with some kind of a clinical outcome --<br/>19 DR. OLIVIER: Right. But we are dealing<br/>20 with antibiotics. And as a first step, if the<br/>21 drug doesn't kill the bug, unless it's got some<br/>22 magical properties like the macrolides do, it's</p>            |



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| 318 | <p>1 unlikely going to have a significant effect on the<br/>2 outcome of the disease.<br/>3 DR. NAMBIAR: But if you do look at<br/>4 clinical outcome in the short term, and 6-minute<br/>5 walk test has come up as an example which, again,<br/>6 has some who like it and some who don't like. And<br/>7 we heard from patients this morning as well that<br/>8 their results on the 6-minute walk test could be<br/>9 highly variable depending on what day it's<br/>10 administered and how they were feeling on that<br/>11 particular day.<br/>12 But again, we don't have a lot of good<br/>13 clinical outcome measures here. So maybe the 6-<br/>14 minute walk test is a starting point. We have to<br/>15 start somewhere and sort of build up on it.<br/>16 We've heard about the use of FEV1, which<br/>17 might be more relevant in a CF population, but I<br/>18 think Dr. O'Donnell mentioned it may not be very<br/>19 helpful in a non-CF patient populations.<br/>20 Are there any other clinical endpoints<br/>21 one could think of besides the 6-minute walk test<br/>22 or an FEV1, a pulmonary function test, which is</p>                              | 320 | <p>1 FEV1 in non-CF bronchiectasis is not correlated<br/>2 well enough that I think it could be used in a<br/>3 trial, anything more than a secondary outcome.<br/>4 DR. OLIVIER: I mean, in our recent look<br/>5 at sort of mortality predictors, it looked almost<br/>6 absolutely useless. We had patients who died with<br/>7 very well preserved FEV1s. Many of the patients<br/>8 came into the follow up period with very high<br/>9 FEV1s, and it didn't seem to correlate well with<br/>10 mortality at all.<br/>11 It's not to exclude PFTs in general. I<br/>12 mean there may be other factors and maybe<br/>13 something like diffusing capacity that might<br/>14 reflect changes in pulmonary vascular involvement<br/>15 that may explain some of the reason why 6-minute<br/>16 walk may be responsive, may be important. But<br/>17 FEV1 in and of itself does not look like a very<br/>18 good predictor, at least not in our hands.<br/>19 DR. WALLACE: I think we need to move on<br/>20 or we'll never eat dinner. Well, there are some<br/>21 other questions especially under the definition of<br/>22 the sputum conversion, all that kind of -- like we</p> |
| 319 | <p>1 probably more helpful to CF population? Is there<br/>2 anything else, from a clinical standpoint, you<br/>3 have found helpful?<br/>4 DR. WINTHROP: I don't know of anything<br/>5 else existing. I think there's a need to develop<br/>6 more combined disease activity measures, and<br/>7 that's something we should do as we go through all<br/>8 these trials together. So those would include<br/>9 objective things, as well as subjective measures.<br/>10 DR. DALEY: I would say that in CF where<br/>11 we know the FEV1 is a very important marker to<br/>12 follow and -- but in NTM, even in CF, we don't<br/>13 know that if you treat them, you reserve that<br/>14 trend of downward with it. There are anecdotes,<br/>15 but in terms of -- even CF where FEV1 has been<br/>16 very useful. In non-CF bronchiectasis, I think<br/>17 FEV1 has not been very useful as a marker of -- I<br/>18 mean, people come in; the CT is better; the micro<br/>19 has been negative for a year, but their FEV1 is<br/>20 worse, and you're trying to figure out how does<br/>21 that -- it just doesn't correlate.<br/>22 My personal clinical experience is that</p> | 321 | <p>1 said -- like Anne said, we haven't -- I mean, it<br/>2 might be we'd all agree on them, but we at least<br/>3 need to bring them up --<br/>4 DR. NAMBIAR: Right. I think it might<br/>5 be more to we need to learn more about it when we<br/>6 have these trials; we use them as exploratory<br/>7 endpoints. That might be the best way to learn<br/>8 about them.<br/>9 I think in the interest of time, we need<br/>10 to keep moving. If there are no other comments<br/>11 about endpoints, I thought we could spend a few<br/>12 minutes talking about -- I skipped number 2<br/>13 because I think everyone was so eager to get the<br/>14 endpoint discussion, and so I jumped ahead. If we<br/>15 could talk about use of controls, if they have to<br/>16 be active control or is there any place for<br/>17 placebo-controlled trials.<br/>18 I think that then ties us back to the<br/>19 patient population because it might be feasible in<br/>20 a certain subgroup of patients to do a placebo-<br/>21 controlled or a delayed therapy option. So I<br/>22 would welcome your thoughts on controlled --</p>  |

