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

Attendees

Jennifer Bogenrief
James Bona
Arthur Chien
Gaby Chien
Selena Daniels
Charles Daley
Gina Eagle
John Farley
Mary Fisher
Jonathan Goldsmith
Soujanya Giambone
Betsy Glaeser
David Griffith
Karen Higgins
Barbara Hudson
David Hughes
Kathleen Keating
Philip Leitman
Marilynn Lundy
Theresa Mullin
Sumathi Nambiar

Attendees (continued)

Anne O'Donnell
Kenneth Olivier
Alexandra Quittner
Hala Shamsuddin
Joseph Toerner
Richard Wallace
Kevin Winthrop
Patricia Yost

C O N T E N T S

6

P R O C E E D I N G S (9:01 a.m.)
Welcome
MS. GIAMBONE: Good morning, everyone. Thank you, all, for being here. Thank you for braving -- we had a really bad commute day, I think. There was a lot of traffic on the roads and I heard from a lot of you that you had to deal with that. Thank you for doing that and for being here.
My name is Soujanya Giambone. I am with the FDA, Center for Drug Evaluation and Research, Office of Strategic Programs. On behalf of all of my FDA colleagues, I'd like to welcome you to today's patient-focused drug development meeting on Non-Tuberculous Mycobacterial Lung Infections, NTM Lung Infections.
We're just very thankful that you're here, and we're looking forward to a really great day of learning from you and listening to you and your perspectives. What I'd like to do is just spend a few minutes going over the agenda and a few housekeeping remarks, and then we'll go ahead

7

and get started.
We're going to start the day today with some FDA presentations. My FDA colleagues will provide an overview of the Patient-Focused Drug Development initiative, background on NTM and current treatment options. Then I'll come back and provide an overview of the discussion format.
We have two topics for today as you know. Topic 1 is on the most significant symptoms of NTM lung infections and how they impact your daily life. Topic 2 is on patient perspectives on current approaches to treating NTM.
For each topic, we have a panel discussion, followed by a group discussion, and we take a break between each of those discussion topics. Then we'll break for lunch. Then in the afternoon, we have a scientific workshop with some really great experts in the field that will be presenting a range of presentations on NTM lung infections, and the epidemiology, and clinical trial design and so forth. So it should be a very interesting discussion.

8

A few housekeeping items. Restrooms are back out into the lobby. If you make a right and go all the way down the hallway, you'll see the restrooms there. We also have a kiosk that you may have seen out in the foyer area. Again, it sells basic coffee, sandwiches, snacks, and so forth, so please make yourself comfortable. If you need to get up and stretch, if you need to go grab a snack or if you need to use the restroom, please feel free to do so. We want you to be as comfortable as possible.
Next thing, you can feel free to pre-order your lunch if you're -- we have that 45-minute lunch break in the middle. But during break, if you'd like to, you're welcome to go and just let them know what you'd like to order, and they'll have it all ready for you if you don't want to have to wait too long in line.
All right. I do have a few notes down here, so I'm just going to go through them for some of the reminders. The shuttle bus that some of you may have taken, the NTM shuttle bus that

9

brought many of you here, it's going to leave at 5:15 p.m.
sharp. If you're going to be taking the bus back, please be sure to be there by 5:15.
Next, just a reminder that we do have the screens around the room so you can feel free to look at any of the screens. We're going to do some polling questions throughout the day. We're going to have the presentations, of course. You can feel free to look along to any of these slides and that'll be great.
This meeting is being transcribed and recorded. In about a week or two weeks or so, the transcript and the recoding of the meeting will be available on the meeting website. Right after the meeting, we'll have the slides for the scientific workshop. They're already posted up there for the second half of the day, the scientific workshop. You'll be able to find the slides there.
I'd been given a notice that you can just go to Google, google.com, and search "FDA NTM" and the very first link that comes up will

10

take you to the slides. Under "Meeting Materials," you can go there, and you'll see the slides for the scientific workshop.

Okay. On that note, let me ask my FDA colleagues to please introduce yourself.

DR. FARLEY: Sure. I'm John Farley, deputy director of the Office of Antimicrobial Products at CDER.

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

DR. TOERNER: I'm Joe Toerner, the deputy director for safety in the Division of Anti-Infective Products at FDA CDER.

DR. SHAMSUDDIN: Hala Shamsuddin, medical officer, Division of Anti-Infective Products.

DR. DANIELS: Selena Daniels, reviewer with clinical outcome assessment staff here at CDER.

DR. GOLDSMITH: Jonathan Goldsmith. I'm the associate director of the Rare Diseases

11

Program in the Office of New Drugs, CDER.

MR. BONA: Jim Bona, the Office of Orphan Products Development.

DR. MULLIN: Good morning. I'm Theresa Mullin. I direct the Office of Strategic Programs in the Center for Drugs.

MS. GIAMBONE: Thank you. We have some colleagues over here.

DR. EGGERS: Sara Eggers, in the Office of Strategic Programs.

MS. CHALASANI: Meghana Chalasani, the same office.

MS. THOMPSON: Graham Thompson, same office.

MS. VAIDYA: Pujita Vaidya, same office.

MS. GIAMBONE: Thank you. Now, I'd like to turn it over to Dr. Farley for his opening remarks. Opening Remarks - John Farley

DR. FARLEY: Good morning, everybody. I want to welcome everyone to this meeting on Patient-Focused Drug Development for Non-Tuberculous Mycobacterial Lung Infections. For

12

the rest of the day, you'll probably hear that abbreviated as NTM because it's a pretty long name.

As I mentioned, I'm from the Office of Anti-Microbial Products within the Office of New Drugs here at FDA. Within our office, the Division of Anti-Infective Products reviews anti-bacterial drugs, including products that can help manage and treat NTM lung infections. This afternoon, the panel discussion will be chaired by Dr. Sumathi Nambiar, the director of that division who is seated to my left.

We, here, at FDA are very happy to see so many patients and patient advocates in the audience. We know a number of you, and we're looking forward to getting to know all of you in the course of the day.

I also understand that we have many more folks joining us on the Web. For those of you in the room, we particularly appreciate you, not only putting up with Washington traffic but then putting up with a security system similar to that

13

that you would face at an airport when you arrived today. At least, they didn't hopefully make you take off your shoes.

Today's meeting is one in a series of FDA's patient-focused drug development meetings, and Dr. Theresa Mullin will be talking about this initiative in more detail in a few minutes. What our division here has done a couple of times, which we found really helpful, is to have experts that we invite through the whole day, so the thought leaders in the country.

Then this afternoon, once they've heard from patients, we get to talk about clinical trial design and moving drug development forward during the latter half of the day, we found that to be a very useful discussion and a useful way of moving forward.

As most of you know, NTM or non-tuberculous mycobacteria represent over a 150 different species of naturally occurring organisms that are found in water and soil. In some people, these organisms infect the airways and lung

14

tissue, and that can cause inflammation in the respiratory system. Symptoms include chronic cough, shortness of breath, fatigue, and a range of other symptoms that we'll be talking about this morning.

Diagnosis of NTM lung disease is often delayed because the symptoms are similar to other lung diseases like emphysema or bronchitis. Dr. Hala Shamsuddin will provide a bit more background on the disease and treatment options for you in a few minutes.

This is a very important meeting for us. We fully understand that NTM lung infections are a serious condition and that there is unmet need for patients.

It's FDA's responsibility to ensure that the benefits of a drug outweigh its risks. Therefore, having this kind of dialogue is extremely valuable for us. What we hear from you today can help us understand how patients view the benefits, as well as the risks of treatments for NTM lung infections.

15

We particularly want to hear from you today about the different ways your symptoms affect your daily life. It is also important to hear what you value in a treatment for NTM infections and what you would like to see in future treatments for you.

It's important to remember that FDA is just one part of the drug development process. We, at FDA, do not develop drugs or conduct clinical trials. Drug companies, often working with researchers or patient communities, are the ones who conduct trials and submit applications for new drugs to us.

However, we work closely with these drug companies throughout their drug development process, and what we hear from you this morning will be helpful to companies, as well as ourselves as clinical trials for new NTM treatments are planned.

This afternoon, we will have a panel of experts specifically discussing some challenges with the design of clinical trials to evaluate new

16

treatments for NTM and some ways forward to meet those challenges.

I know there are a lot of representatives from industry, academia, and others in the room and on the Web. I want to thank you again for being here and being a part of this important discussion.

Now, I'll turn the microphone over to Dr. Theresa Mullin who will talk about our broader efforts in patient-focused drug development.

Presentation - Theresa Mullin

DR. MULLIN: Thank you, John.

Good morning, everyone. I want to echo Dr. Farley in welcoming you here today, and I'm glad you were able to get here on time. I know I got snagged in the traffic a little bit myself.

I'm going to take a few minutes to tell you about this Patient-Focused Drug Development Initiative. This meeting is one that we are able to organize and provide as part of that initiative. As John was saying, one of the most fundamental responsibilities of FDA is to ensure

17

that the benefits outweigh the risks of a drug that we approve or allow to be on the market.

Part of that decision is looking at the clinical context, as we call it, which is to say how severe is this condition, what is the impact on the patient's life, what other treatments that are already available so that we're not allowing anything on the market that offers less benefit or more risk and is not offering as much to the patient as what may already be available.

Those two components are questions we're going to be probing extensively this morning in our meeting: the impact of the disease on your life and what you're doing today to treat your condition and how well that's work or not working for you.

We realize that the patient's perspective on benefit/risk was absolutely critical because patients have that unique perspective of experiencing any benefit that there is to gain from a drug and also experience the harm. So their perspective on benefit risk is

18

extremely important.
Before we started this initiative in 2012, we didn't really have a systematic way to collect that information. We have a patient representative program, which is extremely valuable, but that really allows us to get one person really to -- one or two to provide and speak for the whole community. And we know there's a lot of diversity of experience in the patient communities for each disease.
So this initiative allows us a more systematic way to collect that information, to hear from a broader set of patients, a community of the people who are experiencing a disease and the people who are care partners for those people with the disease.
We started this initiative. We committed to do at least 20 such meetings. This is the 17th meeting. We're going to be doing more 20 because it's been so valuable. We're trying to do as many as we are able to do with the available folks that we have on our staff. Each one focuses

19

on a particular disease and tries to really systematically go at getting that kind of input.
We began, as I said, in September of 2012. We put out a Federal Register notice with about 40 diseases where we asked input on which should we focus on, which diseases should we focus on. We got about 4,500 comments from the public on that list, and we got many more nominations of diseases.
We've worked with the divisions to try to come up with a list that we are working through for this initiative, and we've been learning an awful lot about how to do this and how to actually allow for others to do it as well, collect this kind of information.
Here's a snapshot for you of the diseases that we are covering over this five-year period. As you can see today, we're doing the non-tuberculous mycobacterial lung infections as our meeting focus today.
In each of these meetings, we focus, as I said, on those questions related to impact of

20

the disease on your life and what you're doing to treat it, but we also try to focus questions on what else the review division doctors are interested in probing and trying to understand. It's a unique opportunity to you have you here, so we try to take advantage of that opportunity to learn as much as we can about other aspects.
Sometimes the questions are related to your perspective on benefit and risk, and the tradeoffs, and what constitutes a meaningful benefit. That question has come up sometimes for us also. Your attitude towards participating in trial, your ability to participate in trials, questions of those kinds are very interesting to understand better from the patient's perspective and help give us insight.
After we do these meetings, we leave a docket open to receive more comments. People who were not able to be here or even those of you who are here may think of other things that you want to tell us or share with us, and so we leave a public docket open for a few months to be able to

21

collect additional information.
We take that information, as well as what we hear in the room and on the webcast, and develop a Voice of the Patient Report. It takes us several months to put these together and get them up on our website, but that's where we'll have it.
I think as Soujanya was saying -- I know I at least find things on our website by using Google. I hate to admit that, but that's the easiest way for me to find stuff on our website. So we would recommend you use Google to find the Voice of the Patient Reports.
These reports are a -- we try to capture in the way you describe your experience in your words, and we try hard to not change that, to capture just the way you've told it to us, so it provides a good record for reviewers to subsequently use and refer to when they're doing reviews for drugs that may come in to treat NTM. It also provides information as a basis for other things we might do.

22

For example, if we're trying to -- somebody, a sponsor or patient groups want to work together or separately to form patient-reported outcome tools that could be used in clinical trials to better capture that aspect of your experience from your perspective, it helps to provide some useful input into that kind of further development as well.

With that, I'll stop and thank you again so much for joining us today. And we very much look forward to hearing what you have to tell us. With that, I'll turn it over. Hala Shamsuddin

DR. SHAMSUDDIN: Good morning, and welcome again for being here. This will be a very general overview on NTM lung infections. I will be focusing the talk mainly on the disease in the United States rather than a global overview, and that's mainly due to time restrictions.

Like I said, this is going to be a very brief overview. Non-tuberculous mycobacteria, there are more a hundred and fifty species, and a handful of them cause human disease. You're going

23

to hear some of the names repeated throughout this workshop.

In the United States, mycobacterium avium complex, or referred to as MAC, accounts for most of the cases, approximately 70 to 80 percent with M. abscessus accounting for most of the remainder. The organisms are acquired by inhalation from the environment, and water is thought to be the main source.

This is a map of the United States, and the darker areas represent areas where there are more cases of the disease. As you can see, there are more cases along coastal lines.

Who is at risk for this infection? It's generally people who have underlying lung disease and/or a genetic predisposition. By and large, the major group in the United States tends to be patients who have bronchiectasis, which is a condition where there is damage and scarring of the airways. In that group polls a category of patients with a very specific body type. These tend to be mainly slender women.

24

However, the other categories include patients with cystic fibrosis, chronic obstructive lung disease in smokers, patients who had prior tuberculosis, where this NTM may occur in areas that were previously involved with TB, and then other conditions such as alpha-1 antitrypsin deficiency, which results in lung damage, primary ciliary dyskinesia where people can't clear their secretions, and some people who are immune compromised.

Generally, patients will present with cough, but the other symptoms include shortness of breath, sputum production, coughing of blood, chest pain, fatigue, weight loss, and sometimes fever. As you can see, all these symptoms are not really unique or specific to NTM lung infections. They may occur in patients who have underlying lung disease of any cause or any other infection. On X-ray, you can find cavities or nodules, and generally, there is a positive culture from the sputum or the lung.

How common are these infections in the

25

United States? Generally, NTM lung infection is what we consider an orphan disease, which means it generally affects less than 250,000 people in the United States. But there is a general consensus that the disease is increasing, both in the general population and in patients with cystic fibrosis.

The estimates vary depending on where you are geographically, but approximately 8 per 100,000 people are infected. This number increases with age, approximately 20 per 100,000 people in people older than 50 years of age and to 47 per 100,000 in those older than 70 years of age.

This is a survey of the prevalence of the disease and in how many people is it present. In the Medicare population, as you can see, the increase is both in men and women.

Why are NTM lung infections increasing? There are several possible reasons. The first is probably increased awareness among physicians. The other is increased number of susceptible

individuals. As the population gets older, there are patients with more chronic lung disease; there are more people who are immune compromised; cystic fibrosis patients are surviving longer, and there's possibly increased exposure.

I'm going to switch gears to treatment. And we'll hear more about treatment later this afternoon, so I'm not going to go into it in much detail. But briefly, there are no FDA-approved drugs for NTM lung infections. Physicians in practice will use antibiotics that are approved to treat tuberculosis or other bacterial infections.

In general, these antibiotics that are used, so called "off label" may be used for longer durations and in different populations than those in which they were approved in. Sometimes the side effect profile may be different.

In general, antibiotic combinations are recommended and usually three or more drugs, which may include an injectable drug. But the optimal combination of drugs, the optimal doses, and the optimal duration of both the injectable and the

overall treatment regimen have not really being rigorously evaluated. The treatment is lengthy with the goal of therapies achieving negative sputum cultures for 12 consecutive months.

In a study from 2004 to 2005, the median number of antibiotics that a patient had required range was 5, with a range of 1 to 10. The median number of treatment days was approximately 8 years with a range that was anywhere between 3 months and 20 years. The cost per patient in a year was approximately $20,000, but it could go as high as $70,000. Patients who have M. abscessus were associated with higher treatment cost.

The number of antibiotics used is rather large for a long treatment of time, but the side effect profile is also significant. In the same study, the adverse reactions were reported in 50 percent of patients for those receiving the commonly used drugs and everybody who used the less commonly used drugs.

Now that we've kind of painted a rather grim picture, what are the challenges to

developing a new drug? There are many. The first one is that disease progression really varies by the underlying lung disease, by the appearance on chest X-ray, and by the infecting organism.

A patient who has bronchiectasis and is infected with mycobacterium avium and has nodular disease will have a different disease course than somebody who has cavitary disease or somebody with cystic fibrosis or infected with mycobacterium abscessus.

The response to treatment varies. The progression of the disease varies. The treatment response varies. A drug that works for one NTM species and one patient population does not necessarily work in another NTM species or another patient population. It may be difficult to extrapolate from one population to another or from one organism to another.

Treatments are lengthy; therefore, trials are lengthy. When trials are lengthy, this poses problems with feasibility. Finally, the endpoints for these trials have not been well-

defined, and we will hear more about that in the afternoon as well.

We will need to define assessments in those clinical trials that occur early in the course so we can get a drug to market sooner rather than waiting at least a year for the sputum to be consistently negative.

In conclusion, NTM lung infections are increasing in the United States. The affected populations are mainly patients with bronchiectasis and patients with underlying lung disease. We have no approved FDA therapies for this condition. The currently used treatments are multiple drugs used off label for lengthy periods of time and are associated with significant side effects.

We realize that there is a huge unmet medical need, but having said that, we also have many challenges to drug development that hopefully, we will have a chance to discuss further this afternoon. Thank you. Thank you all for coming again. Overview of Discussion Format

30

MS. GIAMBONE: Thank you to my FDA colleagues for your presentations. What I'd like to do now is go over the discussion format. As I mentioned earlier, we have two topics that we're going to be diving into today.

Topic 1 is on the most significant symptoms of NTM lung infections and how they impact you in your daily life. What we're listening for here is what are the symptoms that are most important to you, that matter most to you, and how do they affect your ability to do activities? Is there something that you can't do as fully as you would like or you can't do at all because of the symptoms that you experience?

We also want to hear how your symptoms have evolved or changed over time. Tell us what it's like on a good day, on an average day, and on your bad days. What do those symptoms look like? How has your symptoms impacted your life, not just physically but emotionally, socially? What are all the different ways that your symptoms have impacted you?

31

In topic 2, we're going to be listening to patient perspectives on their approaches to treating NTM lung infections. Here, what we're listening for is what are you currently doing to treat the NTM lung infection; how well is it -- or is it working; or if not, what's not working about it? What are the downsides that you're experiencing because of your treatment regimen, and what would you look for in an ideal treatment?

We're also in topic 2 going to have a scenario slide that we'll present to patients to hear your immediate thoughts on participating in a clinical trial. We're going to put some information up and talk to you for a few minutes about what are the first things that come to mind.

We are going to have a portion in our afternoon session in the scientific workshop that's going to go on to greater detail on considerations of clinical trial designs and so forth, but we want to first hear some thoughts from you on what matters to you in clinical trials.

32

First, we're going to hear from a panel of patients and caregivers. On that note, could I please have our topic 1 panelists come on up and have a seat?

The purpose of the panel discussion is to really set a solid foundation for our greater discussion. Our panelists have worked so hard over the last few weeks to put their thoughts down, and we really appreciate that you're all here to share them with us. I've had the honor of working with them for the last week and a half, so I know they're going to do an excellent job as will our topic 2 panelists.

Our panel reflects a range of experiences with NTM lung infections, and they'll each have about five minutes to present their remarks. After our panel is done, we're going to then expand on the dialogue, broaden it, to hear from more of you, more patients and caregivers in the audience to provide your perspectives.

What we encourage you to do here is build on what you've heard from the panel. Share,

33

not only what's similar, but what's different for you and how do you experience your symptoms and how they impact you.

Periodically, we'll ask some questions along the way. I'll look to my FDA panel to ask some questions along the way. If you're comfortable to do so, you can raise your hand, and we'll have some microphone runners around the room. They'll come to you, and you can state your name and just present your remarks.

Another way that we're going to be learning from you is through this opportunity to answer polling questions. I believe we've already passed out the clickers. Patient representatives, you should have these clickers in front of you, these little white remote-looking things. This is not a scientific survey. It's completely voluntary.