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| 322 | <p>1 DR. WINTHROP: Yes, I'm glad you went<br/>2 back to number 2 because I think it's really<br/>3 important, and I think it reflects how we'd answer<br/>4 number 3.<br/>5 I might get yelled at by my colleagues.<br/>6 I know have been before. But I'm a big fan of<br/>7 placebo-controlled trials to show that your drug<br/>8 actually does something. While we've heard over<br/>9 and over again today that this is not TB, this is<br/>10 not TB, pretty much everything we've heard up here<br/>11 about trial design has been about TB, and we have<br/>12 approached it similarly.<br/>13 I think TB is very different as well. I<br/>14 mean, we're all in agreement on that. You can't<br/>15 really do a monotherapy trial against placebo and<br/>16 TB. Obviously, you can't. Patients with TB have<br/>17 to be treated. It's a public health concern, and<br/>18 then there's also the patient concern.<br/>19 A lot of people with NTM, as Chuck<br/>20 mentioned and Dave seconded and we've all talked<br/>21 about, don't need to be treated yet. You have<br/>22 this huge pool of NTM. I don't know what</p> | 324 | <p>1 infectious diseases because there's an imperative<br/>2 to treat it right away.<br/>3 DR. O'DONNELL: I thought you had the<br/>4 primate model that we could test this on.<br/>5 DR. WINTHROP: We do, yes.<br/>6 DR. O'DONNELL: Because I think you're<br/>7 right. I mean you hear about people being on<br/>8 quinolones, and you heard about linezolid. And we<br/>9 really don't have any data, right, very good data<br/>10 for stuff that's being done.<br/>11 DR. WINTHROP: I agree. The other issue<br/>12 is why haven't we approached this like<br/>13 bronchiectasis? I mean, for at least a subgroup<br/>14 of people with non-CF bronchiectasis, why aren't<br/>15 we thinking about treating the disease, at least<br/>16 studying the therapies in a similar fashion? I<br/>17 mean those are all monotherapy trials.<br/>18 You got people that are infected with<br/>19 something and you give them something to see what<br/>20 it does to them, or at least does to their<br/>21 bacterial burden. And then there's all the other<br/>22 things to measure.</p>         |
| 323 | <p>1 proportion it is, but I would suggest it's the<br/>2 majority of patients, that when they are<br/>3 incubating their disease for years and years, it<br/>4 take so long to diagnose. If you we could<br/>5 diagnose it earlier, we'd find these people<br/>6 sooner.<br/>7 But I mean there's a lot of people that<br/>8 don't need to be treated right away, and it's a<br/>9 unique group. It's a unique infection where you<br/>10 could actually do a placebo-controlled monotherapy<br/>11 trial, where you're taking your drug and you see<br/>12 if it does anything.<br/>13 If it doesn't do anything, you don't<br/>14 probably need to study it further. It would<br/>15 obviate all of our discussions from 3, 4, and 5<br/>16 because the drug doesn't in vivo activity, and it<br/>17 actually doesn't work. And if it does have<br/>18 activity, then you've move to number 3, 4 and 5<br/>19 figure out how to design a trial and how to<br/>20 actually use the drug.<br/>21 Anyway, I'm a big fan of that. You<br/>22 can't do that with TB. You can't do it with most</p>                                       | 325 | <p>1 Again, those are different diseases, but<br/>2 the point is, you have the luxury of doing it.<br/>3 You can't do that with TB. It's different for all<br/>4 the things that we've talked about. I put it<br/>5 forward for everyone to criticize, but I think<br/>6 that we should think about doing that with our new<br/>7 drugs as they come out. And I do think we should<br/>8 be doing animal models first. We need animal<br/>9 models. We have one. Other people here are<br/>10 working on them, so I do think it's important.<br/>11 DR. NAMBIAR: Just a clarifying<br/>12 question, Dr. Winthrop, so when you said it's<br/>13 doing something, you mean in terms of<br/>14 microbiology? Was that the intent?<br/>15 DR. WINTHROP: Yes.<br/>16 DR. NAMBIAR: So were you planning to<br/>17 look at that at an early time point, so within,<br/>18 say, 4 weeks or 8 weeks of initiating treatment,<br/>19 or were you planning to do it much longer, if a<br/>20 placebo-controlled trial is the way you want to<br/>21 go?<br/>22 DR. WINTHROP: I think it depends on how</p> |

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| 326 | <p>1 the drug works, and I think it depends on the bug<br/>2 we're talking about. So just as everyone has<br/>3 mentioned, abscessus is probably different than<br/>4 MAI, et cetera, and certain drugs have different<br/>5 PK parameters, et cetera. So I think you'd have<br/>6 to design the trial with those things in mind.<br/>7 DR. NAMBIAR: Just from a practical<br/>8 standpoint, would that be challenging, I mean to<br/>9 just put somebody on monotherapy for 6, 8 months<br/>10 and they have M. abscessus? I mean is that --<br/>11 DR. WINTHROP: Let me clarify something.<br/>12 This is not for everybody.<br/>13 DR. NAMBIAR: Okay. That's what I was<br/>14 wondering.<br/>15 DR. WINTHROP: This is not for people<br/>16 with cavitary disease, people who are sick and<br/>17 need to be treated. It's probably not for M.<br/>18 abscessus unless they fit that patient that Dave<br/>19 showed, you know, no progression.<br/>20 I have non-progressing abscessus<br/>21 patients that are always culture positive and<br/>22 they're non- progressive. I mean they don't feel</p> | 328 | <p>1 drugs but that's it.<br/>2 I know there are a lot of unknowns here,<br/>3 but in my mind, this is one of those big areas<br/>4 where we're not talking about TB.<br/>5 DR. OLIVIER: I would ask the question<br/>6 on the opposite end of the spectrum, also<br/>7 understanding all the virtues of placebo-<br/>8 controlled trials about whether a placebo control<br/>9 is always needed. And if you were starting out<br/>10 with patients with refractory disease, and<br/>11 especially now that we know something about what<br/>12 that target population looks like on placebo, is<br/>13 it mandatory to have a placebo in patients that<br/>14 there's no question that the disease needs to be<br/>15 treated, there's no question that they failed what<br/>16 they're on.<br/>17 Especially in early phases of putting<br/>18 drugs first on target disease, could it be<br/>19 conceived that you would have a single-arm study<br/>20 looking at efficacy and sort of compare that to<br/>21 historical effects of the natural history of a<br/>22 similar length of time off drug?</p>                   |
| 327 | <p>1 great, but they're non-progressive. So there are<br/>2 those people out there, but I think they're less<br/>3 frequent for abscessus.<br/>4 DR. DALEY: Kevin, I think just for<br/>5 clarity, though, I think what you're talking about<br/>6 is an early phase study that would be of<br/>7 relatively short duration in a highly selective<br/>8 population. Right?<br/>9 DR. WINTHROP: Yes.<br/>10 DR. DALEY: Okay.<br/>11 DR. NAMBIAR: It's something akin to the<br/>12 EBA studies one does for tuberculosis. I think<br/>13 that's what you had in mind.<br/>14 DR. WINTHROP: I just didn't want to say<br/>15 that because I want it to be different than TB.<br/>16 (Laughter.)<br/>17 DR. WINTHROP: I really tried hard.<br/>18 DR. GRIFFITH: But it's not an EBA<br/>19 study. No, I mean that's very important. This is<br/>20 not 2 weeks. It's 3 months or 4 months. You<br/>21 know, acquired mutational resistance is a<br/>22 phenomenon that we know occurs in a couple of</p>  | 329 | <p>1 DR. GRIFFITH: As Kevin alluded, I think<br/>2 it would be unethical to have a placebo arm in a<br/>3 cavitary patient.<br/>4 DR. OLIVIER: That was one of the<br/>5 competing concerns about where to set the endpoint<br/>6 in a placebo-controlled trial, so you're competing<br/>7 against the ethical aspects of leaving someone on<br/>8 placebo where they definitely meet criteria to be<br/>9 treated versus having a long enough time to see a<br/>10 drug effect. Those two are very dichotomous in<br/>11 terms of where you set that endpoint.<br/>12 DR. NAMBIAR: Okay. If there are no<br/>13 other thoughts on the control arm, just one<br/>14 question, in terms of the optimized background<br/>15 regimen. If one were to go with a trial design<br/>16 where you have a test drug; you add it to the<br/>17 standard of care, whatever one considers as<br/>18 standard of care, and you compare that with the<br/>19 standard of care, and you have to optimize the<br/>20 background regimen.<br/>21 If you truly end up having a very<br/>22 heterogeneous mix of patients, wouldn't that pose</p> |

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| 330 | <p>1 yet another challenge in terms of the background<br/>2 regimen? It would be quite different depending on<br/>3 whom you are treating. I think that was another<br/>4 reason why we had asked if it makes sense to<br/>5 separate out the patients. We would welcome your<br/>6 thoughts.<br/>7 DR. OLIVIER: Well, failing a regimen is<br/>8 failing a regimen. So if the design is to add the<br/>9 drug onto their failing regimen, with the<br/>10 assumption that there are no other viable options<br/>11 to it -- again, it takes into account whether the<br/>12 drug biologically is thought to be active in the<br/>13 two groups that you're mixing. I'm not sure it<br/>14 makes that big of a difference.<br/>15 DR. GRIFFITH: I think the cavitory<br/>16 patients also offer the opportunity of having<br/>17 higher bacterial, mycobacterial loads. It might<br/>18 be a little easier to evaluate efficacy of the<br/>19 drug microbiologically, particularly if you're<br/>20 using a semi-quantitative score.<br/>21 DR. HUGHES: Yes, from the industry<br/>22 side, it's a little bit challenging because we</p>                    | 332 | <p>1 about some practical difficulties. And I think it<br/>2 had come up for discussion this morning, and Dr.<br/>3 Wallace had made a point about how difficult it is<br/>4 for patients to travel 75, 50, 100 miles if they<br/>5 need to.<br/>6 Maybe Dr. Eagle, you can provide your<br/>7 perspective as you're actually doing one of these<br/>8 trials.<br/>9 DR. EAGLE: Yes. The feasibility of<br/>10 these trials, it's very challenging primarily<br/>11 because of the length of time you are expecting<br/>12 the patients to stay in the study. Retention is<br/>13 something that you need to work really hard on.<br/>14 In order to meet the definition of a<br/>15 conversion as it is in the guidelines right now,<br/>16 you do have to have your patients produce sputum<br/>17 every month. Otherwise, how else do you define<br/>18 it? And it is arduous.<br/>19 These centers are not everywhere, but<br/>20 the patients are everywhere, so you need to be<br/>21 able to understand and accommodate their travel.<br/>22 So it has a lot of challenges.</p>   |