It's completely voluntary for patients and patient representatives. It's another way for us at the FDA to hear about the perspectives in the room and also for those on the webcast. We'll

34

do some questions in just a little bit, and you can use your clickers to respond to those questions.

For those of you on the Web, you can also participate in these polling questions by answering them through the webcast. For those of you on the Web -- we have about I believe 70 or so people on the Web so we have a very active Web session going right now.

We can't see you, Web participants, but you're a very, very important part of this meeting. We encourage you to continue providing your thoughts through the webcast. Periodically, I'll check in with my colleagues to provide a summary of what we're hearing on the Web.

We also, towards the end of each topic discussion, will go to the phones, and we'll hear some of the people joining us on the webcast provide their thoughts over the phone.

Last but not the least, a very, very important part of our discussion, another way that we would like to hear from you, is through this

35

public docket. The public docket, you see the website here, and you'll also find it on the slides once they're posted on the Web.

But this docket will be open for two months after this meeting, so until December 15th. It's really a great way to continue the dialogue. I encourage all of you to -- you know, if there's something that you didn't get to share here or if there's something else that comes to mind, please submit those comments in the public docket.

They are all part of this meeting record, and after you submit all your comments, we will go through and read each and every one of those, and they will be incorporated into our summary report. Anybody is welcome to comment, not just patients and patient representatives.

I would like to share some additional resources at the FDA that will be very useful for you. One is the FDA Office of Health and Constituent Affairs, which we call OCHA. You have their contact information here.

Then the other is within the Office of

36

Center Director, we have the Professional Affairs and Stakeholder Engagement team, PASE, which has been collaborating with us to provide outreach for this meeting and help with getting so many of you here, so thank you for that.

We do have some discussion ground rules for today. This meeting is really about the patients and the caregivers to do the talking today. We really have so much to learn from you, and we are looking to you to really lead that dialogue.

FDA is here to listen. We will be in listening mode. We know that there is academia, industry, other government agencies here, and this meeting is very important to you, too. We just ask that you stay in listening mode.

The discussion is going to stay -- we're going to do our best to stay on topic. The discussion is on symptoms and treatments. We know that there's many aspects to treating NTM lung infections, and we're not going to be able to address all of those aspects in this meeting.

37

So whatever else comes to mind that's outside the scope of topic 1 or topic 2, we ask that you share those during the open public comment period, which we took registration for. There's a signup sheet out on the registration desk, and we'll take registration up through lunch break. We'll see how many people sign up, and then we'll see how much time each speaker will have.

Again, I'm going to put another plug-in for the public docket, another place to continue submitting your remarks that you didn't get to say today. The views expressed today are personal opinions, and on that note, respect for one another is paramount.

Finally, let us know how the meeting went for you today. We're going to be passing out evaluation forms probably during break time. They're very important to us, so please fill them out and let us know what worked and didn't work.

All right. First, what we would like to do is do some polling questions. You should all

38

have a clicker, patients and patient representatives. Those of you on the panel, you have it too. Okay. So let's do our first one to practice. Where do you live? Press A for within the DC Metro Area or B for outside of the DC Metro Area.

(Polling audience.)

MR. THOMPSON: Yes, it looks like it's bugged, so maybe just do a show of hands or something for now.

MS. GIAMBONE: Oh, okay. Okay. It looks like we're having a little bit of technical difficulty.

MR. THOMPSON: We're good now.

MS. VAIDYA: No, we're good. The computer was just frozen.

MS. GIAMBONE: Oh, we're good. We're good. Okay. If you see this and this between us over here, you'll know what's going on. Okay, so it looks like it's working. Let's see the results.

MS. VAIDYA: It's a little slow --

39

MS. GIAMBONE: Oh, it's a little slow. Just like traffic today because of that water main break; it's a little slow.

MS. VAIDYA: Why don't we go to the Web first? Sorry.

MS. GIAMBONE: Okay.

MR. THOMPSON: So on the Web, we have about 91 percent outside of DC and 9 percent from inside the DC Metro area.

MS. GIAMBONE: I think we can do a show of hands, right? Oh, there it is. So it looks like most of you actually -- the majority of you came from outside the DC Metro area, so thank you for being here. For all of our local neighbors, thank you also for being here.

Let's go on to the next question. Have you ever been diagnosed as having an NTM lung infection? Press A for yes or B for no.

(Polling audience.)

Okay. It looks like over two-thirds of you in the room said yes, so we are going to hear some really great perspectives from you all today. Thank you.

40

Okay. All right. For your age, press A for younger than 18; B, 18 to 30; C, 31 to 50; D, 51 to 60; E, 61 to 74; or F, 75 or greater.

Yes?

AUDIENCE MEMBER: Is this just for patients or do you want everybody in the room?

MS. GIAMBONE: This is just for patients and patient representatives, yes, and caregivers. Oh, just patients for this one; well, unless you're a caregiver answering on behalf of a patient.

(Polling audience.)

Okay. It looks like just about half of you in the room are within that 61 to 74 age group. But it looks like we have a very nice distribution of folks between 18 to 75 or greater.

Okay. Again, for patients or caregivers answering on behalf of a patient, are you male of female?

(Polling audience.)

Okay. It looks like mostly all of you in the room are female or you are here representing a female.

41

What is the length of time since your NTM diagnosis: A, less than one year ago; B, 1 to 2 years ago; C, 2 to 5 years ago; D, more than 5 years ago; or E, I'm not sure?

(Polling audience.)

Okay. It looks like about half of you in the room have been diagnosed for more than five years. But again, it looks like we have several of you that are within this range of newly diagnosed to about 2 to 5 years ago.

All right. What is your underlying lung condition? A, cystic fibrosis; B, bronchiectasis -- and I apologize if I mispronounce anything -- C, COPD or emphysema; D, her lung disease; E, a condition that's not mentioned here; or F, I don't know?

(Polling audience.

Okay. So almost over 70 percent of you voted for B, followed by let's see -- and it seems that we do have some other -- we have a little bit of everything here. We'll make sure that when we hear from you during the group discussion, if you

can also maybe mention what that underlying lung condition is if you identify that you had another lung disease or a condition not mentioned here.

Okay. Then can I just see what we heard on Web?

MR. THOMPSON: The Web results are pretty much the same as it was in the room. Panel 1 - Comments on Topic 1

MS. GIAMBONE: Okay, great. All right. So on that note, I would like to get started with our panelists for topic 1. You'll just press the red button on your microphone when it's your turn to speak, and when you're done, you just press it to turn it off again. We're going to start with Katie.

MS. KEATING: Good morning, everyone. I thank you from the bottom of my heart for paying attention to NTM. This has been a dream of mine for the past 14 years. I was 39 years old when I started not feeling well, and I've been dealing with this for a long time.

I am speaking on behalf of a lot of

patients who, unfortunately, cannot be here, or on the webinar, or just are too sick to join us today, and also many other friends who were in our original New York City Area support group who have passed away, and others who have passed away throughout the country who we had befriended over the years. The support we have given each other was enormous.

I am just really -- I have hope now that something is going to happen. I am a nurse and long-term care administrator by background, and when I was diagnosed, I researched online, and there were very few articles. Very few. I even went to New York City library and MEDLINE and tried to get everything I possibly could, and there was hardly anything there.

NIH had been studying NTM for 37 years. Mycobacteria was first identified over a hundred years ago. But I felt so alone as a nurse, and I had nowhere to turn to; it took me a period of time, a year searching.

I started looking for a diagnosis, many

different doctors throughout New Jersey, eventually went to National Jewish, and then I traveled throughout the Tri-State area looking for answers because I wasn't going to give up; I wanted a cure. I did not want to deal with this.

I was too young, had too many things to do, and I had a young daughter. So I kept on looking, and eventually I found a support group, and history has gone on.

It is an invisible disorder. I look healthy. And all of us in the group, when we have our support groups, people say to us, "Oh, you look good." And we're like ready to (laughter) shoot them because they don't know how we feel.

People complain if they have a cold, and it wears them down for two or three days, but just imagine having a life that you feel like you're sick half the time. I also compare it to like the manic depressive lung disease. You feel good a few days, and then, all of a sudden you are wiped. It's very hard to live this type of life because you're on an emotional rollercoaster. So again,

I'm really, really happy to be here.

I know we have limited time, so I'll continue. The three symptoms that I experience that have the most impact on my life are fatigue and stamina. My day is based on personal energy. I plan out what I am going to do based on how I feel. When the weather changes, it greatly impacts my energy, humidity, the rain, et cetera; it really impacts what I'm able to do.

I prioritize, of course, on activities of daily living, what I must do, and then add on other. There are some days I could function more than others, and on those days, I get a lot more done because I know that it has this up and down curve.

My stamina is just not what I was. I used to run 7 or 8 miles. When I first was sick with my first NTM infection, I had to take a taxi cab in New York one city block. My sister looked at me like, are you crazy spending money on a cab to go a block? But you get so beat.

Again, it's an invisible disorder. We

46

don't have, unless you're losing weight, the apparent look that other diseases have.

The lack of stamina has affected my ability to work full time. I was at the height of my career, in charge of quality assurance for the state. I could've really done really well in my career, but had to give that up due to this. When you can't plan that you can commit to projects, you are not going to really be productive. I do some per diem work, but there is not -- you're unable to work full time.

I envy people who can get up in the morning, take a shower. Since this is based in water, we don't take showers. We have to watch the water we drink. We only drink certain bottled water. We can't have water in restaurants. Every day, I have to be cognizant of what I can do to avoid an infection.

Not being able to work, of course, takes a toll on your life. It leads to social isolation. We have a support group, which helps us, but it really affects every aspect of your

47

life when you're not able to work full time. And I was 39, so I had financial goals, which unfortunately cannot be met.

Nobody thinks things are going to happen to them. We're like the 21-year-old, you know, guy; nothing is going to happen to us. I didn't think at 39, my life would change overnight. And being at this meeting, I have hope that in my lifetime -- because when I found out it was being studied for 37 years, I thought never in my lifetime, since it was so long, that something would happen. But now, there is hope.

Being a patient, daily, we do airway clearance. We do nasal washes, nebulizers as needed; we go to the lab; we watch our diet. We are constantly in and out of remission.

February and in August are my two critical months because February, flu season, I often get pneumonia; and in August, with the humidity. August, I don't go out. Most people go to barbecues and outdoor events. I have a young daughter. I stay in a lot because I don't want to

48

take the risk of getting sick.

Many of us feel like we should live in a bubble, but then we won't live a quality life. Sometimes we push, and I do go out to places that I'm not -- and then I end up sick. Everybody says to me, "What the heck did you do that for?" But after a while, with every kind of illness, it's easy to get noncompliant. It takes a toll on you over time.

The third symptom is coughing, constantly coughing up into a tissue. Years ago, when I first had this condition, I'd walk to the restroom, but over time, it's gotten worse and you just can't help it. I'm not going to walk to the restroom; you just cough up because the bronchiectasis has gotten worse. You do cough up in tissues, and it's repulsive to some. But I'm just like blinded now because overtime, it just has increased.

Question number 2, specific activities that are important to you that I can't do, I used to run. I can't run; I walk. I watch every

49

water. We can't do planting. We can't wear perfumes, terrified of mold, no hot tubs, no indoor pools. I had to move to a home with hardwood floors, no rugs. Radiator heat is the best because forced air is really bad for people with lung problems. No humidifiers, no fireplaces, no barbecue pits.

I had to leave church recently because the incense, all these respiratory irritants that bother you. We don't go to crowded places, movies in fear of getting a respiratory infection. I travel less frequently.

Again, I was a nurse, but I won't go into a hospital, or a nursing home, or other healthcare facility because I'm fearful of getting sick. I get sick like that, and it doesn't last for two days; it goes often to a pneumonia.

Examples of severe fatigue, it just comes upon you at times. I've been in the grocery store with the shopping cart, but I didn't have the energy to wait in line to check out. That's how severe the fatigue becomes at times. We laugh

50

in our support groups on how it suddenly creeps up on you.

Other things I can't do, exercise. I try to exercise and push, but there are some days I just can't. I know it helps but I just can't.

How does your condition change over time? It has taken a toll, and I try to deal with the new normal, but it has gotten worse, and the duration for recovering is a lot longer.

What makes your symptoms better? Doing everything, all the suggestions that they have on the website to prevent infections makes it better. But at times, after 14 years, you get tired of getting up every morning and doing chest airway clearance. Every patient has a patient burnout after a while.

What worries me most about the condition? When I first researched, there was no new antibiotics on the market. All the money was going into all the psychotropics and all the sexual drugs at that time. Now, there is -- we are being paid attention to, which makes me really

51

happy because years ago, I was worried that I was going to have the infection and there was nothing going to be available. Other worries are --

MS. GIAMBONE: Any final remarks, Katie?

MS. KEATING: Excuse me?

MS. GIAMBONE: Any final remarks?

MS. KEATING: I'm just really, really happy that we are here and that I hope that we can just go forward getting the antibiotics and the research that we really need to improve the quality of life for all of those out there.

MS. GIAMBONE: Thank you, Katie. Thank you so much. Next, we have Barbara.

MS. HUDSON: Good morning. I echo Kathleen's comments about just the gratefulness for everybody that's here, especially those of you at FDA.

Being here for me, although I live in Indiana now, it's a lot like coming home. I spent my whole working career with the Department of Health in Human Services, specifically with the Office of General Counsel advising the public

52

health service. Though I didn't interface a lot with FDA, I do recognize some names still. So it's a lot like coming home for me.

You know, there's a commercial on TV -- I don't watch a lot of TV, but I see this commercial from time-to-time. A woman is walking through the woods, and she begins something like, "I'm only in my 60s," nice long life ahead, big plans.

When I see that commercial, it kind of irks me a little bit because I thought, well, that's me. I'm in my 60s; I love to hike, walking through the woods, big plans, and then unexpectedly, NTM changed some of those plans.

Two years ago, after I retired from this department, I had retina eye surgery, and I had to be face down for two weeks on kind of a cot, and I was about yay off the floor. Well, that's kind of hard. You know, I'm going to sleep face down for two weeks. And at the end of the two weeks, I thought, "Whew, I'm glad that's over with." And I stood up and I coughed. And I haven't stopped

53

coughing since I came from eye surgery.

I met with lots of specialists, pulmonologists, ENT, allergists, internal med, a lot of famous docs even here in the Washington, DC area. Nobody could figure out why I was coughing. Finally, I have a wonderful physician here in Bethesda, and he said, "Barb, let's go to National Jewish." So that was really key.

In 2004, I went to National Jewish. They performed a whole lot of tests, and they diagnosed me with NTM, along with several other diseases:

bronchiectasis; I'm alpha-1 deficient. So we at least knew what we were dealing with.

Physically, I'd say I'm just tired. Last night, I was at the meet and greet, and I was telling the woman and gentleman I was talking with, "Hey, I'm going to faint here in a minute." I had to sit down. I was just so tired, and that's so unusual for me.

I saw both my parents active in their 70s and 80s. Before I got NTM, I was very active.

54

I held a very demanding job in the Office of General Counsel. A couple years after retirement, I was walking, hiking, biking, caring for parents.

I'm now very careful about my energy level as Kathleen said. I may wash windows, but it may take me all day, wash a window, sit down and rest; wash another window, sit down and rest. Things that once took a few minutes may take the whole day.

I wear a mask when I'm in the garage or cleaning to prevent further infection. I no longer fix really large meals. If I want to do anything else during the day, I got to fix a meal that doesn't zap my energy level. Instead of having this much energy, I feel like I've got this much energy, and I'm careful how I allocate it.

I joined exercise classes at the Y. I thought, well, kind of a new city, a good way to know people. I dropped two of those classes just because I couldn't keep up, and those classes were for seniors. There are people in those classes in their 70s and 80s, and I thought, "Good grief."

55

You know, I've always been kind of the leader in the exercise, and now, I can't keep up with people who are much older than I am.

I still exercise a lot. I go to the Y on a daily basis, but it's more individualized. In fact, I'm in a class for cardiac rehab, but I'm getting the exercise, whatever it takes.

My big plans for the 60s have changed. I'm 67 now. I've had NTM for at least two years. But it's affecting not just my physical life. I'm certainly fatigued. I'm certainly coughing. I have a lot of shortness of breath, but it's affecting social life, which I don't like either.

I'm often embarrassed because I've got to excuse myself and go cough up my lungs for an hour. Or I'm going out to lunch with a friend, and I have to call and say, "You know, I've got to cough up for another 45 minutes or so, and then we'll have lunch."

Recently, I was trying to clear my lungs. I was, I guess, sitting on the front stoop or whatever, cough-spit, cough-spit, you know. My

56

neighbor came rushing over. I had no idea she could hear me, but she came rushing over. "Should I call 911?" I said, "No, go back. I'll go in the house and finish coughing." It's just an embarrassment a lot of times.

I guess I have some fear of the future. I'm single. I thought, well, gee, I could take good care of myself. I'm physically active. But now, I don't know. I've declined a lot in the last couple of years. What's the next couple of years going to be like?

The next panel will talk a little bit more about treatment. I began treatment in August, late August, and three weeks later, I was so sick. In fact, last week, I was in bed three days, just shaking and thinking, well, am I going to be able to be here or not?

So I came off the drugs, but I don't know what the future holds for me who can't take the three-drug cocktail. What are you going to look two years from now or four years from now?

I guess my goal is to push myself as

57

much as I can to remain active, notwithstanding the fatigue, the shortness of breath, the coughing, but to remain positive as I go through the future.

As with Kathleen, I remain hopeful that together, we can work together to find some answers, maybe not the final answer but at least the next step forward. How do we get this before the people -- even in the department, how do we get it before the Commissioner of FDA? How do we get this issue before the secretary of HHS?

Those are the things, and I look forward to any questions you have later.

MS. GIAMBONE: Thank you so much, Barbara.

Philip?

MR. LEITMAN: I'm delighted to be here. Those of you who have met me before know that I usually have some notes, and then usually, I listen to what people have to say and go in a different direction. Today is no exception.

I'm here because Fern is not, because

58

she cannot speak for the illness that she battled from the time she was in her 40s. I'm not going to into defining what NTM is or any of that because that's been done.

What I'd like to talk about is what it does. Frankly, you can't separate symptoms and impacts on daily life of the disease from the treatment because they really do go hand in hand. Both affect the ability to live and the quality of life.

In Fern's case, she was on multiple drugs for 18 years. She had -- and this is not a misquote -- over 26,000 IV infusions during the period of her treatment. They were difficult to tolerate. I'm delighted so many patients are here, doctors, scientists, and FDA.

In her case, we knew that the treatments extended her life. From the time she was diagnosed until the very last day, there was this smile on her face and optimism, but it did have an impact. What we're hearing from Katie, Barbara, what I'm sure you're going to say, Marilynn and

59

others, is fatigue, the inability to be spontaneous, get up, take a quick shower, go out and live your life.

Your life changes because your life is planned around the treatments and the impacts of the disease. From the treatments, Fern had loss of hearing, not complete, but she could read lips. Her eyesight was affected. She was still able to drive until she didn't have enough energy to do that. Part of that was from the disease, the long term inflammation. Part of it was from the drugs. We know that.

So while treatments help, they extend life, at times, improve life, those treatments are not a cure. In fact, I would challenge anybody to define a cure for NTM because we really don't know what a cure means because even if you're culture negative, it comes back.

So we need to start by defining what are the goals. In my mind, the goals are to extend life and improve quality of life, reduce the amount of fatigue, increase stamina, decrease the

60

number of exacerbations because everybody with this disease has an exacerbation.

We need to have treatments that will be less toxic and more effective. And I'm thrilled because you all are listening. So many patients are here whereas years ago, we would've come to an empty room. So many doctors are looking at it, and industry is here. They were here with us last night; they're here now.

While we heard earlier that the treatments are off label, one of the things needed is to really have some trials to understand the existing treatments that are used off label, what do they really do? What's the role of the new drugs because we know that they're needed, but we need to better understand the current treatments and what that means.

There is a history of drug resistance that's acquired over time. We now know from more sophisticated testing over the last few years that if you have a certain gene, certain strains, they're going to be more inherently resistant.

61

But with the newer technology, those treatments can be refined. But we know this is very different than typical drug approval because many patients are on treatment for a very, very long time, many months to many years, and that has a different impact.