| 331 | <p>1 would end up having to provide perhaps three or<br/>2 four different drugs, none of which are approved.<br/>3 They would, therefore, all be experimental at that<br/>4 time. I think just leaving it as optimized<br/>5 background regimen, plus or minus the<br/>6 experimental, is a much more pragmatic way to go.<br/>7 DR. EAGLE: And I would just add what<br/>8 Dr. Farley said earlier about the perils of<br/>9 randomization. And I think that -- I mean, that<br/>10 can sort it out to a degree.<br/>11 DR. HUGHES: Or you stratify by site or<br/>12 collect cluster of sites.<br/>13 DR. EAGLE: Yes, or I mean even stratify<br/>14 it by whether someone has interrupted treatment or<br/>15 not. What we find in the refractory population is<br/>16 that patients that are on treatment for a long<br/>17 time, and they do take holidays because of the<br/>18 toxicities and it's not working anyway. That's an<br/>19 area where you can potentially stratify as well.<br/>20 DR. NAMBIAR: If there are no more<br/>21 comments about clinical trial design itself, I<br/>22 thought we could spend a few minutes just talking</p> | 333 | <p>1 I think one of the things that we're<br/>2 been told particularly by the physicians that were<br/>3 in our last study is that these patients need to<br/>4 just be hand-held basically because it's a lot of<br/>5 -- it's arduous.<br/>6 They've got their comorbidities; they've<br/>7 got underlying lung disease; they're on all these<br/>8 medications. I think what we need to do is<br/>9 actually just pay attention to all of that and<br/>10 just help them along.<br/>11 DR. GRIFFITH: Dr. Daley asked me to say<br/>12 that monthly visits were not practical.<br/>13 DR. OLIVIER: And I would just reiterate<br/>14 that and the fact that I don't think the visits<br/>15 need to be monthly. And again, patients can very<br/>16 easily be trained to do standardized collection of<br/>17 sputum and they have that sent directly from<br/>18 wherever they are to wherever the core lab is. So<br/>19 that takes care of your microbiologic outcome.<br/>20 The PROs can be administered remotely.<br/>21 We're not talking about other measurements that<br/>22 are that difficult to do. Things like 6-minute</p> |

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| 334 | <p>1 walk or PFTs are fairly standardized by<br/>2 guidelines.<br/>3 I think if we can think outside the box<br/>4 instead of having everything tightly controlled in<br/>5 a relatively few research centers and space out<br/>6 the actual visits a bit, we could probably still<br/>7 maintain the frequency of data collection that we<br/>8 would need for the trial.<br/>9 DR. WALLACE: You could also arrange to<br/>10 have blood drawn and sent to the centers. I mean<br/>11 I think you could do essentially -- and this is<br/>12 one place where doing a complete physical exam<br/>13 probably is not -- I mean it's -- we fill out the<br/>14 forms, but it really doesn't add much, and<br/>15 probably not totally essential that we do it if<br/>16 you really felt like it needed to be done.<br/>17 DR. WINTHROP: Yes. I think taking more<br/>18 of a pragmatic trial approach in the future would<br/>19 be useful. I echo --<br/>20 DR. WALLACE: You know, it takes them<br/>21 all day to come to clinic, prepare, come early,<br/>22 blood drawn, whatever needs to be down, sitting</p>                 | 336 | <p>1 because of those high evaporative pressures.<br/>2 DR. NAMBIAR: Right.<br/>3 DR. O'DONNELL: Could I ask one last<br/>4 question of the panel, the serology data that I<br/>5 showed, the IgE? Does anybody think that has any<br/>6 value as, say, some kind of marker in a trial?<br/>7 DR. WINTHROP: No.<br/>8 (Laughter.)<br/>9 DR. OLIVIER: I think that this is a<br/>10 discussion that's been going on for many, many<br/>11 years of trying to find both a sero diagnosis and<br/>12 sero marker. I mean it may. It might be<br/>13 something interesting to put in as an exploratory<br/>14 variable.<br/>15 DR. WINTHROP: I'm joking. I think you<br/>16 should look at it. But I think there probably are<br/>17 sero markers out there, but that's probably just<br/>18 not the most useful.<br/>19 DR. NAMBIAR: If the panel doesn't mind,<br/>20 I just had one last question. I think we heard in<br/>21 a couple of presentations that the likelihood of<br/>22 reinfection is so high; 60, 70 percent of</p> |
| 335 | <p>1 there, they miss lunch, and they're exhausted when<br/>2 they get home. So by the time they've done that<br/>3 four or five times, they start thinking, well,<br/>4 gee, I don't want to go today.<br/>5 I agree with Gina. It's very hard on<br/>6 them even though they want to be part of the<br/>7 study. It requires a whole day's worth of -- I<br/>8 mean, these are people, they're sick, so they get<br/>9 fatigued relatively easily, and they may be down<br/>10 for a week after they make the visit.<br/>11 DR. NAMBIAR: Yes, there's an<br/>12 interesting comment from one of our patients this<br/>13 morning about how they spend six months in Florida<br/>14 and six months in another state. To be in a<br/>15 clinical trial and to be geographically that<br/>16 separate is really challenging.