I think that many of the patients, including my wife, took the approach that there were some calculated risks in order to extend life and try to improve quality. Those are individual decisions made with their physicians.

I will tell you from a personal point of view, in 2009, with the help of a physician, a drug company, and approvals, Fern was given a drug on a compassionate use basis before it got on the market.

It extended her life for five years. She saw our grandchildren grow. Everybody in this room who has the disease, every family member wants that same opportunity. That's why we're here. This is different than something that is a short term treatment.

62

I echo what all the patients are saying, and thank you.

MS. GIAMBONE: Thank you so much, Philip.

Now, we have Marilynn.

MS. LUNDY: Well, I'm thankful to be here, and I'm fortunate to be here. I think I can come from a little bit of a different viewpoint than the people that have spoken. So I'm not going to repeat a lot of the symptoms that caused me to be diagnosed, finally after five years, took me to be diagnosed.

I began to feel tired and so forth. This was about 15 years ago. I probably would've contributed a lot of the symptoms that we have to maybe aging, because at one time or another, I had every one of those symptoms that was up there on the board this morning, except I never lost much weight.

But the one symptom for me that actually got me through those five years to finally get a diagnosis was every morning, getting up and

63

coughing up green sputum. For me, that has been the biggest thing that I've had to deal with. And it has affected everything in my life, and still does.

After I was diagnosed, I was on antibiotics for five years, and I have been off of any medications for about two and a half years. I guess I maybe represent life after drugs or life after medication. I can tell you that I still have symptoms. I still get up every morning and cough up sputum, which my sister, who's been staying with me the last couple of days, can attest to.

I still have those days when I get up, and it doesn't seem like there's any known reason, but I cannot function very well. I can't think straight. I ache all over. Those days, if I can, I cancel everything and try to lay low.

In spite of the fact that I'm stabilized, my lung scans don't show that there's much more deterioration going on -- and that's one of the reasons why I'm not on medications right

64

now -- and I have been feeling pretty well most of the time. However, the symptoms of that nature, who knows --

I mean it feels as though we don't even know why suddenly those days happen. Unfortunately, a lot of times, it's on the weekend. That's the first thing for me as a patient that went, because I worked full time through all the medication, had to work. I live alone. I've never been married, don't have -- I'm not independently wealthy or anything, so I have to make a living. And through all this, I have worked five days a week at least.

However, I'm an interior designer, and I had to change my career totally because there's nothing that can get me coughing faster than being on a construction site with a lot of dust and, you know, the nature of a construction site.

I used to be there at 7:00 in the morning, going over things with the contractors and being sure that it was done the way I planned it to be done, and I can't do that anymore. I

65

still do a little decorating, but I can't make the kind of money that I used to make.

Another thing that I did, I did a lot of presentations. I traveled around the country on media tours for some corporations as an interior designer. I even wrote a book on public speaking just about 15 years ago when I started to feel so poorly.

I have not been able to do that. A lot of my clients came from those presentations and so forth, but to stand up and give a presentation without coughing or without being totally fatigued, it was pretty impossible.

The good news is that I was just at NIH yesterday, and as I said, things are looking good. My scans are -- everything is stabilized and so forth. And I won't have to come back again for a couple of years.

But that doesn't mean that the symptoms are gone. As long as there's bronchiectasis -- and we don't even have a clue about, it seems to me, about bronchiectasis and how to deal with it,

66

that's the underlying disease that I have, and that's there. The airways are already ruptured, and they are just sitting there waiting for MAI or some other bacteria to come and move in.

I do a lot, of course, to prevent it. I was part of the Falkenheim's water research and found that in my building, 600 apartments in New York City, that the water in the pipes in my building, everything in my building has the exact strain of MAI that I was diagnosed with initially.

I talked to Dr. Falkenheim about what can I do about this? At that time -- I understand there's now some filters that we may be able to get for our homes. But there was nothing at that time. And he said the only thing to do was to boil my water. So I do that every day. I boil all my drinking water, all the water that I cook with.

There are so many things that I do now to prevent and to take care of myself, and as Katie was saying, to prevent myself from being exposed so that I don't have as many exacerbations. I had one a month ago, and I had

67

one two months before that.

It's not like a normal cold. You're out for at least a week with a fever and flu-like symptoms, I ache all over kind of thing. If you want to live your life, you're going to be exposed to these things.

I'll end on the high notes for me. When Dr. Oliviaz [ph] asked me yesterday what was new, I said, "Well, what do you mean?" What category are we talking about? And so suddenly I realized, well, what's really new with me is that for the first time, in a long time, I was able to -- I've always been singing all my life. There was a period of time when I was on the meds when I couldn't sing at all. I had no voice.

I don't know if you can tell what's happening in my voice right now. This stuff is hanging down there, et cetera. Well, I wasn't even able to sing at all. Sometimes I couldn't speak very much either.

So for the first time in many years, in June, I gave a performance on stage, off Broadway,

68

so to speak, and sang. That's been very exciting to me, to be able to sing again.

I also was able to give an hour's presentation, standing, with 15 minutes questions afterwards for the first time again in about 15 years.

So I'm one of the very fortunate people that has really benefited from all the research and everything that's happened in recent years, and I mean recent. I mean, when I -- you know, in New York City, it took five years to be diagnosed. That tells you how few people, even the medical profession, understood very little at that point.

Today, through all the research and because of my experience, every research project that comes my way, I participate in because I want to be able to educate and have everybody know and understand this disease.

This is great to be here today, and this is so different than it was before all this happened. When I was first diagnosed, the only thing that was online was people that had HIV or

69

AIDS, and I was terrified. I thought, well, it won't be long before I'm dead, you know?

Then I found the support group -- I'm in the same support group as Katie -- and found out that it didn't necessarily mean you're going to die of this disease, but it looks like I'm going to have it the rest of my life.

MS. GIAMBONE: Thank you. Thank you so much, Marilynn. Thank you for sharing that really positive story about being able to sing recently. That's really very nice to hear.

I would like to ask everyone to give our panelists a round of applause.

(Applause.) Large Group Facilitated Discussion on Topic 1

MS. GIAMBONE: Thank you for working so hard to prepare your comments and for being so courageous and sharing them with us.

What I'd like to do is a few show-of-hands exercise now. How many of you felt that you heard -- that what our panelists said that some of it resonated with you?

70

(Show of hands.)
Many, many hands. Okay, I see at least a dozen hands that have been raised. That's great to hear that there's a lot of similar experiences, and I know there must be some that are not similar, too, so we look forward to hearing them.
But I also want to ask, we heard some very interesting concepts, and I want to see by a show of hands if these also resonate with you. Katie mentioned weather changes are -- that's a trigger for some of the symptoms. How many of you feel the same way?
(Show of hands.)
MS. GIAMBONE: I see about 16 hands or so, 16 or 17 hands.
We also heard about having to pace yourself for activities during the day. How about that? How many does that resonate with?
(Show of hands.)
MS. GIAMBONE: Again, another 16, 18 hands I think I see.
Marilynn brought up this difficulty in

71

thinking. How about that? How about that concept, which again we'll dive into in just a little bit? But I just want to see how many of you.
(Show of hands.)
MS. GIAMBONE: So I'm seeing about 10 hands or so raised on that.
All right. Great. Why don't we get our clickers out? I want to do a polling question, which is going to help kick off this discussion. So again, patients and caregivers, if you can grab your clicker.
Of all the symptoms you have experienced because of your NTM lung infection, which do you consider to have the most significant impact on your daily life? You can choose up to three symptoms: A, chronic cough; B, coughing up blood, phlegm or mucous, and mucous; C, shortness of breath or other breathing difficulties; D, fever or night sweats; E, loss of appetite; F, weight loss; G, fatigue or lack of energy; H, pain such as chest pain or shoulder pain; or I, other

72

symptoms not mentioned.
Again, for those of you on the Web, you can answer through the webcast.
(Polling audience.)
It looks like 80 percent of you voted for G, fatigue or lack of energy, so we'll definitely hear more on that. Then we see almost 40 percent or so cough; coughing up blood, phlegm and mucous; and shortness of breath, so we'll touch on those as well.
We have several people that identified fever and night sweats, pain. We also have people that identified other symptoms not mentioned, so we'll be sure to get to those as well to hear from you.
How about on the Web, what do we see?
MR. THOMPSON: Pretty similar. We have 45 percent for chronic cough, 48 for coughing up blood or mucous, 45 for shortness of breath, 21 for fever and night sweats, 12 for loss of appetite, 9 for weight loss, 75 percent for fatigue or lack of energy, 15 percent for pain,

73

and 6 percent for other symptoms not mentioned.
MS. GIAMBONE: Great. Thank you. Let's start with fatigue. Many of you voted for that, and we heard it on the panel, too. What I'd like to ask is if you can describe to us, how do you experience the fatigue? And as Philip mentioned, can you talk about maybe what exacerbates it or what triggers it? How do you cope with that?
One sec, we have a microphone coming to you.
MS. WEINER: Thank you. My name is Marcy Weiner. I was diagnosed about eight and a half years ago. The fatigue, as one of our panelists stated, can come on very suddenly. If I lie down, instead of taking maybe a doze for 10 or 20 minutes, which would've been normal, it might be three and a half or four hours later I wake up, and you're not refreshed. I could maybe not find that I could move.
Now, I'm fortunate so far to have a lighter case. But this still can happen. It's totally unpredictable. And you may not have any

74

other symptoms along with it. There may be, at the time, no necessarily increase in sputum or no night sweats or fevers, which you could put towards TB, et cetera, like that.

I think this is the one thing. You heard this from the panelists, but it's very dramatic at times. You could be driving along in the car between Massachusetts and Connecticut and all of sudden have to pull off to the side of the road, literally, and take that -- and know because you know your eyes are closing, and you're going to just bottom out.

MS. GIAMBONE: Okay. So fatigue that comes on very abruptly. Marcy, as you mentioned, sometimes sleep is not even help -- it doesn't help refresh you. Okay. Thank you, Marcy.

FEMALE SPEAKER: With the fatigue, as I -- it actually is brought on even more so with the constant coughing, as you can tell, that it wears you down. Constant coughing all the time creates more fatigue, so it's kind of a vicious circle.

In addition to that, I cannot sleep

75

through the night, so I don't get a lot of rest at nighttime, and that unfortunately also contributes to fatigue as well.

MS. GIAMBONE: Thank you. Is it the cough -- what is it that you're not able to -- what's impacting you not being able to sleep? Is it the cough keeping you up?

FEMALE SPEAKER: My coughing.

MS. GIAMBONE: Okay.

FEMALE SPEAKER: Yes.

MS. GIAMBONE: All right. Thank you so much. We have a hand over here.

JACQUELINE: Hi. My name is Jacqueline. I'm 53 years old, and I've been battling this for 40 years. The fatigue is just the tip of the iceberg because with the fatigue comes confusion. It comes with just so much you cannot even believe.

My way of dealing with this after 30 years was I will just take -- I am blessed because hydrocodone makes me awake, not fall asleep, so I can do my housework and take care of my daughter,

76

my stepdaughter, that I homeschool.

But obviously, this is bad because who wants to operate under the influence almost every day of their life and not be able to drive? My daughter goes to the NIH out here, and my husband cannot even let me drive her because what if I get tired? Either that or I'm under the influence, and it's just got a good idea. It folds into everything.

MS. GIAMBONE: Thank you. Thank you. Katie, did you want to say something?

MS. KEATING: I'd like to say something also on that note. Since fatigue is so unpredictable, I also was driving. I tried to go back to work a couple of years ago. I have a very good driving record that I just -- suddenly, it came on me. It went through the stop sign, got pulled over.

Then a few weeks later, I went to pick up my daughter at school, and I was speeding. I never had a speeding ticket in my life. But again, it came on suddenly. I didn't feel well.

77

I was trying to go back to work and doing everything I wanted to do.

It's just hard to accept, to surrender, to give in, but that's how suddenly it comes upon you. When you have a young child -- I didn't get into [indiscernible]. But when I first had my first MAC infections, the first few in the early years, I couldn't even do my daughter's homework, check it.

Big thing was rest up just so I could sign her papers. You know, in the beginning of the year, they give you a ton of papers. That was like a big accomplishment. That's how minimal energy.

When you go through chemo -- I have friends that went through chemo recently, and you feel beat for a period of time; you take off the weekend. Six months later, you go back to work.

This is no getting-better-and-go-back-to- work. You just go through ups and downs. It's just -- I often call it like microbial prison because you're never out of the sentence of -- you

78

know, we innocently got this disease. We took a shower one day, and it totally changed your life.

MS. GIAMBONE: Thank you, Katie.

MS. KEATING: You're welcome.

MS. GIAMBONE: We can hear you, Donna.

DONNA: My name is Donna. I think my fatigue comes from lack of sleep, finding a good position, so I'm not wheezing; not so much coughing but the wheezing is terrible and mostly in a prone position.

What also keeps me up at night is the fear of the future, which Barbara had touched on, and being a pulmonary cripple, which I've been told I might be someday as a result of -- they can't even operate on my lung. That's how bad it is. And they said if I do have a pneumonectomy, I'd become a pulmonary cripple. So the fear and the anxiety is what keeps me up at night.

MS. GIAMBONE: Okay. I'd like to ask, is there a sort of -- I know that we heard that fatigue is abrupt, but we're also hearing -- I'm hearing sort of a daily battle with it, too, a

79

daily sense of fatigue, tiredness.

Is that accurate that you're also having a daily battle with fatigue? No? I'm seeing many head nods, but I'm also seeing a no here. One second.

DEBORAH: I didn't know I would be talking. Mine is a little different. I always have bronchitis. Seasonal change, I went to my doctor, he gave me my typical antibiotic. And then as I was walking out, he said, you know what, let's take an X-ray of your chest, make sure you don't have pneumonia, which I did not have.

But they found little nodules here and there, and the radiologist said since he had nothing to compare it to, he wanted CAT scan every six months for two years, which I did. Never coughed, never sick.

Eighteen months later, a cavity formed in the upper right. I saw a pulmonary specialist. He said, I'm doing a full PET scan to make sure it's nothing cancerous, but I think I know what you have, and you'll be in a lot of antibiotics

80

for a long time.

I stayed on the cocktail, the three for two and a half years. And by then, I saw an infectious disease doctor. He said, let's give your body a holiday from the drugs. Of course, I felt fine, but I never had a negative sputum. By then, I was diagnosed with MAC.

While I walked out of the office, I think two minutes later, I start coughing. My husband said to me, Oh, my God, they just turned on the cough. So I coughed enough that I started bleeding a little and scared me half to death, still never fatigued to this day.

I went to Denver. I saw Dr. Eisman. I saw Dr. Daley. They said because I'm so healthy, I should have -- I had millions of tests, and I did have -- Dr. Mitchell did a lung resection in my upper right and my middle lobe. I did very well with that and stayed with medicine another year or so.

I was negative for about three and a half years, and this February, I had one positive

81

sputum, again, not sick really, but they have me back on my medicine. I've had now 7 negatives, but I have to stay on the meds. I'm assuming I'll be on meds off on the rest of my life.

MS. GIAMBONE: Thank you, Deborah.

DEBORAH: That's my story.

MS. GIAMBONE: Thank you, Deborah. And we'll definitely be hearing more about treatment regimens in topic 2. But you bring up cough, and that's a good lead in to the other symptoms that you've all identified: chronic cough; coughing up blood, phlegm and mucous; and then also breathing difficulties, which I know you had mentioned.

Can we hear some perspectives on the cough? Tell us about how you're experiencing that cough? Is there a good day? What triggers the bad day? Would anybody like to share? I thought I saw a hand here. Okay.

JAQUELINE: Hi. The cough is something. I've had an AVI vest since 1999 that I had to wear for 3 to 5 hours a day to clear my lungs. I've had the first flutter valve. I now have a brand

82

new AFLOW VASP that you can actually walk around with and not sit at a corner two feet away from a wall for 3 to 5 hours a day. That brings on depression. I mean, who wants to sit in a corner for 4 hours a day?

So now, I have a new vest, but the cough causes so much pain. You're always pulling muscles, and it makes you so tired. It leads right into the fatigue when you cough. It just creates like a horrible syndrome.

MS. GIAMBONE: So the cough is bringing on pain, and it's also impacting -- it's also triggering the fatigue.

JAQUELINE: Yes. If one of you put on a vest, one of the precaution types of vest, and you wore it for a half hour, it would do you all in. I mean, it would just do you in. Everybody would have to take a nap. And then to cough on top of it, each one of you at that table would need to take a nap and take some Tylenol.

MS. GIAMBONE: Thank you. And your name?

83

JAQUELINE: My name is Jaqueline.

MS. GIAMBONE: Jaqueline. Thank you, Jaqueline. We have a comment here.

DOROTHY: I'm Dorothy. Two years ago, I started using the sodium chloride 7 percent solution twice a day, and I haven't had pneumonia since. But I cough a great deal, and the only thing that will stop it is a cough drop.

Yesterday in the afternoon, I coughed three times; twice, I was on the phone, had to hang up and wait until I could it under control before I called back. Twice this morning, I've been doing it, too.

MS. GIAMBONE: Thank you, Dorothy. We have a comment here.

BETSY: Hi, I'm Betsy. When I start trying to talk, I start coughing. I cough like episodes. Well, it will go on for 5 or 10 minutes just coughing. I mean I walk up the street and suddenly I'm seized with this huge coughing episode. I just have to stop. People think I'm dying or something awful. They keep offering

84

lozenges, which really don't help much. Water, I carry water with me everywhere. It just doesn't stop. It doesn't stop the cough.

It's really affected my life in a horrible way in terms of socializing and even volunteering. Nobody even wants me around because you may say you're not contagious but people don't believe that. Most people say, oh, yeah, and I can clear a subway car, or a bus.

(Laughter)

So if you want a seat, just watch me.

Anyway, it's exhausting as everybody has been saying. It's really exhausting. I'm quiet until I start trying to talk or eat. Even when eating, it seems to trigger a lot of coughing.

So I don't know. I'm working on it from a lot of different angles: swallowing therapy, acid reflux. I'm looking everywhere to try to deal with it, but so far, not much luck.

MS. GIAMBONE: Thank you, Betsy. Can I ask you, how many episodes of coughing do you typically experience?

85

BETSY: A day?

MS. GIAMBONE: In a day.

BETSY: Average day, maybe four.

MS. GIAMBONE: Four episodes.

BETSY: At least. I mean it could be more, but four, yeah. Yeah.

MS. GIAMBONE: Okay. Does that resonate with others about four or so -- just sounds like about 10, 15 minutes of coughing episodes a day? Does that sound similar to your experience? So I'm hearing some, it depends, but I'm seeing head nods also. Okay.

We're hearing that talking, eating can trigger cough, weather changes, it sounds like. What other triggers the cough? I see some hands here.

MS. WEINER: Yes, mold, and I think that is the tie-in with the rainy weather. I've noticed if I'm in the Caribbean -- or I went to Hawaii for our 50th wedding anniversary, rained the whole week, huge reaction. It was very dramatic, and I was really upset that the place we

86

were staying at, which had dehumidifiers, never offered them.

But I think the mold -- I've talked with Joe about this before, I think they're doing some research in France, perhaps in Paris, one of the institutes on this tie-in. And I'd like to see a little bit more of that.

MS. GIAMBONE: Thank you. Marcy, right? Okay, thank you, Marcy.

Continuing -- yes, Marilynn?

MS. LUNDY: I have an extreme coughing story, again a travel story. Traveling changes dramatically when you have this disease. I was in treatment early on, and towards the end of a trip, and I got an exacerbation and was really sick and coughing very, very badly.

It was the end of the trip, and I got home and realized that I wasn't cognitive like I usually am. My mind was working properly but -- and I went to a meeting, and people said, you need to see a neurologist. And it turned out that I had a broken blood vessel in my brain.

87

They did everything to try to diagnose where that came from. They were down behind the heart too see if there were any holes there and so forth and so on. And in the end, they said it's conceivable that it could've been from the coughing.

Luckily for me, it went away in a week. I understand that that's called a mini-stroke. They didn't call it that. They said a broken blood vessel. But the coughing can be really, really unbelievably extreme, especially during an exacerbation.

MS. GIAMBONE: Thank you, Marilynn.

We'll take one comment from Barbara, and then I'm going to check in with the Web.

MS. HUDSON: Well, I was just going to say, the first year I was coughing, I broke two ribs and a vertebrae in my back.