<br/>17 It seems like it's a perfect setting<br/>18 where the PI and the local -- the primary care<br/>19 physician have to sort of collaborate and work<br/>20 hand-in-hand to make this work.<br/>21 DR. EAGLE: Fortunately, the most common<br/>22 destination is where most of our centers are</p> | 337 | <p>1 patients, in fact, have reinfection. And the way<br/>2 we are looking to design to trials, we are<br/>3 requiring regular visits while on therapy, but<br/>4 certainly a visit, at some point, after treatment<br/>5 is complete. Again, as I said earlier, we picked<br/>6 three months, but it could be short; it could be<br/>7 longer.<br/>8 It seems very important at that point<br/>9 one has to differentiate if it's truly a relapse<br/>10 of the infection that they started or if it's<br/>11 truly a reinfection, especially given the numbers<br/>12 are so high.<br/>13 Any thoughts on how we might address<br/>14 that?<br/>15 DR. OLIVIER: I think it's imperative<br/>16 that the islets be banked. I mean Richard will<br/>17 tell you that's really the only way you can tell,<br/>18 is to be able to compare those microbiologic<br/>19 recurrences off treatment to what they started<br/>20 with.<br/>21 DR. NAMBIAR: Okay.<br/>22 DR. WALLACE: In the last trial, the</p>                           |

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| 338 | <p>1 broth bottles can be saved, so we saved every<br/>2 positive that the patient has. As we said,<br/>3 sometimes, there'll be a positive in the middle of<br/>4 five negatives, and you want to know if that's the<br/>5 same or not. If you don't have the bottle, then<br/>6 we got to turn it over to you, and you don't know<br/>7 what it is.</p> <p>8       So banking those organism -- all of the<br/>9 islets, even the screen islets, turn out to be<br/>10 important sometimes when you want to go back and<br/>11 they have a late positive and you want to compare<br/>12 them. It's not difficult to do. You just have to<br/>13 be the mindset. You just set up to do it. And<br/>14 I'd like to think that one of these days, most<br/>15 labs will be doing it because for long term<br/>16 follow-up, these are long term patients.</p> <p>17       It's not like they show up with an E.<br/>18 coli urinary infection, and you treat it, and you<br/>19 throw the organism away. These are often patients<br/>20 for life, and they're complicated, and being able<br/>21 to evaluate them, especially in the study --<br/>22       Think of the studies, think of the --</p> | 340 | <p>1 physicians treating patients in the clinic.<br/>2       From what I understand, you can tell me<br/>3 -- you're in a great lab. But when we look at<br/>4 some of the patients coming in and they have their<br/>5 history, they have a history of MAC, but sometimes<br/>6 those labs don't even separate intracellulare from<br/>7 avium. Sometimes that's all you need if you're<br/>8 going to have a relapse. I mean at the very basic<br/>9 level, if you get a different species, you don't<br/>10 have to go any further but that's not even done.</p> <p>11       DR. NAMBIAR: Okay. So I think we're<br/>12 running out of time. Dr. Farley has reminded me<br/>13 only three times that I need to stop talking.<br/>14 With that, I'll thank all the panel members. I<br/>15 think this was very helpful. And we'll have to<br/>16 take all this back and put our heads together and<br/>17 hopefully design better trials as we move forward.<br/>18       With that, I'll turn it back to Dr.<br/>19 Farley. Open Public Comment Session</p> <p>20       DR. FARLEY: This has been great. As<br/>21 with most federal meetings, we will invite a<br/>22 period of open public comment. If you signed up</p> |
| 339 | <p>1 the British Research Council did that M. kansasii<br/>2 study. They didn't save the islets, and they had a<br/>3 bunch of relapses, which could have easily have<br/>4 been new infections. But they didn't save the<br/>5 islets, so the study kind of went down in flames<br/>6 in the sense that we don't -- they were all about<br/>7 the 5 percent relapse rate. If you accept all<br/>8 those as being true relapses, it killed them.</p> <p>9       DR. EAGLE: I think when we do see the -<br/>10 - we have a patient that's negative and then comes<br/>11 positive, pretty much parallels the numbers that<br/>12 you had with respect to which ones are new<br/>13 infections or which ones are relapse.</p> <p>14       It is a very important question. The<br/>15 difference in the meaning of what each of those<br/>16 is, is huge. We did look at it in the last study,<br/>17 and we're definitely looking at it in the next<br/>18 study.</p> <p>19       It's very important, but it needs to --<br/>20 after the study, this is within a clinical trial,<br/>21 and it's well and good, but I think it needs to<br/>22 also be information that's available for</p>        | 341 | <p>1 for this earlier and you didn't actually know what<br/>2 you were signing, it's perfectly fine to pass.</p> <p>3       I'm going to ask Meghana to help by<br/>4 using the hand mic. Open public comments, speaker<br/>5 number 1 is Dr. Renu Gupta. We would ask you to<br/>6 limit your comments to three minutes.</p> <p>7       DR. GUPTA: Good afternoon. Thank you<br/>8 very much for giving me the opportunity to speak.<br/>9 My name is Renu Gupta. I am a physician,<br/>10 infectious diseases, and I am working as an<br/>11 independent consultant. I was formerly working<br/>12 with Insmmed.</p> <p>13       I just really have a couple of points to<br/>14 make. I would like to thank the agency for<br/>15 holding this forum today. And although NTM lung<br/>16 disease is an orphan disease, it today does not<br/>17 feel like a neglected disease. This momentum that<br/>18 we have started to gain with all our patients<br/>19 here, our clinicians and researchers and the<br/>20 agency needs to be sustained.</p> <p>21       I have only a couple of points, which<br/>22 probably echo what has been discussed today,</p>  |