MS. KEATING: I was going to say the same.

MS. HUDSON: The coughing for me may start 10 minutes of trying to clear it. But it

88

could go on for a good 90 minutes, and I'm just down on the floor, on my knees, grabbing my ribs, hacking. So it's not your standard little cough.

MS. GIAMBONE: Barbara, that severe cough that you just mentioned that can last 90 minutes, is that something you experience on a daily basis or how frequently --

MS. HUDSON: It is.

MS. GIAMBONE: Okay.

MS. HUDSON: And I even got a little fearful of coming up here. Usually, I can delay it if I chew gum or something. But I would say 2 to 3 hours a day, I'm coughing a lot, a heavy cough, trying to clear my lungs.

MS. GIAMBONE: Is there a time of day that you experience it?

MS. HUDSON: It doesn't matter. Sometimes using the Aerobika, which is to shake your airways and clear your lungs -- and I can start clearing my lungs, but then it never ends. You know, it's like an eternal fountain there that I'm coughing for 1 to 2 hours, and sometimes I

89

just say to myself, "Well, enough," you know. I just start chewing gum and say, "Let's end this."

MS. GIAMBONE: Okay. Thank you, Barbara. When you mentioned about coughing so hard that you've broken some ribs, I saw a lot of head nods. But I just wanted to turn back to the audience. By a show of hands, how many of you have experienced that sort of severe cough and you've broken ribs?

(Show of hands.)

MS. GIAMBONE: One, two, three, four, five, six, seven -- about seven hands -- eight hands, okay. Thank you.

Let me check in with the Web quickly to see what's coming in, what our Web participants saying.

MS. CHALASANI: So we have 115 participants on the Web with us today, and many of them are echoing what we've been hearing in the room so far. They also say difficulty thinking is a problem. They discuss fatigue. One participant commented on sudden fatigue, which is when she

90

just wants to put her head down on a steering wheel when she's driving. Another participant commented that it's like walking through molasses throughout the day.

As far as triggers, we've heard weather again. Scents are a huge trigger that make them cough and give them shortness of breath. One participant noted that lying down just flat is a trigger as well for them, and so she's afraid to lay down.

Another participant noted that it's just a full time job trying to stay well, especially participants with reflux. This participant has to set an alarm clock after each time he drinks 5 ounces just to make sure that he's able to take care of himself well.

MS. GIAMBONE: Thank you. Thank you for that.

FDA panel, any questions?

(No response.)

Okay. Yes?

FEMALE SPEAKER: Nobody mentioned the

91

coughing, which leads me sometimes to vomit, which is a vicious cycle because I lose my appetite, I don't eat. And I can go for two, three days without eating anything. So it's like a vicious cycle. You know, I could cough so badly that I end up throwing up my guts.

MS. GIAMBONE: And you're losing the appetite because you're just not able to keep it down with the cough, and you just don't feel like eating?

FEMALE SPEAKER: You just don't want to eat.

MS. GIAMBONE: Okay.

FEMALE SPEAKER: You just have that total loss of appetite. Like I said, I can go for two days without eating. I'll drink a protein drink, cough, and it comes right up.

MS. GIAMBONE: Okay. Thank you for sharing that.

Let's look at some of -- a few of you mentioned from other symptoms here, shortness of breath, breathing difficulties, and then a few of

92

you also mentioned other symptoms not mentioned. I'd like to open it up to see if you'd like to share with you some of the breathing difficulties that you mentioned here. What do you experience and how do you experience it?

ANDREA: Thank you. Shortness of breath impacts everything. I have to walk at my pace going down the street, or I end up very winded. Even when I do the suggested breathing, I cannot talk and walk because I don't have enough air or talk on the phone.

I have grandchildren. The fatigue, the chronic fatigue, shortness of breath impacts my interactions with them. I didn't know if you're going to get to loss of -- not loss of appetite, but weight loss, which since I'm on a diabetic diet is impossible.

You can say things that I would eat, that I enjoy, I cannot eat. So protein drinks and this and that. And I manage to just barely keep my weight at -- but I eat all day long. I'll have to work at it constantly. And since I'm watching

93

how much sugar, it's turned into -- I mean all the other things, you pace yourself. You pick the primary thing you have to do that day.

Every once in a while, I have a day where I go through things and get a bunch of things done. But mostly, I do one thing, and then I have to take a nap. I mean, I pretty much go about my business, but it certainly dominates everything I do.

MS. GIAMBONE: Okay. And your name?

ANDREA: I'm Andrea.

MS. GIAMBONE: Andrea, let me ask. You mentioned that you're not able to eat. Again, is it the coughing? We heard earlier that coughing leads to vomiting and that's leading to loss of appetite. What's leading to your loss of appetite?

ANDREA: I don't have a loss of appetite; I eat all the time, but it doesn't --

MS. GIAMBONE: Oh, but the weight -- okay, the weight loss, right.

ANDREA: I mean it's affected by this diabetic diet. Before I was on it, I've been --

94

I've been sick for 18 years. I've been on antibiotics constantly for 9 years, 8 years, whatever. And my sputum is negative, but when I go off it, within two or three weeks, the MAI is back. Plus, Nocardia and Aspergillus, so it's really a constant battle.

MS. GIAMBONE: Thank you. Graham, Meghana, do we have anybody that's waiting on the phone? Okay. So we'll take two callers on the phone. But before we go there, I'd like to ask if there's other symptoms that have not been mentioned through this polling? Is there something that you'd like to share?

Philip, I saw you -- let's hear -- Marilynn?

MS. LUNDY: One of the symptoms that I still am dealing with, often in the support group, a lot of the people seem to have GERD and have been diagnosed with GERD. I'm not sure that I really have GERD, but I belch a lot.

There seems to be air pockets in my system, and I'm not sure what causes it. But it

95

does seem to be a symptom with most of us to have to deal with. And it's not acid reflux or anything like that. It's just like trapped air in parts of the body. I don't know how to explain it other than that.

MS. GIAMBONE: Okay. Okay.

MS. LUNDY: And I'm still dealing with that. Again, my sister can attest to that.

MS. GIAMBONE: Do others experience that by a show of hands?

(Show of hands.)

MS. GIAMBONE: Okay. Gastric issues, I'm hearing. I'm seeing a lot of -- oh, okay, let's see. Keep your hands up real quick. One, two, three, four -- 14 hands, 15 hands raised for that, okay. Other issues not mentioned? We have a hand back there, back there, Sarah, with the black dress. Right there.

MS. PEFFERS: Hi. I'm Mel Peffers. It was bronchiectasis, and then NTM diagnosis, like 10 years apart each. I get joint pain with the night sweats and the fever, and it's like really

96

bad. And it comes and goes. So I just throw in joint pain, and I don't know if other people have that --

MS. GIAMBONE: Okay.

MS. PEFFERS: -- as well as muscle, fatigue and aches. Thanks.

MS. GIAMBONE: Okay. Let's do another show of hands, joint pain?

(Show of hands.)

MS. GIAMBONE: Okay. I'm seeing about eight hands. And we saw others also identify -- we have fever and night sweats, okay. So it looks like others also experience that.

I know we're getting close to the break time here, so I'd like to see from our phone panelists if I have somebody lined up. So go ahead, Graham.

MR. THOMPSON: Operator, can you open the first line?

OPERATOR: Yes, your line is now open.

MS. STEINBERG: Hello?

MS. GIAMBONE: Yes, hello?

97

MS. STEINBERG: How are you?

MS. GIAMBONE: Very good. How are you?

MS. STEINBERG: Okay. So I'm Esther Steinberg. I'm the coordinator and support group leader in Canada. I want to thank you very much for this webcast because it allows many of us to have the access to information sharing that we would otherwise not have.

In Toronto and across Canada where the temperature is changed, I can see from all the patients that everybody is now getting sicker than they were two weeks ago and developing all the symptoms. Right now, I'm watching you from my bed. I can't stop coughing. For a while, I was able to come off the meds, but now I'm going to have to go on.

Listening to everyone at the meeting, we all share the same symptoms, the same pain, the same concerns. We're appreciative.

The one thing I have to say, I know that Philip is there, and I have to add how grateful that we all are to Philip and his late wife, Fern,

98

for all that they have done to bring this disease to the forefront, give us a voice that would not otherwise have been heard.

Philip, if you can hear me, thank you very much.

(Applause.)

MS. GIAMBONE: Thank you so much for your comment.

MS. STEINBERG: There isn't a lot that I can add. It's repeated, it's so common to all of us to watch all this going on and hoping that one day that someone will develop a drug, something that would make our life easier.

I would say that from people that I know, 90 percent of the people push forward through all the symptoms and do whatever they can to give themselves what we now call a new normal life and to keep up the good fight.

MS. GIAMBONE: Thank you so much. There were a lot of people that were nodding along with you, so thank you for sharing that. And we have time for one more caller.

99

Operator, could you open up the line?

OPERATOR: Yes. Cynthia, your line is now open.

CYNTHIA: Thank you.

MS. GIAMBONE: Yes, we can hear you.

CYNTHIA: Hi. I wanted to comment that many of us have what doctors refer to as asthmatic component to the illness. That's why one of the things that would bring on my coughing is exposure to a vast array of lung irritants from diesel fumes to perfumes, anything sprayed that has scent in it, also VOCS or volatile organic compounds from glue, paint, et cetera, air conditioning, sprayed sunscreens. [Indiscernible] used to set off quite a hacking episode.

I don't think that's true of everyone, but it was certainly true for me. I was lucky enough to be a candidate and had a successful middle lobectomy, which greatly improved my condition and reduced that sensitivity. But it's still there.

I fear in the future it may come back.

100

And even now when I'm not as sensitive, I'm aware that those things do irritate my lungs, so I'm kind of scared of being in situations where those thing are present.

Cigarette smoke and campfire smoke are some of the worst. Unfortunately, I can't camp anymore because of that. It's almost impossible to go camping in America without campfires around you.

Anyway, thanks for letting me comment and thank you for doing this.

MS. GIAMBONE: Thank you so much for your comment. Yes, and I believe what you said on the phone, I know others have also mention that smells, different scents can trigger this. So thank you for sharing that.

We are now at break time, but thank you for an incredibly rich discussion on topic 1. And we'll see you back in 15 minutes for our topic 2 discussion.

(Applause.)

(Whereupon, at 10:49 a.m., a recess was

101

taken.)

MS. GIAMBONE: So we're going to go ahead and get started. We had a really great discussion in topic 1. We couldn't get to everything because there was so much to share, and there are so many aspects to it as we talked about.

Again, I'm going to really encourage you to go that public docket. Please, please submit your comments there. They're so important to us, and we will read through every one of them. So if we didn't get to something in topic 1, or if you didn't get share something in topic 1, please do go there, go to the public docket and submit it there.

We also heard some very interesting things that came up during break, which I want to just mention. We heard a symptom that was mentioned. She said, "You know, I'm a little embarrassed to tell you this, but one of the symptoms that many patients experience is, because of the chronic cough, hemorrhoids and leaking."

So by a show of hands, can we see if others also experience that because of the cough?

(Show of hands.)

MS. GIAMBONE: Okay. So I see 11 hands raised, but I'm also hearing that a lot of people may not feel comfortable to raise their hand with that. It's noted that it is a significant -- it's something that definitely does impact you very much.

There were two other questions that came up. Again, we'll do a show of hands for this one. If you were working at the time of your diagnosis, how many of you either had to stop working or you had to significantly alter your work schedule because of your diagnosis? Okay, let's see.

(Show of hands.)

MS. GIAMBONE: Let's see. I'm seeing 17 hands raised, but it definitely sounds like it's a very, very important aspect of this. Okay.

Then last but not the least, and I think this is really a place for the public docket again, one question that we did have raised from

the FDA panel was with the fatigue. If you experience it even at rest, or if you experience it only during activity.

So keep that in mind, and if you can take that and answer that in the docket, it's going to be very helpful for us to read through. You can see so many really important considerations that came up in topic 1. Panel 2 Comments on Topic 2

MS. GIAMBONE: Now, we're ready to start topic 2. Again, we have five panelists here, and they've worked very, very hard to put these comments together, so thank you for that.

Topic 2 is on patient perspectives to treating their NTM lung infections. What's working, what's not working, what are the downsides, and what do you look for in an ideal treatment. So that's what we're focused on for this segment.

On that, I'd like to get started. Betsy, we have you going first.

MS. GLAESER: Well, I'm 76, and I've had

NTM for 16 years, and probably bronchiectasis for even longer than that. I started with avium in '99, but beginning two years later and until today, I've had abscessus. Surgery was never an option, much too much damage by the time I was diagnosed.

Recently, the avium has reappeared and joined the abscessus, which probably is somewhat unusual. I have never had a negative abscessus culture and have never been off an average of 6 to 7 drugs a day targeting NTM, the bacterial, and fungal infections.

My NTM symptoms -- and I know from my New York group, my symptoms are just what you all have discussed, and my airway clearance, including the saline rinse, which is a good idea, and my non-prescription meds that are not unusual, so I'm not going to talk about them.

As expected, I have lost lung function. My PFTs are now in the 45, 65 percent of predicted range. Drugs have slowed, but they've not stopped the deterioration. Of course, bronchiectasis

progresses.

I want to emphasize the huge importance of exercise. In my case, training in a gym, plus the usual New York walking to my quality of life. Exercise is my only secret weapon, and it's the reason some people say I'm better than my numbers.

Looking first at NTM medications, I started off with the standard 3-drug cocktail:

clarithromycin, ethambutol, rifampin.

But I stayed on this when they added meds for abscessus two years later.

If I start a drug and can tolerate it, and it's not proved to be useless or to interfere with a drug I need more, I will be kept on it. The infections being treated are recurrent and chronic.

Fluoroquinolones were added in '01, and after cipro and Levaquin had side effects, I moved on to moxifloxacin -- you know it as Avelox -- and I still take it. Many drugs have been with me for 10 to 16 years.

Now, at times, the drugs for abscessus

106

were stopped because of toxic, sometimes life-threatening side effects. Initial treatment involved IV, EMI, and then meropenem, followed by IV cefoxitin. Desensitization bought only limited time. All three drugs were effective, but they produced, for me, anaphylactic type reactions, and they sent me to the emergency room.

In 2006, still searching for something to combat abscessus, I was started on linezolid. I took it for a full year. I felt great, but I had to stop because I developed neuropathy, numb toes in both feet, which never improved. But it was the most effective drug for my NTM that I'd ever taken, and it was an oral, not an IV.

I inhaled generic amikacin for 8 months in 2009. While improving energy, reducing cough, and hitting two infections, amikacin left me with serious life-limiting, not threatening but limiting, side effects, which appeared quite suddenly.

I now have two hearing aids, I suffered severe vertigo initially, and I'm still sensitive

107

to certain stimuli. I made the mistake of riding backwards coming to Washington on the train yesterday; that was a terrible mistake. The damage to my vestibular, which is your inner ear, produces frequent dizziness and poor balance. I'm a fall risk three times this year.

Now, beginning about five years after diagnosis, half of my meds were targeting gram positive and negative infections, which then became more active. Pseudomonas is recurrent and common in NTM and CF patients. Effective drugs for me were the IV aztreonam, taken for six months in '04, and the inhaled generic amikacin that I mentioned.

Klebsiella pneumoniae is my most stubborn recurring drug. Of no use was IV tigecycline for 11 months in '07 despite high sensitivity in the lab. Augmentin was ineffective. But the inhaled generic amikacin, I mentioned, hit both the Pseudomonas and the Klebsiella. It was an enormous surprise that it hit the Klebsiella, and perhaps it was due to synergies with other

108

drugs.

Recently, after two and a half years on nebulized aztreonam called Cayston, neither my Klebsiella nor Pseudomonas shows up in cultures. It's unclear why, but Cayston has been a fantastic drug for me. I have more treadmill stamina -- yes, I do treadmill and I do weights and so on -- higher saturation, energy, mental acuity, and I'm clearly stronger than three years ago. I no longer take the portable oxygen concentrator to the gym.

Serratia was treated by Bactrim from '05, and I still take it. I do wonder if the NTM patient is producing something particular, which is very appealing to all these bugs. Fungal infections have been with me for all 16 years in different forms and locations treated by posaconazole and fluconazole.

Statistics in '99 predicted I should have died years ago. My lungs deteriorate slowly but steadily, but I'm not on any drugs right now, specifically for abscessus, and there are now no

109

new NTM-focused drugs which would work for me that I'm aware of.

I know I'm out of time or close. I'd just like another minute to list some ideas for new or improved treatments: a fast approval of inhaled drugs, especially liposomal whose higher concentration in even my damaged lungs penetrates more than IV. Look at longer-term drug side effects.

I mean I'm on drugs for 16 years, but my amikacin damage occurred after 8 months, 5 days a week. Study of breakpoints and risk would be helpful. Drugs to combat resistance, common NTM infections like Klebsiella, an ESBL producer, or certain abscessus species like mine are resistant.

Faster NTM species identification by more labs would permit drugs to target specific species. Then FDA approvals should support the resulting new drugs, which will become available from this species identification.

Encouragement of treatments based on genetic research, identifying NTM and diseases

110

with relevant profiles and genetic mutation. Is there anything to increase energy without undesirable side effects? How about Ritalin for NTM?

(Laughter.)

MS. GLAESER: Two studies I participated in could lead to effective treatment. One was a proof of concept, testing whether sildenafil, Viagra, increased ciliary beat frequency, which is too slow in NTM and CF patients, thus increasing lung protective performance.

The test was would the Viagra increase the ciliary beat? It did. Incidentally, Viagra did nothing for me except it gave me a headache, for two days. Disappointing.

This work could lead to strategies to reduce NTM vulnerability initially and as part of treatment. Second, I participated in a research effort testing interferon gamma against NTM. Immunology could be a very fruitful route.

In conclusion, my present level of functioning owes everything to great doctors and

111

the aggressive use of our present multiple long-term meds mainly adapted from other diseases like TB, also, my own competitive drive not to let NTM beat me, initially, not before I saw my first grandchild. But he's 10 now, so now I'm going for a high school graduation.

Still, my personal NTM future is not reassuring without new approaches to NTM drugs, which I trust this important FDA conference will encourage. Thank you for letting me speak.

MS. GIAMBONE: Thank you, Betsy.

(Applause.)

Next, we have Patricia.

MS. YOST: Good morning. My name is Patricia Yost, and I am from Bucks County, Pennsylvania. I'm a retired middle school and high school English and theater teacher of 33 years. I was diagnosed with mycobacterium avium and bronchiectasis in 1995 at age 38.

I have been under treatment, in other words, taking medicines and dealing with my disease since 1995. As it has always been active

112

and producing positive sputum results, I have never had a negative sputum culture.

My medicine treatment for that past 20 years has included many different drugs taken every day and administered orally, intravenously, nebulized, and inhaled in the attempt to slow the growth of the bacteria, as well as to minimize the damaging effects to my lungs.

Currently, I take clarithromycin, Biaxin, and rifampin to slow the growth of the disease; ipratropium bromide and albuterol to help bring up more mucous and sputum to try to avoid yet another bout with pneumonia; decongestants to help dry up excess mucous; Prilosec for my acid reflux; Prozac for the negative emotional effects of dealing with a chronic disease; and vitamins and probiotics to balance the negative effects of the medications on my digestive system and the many yeast infections including thrush.

Additionally, I was recently accepted and admitted to the current clinical trial at the University of Pennsylvania for the inhaled

113

liposomal, amikacin; so I am also taking the inhaled liposomal amikacin through a nebulizer every day as well.

In the past, I have taken ethambutol and voriconazole. However, these medications were discontinued because of their damaging effects to my optic nerve. I had taken Levaquin after a severe pneumonia requiring a chest tube for drainage back in 2008, but that was stopped so that I would not build resistance to that drug in case I needed it again for something.

The non-drug therapies for my disease include the daily use of the percussion vest therapy, the use of the Acapella device, exercise, meditation and prayer, and my very supportive family, especially my wonderful husband who is very understanding and helps.

All of my treatments have helped in slowing down the growth of the disease and clearing the increased mucous from my lungs over the years, but the disease continues to grow and damage my lungs and diminish my lung capacity.

114

I retired early from teaching and no longer can participate in my theater or music activities because the constant coughing from bringing up the sputum has affected my vocal chords, which is obvious, and the medications cause nausea and increased acid reflux, fatigue, itchy skin, lingering hearing and eyesight problems, restless sleep, and numbness in my toes.