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| <p style="text-align: right;">342</p> <p>1 nothing novel. One is the unmet need and the<br/> 2 seriousness. We need a strengthening of our<br/> 3 infrastructure within United States at a minimum.<br/> 4 And by that, I mean if we can have increased<br/> 5 outreach to primary care physicians and also<br/> 6 pulmonology centers outside the Centers of<br/> 7 Excellence, so that we can have increased<br/> 8 awareness around diagnosis of the disease. This<br/> 9 has been discussed for many years, but we now need<br/> 10 to put a system in place, an infrastructure.<br/> 11 The CF Foundation's registry is a model<br/> 12 and the TDN is a model. I only illustrate that<br/> 13 because I've had the good fortune of working with<br/> 14 their team and learning over time as to how<br/> 15 successful that has been in terms of outreach for<br/> 16 patients, and that clearly had an impact in<br/> 17 drawing patients into clinical trials.<br/> 18 We have an NTM registry, which is a<br/> 19 module of the bronchiectasis registry with 13<br/> 20 sites. I've been talking to stakeholders and<br/> 21 making a plea for a stronger public and private<br/> 22 sector partnership. I think this registry and the</p> | <p style="text-align: right;">344</p> <p>1 underlying inflammatory cascade in the lungs of<br/> 2 these patients. Thank you very much.<br/> 3 DR. FARLEY: Next, we have Ms. Mary<br/> 4 Fisher. Could you identify yourself? It's right<br/> 5 here.<br/> 6 MS. FISHER: I just want to make a<br/> 7 comment regarding clofazimine. As I alluded to it<br/> 8 when I was on the panel, I started clofazimine<br/> 9 back in 2011. For those of you who don't know<br/> 10 clofazimine, it was a medication that was used to<br/> 11 treat Hansen's disease or leprosy.<br/> 12 It no longer is available commercially.<br/> 13 When they prescribed it for me, my physician had<br/> 14 to fill out reams of paper, jump through a<br/> 15 thousand hoops just to get it approved. Once it<br/> 16 was approved, then my physician had to order it<br/> 17 from the pharmacy in Louisiana. It had to be<br/> 18 delivered to the physician office, and then I had<br/> 19 to drive an hour to go get it.<br/> 20 My concern is that medication is an old<br/> 21 medication. I understand when they started using<br/> 22 it, it was investigational. However, I have been</p>                 |
| <p style="text-align: right;">343</p> <p>1 benefits of a registry pre-approval and post-<br/> 2 approval are immense.<br/> 3 The last thing that I would say is<br/> 4 related directly to the drugs currently being used<br/> 5 and the drugs in development, is that if we could<br/> 6 come up with a model of cooperative groups like we<br/> 7 have in oncology or we have in mycology with<br/> 8 significant funding and backing from the NIH and<br/> 9 some investment from the biopharmaceutical<br/> 10 industry, that those cooperative groups could take<br/> 11 on the mission of NTM- focused-related research<br/> 12 agenda. I know the ADS has that in their mission<br/> 13 as well. ADS cannot do it alone.<br/> 14 So that would also lend itself to<br/> 15 looking at current regimens and evaluating -- and<br/> 16 I believe there are ways one can do that in<br/> 17 cooperative group studies.<br/> 18 Lastly, a plea for my colleagues in the<br/> 19 biopharmaceutical industry to go to their<br/> 20 management and ask for greater investment in both<br/> 21 diagnostics and small molecules and biologics for<br/> 22 treating the bacteria and also for improving the</p>                                       | <p style="text-align: right;">345</p> <p>1 on it for four years, and I'm sure there's quite a<br/> 2 few people in here that have probably been on it<br/> 3 or are on it.<br/> 4 I don't have any side effects. The one<br/> 5 side effect that is very common; that I would've<br/> 6 loved to have had was the bronze skin. I'd love<br/> 7 to have a tan year around but I never got it.<br/> 8 Anyway, what I am requesting is if we<br/> 9 cannot streamline that process of getting that<br/> 10 medication to us. I have to still call my<br/> 11 physician's office, and then when they went to<br/> 12 request it again this year, the process changed.<br/> 13 In January, they decided that they no<br/> 14 longer were going to pay the postage, which I have<br/> 15 no problem with. However, that was not<br/> 16 communicated to my physician's office until April.<br/> 17 When I went to get it renewed, they tried to<br/> 18 reorder it the old way. They told them it wasn't<br/> 19 the proper way.<br/> 20 The incompetence in the doctor's office<br/> 21 didn't get it done, and I was a week without the<br/> 22 medication after many, many phone calls to the</p> |