Additionally, it is inconvenient to travel as I must bring my vest and nebulizer machines with me, as well as administer my other treatments twice a day.

In conclusion, having NTM and treating NTM is a daily struggle and has been for me for the past 20 years. As there is no cure, I will continue to deal with its impact and the impact of the treatments for years to come. I hope and pray that something will work to minimize the negative effects and perhaps grant me the possibility of finally getting a negative sputum culture and a reprieve from taking medicines every day.

Thank you for your time and considerate

115

compassion to learn the patients' perspectives concerning the effects and impact of the disease and its treatments. Also, thank you for encouraging the research and clinical trials from new medications and treatments to help in our daily struggle for a normal and healthy life free from this insidious disease. Thank you.

MS. GIAMBONE: Thank you so much, Patricia.

(Applause.)

Next, we have Gaby and her son, Arthur.

MS. CHIEN: Good morning, gentlemen, ladies. Thank you for allowing me to speak today. My name is Gaby Chien. I'm retired after running an international business for 30 years. I'm 77 years old and a proud mother of my three children.

This is my son, Arthur, who encouraged me to come over today to have my voice to speak out for the NTM patients.

Thank you, Arthur. He says, "Mom, in case you're short of breath, I will continue your testimony today."

116

I'm here today to personally highlight the devastating effect of M. abscessus and to implore the FDA to take steps immediately to advance treatment that's existing today, yet are not made available to those who suffer from NTM and are short on time like me. My full commitment has been submitted for the record, so I will get to the heart of it.

Diagnosis in 2010. I have undergone various treatment approaches. I have taken at least 10 and different kinds of antibiotics from [indiscernible] to pills to inhale. Those include cefoxitin, tigecycline, Flovent, cipro, to name a few.

With little known about M. abscessus, I was like a human experiment. My reaction was invariable from loss, my balance, and the rashes from across my body from the leg, itch, red, swollen, through the arms and the face.

I have a blurred vision and I paint. Fatigue, shortness of breath, sweat and a loss of hearing and the loss of sensation on my lips and

117

my tongue are a few of the side effects I record.

This was the only known approach, one that has required me to eliminate trouble, restrict all physical activities including exercise, remain indoors. At times, I can barely hold conversation with my children, with my friends, with my grandchildren, and so on.

I beg the FDA a fast track treatment where they be promising drugs that should be given priority to become clinical trials to support other drugs already in that process.

I am also here to tell you we need accessibility of this treatment, that healthcare system is taking a toll on us. I'm currently on triple therapy of antibiotics. Those are macin [ph], amikacin, and linezolid, Zyvox; the project treatment duration, 18 months.

The cost of linezolid, a month's supply, is $6,000. Because my insurance company, United Healthcare has denied the coverage saying NTM is an off label use, it cannot approve. My Medicare Part D benefits refuse to cover as well as the

118

AARP Medicare Complete.
Tens of thousands of dollars in cash for this one medication that has benefited fully from its patent period is not what our government would tell me and my fellow NTM patients is the best we can do, when in other countries, linezolid is sold for under $600 a month without insurance.
I have been a taxpayer, law-abiding citizen my entire life. I beg this panel, for we want to live to use the retirement years I have earned to be with my family, my children, and my grandchildren.
Please, urgently help me and my fellow sufferees by making the currently available options like linezolid obtainable and to be a force in urgently supporting present research to help us overcome NTM.
Thank you with all my heart. I pray the next time we meet, we'll be celebrating progress. Thank you.
(Applause.)
MS. GIAMBONE: Thank you, Gaby. Thank

119

you so much, Gaby. Next, we have Jennifer.
MS. BOGENRIEF: Hi. My name is Jennifer. I was 35 years old when doctors found a spot in my lung, and I was diagnosed with M. xenopi in December of 2011, and I completed treatment in December of 2013.
I went through intense treatment, and I'll tell you about that. I'm currently clear of infection although the stories that I'm hearing today are terrifying because I have been told by my doctor that there's a very high likelihood that I will have recurrence, if not of M. xenopi, of some other strain.
After having a lung wedge resection surgery to remove the nodule in my right lung in November of 2011, I was diagnosed with M. xenopi, which is considered rare in the United States so treatment was very unknown.
My physicians at Johns Hopkins, which I was lucky enough to go to -- that was the first place that I went for treatment -- they were able

120

to consult with physicians at National Jewish Health to develop a treatment protocol.
Johns Hopkins had told me at the time that they had not seen M. xenopi since 1999, so they weren't really sure what to do with it, which when you're that young and you're looking to -- you're just starting, I had recently been married, it's not a very good outlook for your future when you're being told that they don't know what to do, how to treat you.
I had a port put in, and I did 8 months of amikacin infusions. I did those three times a week; it was 750 milligrams. Then I did, on top of that, and then going beyond, I did 22 months of antibiotic treatment: azithromycin 500 milligrams once a day; ethambutol 400 milligrams twice a day; rifampin 300 milligrams twice a day; and isoniazid -- I never know how to pronounce that one -- 150 milligrams twice a day.
I also too Vitamin B6 because I developed neuropathy, I believe, from the amikacin fairly early on. My legs, feet and hands and even

121

arms would fall asleep in a pretty quick amount of time, which is a problem because my job involved sitting at a computer, so I was constantly moving around to try and to keep myself awake.
I also took probiotics. I ate yogurt daily to help with my upset stomach, and I started acupuncture. I haven't heard that mentioned yet. Acupuncture for me was critical, and I continue it now.
All of these medications were an addition to my usual medications for asthma, which I've had since I was seven. Asthma kind of complicated things for me because it's difficult when you have shortness of breath to understand whether it's from the asthma or if it's from the infection.
For me, we talked a lot about fatigue today, and I did have a lot of fatigue, but it hit me after I had my surgery. It was completely overwhelming. I was a very active person before my infection, and it greatly reduced -- I basically became a couch potato. It was all I

122

could do to go to work and then come home at the end of the day, which was a shorter day than it had been previously because of the fatigue.

Thank goodness my husband is a good cook and he doesn't mind cooking because I did not have the energy to cook, and he was a lifesaver for me. He was very supportive.

The symptoms that my treatments addressed were I had a very painful cough. It almost sounded like barking that often left me doubled-over. And it was infrequent, so at first, I didn't realize that there was something that should be addressed necessarily.

I know with asthma and allergies, I have a history of bronchitis and pneumonia, and so you never really know at first, before a diagnosis that something is more seriously wrong. The cough went away right after surgery, and I had shortness of breath also that actually was the first thing that I noticed back in 2009. That gradually went away as I recovered from the surgery.

The prescription medications,

123

antibiotics seem to have gotten rid of the infection for me. My CT scans have improved, and they continue to improve after the treatment ended, which was sort of surprising to me that even a year later, my scans were still improving after I ended the antibiotics.

The Vitamin B6 helped with the neuropathy as well as the acupuncture, which I've mentioned. My acupuncturist was addressing lungs, liver, and kidney function, which suffered because of the antibiotics. I was doing weekly blood draws to monitor liver and kidney function. And at one point, I was told by my doctor that if things didn't improve the next time, I would have to discontinue -- I believe it was the rifampin. I can't remember for sure but --

I started acupuncture actually right after that. And within a week, my liver and kidney function was better. So I very firmly believe in acupuncture, and I really wish that it was something that was covered by insurance across the board because I think it is very helpful.

124

There weren't any changes to my treatment regimen until my treatment ended, and it was determined to be effective. I stopped the amikacin after 8 months on advice from National Jewish Health, and I ended all of the other antibiotics after 22 months. That decision was made after my CT scans showed improvement, and I had a negative sputum culture, which actually, I've never had a positive sputum culture.

Unlike what sounds like most people here, I have not had a problem with excessive -- with coughing up sputum. I had a cough, but it was a non-productive cough that was sort of frustrating because they couldn't test anything to find out what I had, which was part of why I needed to have the surgery, that, and to get rid of the nodule.

Like I said, I currently don't really have symptoms. I do still have asthma, and I always kind of wonder when I'm feeling a little bit worse, is it coming back. The treatment seems to have reversed my disease. Talking about how

125

the therapy improved my ability to do activities that were important to me, I was able to do infusions at home because of my port and a weekly home nurse visit, which allowed me to continue working full time, which was really important to me.

I barely had any savings at the time that this started. I was pretty young, and I needed to work. And my husband, he works too. We both needed to be working. Washington, DC is where we live, and it's an expensive place to live, and working was critical to me. In addition to the fact that I think that if I hadn't been able to work, I would've slept my life away on the couch and in bed because really, getting up and going to work every day was what kept me going.

MS. GIAMBONE: Jennifer, any final remarks on what you look for in an ideal treatment?

MS. BOGENRIEF: Sure. Let's see. One of the things I wanted to mention was the antibiotic schedule was complicated. Some of the

126

foods have to be taken with -- some of the medication has to be taken with food; some has to be taken on an empty stomach. That's difficult especially when you're trying to travel. And I used to travel; didn't travel as much going through the treatment.

I think I've talked about a lot of things. Some of the things about ideal treatment, better upfront communication from the physician about what the treatment entails. And I think that as we hear stories from other patients, it becomes more clear what maybe works for some people and what doesn't. And it's difficult because different drugs work for different people.

But in the beginning, it was very unclear to me what the treatment would be like, and I was originally told that it would be up to 6 months, and then it ended up being 22 months.

In the middle of all of this, my husband I wanted to start a family, and that is something that you cannot do when you're taking five antibiotics, including amikacin infusions. And we

127

weren't able to do that, and we have not yet been able to do that. And that is something that is a big impact on a person's life when a disease impacts that ability to have a family.

One other important thing was coordination between the infectious disease doctor and the primary care physician was very important for me because they were great about talking to each other and being very responsive to me. Thank you for this opportunity.

MS. GIAMBONE: Thank you so much, Jennifer.

(Applause.)

MS. GIAMBONE: And finally, we have Mary.

MS. FISHER: Hi. I'm Mary Fisher, and I'm from Northern Michigan. I originally started getting sick in 2006 with a cough and fatigue. To make a long story short, living in rural Michigan, there was nobody that had a clue what was going on, and I ended up with a right middle lobe resection thinking I had cancer, which turned out

128

to be a granuloma, which nobody bothered to culture. And 10 months later, I was sick again.

I was finally diagnosed with NTM abscessus in 2008. At that time, they put me on IV amikacin, IV cefoxitin, and oral azithromycin. After three months, they removed the amikacin and the cefoxitin due to increased kidney function tests.

For the past seven years, with a few drug holidays here and there, I have remained on inhaled amikacin and oral azithromycin. In 2011, the investigational drug clofazimine was added to the regimen as research showed that it had a synergistic effect with amikacin.

Over the course of my illness, I've had five cycles of IV cefoxitin, one round of IV imipenem, and two rounds of tigecycline. Even though my sputum cultures indicated sensitivity to these medications, I rarely converted to a negative.

To my knowledge at that this point for my particular abscessus, there are no other

129

antibiotics that are available for me to try.

I've also developed neuropathy, nerve pain and muscle spasms due to the two chest surgeries that I had. After the second surgery is when they started me on Lyrica, which had minimal effect. I've had better results with a heating pad and massage therapy.

During the time I had only three negative cultures, prior to my second surgery, they started IV tigecycline. When the damaged lung was cultured, it was negative. However, tigecycline was discontinued due to the low protein and albumin levels along with decreased blood sugars. Two months after it was withdrawn, the sputum returned positive.

Prior to my diagnosis, I was very active and extremely independent. I cleaned my own home, planted my flower gardens, traveled quite a bit, and took care of my horses. After years of antibiotics, my disease only progressed, and I no longer could do those activities due to decreased energy and stamina.

130

I had to hire somebody to help clean the house, help with my flower gardens. But when I was told to find someone to take care of my horse, that's when I drew the line. I said, you cannot take away the only activity that brings me the most pleasure.

When I feel down or depressed, I will go to the barn or pasture and just seeing her brightens my day. Spending time with her allows me to forget about my illness for a while.

The most significant downsides for me are the timing of multiple medications. I take azithromycin, which can be taken with or without food, but they recommend without food for better absorption.

The clofazimine needs to be taken with food. Omeprazole needs to be taken 30 minutes before you eat. Calcium should not be taken two hours before your antibiotics because it has neutralizing effect. Probiotics should not be taken 3 to 4 hours next to the antibiotics because it will render them useless.

131

I also take another medication that has to be taken four times a day. Three times a week, I need an hour or two to take my inhaled amikacin. When IV antibiotics enter the regimen, they are usually 2 to 3 times a day.

Finally, I need to incorporate one hour of exercise four times a week. I echo what Betsy says. My pulmonary rehab and exercise have been my lifesavers. It's very hard to work, plan any social activities or get projects done around the house when my days are dictated by all these treatments.

The whole process is very difficult and frustrating. I would like to see medications that are developed that do not have so many interactions that require so much time and effort to take, that you can have simplelize [ph] the process.

I would also like to see a medication if we cannot find a cure that would at least suppress or put the infection into remission for more than a few months while decreasing the further damage

132

of my lungs.

MS. GIAMBONE: Thank you so much, Mary.

(Applause.)

MS. GIAMBONE: Thank you to all of our panelists. I know we've clapped after each one of you has spoken, but collectively, you've all just done such a great job preparing for all of this and being here and sharing those stories with us, so thank you so much. Large Group Facilitated Discussion on Topic 2

MS. GIAMBONE: So once again, I'm going to ask the question by a show of hands, what you heard today on the panel, how much of it resonates with you? Similar experiences?

(Show of hands.)

We see about 12 or 13 hands raised. Another few exercises of show of hands. We heard through the panel that you've had to try many different medications and you've had to stop for various reasons.

You stopped for bad side effects, so let's see a show of hands there. How many of had

133

that experience? So you stopped taking medication because of the side effects.

(Show of hands.)

MS. GIAMBONE: So I see about six hands.

You've stopped because the medication stopped working. So let's see some hands for that.

(Show of hands.)

MS. GIAMBONE: I see about seven hands. And then I also heard that you had to stop so you would not get desensitized to that particular medication. Let's see.

(Show of hands)

MS. GIAMBONE: I see one hand for that -- actually, I see three hands for that. Okay, great. Thank you for sharing that.

Now, we have a polling question. All right. So everybody who answered before, patients and caregivers, let's get your clickers out. Have you ever used any of the following drug therapies to help treat the NTM lung infection? A, oral antibacterials; B, IV antibacterials; C, steroids;

134

D, inhaled therapies; E, other prescription medication such as pain medication; F, other drugs not mentioned; or G, I'm not sure?

AUDIENCE: (Inaudible).

MS. GIAMBONE: Sorry? Yes, you can check all that apply.

(Polling audience.)

MS. GIAMBONE: Okay. So it looks like actually nearly all of you that are responding are taking or have taken oral antibacterials, followed by B and D, so IV antibacterials and D, inhaled therapies. And then it looks like we also have a nice range of other ones, too, including some drug therapies not mentioned here.

What are we seeing on the Web?

MR. THOMPSON: Similar for the oral antibacterial, about 85 percent; only 21 percent for intravenous antibacterial; 46 percent for steroids, which is more than in the room, 40 percent for inhaled therapies; and then around 20 percent for the rest.

MS. GIAMBONE: Okay. Thank you.

135

So what I'd like to do is kind of open this up to any of what you've answered here. But the question that I'd like to ask you is, what symptom is your medication -- what is it for and how do you know that it's working? How do you know that the medication that you're taking is actually making a positive difference? And then we're going to spend some time hearing about the downsides.

But how do you know that a medication is working for you? What symptom is improving? Let's see. Why don't we go to --

JEANNE: Hello, my name is Jeanne, and I'm from around Dayton. I was diagnosed two years ago with MAC and about a year later with abscessus. I also have Staph, which has been my biggest problem.

My treatment, they have not put me on treatment for either the MAC or the abscessus because the Staph has been the biggest problem. I was on Duricef for a while; that did not work.

Currently, I'm on cephalexin. I took it

136

for 10 days, and now they have me on a daily regimen with it. And I tell you what, I feel so much better. I can work better now.

I'm a retired nurse, but I go back now and help them in cardiology once a week for sure and then vacations, then whenever they can use me, and I'm agreeing to come in. But this is the first time in a year that I can say that I feel better.

My energy is better. My appetite is better. I'm now maintaining my weight. I have lost 16 pounds in the last year, unavoidable because there was no appetite. This wonderful man here made a special trip out for ice cream one night because that's the only thing I felt like I could eat. I call it swallow food. You don't have to use any energy. You just put it in and it goes down.

So this is helping me right now. They're not sure if and when -- my two doctors, ID doctors -- I have one in Florida that I see during the winter when I'm there, and one in Ohio when

137

we're there in the summer. And they are both in total agreement that, well, it's definitely not time, and they're not sure if it ever will be.

MS. GIAMBONE: Thank you.

JEANNE: I don't know. Listening to all of you, it makes me question some of this. But I will say that the doctor that I see in Florida is very closely associated with National Jewish Hospital. And he's offered to send me there, but he said they would turn around and send me right back to him. So I'm comfortable with that.

MS. GIAMBONE: Thank you so much for sharing that.

How about some of the downsides that you're experiencing with these therapies? Can you talk about what it is you're taking and specifically what is the downside that you're experiencing?

LAURA: My name is Laura. In 2006, at the age of 46, I was diagnosed with NTM, and then one year later, I entered the NTM study at the wonderful National Institute for Health. While I

138

was there, I discovered I was also ZZ alpha 1 antitrypsin deficient patient. So I started on the cocktail of three oral antibiotics, every one which has been mentioned up here, linezolid, ethambutol, rifampin, azithromycin.

After five years, they added clofazimine. I never had any serious side effects, upset stomach. I was very fortunate. I tolerated them. But after six years and I'm up to four oral antibiotics, I had peripheral neuropathy. I have hearing loss. I have ringing in my ears.

What else? My FEV1, when I was first entered in the study, was 92 percent, and I'm now down to the mid-70 percent, so the drugs just weren't working. But then in 2013, I entered the clinical trial for the inhaled form of liposomal form of amikacin, and 60 days later, I cultured negative, and I've cultured negative ever since.

That's kind of the negative and the positive of what the oral antibiotics were doing for me and then how positive the inhaled therapy has worked for me. I actually have a sputum

139

sample up in NIH this week, and I'm keeping my fingers crossed I'm still negative.

MS. GIAMBONE: Great to hear. Thank you so much. And your name, sorry?

LAURA: Laura.

MS. GIAMBONE: Laura. Thank you, Laura, for your comments.

LAURA: Yes, thank you. Thank you for this meeting here.

MS. GIAMBONE: So I do want to do a show of hands here. Laura, you mentioned that the inhaled therapies are working. Is it that the inhaled therapy is working better for you, and is it easier for you, too, also to take inhaled therapy?

LAURA: I tried malfunction.]

FEMALE SPEAKER: We can't hear her.

MS. GIAMBONE: Still can't hear? Okay. Go ahead.

LAURA: So the inhaled therapy was not that difficult. It was a little tedious because

140

there was a nebulizer you had to keep clean. And I travel for my job, so I had to take it with me on an airplane and do it in a hotel room, and then sterilize the equipment. But it was very effective. I mean within 60 days, I was culturing negative.

MS. GIAMBONE: Okay, great. Thank you for that.

But I did want to do a show of hands for is that we've heard a range of downsides. We've heard neuropathy from several people, and I just want to do a show of hands if others also experience that as a significant downside to the treatments.

(Show of hands.)

MS. GIAMBONE: I see about 8 hands raised -- or 9 hands raised for that.

I've also heard mentioned vision loss, hearing loss. Again, others with that also?

(Show of hands.)

MS. GIAMBONE: I see 11 hands there.

Okay. So let me check in with the Web

141

quickly and see what we're hearing there.

MS. CHALASANI: Sure. We have 130 participants now on the Web and a very active conversation, much echoing what we've heard in the room that some people say that they know when the meds are working because their cough is not as deep or the choking mucous sort of eases up.

But just as many participants are saying that they have no idea that the drug is helping them. They only know when they go into to go their lab results, and that's when they know that it's actually helping them.

Lots of talk about vision and hearing loss, and then some non-drug therapies mentioned, include behavioral changes, adding postural and nutritional behavior modifications. And there's some talk about a hypertonic saline solution as well.

MS. GIAMBONE: Okay, great. Any other comments on either the therapies that are up here or a drug therapy not mentioned, what was that therapy; how did you experience it, what was the

142

down side of it?
MS. BRESLAWSKY: Hi. My name is Debbie Breslawsky. I would like to say a couple of things. I'll keep it short.
One is I was on inhaled amikacin as well as IV, and I found that I was able to tolerate the inhaled much better than the IV. In fact, I had to be taken off the IV because of tinnitus, a ringing in the ears.
Perhaps maybe there should be a focus, if there has to be, on inhaled, which goes straight into the lungs rather than any other type, not to say we want to discord anything else.
But the other thing I would to bring up is that I know that we have some really tough side effects from some of these meds. I'm probably speaking for many people in this room, but probably not everybody, depending on what the side effects are.
We're in a situation right now that we have limited options. I, for one, would take the side effects of these drugs or of any other new

143

drugs knowing that there are no other options and knowing that the progression won't go any further than what it is or progress slowly.
I just wanted to mention that because these side effects are tough, and I have to say I've had many myself, but I've just stuck with it. Probably they weren't as bad as some other people's descriptions, but I just rather have the drugs and not have the drugs, and not fear that I'm going to get really bad in the future. I wanted to make that point.
MS. GIAMBONE: Thank you for sharing that. In just a few moments, we will talk on a similar issue. We're going to have a scenario that goes right into that, what you just brought up.
Yes, we have one comment here.
FEMALE SPEAKER: I just like to say there are two fairly non-invasive medical therapies that really helped me. I was told if I had bronchiectasis to get a test for a sleep study, sleep apnea. And so CPAP really helped

144

with the fatigue, even though I still have fatigue. Seven percent saline and the Aerobika that I was told about at National Jewish were extremely helpful for immediately bringing up mucous, and just amazing for me.
Then weight training reversed my osteoporosis, and food. I avoid dairy. I don't know if it's the lactose. I really would like a study on dairy, inflammation for the GI and lungs.
MS. GIAMBONE: Thank you so much. Any other -- yes, we had one.
FEMALE SPEAKER: Sorry. It's me again. I'll make it quick. I did probably the three that we all start with, rifampin, azithromycin. By the way, that may have orange -- it's totally orange. I mean, there's no way around that. There's weird side effects. But you do that.
I then keep getting the sputum samples, and then went on an inhaled amikacin. For me, it was it was awesome in the clinical trial. I had a little nebulizer I could travel with. I just put that thing -- you could go through TSA. You bring

145

your drug stuff. You can travel with that puppy; it was great.
For me, the inhaled amikacin, way to go. The better symptoms were -- yeah, I produced a lot of phlegm, but then afterwards, I got the clean sputum sample results. Yay! I got a negative, and gained 10 pounds. Boom! It was like the weight came right back on. So that was great, and it wasn't like I changed my diet or started eating more. The NTM was obviously yummy eating that.
But one other thing I'd like to bring up is I love the goals Phil put out, which he had three, which was really nice. He was like extended life, quality of life, and less toxic drugs. But one other one I'd like to add -- because it's not even on the agenda -- early diagnosis.
Every single one of us will have stories. I went 10 years before -- well, I went 10 years before bronchiectasis diagnosis; then I had 10 years before the NTM. People send sputum samples out. They don't have the right paperwork.

146

You don't know where to send the sputum samples out. Earlier diagnosis I think will definitely help because everybody is like, Oh, you're so young.

I think I'm going to check white privilege here. I have good health insurance. I kept going to doctors. People saying, oh, it's TB; oh, it's cystic fibrosis; oh, it's this. I kept going.

I think there's a lot of other people outside of my demographic that have these sorts of diseases. Earlier diagnosis and better diagnosis I think could really help. So there.

MS. GIAMBONE: Thank you for sharing that.

I'm hearing a lot of people say that inhaled therapies have worked a little bit better for them than the oral therapies. Okay. Let's take one more comment.

DEBBIE: I'd just like to echo what Gaby was saying about linezolid. I am fortunate to be a nuisance to my insurance company and my

147

employer, who provides lifetime health insurance for which I am very grateful. But I did not get my linezolid covered without a major, major battle.

I am also fortunate not to be on Medicare yet, and yet linezolid was the only drug that my sputum sample showed was going to be effective. I think it's crazy that those sorts of medications, because they're off label, won't be covered.

I fought a battle, and it cost me $300 a month as opposed to $2500. And I would've paid out of pocket, but not everyone is in that position. And you shouldn't have to fight for a medicine that medical tests show should help your disease.

MS. GIAMBONE: Thank you for sharing that. And your name?

DEBBIE: Debbie.

MS. GIAMBONE: Debbie. Thank you, Debbie.

Okay. Let's do a quick polling

148

question. We've heard a lot of other therapies that you're also using such as acupuncture. I do want to make sure we get to the next polling question. Then we won't spend too much time on it. We'll go into the scenario question, where we're going to hear your thoughts on if you would participate in a hypothetical trial given some data.

So let's answer this question so we have the results recorded, and then we'll go forward.

Besides your drug therapies, what else are you doing to manage any symptoms you have experienced because of your NTM lung infection? A, cough medicines; B, supplemental oxygen; C, pulmonary rehab; D, breathing exercises; E, dietary supplements; F, diet modifications; G, complimentary or alternative therapies; H, other therapies not mentioned; or I, I'm not doing or taking any therapies to treat symptoms?

While we're answering that, I'm just going to put a plug-in for those on the webcast. If you're interested in sharing some comments on

149

ideal treatments by phone, we'll check in, in just a little bit.

So it looks like over half of you in the room are doing some breathing exercises or relaxation techniques, dietary supplements, and then it looks we have a good range of everything else to pulmonary rehab, diet modifications. Okay, great.

What did we see on the Web for this?

MR. THOMPSON: For cough medicine, supplemental oxygen and pulmonary rehabilitation, around 15 percent for each; 53 percent, breathing exercise/relaxation techniques; 56 percent, dietary supplements; 40 percent, diet modifications and alternative oral therapies; and then 20 percent, therapies not mentioned.

MS. GIAMBONE: Thank you. Okay. Let's go to our scenario question. I'm going to read this out loud in just a second, but the scenario question is we're going to present you with this scenario regarding a clinical study. We're not giving you a lot of data here. This is just the

150

hypothetical. But what's important to us is some of the first considerations or questions that come to mind. We want to hear what those are.

Then like I said, in the afternoon, we're going to have a discussion on clinical trial design. But for now, we want to hear your immediate thoughts when you imagine that you've been invited to participate in a clinical trial to study an experimental antibiotic treatment for NTM lung infections.

The purpose of the study is to better understand how well this treatment works and its safety. The clinical trial lasts two years and clinical visits will occur every month for two years in addition to your regular doctor's visits.

These visits will involve monthly sputum collections, lab tests, lung function tests, and other lab tests as needed. Treatments may involve either IV medication or inhaled therapy, and treatment will be given in addition to your standard of care.

Given just this amount of information,

151

what thoughts or questions come to your mind when you hear this scenario? It can be anything. What's the first thing that comes to your mind when you see this and how you would consider participating?

DEBORAH: Probably, the first question comes to my mind since I'd been on IVs and I've gone on inhaled, why 1 to 2 hours?

MS. GIAMBONE: So why is the IV --

DEBORAH: Why the length of time.

MS. GIAMBONE: Okay. Why that length of time.

DEBORAH: I'm not saying I wouldn't do it, but that's the first thing that I thought.

MS. GIAMBONE: Sure. Okay, thank you, Deborah. Philip?

MR. LEITMAN: If the patient is not already on IV, in order to participate in IV, they're going to have to have something inserted. That seems very, very challenging to me.

MS. GIAMBONE: Okay. Thank you, Philip.

Other thoughts?

152

FEMALE SPEAKER: Do I have to stop the meds I'm currently on to participate?

MS. GIAMBONE: Okay. Do you have to stop the meds that you're currently on to participate? I saw a lot of heads nodding for that. But it's in addition to your -- FDA panel, you'll have to chime in here. This is in addition to the standard of care.

So you wouldn't be stopping, right? Is that what I'm understanding? Okay. Good question. Thank you for asking.

We have another -- sorry. Yes, Patricia?

MS. YOST: Sign me up.

(Laughter)

MS. GIAMBONE: Sign you up. Got it. So regardless of the risks that have been identified, you want to go ahead and take -- okay. We'll take one more comment.

DR. WALLACE: I'm going to say this from a practical standpoint because I try to recruit patients. Having patients come who live 50, 100,

153

150 miles away every month is almost impossible. Many of these people can't drive by themselves; they have to have someone come with them.

That one marker, which is often required for these studies, often will take out at least two-thirds of the potential patients because it's not a practical possibility just because of the complexity of their disease and how far they live away. This is an issue for every orphan disease where everybody doesn't live in the same town where the study is being done.

MS. GIAMBONE: Thank you. So the burden of how frequently you'll need to go in. Okay. I see several more hands raised.

FEMALE SPEAKER: The visits are monthly. How often are the treatments administered?

MS. GIAMBONE: Okay. How often are the treatments administered? Okay. And then let's just take one more comment, and then we'll dive into ideal treatments.

FEMALE SPEAKER: Yes, addressing this gentleman's comments, if various centers were --

154

most of my clinical trials have been at NIH. I live in New York. It would be a major hassle. I go regularly but not once a month. But if my New York doctor could administer whatever, it would make a huge difference.

MS. GIAMBONE: Okay. So if your current doctor-- or the one that you go to, if you could get --

FEMALE SPEAKER: My New York doctor rather than my NIH doctor.

MS. GIAMBONE: Got it.

FEMALE SPEAKER: They talk to each other all the time anyway.

MS. GIAMBONE: Thank you. It looks like there's definitely a lot of considerations here, and I'm going to ask that you please submit those considerations to the docket just so we can move on --

FEMALE SPEAKER: May I say one more quick thing?

MS. GIAMBONE: Yes.

FEMALE SPEAKER: I was wondering -- and

155

there were times I'd like to participate in a clinical trial -- and there's many of us that live in the Northeast, let's say, for part of the year, and then they go to Florida or California.

I was wondering if the clinical trials could be set up where you can switch locations and the centers could share information or pass it on.

MS. GIAMBONE: Okay. So it definitely appears that the travel to this and the burden of getting to the doctor is a major issue.

I know we're approaching lunchtime, so I do not want to keep you very long. But do we have anybody on the phone, Graham and Meghana?

MR. THOMPSON: Operator, can you open up Cynthia's line?

MS. GIAMBONE: We'll take one comment on what you look for in an ideal treatment.

OPERATOR: Cynthia, your line is now open.

MS. GIAMBONE: Hi. Cynthia?

CYNTHIA: Thank you. Hi. An ideal treatment for me would be one that does little

156

harm. I kind of think of antibiotics as a shock and awe for us, and they're absolutely essential, and thank God we have them.

But I know many of us suffer from other health issues. I myself have osteoporosis and children [indiscernible]. And some of my meds, the Symbicort and corticosteroids that we take lessen the bone density. And I'm kind of really worried about getting frail bones, and exercise seems to be key to staying well. And I think it's poorly understood the long-term effects of the use of these toxic antibiotics on our overall health.

I'm hopeful that in the future, they can look to biologics and cellular mechanisms to weaken the tough cell walls that keep meds from getting at the bug, so that we could perhaps really make that shock and awe much more effective, so we have to take it for a shorter periods of time and less toxic drugs.

MS. GIAMBONE: Thank you, Cynthia.

CYNTHIA: Thank you.

MS. GIAMBONE: Thank you, Cynthia. So

157

drugs with minimal side effects, I heard, and exploring biologics.

Other thoughts on ideal treatment, what you look for? Yes?

MS. BUONVIRI: Hi. I've been a patient for 10 years, and I've been treated for MAC. I've been treated for abscessus twice with IVs and orals. Just for the record, I went to National Jewish in February after 8 years of being urged to do so by my doctors at Johns Hopkins. And I was treated by Dr. Drummond with lifestyle changes and exercise and a nebulizer. I just got back two weeks ago, and the first time I had a CT scan improvement without drugs. And I am eternally grateful to Dr. Drummond for that.

But my ideal treatment has to do with something that's being advertised in magazines as a lung treatment, and that is stem cells. I've heard no one mention that. I've taken it to my doctors. They don't know that much about it.

I would like to know what the status of it is. It's being practiced throughout the

158

country at multiple locations by a group called The Lung Institute. I have spoken with them. It sounds like the greatest thing since sliced bread. They take your own stem cells and they transplant them, and supposedly, it helps your lung function and a repair of your lungs.

I'd like to submit that for consideration. I'd like to know any comments or responses about what it is, and how it fits in the FDA plans, and what's known about it.

MS. GIAMBONE: Thank you so much. And your name?

MS. BUONVIRI: Lynn Buonviri.

MS. GIAMBONE: Thank you so much, Lynn.

Okay. Another comment on ideal treatment? Yes, Marilynn, the mic is coming to you.

MS. LUNDY: Thank you. Dealing with the sleep issues when you're on medications, I think, is underrated. It's one of the most important things for me, and I've realized as time has gone on, that those five years, I hardly ever got a

159

good night's sleep.

Part of the reason is because there does seem to be some diuretic action -- I'm not sure which one it comes from or whatever, but I was up peeing at least five times a night. It's really difficult to get back to sleep. So you are sleep deprived, at least most people that I know, and myself.

If they could come up with some kind of medications that were effective and that you could still get some sleep -- and you're supposed to get so much more sleep when you have this disease because you're weary all the time, and that's part of the fatigue, is you never got a good night's sleep. Five years on no sleep is pretty difficult and psychologically a huge problem.

MS. GIAMBONE: Thank you, Marilynn.

So we are approaching closing, but I do have a question for you as a show of hands that I know the FDA panel identified would be helpful for them to know.

How many of you have had to take a 6-

160

minute walk test as a way to measure the progression? Let's see. How many of you have taken a 6-minute walk test? Is there a different name for it or is that the name? Okay, that's the name.

(Show of hands.)

MS. GIAMBONE: All right. So just keep your hands up for a second while we do a quick count. I'm seeing 19 hands raised on that one, so it does seem that way.

Just very quickly, which symptom gets in the way of you not being able to maybe do your 6-minute walk test as well as you would like? Is it like the shortness of breath? Is it -- the stamina? Okay.

MS. KEATING: [Inaudible - off mic.] -- tomorrow it rains, and your 6-minute will be off. So it's really not a valid test. In my eyes, I don't --

MS. GIAMBONE: Okay.

MS. KEATING: Some days I can walk forever and some days I can't walk a block.

161

MS. GIAMBONE: Okay. So I'm hearing stamina and take one more comment here.

FEMALE SPEAKER: It's just a comment. I have cold hands. The finger measure of blood oxygen doesn't work. Hence, unless everybody starts getting the thing that sits on your head, it's just not valid. And I can't do it in the gym because the reading falls down to 95, 96. And if you want valid measurements, then this equipment has to be available.

MS. GIAMBONE: Okay. Thank you so much. Thank you.

Any final questions from FDA? I really don't want to take up your lunchtime? No questions?

(No response.)

MS. GIAMBONE: You're all extraordinary. Thank you so much for sharing these stories with us. We've learned so much from you. And please, submit to the docket to continue this discussion. Thank you. We'll reconvene at 1:10.

(Whereupon, at 12:20 p.m., a lunch

recess was taken.)

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

(1:13 p.m.)

DR. FARLEY: I want to thank everybody for their input this morning, which was extremely valuable. We have an afternoon agenda focused on helping us, first of all, kind of have the same background information and also talk about the way forward.

We have Ken Olivier from NIH who many of you know, who's going to talk about the epidemiology and natural history of the disease. Dave Griffith is going to talk about treatment guidelines and what the current standard of care is.

Hala is going to share with you the review considerations for new drugs in the United States, what authority the FDA has from Congress, and we'll talk a little bit about kind of what authorities we don't actually have. That's also very helpful, I think, for folks to understand.

Selena Daniels and Alexandra Quittner

are going to tag team around taking input from patients and translating that into clinical trial endpoints. Then lastly, Dr. O'Donnell, who has really been in the trenches working on clinical trials, is going to talk about the challenges that we face to-date, and then we're going to move on to a panel discussion.

I want to thank particularly all of our panelists for taking time out of their schedules to be with us. I'm going to give them a chance to introduce themselves starting with Chuck Daley on my left.

DR. DALEY: Hi. I'm Chuck Daley from National Jewish.

DR. GRIFFITH: Dave Griffith from University of Texas Health Science Center in Tyler, Texas.

DR. QUITTNER: I'm Alexandra Quittner from the University of Miami.

DR. DANIELS: Selena Daniels. I'm a reviewer on the clinical outcome assessment staff here at FDA.

DR. FARLEY: Give us a chance to fix the mics. While we're working on that, just to remind the panelists that our patients told you very loud and clear that some of them struggle with hearing issues. There'll be no mumbling into the microphone, so speak loudly and make sure your mic is on. And this is a crisis; we will fix it.

DR. SHAMSUDDIN: Hala Shamsuddin, Division of Anti-Infective Products, FDA.

DR. WINTHROP: Hi. Kevin Winthrop from Oregon Health Science University in Portland, Oregon.

DR. NAMBIAR: Sumathi Nambiar, director of Division Anti-Infective Products.

DR. FARLEY: John Farley from FDA, and this isn't working either. This is bad. John Farley from FDA.

(Laughter.)

DR. TOERNER: I'm Joe Toerner from FDA.

DR. OLIVIER: Ken Olivier from the National Heart, Lung, and Blood Institute.

DR. HUGHES: David Hughes, global

program head, clinical development from Novartis Pharma.

DR. O'DONNELL: Anne O'Donnell from Georgetown University here in DC.

DR. HIGGINS: Karen Higgins. I'm a statistician supporting the Division of Anti-Infective Products.

DR. WALLACE: I'm Richard Wallace. I'm from the University of Texas Health Center in Tyler.

DR. EAGLE: Hi. I'm Gina Eagle. I'm working on the clinical development of Arikace at Insmed Incorporated.

DR. FARLEY: Thanks. I think this one is still working, which is great. I'm going to invite Ken Olivier to the podium. He's senior clinician and chief of the Pulmonary Clinical Medicine Section at the National Heart, Lung, and Blood Institute, which is part of the National Institutes of Health. Presentation - Kenneth Olivier

DR. OLIVIER: Thank you very much, John.

166

It's a pleasure to be here. I just want to start with a brief story.

When I got to the NIH a little more than 10 years ago, I was all excited and ready to get started, and I did a lot of cold calls to members of the pharmaceutical industry saying I have this terrible disease, NTM, and would you be interested in taking your drug and studying it in NTM patients?

Most of those calls weren't returned, but one of the companies that did return it asked me, well, how many people have this disease; what do they look like; what are their comorbidities; where do they live; what's the natural history of the disease?

I was armed with the data in the first two slides that I'll show you, and it became quickly apparent that we needed to do some updating of that data. I was very fortunate, at that time, to meet Becky Prevots, who's sitting in the front here, who is a phenomenal epidemiologist. And for the last 10 years, we've

167

sought to address a number of these issues.

I'm very happy to also have Jen Adjemian and Sara Strollo from our epidemiology group here. A lot of the data that I'll show has been collected primarily from them with the hopes of trying to shed some light on these areas as a place to start for drug development.

The current status of what we knew about the epidemiology of this disease sort of began with studies that were done in the late 1950s and 1960s. These were fairly elegant studies where they did a series of skin tests with antigens that were prepared from the Mycobacterium, looking to try assess where exposure was occurring in the U.S.

They were using the model of the standard PPD reflecting exposure infection from tuberculosis. And this was done in lifetime, single-county naval recruits. These were essentially all white males between the age of 17 and 21 years.

They were aggregated in basic training,

168

so they did this series of skins tests. They asked them where they had lived all their life, and they generated this map of the U.S. to kind of give you an idea of where exposure was most prevalent. And it showed this concentration along the Southeastern U.S., up along the West Coast, and in the Hawaiian Islands.

It told us very little about who was actually infected, actually told us nothing about who was infected with these organisms. We had to wait a bit for that data. It came from a study that was conducted by folks at the CDC.

At that time, all positive mycobacterial islets were referred to state epidemiology labs for identification of the mycobacteria. So this was a study that surveyed those state labs to identify positive islets.