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| 346 | <p>1 office to remind them to get the drug.<br/> 2 Now, I'm responsible for generating the<br/> 3 postage. I'm responsible for sending the email<br/> 4 with the postage, but it still goes to the<br/> 5 doctor's office, and I have to go pick it up. I<br/> 6 don't understand why that can't come directly to<br/> 7 me. If I'm doing all the work, I'm doing all the<br/> 8 generation, why is it that I have to still jump<br/> 9 through the hoop? And I can guarantee you my<br/> 10 physician doesn't even know when it arrives. It<br/> 11 gets to the receptionist, they call me, I pick it<br/> 12 up.<br/> 13 So I am just asking for them to look at<br/> 14 that and see if that drug cannot come off that<br/> 15 investigational and streamline the process for us<br/> 16 to get that medication.<br/> 17 DR. FARLEY: Thanks. So people don't<br/> 18 say something in a vacuum, so we might've talk to<br/> 19 you on the phone a bunch of times because we<br/> 20 actually have about three full time equivalents<br/> 21 working on the clofazimine expanded access<br/> 22 program. We have heard you loud and clear and</p> | 348 | <p>1 first would be early diagnosis perhaps through a<br/> 2 skin test such as they do for TB, and is that a<br/> 3 possibility, and is anybody working on that? It<br/> 4 seems to me it should be feasible. I just don't<br/> 5 know.<br/> 6 The second issue is something that Dr.<br/> 7 Gupta brought up, which is the inflammatory<br/> 8 cascade. I'm very well aware of that, and<br/> 9 oftentimes, when I try to bring in some sputum,<br/> 10 I'm really getting what looks like to me to be<br/> 11 inflammatory. It's white and cloudy, but it's<br/> 12 just really inflammatory and not necessarily<br/> 13 bacterial.<br/> 14 As a patient, I say, okay, maybe I<br/> 15 should try antihistamines, this or that, what<br/> 16 about low dose aspirin? But I don't hear anybody,<br/> 17 really, as far as the medical and the<br/> 18 pharmaceuticals, trying to deal with this cascade<br/> 19 in the lungs, inflammatory in the lungs. I think<br/> 20 that's very critical especially with us with<br/> 21 bronchiectasis. I think it's perhaps the number<br/> 22 one thing that we need to do for bronchiectasis</p>   |
| 347 | <p>1 we're working very hard to streamline it.<br/> 2 Part of it is that because it's not<br/> 3 marketed in the United States, it is only<br/> 4 available through the single-patient IND program,<br/> 5 and those regulations, unfortunately, require us<br/> 6 to deliver it to the physician, not to the<br/> 7 patient, even though the patient paid us to<br/> 8 deliver it to the physician.<br/> 9 But we are working hard on streamlining<br/> 10 it, and it's a priority here at the FDA to get<br/> 11 that done. Be patient, and we appreciate your<br/> 12 patience so far. Part of it is that through that<br/> 13 that process, we actually have gotten to know a<br/> 14 fair number of the patients.<br/> 15 We find that really helpful because we<br/> 16 got to talk to you and we know kind of more of<br/> 17 what your life is like and we're more connected to<br/> 18 what you're going through. But there might be a<br/> 19 better way to do that. We hear you.<br/> 20 Next is Marcy -- W-E-I-N-E? Weiner,<br/> 21 sorry.<br/> 22 MS. WEINER: I have three things. The</p>   | 349 | <p>1 patients.<br/> 2 Third, I know it's an old one. I think<br/> 3 it has some eucalyptus in it, which is a known<br/> 4 antibacterial. It was used in the Vicks VapoRub.<br/> 5 Those of us that are old enough remember our<br/> 6 mothers putting this in a vaporizer, rubbing it on<br/> 7 our chests. But it also helped to break things up<br/> 8 and brought relief and perhaps in a more modern<br/> 9 form in delivering and through either an inhaled<br/> 10 or nebulized form, eucalyptus could be used.<br/> 11 I mean this has such strong<br/> 12 antibacterial properties. I just can't believe<br/> 13 that we're utilizing this in any fashion. Now, as<br/> 14 a person who did microbiology so many years ago,<br/> 15 I'm probably useless for you. But I just can't<br/> 16 think -- it's a thought to spark some kind of<br/> 17 look-into. It's very easily accessible. They<br/> 18 have a lot of it in Australia -- I brought some<br/> 19 back -- and in California. You go to a spa in<br/> 20 Arizona, they're going to have little bottles of<br/> 21 it.<br/> 22 For the ladies with bronchiectasis that</p> |



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| 350 | <p>1 are told they cannot take showers but they have to<br/>2 take baths, put five or six drops, little drops,<br/>3 of that in and get the benefit of it. I mean I<br/>4 think for scientific purposes, it would be good to<br/>5 have something looked into.<br/>6 DR. FARLEY: Ms. Deborah Schwartz.<br/>7 MS. SCHWARTZ: Very quick question, I<br/>8 just wondered how many people here have cavitory<br/>9 disease, if anyone just had surgery and<br/>10 reoccurrence after surgery.<br/>11 DR. FARLEY: Did you want folks to raise<br/>12 their hand?<br/>13 DR. WALLACE: I can tell you it happens.<br/>14 Remember that surgery is a de-bulking procedure.<br/>15 It does not --<br/>16 MS. SCHWARTZ: I had two surgeries<br/>17 [inaudible - off mic.]<br/>18 DR. WALLACE: Did you have them on both<br/>19 sides or on the same side?<br/>20 MS. SCHWARTZ: Upper right and middle<br/>21 left by Dr. Mitchell. For four years, I had<br/>22 negative sputums. I had one positive in February.</p>   | 352 | <p>1 there's a right answer here, but that would be my<br/>2 approach. Closing Remarks and Adjourn<br/>3 DR. FARLEY: Okay, great. Thanks very<br/>4 much, everyone. Before I forget, I need to<br/>5 announce there is a shuttle bus -- Phil are you<br/>6 involved with the shuttle bus? You're not. Okay.<br/>7 But there is a shuttle bus that some of you came<br/>8 on. It's leaving from the circle out front at<br/>9 5:15. We're around. If you have trouble finding<br/>10 the way you came back in, let us know, and we'll<br/>11 get you headed in the right direction.<br/>12 I want to thank everyone, particularly<br/>13 the patients who I know have traveled. Many of<br/>14 you have traveled a very long way. I was told at<br/>15 lunch by the patient-focused drug development<br/>16 group that is one of the best meetings we've had<br/>17 in terms of the quality of feedback that we've<br/>18 gotten from patients. This has been extremely<br/>19 helpful to us.<br/>20 I can tell you from early on in the HIV<br/>21 epidemic that the progress that got made, got made<br/>22 because patients and academics and developers of</p> |
| 351 | <p>1 Dr. Daley and my doctors decide I should go back<br/>2 on medication, and I did, but I've never had<br/>3 another positive sputum, and they still want me to<br/>4 stay on it for 18 months.<br/>5 I guess they're worried about cavitory<br/>6 disease again. I don't know. But anyway, I'm<br/>7 taking the medication. I'm doing okay. Inhaled<br/>8 amikacin, I like very much, but I only had one<br/>9 positive four years after surgery.<br/>10 DR. WALLACE: I'll just say that our<br/>11 experience from fingerprinting is that people who<br/>12 have relapse with the same strain almost all do so<br/>13 within six months. I've never seen a relapse with<br/>14 the same strain after a year. So almost<br/>15 certainly, your islet is a different islet --<br/>16 MS. SCHWARTZ: It is a different one.<br/>17 It's intracellular.<br/>18 DR. WALLACE: And so on the basis of a<br/>19 single -- I can understand why they're concerned,<br/>20 but the answer is we would not put you back on<br/>21 medicine for a single positive. We just collect<br/>22 samples and follow you. I mean I don't know that</p> | 353 | <p>1 drugs and regulators were talking on a regular<br/>2 basis and knew each other and working together.<br/>3 And I'm seeing that happening in NTM, and I'm very<br/>4 excited about that, and you've been a big part of<br/>5 that process.<br/>6 I want to thank the panel in particular<br/>7 for taking time out of your schedule. This has<br/>8 been very valuable to the division as they begin<br/>9 to work on clinical trials.<br/>10 I know that there are some companies<br/>11 here who are thinking of working in this area.<br/>12 And we want to encourage you, and we also want to<br/>13 remind you that the division is available to meet<br/>14 with you at any point in your program,<br/>15 particularly early under the pre-IND program and<br/>16 provide you regulatory advice. That's a fairly<br/>17 easy thing to access. If you don't know how, just<br/>18 look up Sumathi or I, and we'll get you pointed to<br/>19 the right person.<br/>20 With that, I want to thank everybody for<br/>21 a great meeting, and we look forward to seeing<br/>22 many of you again soon and talking further as we</p>                          |

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| <p style="text-align: right;">354</p> <p>1 begin to make progress, continue to make progress<br/>2 in this area. Thanks very much and safe travels,<br/>3 everyone.<br/>4 (Applause.)<br/>5 (Whereupon, at 4:57 p.m., the meeting<br/>6 was adjourned.)<br/>7<br/>8<br/>9<br/>10<br/>11<br/>12<br/>13<br/>14<br/>15<br/>16<br/>17<br/>18<br/>19<br/>20<br/>21<br/>22</p> | <p style="text-align: right;">355</p> <p>1 CERTIFICATE OF REPORTER<br/>2 I, Janet Evans-Watkins, the officer before whom<br/>3 the foregoing proceedings were taken, do hereby<br/>4 certify that the proceedings were taken by me in<br/>5 stenotype and thereafter reduced to typewriting<br/>6 under my direction; that said proceedings are a<br/>7 true record; that I am neither counsel for,<br/>8 related to, nor employed by any of the parties to<br/>9 the action in these proceedings were taken; and,<br/>10 further, that I am not a relative or employee of<br/>11 any counsel or attorney employed by the parties<br/>12 hereto, nor financially or otherwise interested in<br/>13 the outcome of this action.<br/>14<br/>15<br/>16<br/>17 JANET EVANS-WATKINS<br/>Notary Public in and for the<br/>State of Maryland<br/>18<br/>19<br/>20<br/>21 My commission expires: July 8, 2016<br/>22</p> |
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