They had a limited amount of metadata associated with that, that they knew something about things like the gender of the patient, but nothing enough to establish a case definition. But it generated a very similar map of where the

169

concentration of disease was. And again, if you look at this map, the Southeastern U.S. stood out prominently, the West Coast, and the Hawaiian Islands.

After that time, and especially in recent years with the advent of DNA probes and the ability for basically any lab that was culturing mycobacteria to tell whether it was TB or not, a variety of other factors led to sort of a drying up of that pipeline of islets to the state mycobacterial lab, making this study design no longer feasible.

So when Becky and I got together and started talking about this problem, we tossed around several ideas of how to get at it. One of the things that was very attractive was putting together a consortium of integrated healthcare systems. The model of this was Kaiser Permanente on the West Coast where you have a fairly stable beneficiary population.

You have years, at that time, of electronic medical records where we could go in

170

and search for positive islets and then link those islets within the system to get demographics of the patients, to link into billing records, to establish how often the correct diagnosis was made once we had established an islet case definition, and to link into radiographic records and other areas of the system to tell more about the patients.

This study was done in collaboration with four of these large centers, the two West Coast, Kaiser Permanente, a health group in Seattle, one in Colorado, and the Geisinger System on the East Coast. This study had a beneficiary population of about 4 million people, and it gave us at least a snapshot of people that were in those types of healthcare systems to look at overall prevalence.

In the study, we looked at a period from 1997 to 2007, and the average age adjusted period prevalence between the years of 2004 and 2006 was around 5.5 per 100,000. So this was a bit higher than the study that had been done in the '70s by

171

the CDC where the estimated case prevalence was around 2.8 per 100,000. If you use average census data from 2005, that equates to about 16,000 people in the U.S.

Some important things that we noticed from the study was that the prevalence was increasing at rate of about 3 percent per year, and we were able to do things like compare the prevalence of tuberculosis to that of non-tuberculous mycobacterium and look at the differences in the patient population between the two.

One of the striking things that you can see from this slide is that there's definitely an age correlation with the prevalence of both mycobacterial islets, but it's even more dramatic for non-tuberculous mycobacteria that are showing up as the sort of greenish-blue and fuchsia bars there as opposed to TB in the brown and green.

The other striking difference was the gender mix, which was almost exactly the opposite of TB. In this older age range population, men

172

predominated in the prevalence of TB,.whereas in the older population, women very much predominated. In that over 60 group, as you went up in age by decade, the relative proportion of men to women increased even more dramatically.

There were other similar studies that were done, and I should acknowledge people in the room like Kevin Winthrop who has done quite a bit of work at this, and Ted Marras, who is not here, from Ontario and did similar types of studies that sort of corroborated these studies together to give us a clearer picture of this.

This also was an islet-based study done in the Province of Ontario in Canada, where they did a similar type study of identifying a case definition, in this case greater than or equal to two positive sputum or one bronchoscopy or biopsy specimen as equating to a positive case and then looked at how that changed over a period of time.

They also looked at the differences in species with MAC being most prominent similar to the study that we had done in the HMOs, M. xenopi

173

being very prominent and M. abscessus as well.

On the graph, the bottom line on that depicts the case prevalence change over that period of time and, or disease prevalence, and the top is the isolation prevalence, finding at least one positive culture.

You can see that they're both increasing at about the same rate, about 6 and a half percent per year and that the case definition was met by somewhat less than a half of the total people having a single positive islet.

When we looked in the HMO study, kind of further looking at how people diagnosed the disease once they met the case definition based on the number of positive cultures, we found that about a third or less of people correctly identified them and assigned the correct billing code to them.

That's an important note. When we looked in that HMO study and saw that the predominance of patients was in the over 60 age group, that gave us the opportunity to look at

174

another very important database in the U.S., the U.S. Medicare database, which over 95 percent of the U.S. population age 65 or older has that as a billing source. So it actually serves as a potentially very useful source of epidemiologic data in that age group.

However, the definitions there are based entirely on billing codes as opposed to the prior two studies that were based on detecting positive islets. So we know that these data likely underestimate to a significant a degree the number of patients that have the disease in this age group.

However, it allowed us to do several things, and one of them was to compare the prevalence or the change in prevalence of disease-related NTM to the prevalence of bronchiectasis, the setting that we most commonly find the organisms in the U.S.

The top two lines in the graph represent the increase in prevalence in women in the red versus men in the blue of bronchiectasis in

175

general. You can see that that's increasing at a steady rate over the 7 years of the data that we analyzed.

In the bottom graph, it's a similarly constructed graph looking at the increase in prevalence of NTM over that period of time, where you can really see that the pace of increase in women is sort of exceeding that in men and that the overall prevalence of NTM disease was, on average, about 10 percent of the prevalence of bronchiectasis.

This is a recent study that was done by Sara Strollo and others in Becky's group, looking at the burden of organisms or burden of having NTM disease in the U.S. in terms of cost in medical care utilization. This study actually built upon prior studies that were done. It looked at the Medicare data, and it made several assumptions based on that. It looked at the HMO data that had been collected, and it used a relatively large survey of physician practices to determine things like often patients were treated when they had the

176

diagnosis made, and what they were treated with.

It sought to estimate annual medical cost. Again, this was extrapolated from both the Medicare and practice survey studies. The assumptions in this are fairly important. Seventy-three percent of cases were assumed to be missed based on the ICD coding that we had derived from prior studies.

We estimated that 31 percent of NTM cases were younger than age 65 because if we focused just on the Medicare data, that's the only data that we have that information directly from. We estimated an 8 percent annual increase in prevalence based on prior studies as well.

If you look, given all those assumptions, the estimate was that about 86,000 people in the U.S. had this disease. The cost is listed right under that in the table. So if these patients impacted the healthcare systems once, the total cost in the U.S. was around $815,000. Now, this really doesn't account for things like missed work days. This is only looking at healthcare-

177

associated costs.

If you increased that by one, two, or three additional visits, the cost goes up considerably until you very quickly get up over a billion dollars a year. Eighty percent of the costs in the study were attributed to prescription medication costs. So the things we're talking about today in this room have a significant impact in terms of what this is costing to treat with the current regimens.

The other thing that these studies enabled us to do was to look at associated risk factors from an environmental or atmospheric exposure standpoint. These are the same data I showed previously but now mapped out similarly to how those early studies in the '50s, '60, and '70s were mapped. And basically, the darker the colors, the higher the prevalence of both bronchiectasis and NTM.

If you look at the general geographic distribution, particularly the NTM map, it looks very similar to the original studies done with

178

skin tests, very similar to the distribution in the CDC survey study with a predominance in the Southeastern U.S., up along the West Coast and the state of Hawaii.

If you look at where many of these patients may come from in the broader picture, looking at bronchiectasis in the top, there's a relatively similar distribution of disease as well.

This allowed us to sort of link where these patients are with certain conditions that may be prevalent in the environment to look at potential risk. And using a technique called spatial cluster analysis, which Jen Adjemian knows quite well and led these studies, if you take counties where there's a high prevalence of NTM disease and you compare that to clusters of counties where there's a very low prevalence of disease, you can then link those geographic areas into large databases such as the National Oceanographic and Atmospheric Association Database, and then derive certain environmental

179

risks.

From looking at this, things like the amount of surface water in the area and particularly atmospheric qualities like the ability for a droplet to remain suspended that's large enough for mycobacteria to remain viable and then be inhaled to cause disease, a quality that's called evapotranspiration, which relates in a bit to relative humidity -- if you look at those odds ratios, that factor actually turns out to be quite significant.

We've also looked at this in a known high risk population. The excellent introductory talk that was given this morning noted CF as being one of the high risk groups. If we break down data from CF patient registry, which collects data on essentially over 90 percent of CF patients throughout the U.S.

and has been doing this over a number of years, we can get some very useful pictures of risk factors and distribution of disease from this as well.

180

In 2010, the registry started collecting very specific data with regard to NTM culturing, NTM positivity, and the species associated with that as well. During the time period listed, there were about 18,000 patients over the age of 12 in the registry. And of those who had cultures done, about 14 percent of these patients were positive either for M. avium complex or M. abscessus.

So this is an exceedingly high prevalence in this disease relative to what we've seen in the general population. There were four significant geospatial clusters, which are shown in the red circles on this map, that turned out to be very high prevalent areas, based on the registry data.

Again, when we link that in to atmospheric conditions, the saturated vapor pressure or evapotranspiration comes out as being a very significant climatic risk.

In terms of the significance of the disease and sort of what the natural history is

181

like, in cystic fibrosis, lung function parameters such as the FEV1 have been used in a number of drug trials. And many people equate the progression of disease in CF or the definitions of exacerbations in CF to changes in lung function.

This is from a study that was done at the University of North Carolina where they looked at about 800 patients. They looked at the change in lung function over time by age, which is along the bottom axis, and they compared those patients that had no NTM to those that had Mycobacterium abscessus.

As many of you in the room know, Mycobacterium abscessus can be a particularly virulent organism particularly in the setting of cystic fibrosis. They were able to show a significant change in decline in FEV1 over time.

If you look at where the other mycobacteria fall on this graph such as Mycobacterium avium complex, they were almost exactly in the middle of these two lines. So the data were most striking for Mycobacterium

182

abscessus.
I'm not sure that these lines would necessarily look the same in non-cystic fibrosis patients or that FEV1 necessarily shows the same responsiveness, but we don't have this type of detailed data in those patients to indicate that.
Unfortunately, there have been several studies that have looked at mortality in this disease, and I think it's worth discussing these a little bit to kind of give an idea of the significance of this disease. This is not just a bothersome disease, but it can be a disease that's quite severe in some patients that they do die from.
This is a study done in Japan that looked at a couple of things. It coupled islet-based definitions with known death rates in the country to look at mortality related to NTM disease. It also derived prevalence from that as well, and it noted several interesting things.
The bar graphs noted increase in mortality by gender and noticed that it was sort

183

of steadily increasing over that time period until the year of 2000 in both sexes. After that time, the mortality seems to be increasing preferentially in women.
The map of Japan there looked at where these deaths were occurring, and again, there was a similar sort of geographic predominance. The areas in the darker colors were in the southern part of Japan, basically warmer climates, more humid areas than in the northern parts of the country. They estimated the prevalence in Japan to be between 33 and 65 per 100,000 so significantly higher than what had been seen in the U.S.
Then they looked in a single center at the persistence of islets over time. This give you an idea of the marked difference between looking at the epidemiology of a disease like influenza which is present for only a small period of time, or diseases like diabetes where once you have it, it's present basically for a lifetime. And they found that over 50 percent of patients

184

diagnosed with MAC remain culture positive at two years, and a third of them or more were culture positive out to five years from that isolation.
There have been several studies now that have reported 5-year mortality from this disease. Again, a study from Japan showed the 5-year mortality to be around 25 percent. A second study from Japan showed around 28 percent. Claire Andrejak did a study in Denmark showing a much higher prevalence of 40 percent. One thing to keep in mind with this study is it was predominantly cavitary disease.
A general theme of many of these studies is that the prognosis in cavitary disease is significantly different from those in the sort of nodular bronchiectasis disease that we see in the U.S.
Then finally, Finland, 28 percent and in a recent study that we've done at the NIH -- it's not yet been published -- we saw a similar mortality of 25 percent.
In our data at the NIH, we were able to

185

look at specific risk factors for disease. And again, fibrocavitary disease, if you look at the difference in survival, median survival, on the left, it was around 9 years for those that had fibrocavitary disease versus 13 years for those without fibrocavitary disease.
The other significant risk factor was the presence of pulmonary hypertension, raising the question about whether there may be some vascular component to the disease. But those with pulmonary hypertension had a median survival of around 7 years versus greater than 18 with no pulmonary hypertension.
In summary, the U.S. prevalence is difficult to assess. It's probably somewhere between 16 and 84,000, maybe even more than that if you factor in all the patients with disease that never comes to medical attention. It appears to be increased in women in age over 60. There's considerable geographic variability to the disease, which likely reflects in part environmental influences.

186

The disease burden in costs are quite substantial, and it adversely affects lung function. At least in cystic fibrosis, it appears to be associated with increased mortality. Thank you very much.

(Applause.)

DR. FARLEY: Thanks, Dr. Olivier. If there are any questions, we'll take some after the second talk.

I'd like to invite Dr. Dave Griffith, Professor of Medicine at the University of Texas Health Science Center in Tyler, Texas.

Presentation - David Griffith

DR. GRIFFITH: Thank you very much. It's wonderful to see everybody here. I very much appreciate the opportunity to be here today.

I'm going to talk about the much-maligned treatment guidelines for NTM disease. Very quickly, my conflict of interest statement. I am and was a co-investigator on the Insmed-sponsored inhaled liposomal amikacin trials.

The 2007 NTM guidelines were not the

187

first guidelines to be published. There were two, at least, in 1990 and 1997. I would only point out that my friend, mentor and colleague, Dr. Wallace, shepherded those two through. I think you had three or four co-authors on each of those, whereas we had a host of thousands on the 2007 guidelines.

I want to take you through a little bit of the process of those 2007 guidelines. I was struck by a similarity between that process and a famous movie. This is really the agony of the NTM guidelines. I'd like to apologize to John and Walter Huston.

In about 2003, 2004, some of our colleagues were sitting around deciding that we weren't doing very well and we needed to update the guidelines. By the way, I don't need to tell you who old Dave is in these slides.

A bunch of us, old guys, mostly, with apologies to Gwen Hewitt, got together and put together an update on the old guidelines. But unfortunately, not everybody knew that they didn't

188

know a lot about NTM and not everyone embraced them.

So when they were released, again, not everyone knew that they needed what was published in the guidelines. I'd just like to say for you cinematic purists that if you substitute the word "badges" in this slide, this is the actual quote from the movie, not the shortened version that you get quite often.

We had to think again, where did we go wrong; what did we do that we should've done, or what didn't we do that we should've done better? I think that's what we're going to try to tackle, again, with this next group of guidelines.

Why do you have to have guidelines for NTM disease? Well, number one, this ain't TB. Number two -- let me rephrase that. This ain't TB.

If I had one message that I would like to send to my FDA colleagues is that when you evaluate treatments and protocols for treating NTM disease, you cannot look through the lenses that

189

you looked through when you evaluate protocols for tuberculosis. There are similarities. They are not identical. And I'm going to point out a few of those.

The guidelines are actually sometimes helpful, believe it or not, for both diagnosing disease and for successfully treating NTM disease. If you follow what's recommended in the guidelines, at a minimum, you usually don't make things worse. And I think they can be instructive. I think that they are educational.

As folks have mentioned, this is not an area where a lot of physicians have expertise. If you want to go to one place, I think that was one area where the 2007 guidelines did prove to be fairly successful. People could go to that document and at least get a little bit of information. I'm going to talk a little bit more about that as we go along.

But let's face it, you can't have a single document that's adequate for 160 different species. They vary by virulence; the host varies

190

in terms of susceptibility. Of course, the NTM can infect a number of different areas obviously other than the lung.

The guidelines do not take the place of knowing something about the diseases. I mean theoretically, we shouldn't need this. Theoretically, clinicians should know what the significance of Mycobacterium kansasii is in a particular patient. They should know what the significance of Mycobacterium abscessus and know the insignificance of Mycobacterium gordonae. But they don't. That's why we are stuck with this process. It's an impossible task, but we do the best that we can.

We know that in contrast to tuberculosis, getting an NTM respiratory islet doesn't necessarily mean that someone has NTM disease. We know that there are frequent contaminants. Mycobacterium gordonae, for instance, I don't know that I've seen a case of M. gordonae lung disease. I'm sure some of the panel members probably have. But it's the third most

191

commonly isolated NTM in the state of Texas, but it almost never causes disease.

We know that that NTM are in tap water and can contaminate specimens. And frequently, people who have NTM in their sputum don't get worse with time. I think I have an example of that.

Making the diagnosis of NTM disease doesn't mean that somebody needs to start therapy, and that's based on careful risk and benefit analysis. I'm mentioning this because the guidelines do tell you how to diagnose the disease. They give you criteria for diagnosing disease, but it's not enough. You have to know something about the bug, the source, the patient. All of that is always, always true.

If you have a positive test, that is not necessarily a diagnosis. And here, I've just listed a few of the considerations that all of us go through when we try to decide, what is the risk benefit ratio for an individual patient.

I thought I would just show this very

192

nice lady that I followed for some time. This lady was 75 years old when I first saw her, not a terribly abnormal chest X-ray, but she had bronchiectasis and her sputum was consistently culture positive for MAC.

I have followed her now for 12 years. Out of 70 sputum AFB cultures, 35 were positive for MAC. The lady is doing fine. She feels okay, no radiographic progression, and I've never put her on medicine.

The point being just, the guidelines don't necessarily tell you what to do with an individual patient, particularly with this regard. But the other thing, which I hope everyone here appreciates, is it's important to have a very close relationship with your doctor.

This nice lady, I think she comes sees me every six months or so. And she always says, "Why do I keep coming to see you?" Partly because, as Ken said, we don't necessarily know what the natural history of these diseases are,

193

and I don't know that someday this patient won't need therapy for MAC disease. At any rate, just an example of what is necessary in addition to the guidelines.

These are the treatment recommendations for MAC lung disease. I think the folks are pretty familiar with them. For the disease associated with bronchiectasis, it's macrolide-based, usually three times a week. For cavitary disease, we think it's daily, frequently with an injectable agent.

This is a study that we published not too long ago of our population of patients with bronchiectasis and MAC lung disease receiving three times a week therapy. As you can see, it was successful in the majority of our patients.

We did find kind of a disturbing, the finding of microbiologic recurrence of MAC, which frequently was due to reinfection as opposed to disease relapse. Nevertheless, most people had microbiologic improvement on therapy. Fortunately, essentially, none of them developed

194

resistance to macrolides on therapy.
I put this slide in -- this is from South Korea -- to point out that it's not just in Texas where this particular approach is successful, but it also happens other places.
This is an example of where the guidelines, I think, are pretty good. We didn't have this data when we made the recommendation in 2007, but fortunately, the data that we had has borne out the success of this particular approach.
In terms of the recommendations of the guidelines, most of the time, with bronchiectasis, you do get favorable microbiologic response, and these regimens do not promote the emergence of resistance to macrolides.
I'm not going to spend much time -- actually, I had not seen Ken's data on cavitary disease. That's very important data. As you can see, I think cavitary disease is not just associated with all-cause mortality, but like tuberculosis is probably likely associated with significant long-term respiratory impairment.

195

Now, we're a little underrepresented today in terms of this aspect of NTM disease. Interestingly, our European colleagues see a lot more cavitary disease than we do, frequently from organisms. I heard someone speaking early about Mycobacterium xenopi. That is a bug associated with cavitary disease frequently in Northern Europe and a high mortality.
I think this is an area also where we need a lot more information, and I think we can make a significant impact on the disease with appropriate therapy. I also think it will probably need a little bit different approach when we design studies.
I know there's a lot of nihilism about treating these diseases and pessimism, but I just wanted to show you an example of a patient that I had successfully treated with medication alone.
Many of you also know that these patients also do well with surgery, or that least their disease does well with surgery. So it's certainly not a hopeless process by any stretch.

196

This is a big problem, of course. The introduction to macrolides some 20 years ago changed the landscape for treating MAC, both disseminated disease and pulmonary disease.
It's one of those areas where if you don't manage MAC correctly, you can, I guess, do harm. I hope that that's not overly judgmental. But this is an area where the guidelines -- this is part of the education aspect of the guidelines.
Not every drug that you give for MAC, as many of you know, has a correlation between what's seen in the laboratory and what happens in the patient. The macrolides are an important exception to that.
If the bug is sensitive in the lab, it's going to be effective in the person. If it's resistant in the lab, it's not going to be effective in the person. So taking a macrolide-susceptible bug and making it macrolide-resistant or allowing it to become resistant is a big deal.
I just wanted put up just a little bit about some of the risk factors that we can

197

identify for that occurring. I bring it up because we don't think of MAC disease generally as being associated with high mortality, but I can tell you that if you have a macrolide-resistant MAC islet and you have cavitary disease, that is a fatal process.
It would be nice -- I hope that Ken can pull some data on that out of his data set. This is one area where following the guidelines makes a big difference in terms of patients. Forgive me. This is the CAT scan for the individual I just showed.
I won't go into any detail here about the treatment of these patients but it is, of course, extremely difficult. And frankly, in the setting of the type of individual I just showed, it is almost impossible to treat.
This gets into the education part of the guidelines. TB is relatively easy here. If the lab says the drug works in the lab, then you know it works in the person. That is not the case with NTM, with two exceptions: the macrolides and

198

amikacin.
The reason I want to belabor this point is doctors are not born with this knowledge. If all you know is TB, you don't know that you have to take steps to protect macrolide and amikacin more so than you do for other drugs.
This type of resistance is called mutational, or acquired mutational resistance, very familiar to people who treat TB, but not that familiar to physicians who take care of MAC patients.
Again, I hope that in this next guidelines process, we preserve that aspect of it. It's not directly related to therapeutic recommendations, but physicians have to know that so that they protect their patients against the emergence of resistance to these two very, very potent drugs, very powerful drugs: amikacin and the macrolides.
Just very quickly, again, there are many counterintuitive aspects of treatment of non-tuberculous mycobacterial diseases. For instance,

199

it's not clear that the level of a drug in your blood makes a difference or correlates with how you respond to that drug.
Of course, the big one is the one where it doesn't necessarily correlate -- that the finding in the laboratory on how the bug responds to the antibiotic doesn't necessarily correlate with what happens in your body.
I would just like to point out, again, physicians don't know this at birth. For instance, this is a patient who had their MAC islet sent to a reference laboratory. It was reported as resistant to ethambutol.
We know that whether the islet is resistant or susceptible to ethambutol doesn't matter in terms of the response of that patient to ethambutol in their treatment regimen. Ethambutol is important for protecting the macrolide, for keeping people from becoming macrolide-resistant.
Well, this patient's doctor saw the resistant label next to ethambutol, and he stopped it. And instead, he substituted fluoroquinolone,

200

which is of a questionable value. At any rate, this individual ended up becoming macrolide-resistant; another example of the process of education that's necessary for physicians to adequately care for patients with NTM disease.
Now, we come back to -- we don't need no stinking NTM guidelines. Becky [sic] Adjemian and the folks at NIH did a survey of physicians in the United States to see how well they complied with the NTM guidelines from 2007. And the short answer is they didn't. People treated this stuff in every possible way. It was just astounding. Almost no one in the survey treated patients according to the guidelines. You can take that for what it's worth.
Just very briefly, let me close with the new guidelines committee is composed of four different societies, two from your Europe, two from the United States.
This is a different document. This will be a different critter. The last document was almost a reference paper. This one will be

201

question-focused. They're called PICO-based questions.
Just to give you an example, this is a recent guideline for pulmonary fibrosis, and it basically asks seven questions. And the questions were, should patients be treated with A, or B, or C, or D, or E or F?
Frankly, I don't know how we're going to do that kind of a document for NTM because I can come up with seven questions for MAC without discussing any other mycobacterial pathogen. But nevertheless, we're struggling with it.
Dr. Daley is chairing this effort. It will be a different document. I hope we preserve the educational aspect to it, that a physician doesn't just go it, go to the bottom line that's in bold print and take that home to treat the patients. I hope they learn something about NTM disease.
I will close with a slide that I like to use in essentially all my talks. This is from Dr. Emanuel Wolinsky who is one of the fathers of NTM

202

disease. Many of you know, in most instances, I'd rather treat a patient with multi-drug resistant TB than someone who has macrolide-resistant MAC, although they're both quite difficult. So we certainly still need help, and hopefully we'll get some from the FDA. Thank you very much.

(Applause.)

DR. FARLEY: I think we'll pause and see if there are any burning questions for Dr. Olivier or Dr. Griffith. Any questions that folks in the audience would like to ask? I see a hand over there.

FEMALE SPEAKER: My question is for Dr. Olivier. If I understood your epidemiological charts, it would appear that the prevalence as we understand it of NTM disease in the U.S. is much lower than in Japan. Is that, in your opinion, because we measure it less well or because there's something in people in Japan or in the environment that makes it more common?

DR. OLIVIER: It's a very good question, and I think when we talk about etiology of

203

disease, we need to consider both the opportunities for exposure and other risk factors that might go along with that.

In many of these studies in the U.S. and in Japan, many of these of patients had relatively few other comorbidities associated with their disease. But you have to think about things such as genetic risks. And we know from other genetic diseases that those genetic risks can vary considerably based on ethnicity and geographical background.

There may be differences in methodology; there may be differences in sensitivity to the disease. If you just weigh the amount of literature on this disease coming out of Japan and South Korea, it vastly outweighs the amount of literature coming out of the U.S.

Maybe people are more aware. Maybe they're looking for it more. But there could be a variety of issues why that difference in mortality occurs. Some may actually be attributed to just differences in study design and technique.

204

MALE SPEAKER: I had a question. I'm not sure who on the panel would be best to answer it. We heard earlier today about bronchiectasis as a risk factor for NTM. My question is, does bronchiectasis cause NTM or does NTM cause bronchiectasis? Or do we really know?

DR. OLIVIER: The answer is yes.

(Laughter.)

This is sort of like the chicken and the egg argument about what comes first. Our group has been very interested in looking at genetic risks of this.

My former boss and I used to argue about this all the time. If we knew what the truth was, if we knew what the generic risks were, would they be risk factors for the development of bronchiectasis, and then having that altered airway clearance predisposes you to having whatever you're inhaling stick in the airway and cause problems.

On his side of the fence would be identify genetic risks that make it more likely

205

for mycobacteria to cause disease because the parts of the immune system that are responsible for clearing the mycobacteria are defective.

We, in the recent past, have done a fairly large study trying to get some preliminary evidence about what the genetic risk factors are like. And the results of that probably suggests that both are right, that when we have looked at genes that associate with causes of bronchiectasis and genes that associate with a part of the immune system that controls mycobacterium, in general, the patients that have NTM associated with bronchiectasis have a much higher frequency of variation in those genes in both of those groups than the general population does.

This study only scratched the surface. There's a lot more work that needs to be done to better understand the significance of the genetic abnormalities that we found. But it's likely what's called an oligogenic disease as opposed to cystic fibrosis where one gene results in the manifestation of disease.

206

It may be that you need a minor change in genes controlling for bronchiectasis, coupled with a minor change in genes that control mycobacterium, coupled with enough environmental risk exposure time to go by to result in this disease occurring in this population in the age range that it does.

DR. WALLACE: John, can I make one comment?

DR. FARLEY: Absolutely, Dr. Wallace.

DR. WALLACE: David's data about follow-ups on patients who were treated with standard regimens for MAC, you'll make note that in the follow-up, which was only two or three years, 50 percent of the patients developed one or more positive cultures for MAC, most of which were not of the same genetic type as the original islet.

When you look at studies or long terms studies, and this especially applies to the Japanese studies, you have no idea if you have may have successfully treated those patients and they now have another episode. They're all assumed to

207

have the same episode and they're all assumed to be treatment failures.

We've been very slow in adopting the willingness to do both species identification and to do fingerprinting. I mean, I know it's -- I preach on this a lot. But it's impossible to analyze --

One of you who says, gee, I've had MAC for 10 years; they've treated me five times. You could've had five episodes with five different organisms. I mean that means you were successfully treated for each of those episodes and then because either of your individual risk factors or occupational risk factors, you acquired it more than once.

All of this data is kind of tainted by the fact that we have no knowledge about whether all of these people that die of MAC, did they have a single episode that they never got rid of or they couldn't stay away from MAC?

My wife has a saying that "you're never cured of MAC" and by that means you never stay

208

away from it. You're always exposed to it. And sooner or later, if you have it once, you're going to have positive cultures again.

It taints a little bit the data because we don't have that piece of information. This is always an encouragement of how important that is to analyze this data and hopefully sometime in the future, we'll do this with more regularity.

DR. FARLEY: Great. Thanks. That was very helpful.

So we're going to turn our attention to clinical trial design. When the FDA recruits physicians, we actually are looking for real docs. And our next speaker is one of those folks. I've had the delight, really, over the last -- since I've been at the FDA working with Dr. Shamsuddin. She was, prior to coming to the FDA, an infectious disease physician caring for very sick immunosuppressed patients. And many of you do know her because she was the point person for the clofazimine expanded access program for quite some time.

209

She's going to talk about review considerations for new drugs, focusing on the standards, which were established by Congress in 1962. The FDA was granted the authority by Congress to follow those standards and review drugs based on those standards, as well as some other review considerations. Thanks, Hala.

Presentation - Hala Shamsuddin

DR. SHAMSUDDIN: Thank you. We'll switch gears here and talk about review considerations for new drugs. Hearing this morning about safety, I'm going to start by saying that I will be discussing mostly efficacy because a lot of times, you cannot really interpret safety except in the context of efficacy. The risk benefit evaluation really depends on each patient population. If you don't hear much about adverse reactions, that is why.

Before I start with how to evaluate clinical trials and evaluate efficacy, I'd like to have a shout out for our nonclinical disciplines because there is a lot of work that goes even

before a clinical trial is started. And that really includes chemistry and manufacturing controls where you have to assure that the drug can be safely, and reliably, and consistently manufactured without a lot of impurities, and that the drug is stable.

There's some toxicology studies that go on with evaluation of safety in animals because that gives us an idea of what safety signals to follow in the course of a clinical trial.

There's some data about pharmacology, how that drug is handled in the body, and in vitro antimicrobial activity, how active is it and against what species. And finally if there's any animal model of infection in which the drug is active.

Having said that, for any drug to obtain market authorization or approval, the drug must show substantial evidence of efficacy, and this is according to Section 505(d) of the Food, Drug, and Cosmetic Act that this is shown through adequate and well-controlled investigations. We interpret

investigations to mean trials.

According to the Code of Federal Regulations, an adequate and well-controlled clinical trial is done to distinguish the effects of a drug from other influences such as spontaneous change in the course of the disease, placebo effect or biased observation.

The Code goes on to describe the different types of adequate and well-controlled trials. It describes five types. The first four are all randomized trials. The test drug, the patient is either randomized to receive the test drug or placebo, and that's the placebo concurrent trial; randomized to receive the test drug or no treatment at all; or is randomized to receive one or more doses of the test drug.

We can also have a trial where the control is active. It is a randomized trial in which the test drug is compared to another drug that is known to be effective for this condition.

Finally, we have historical control trials where the test drug is compared to

historical experience. And we generally reserve these types of trials for special circumstances.

Another way really to think about these trials is to categorize them in to two categories:

either a trial design to show superiority or a trial design to show non-inferiority.

For a superiority trial, the trial is designed to show that the test drug is better than the comparator; it's more effective than the comparator whatever that comparator might be. It may be designed to show it's better than placebo, no treatment, one dose better than another, or it's better than what is available.

The advantage of these trials is that they are really a direct assessment of the drug benefit. They also can assess any outcome of interest regardless of what historical trials have assessed.

Non-inferiority trials, on the other hand, are designed to show that the test drug is not worse than the active comparator by a certain

prespecified degree, which we refer to as the non-inferiority margin.

These trials are done when it's really not ethical to do a placebo trial, or when I don't think I can be superior than what is available, but I may have some other advantage.

The disadvantage of these trials is that the active comparator should be known to be effective in that population, and the magnitude of that effect, we should be able to estimate that compared to placebo from previous trials.

We also should be able to estimate the magnitude of the effect in that particular population of interest. A drug that may have a treatment effect in one population may not have it in another.

We also would like to know that this treatment effect can be estimated for that particular outcome of interest. If previous trials had evaluated mortality and I know the effect on survival, I may not be able to extrapolate that for a trial that's evaluating a

214

patient-reported outcome, for example.
All of these disadvantages really pose challenges for us, and they pose challenges and limits as to the choice of the study population and the choice of the outcome measure that we are measuring in that trial.
It is very possible that a study cannot support the efficacy if we cannot find historical evidence of the active comparator. If a trial comes in and they say, this is my active comparator and I really don't know what is the treatment effect of that active comparator, it could be very difficult to show that I'm no worse than that because I don't know what the treatment effect is.
How does this apply to NTM lung infection trials? There are several designs that can be considered. The first one is an add-on trial where a test drug or test drug combination is added to a background regimen and then compared to the background regimen alone or the background regimen with placebo. This test drug plus

215

background regimen versus background regimen has been used in MDR TB trials in the past.
You can also compare new regimens. You can have one combination compared to another or you can have one combination compared to placebo or no-treatment if that population you are studying in whom delayed treatment may be clinically acceptable.
You can also design a non-inferiority trial where you can substitute one test drug for a drug in the background regimen. This has also been used in TB to allow treatment shortening.
If feasible, you can also compare one new regimen to another. You can say, I'm not inferior to this other regimen but I do offer some advantage such as mitigation of toxicity.
We think that non-inferiority trials are going to be extremely challenging for NTM lung infections mainly because we don't know what the treatment effect of a single drug substitution is for efficacy. We don't know if we shorten therapy, again, what the treatment effect for that

216

shortened duration is going to be.
What complicates matters further is that combination therapy is recommended and in general, this would complicate the trial design for a new regimen because in general, we require that any new drug must be demonstrated to make a contribution to the overall regimen. If I have a regimen that's composed of three or four drugs, I will need to know that each drug makes a certain contribution.
The trial designs that we talked about generally are for demonstrating the efficacy contribution of a drug. But that may be difficult unless the drug is an add-on trial.
In addition, a new test drug may not offer much advantage as far as efficacy. It may be preventing emergence of resistance or mitigating toxicity.
For these situations, the FDA has published a guidance for industry, which I will refer you to, and I will not go into more detail. It's about co-development of two or more

217

investigational drugs for use in combination.
I'm going to switch gears here and talk about trial endpoints. We talked about demonstrating efficacy, but, really, what do we mean by that?
The trial should measure something. What we would like it to measure is a clinically meaningful outcome. A clinical trial should measure a clinically meaningful outcome that is a direct measure of how a patient feels, functions, or survives.
This includes, obviously, improved` survival, or improvement of symptoms or functional capacity, or a prevention of disease complication. A good example here would be treatment of latent tuberculosis where patients are totally asymptomatic, but the treatment is given to prevent active disease in the future.
Switching a little just to introduce the concept of a biomarker and a surrogate biomarker, because we do make the distinction between the two, according to the Biomarkers Definition

218

Working Group, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic process, or pharmacologic responses to an intervention.

You can think of a blood pressure measurement as a biomarker, microbiologic culture as a biomarker, radiologic appearance on X-ray as a biomarker.

A surrogate is a lab measurement or a physical sign that is used as a substitute for clinically meaningful outcome. According to the Code of Federal Regulations, this should be reasonably likely to predict a clinical benefit.

Examples of that are, for example, drugs that are approved for hypertension. You show an effect on blood pressure because blood pressure has been demonstrated to be predictive of future cardiovascular outcomes. Another good example would be HIV viral load where that has been correlated with survival.

A surrogate is a biomarker, but not

219

every biomarker is a surrogate. For a biomarker to be established as a surrogate that is predictive of a clinical outcome, we need to have evidence that the changes in this biomarker will correlate with the changes of the clinical outcome. And once established, a surrogate will allow development.

Again, a good example is HIV viral load where drugs are approved on the basis of decreased viral load because, again, that has been demonstrated to correlate with mortality.

If a drug receives accelerated approval under Subpart H on the basis of a surrogate biomarker, at times, a confirmatory trial that assesses the clinical outcome is still required.

A good example here is TB drugs. Although TB drugs receive accelerated approval based on culture conversion to negative, we still require a confirmatory trial that shows a relapse free survival.

How does this apply to NTM lung infections? We have several endpoints that are

220

consideration in NTM infection trials, and we are certainly open to suggestions for other outcomes.

The first is survival. The trial that measures survival is likely to be quite lengthy because the treatments are lengthy. We can have a trial that evaluates measures of symptoms or function. And examples of those may be clinician-reported outcomes. But some of these may be difficult for some symptoms. One symptom you heard about this morning was debilitating fatigue. A clinician is going to have a hard time reporting that.

The other one is patient-reported outcomes or for short, PROs. We're going to hear a lot more about that in the next talk, but these require development and they require validation. The validation has to be in the population under study. A PRO developed for patients with bronchiectasis may or may not apply to patients who have cystic fibrosis, for example.

Another measure of function is the 6-minute walk test, which we heard a little about

221

this morning, or any other functional assessment, FEV1, for example. However, the degree of change that is meaningful to a patient should be defined.

Finally, surrogate biomarkers, one example of that is microbiologic evaluations. Sputum culture conversion to negative may be one biomarker that, if studies show a correlation with improved survival or function, may serve as surrogate biomarkers.

This is similar to TB trials. However, in this disease, we have a lot unanswered questions. We don't know how many consecutive negative cultures we need. We don't know the timing. Is it at 3 months, at 6 months, at 12 months? Should it be during therapy? Should it be after therapy? We don't know how this correlates with clinical outcomes yet.

We're also open to suggestions for other surrogates, for example, radiologic evaluations. However, these are exactly the same considerations as microbiologic surrogates.

In conclusion, a drug needs to show

222

substantial evidence of efficacy for a clinically meaningful outcome evaluated in an adequate and well-controlled trials. Surrogate markers can be used for approval if the surrogate has been shown to predict and correlate with a clinically meaningful outcome.

Patient-reported outcomes have to be validated, but once validated, they can be used as a basis for approval. And finally, it is feasible to co-develop a new test drug combination in certain situations. Thank you.

(Applause.)

DR. FARLEY: Thanks, Hala.

You're going to be hearing a lot of discussion for the rest of the day, I'd say, about the endpoints in clinical trials because the design of the clinical trial itself and -- I'll just throw out something provocative and the panel can pick up on it later. But it seems in this disease that the most straightforward way to an adequate and well-controlled trial to meet the Congressional standard would be to show that

223

you're better than a placebo or better than something else, and that's the superiority trial that Dr. Shamsuddin was talking about.

But the endpoint and getting to an endpoint that means something to patients is challenging in this particular disease. One of the most straightforward ways that it would seem to do it would be to take the input that we got from you this morning and in other fora and try and turn that into an instrument, which we call a patient-reported outcome measure.

But one of the things I've learned in the last six years since I've been is that that's a lot harder than it sounds initially. Drs. Daniels and Quittner are going to walk through that a little bit for you, as well as provide you an example of a work in progress.

Presentation - Selena Daniels

DR. DANIELS: Good afternoon. My name is Selena Daniels, and as I mentioned earlier, I'm a reviewer on the clinical outcome assessment staff here at FDA. And just to give you a little

224

idea of what the group does, we provide advice to review divisions upon request in regards to clinical outcome assessments, which can include physician questionnaires and mostly importantly patient questionnaires.

We review these questionnaires to ensure that they're measuring the most important symptoms and impact to patients and that they're measuring these concepts in a reliable and accurate manner.

Today, I will briefly present on how we utilize information from patient-focused drug development meetings and how we aim to incorporate patient input in to clinical study endpoints.

You may be wondering how do we use the information from patient-focused drug development meetings. We have these meetings, but where do we go from here? How do we take this valuable information and generate clinically relevant patient-focused endpoints and place them in clinical studies?

I'm hoping that I'll be able to answer at least some of these questions in the next few

225

slides.

One of the main advantages in having patient-focused drug development meetings is that it gives all stakeholders the opportunity to listen to the patients' voice. We find it very useful to hear the patient experience, particularly to hear what's most important to the patient from their perspective and how they describe their symptoms and impacts in their own words.

We hope that it helps give drug sponsors ideas about what important symptoms and impact to measure in clinical studies and later make the investment to select or develop questionnaires to include in these studies, as well as engage with FDA for discussion.

The information from these meetings also helps informs how we review patient questionnaires here at FDA. It makes sure that you guys, the drug developers, are adequately assessing the patients' perspective from their medical condition.

226

While the patient-focused drug development meetings provide initial input, we also encourage drug sponsors, as well as other researchers who are developing these questionnaires to engage with additional patients either in one-on-one interviews or focus groups, as well as physicians and other experts.

The goal of this is to confirm that the questionnaire includes important yet relevant information and that to ensure that the questions and instructions of the questionnaires are clear and understandable to patients.

Another advantage of these meetings is that it helps us to think about clinical study endpoints. What's an endpoint? In the case of a patient questionnaire, the study endpoint could be the questionnaire score, and that's how it's going to be analyzed in the clinical study.

For example, if patients are reporting that the most important treatment benefit to them is symptom improvement, then we will want to encourage drug sponsors to select or develop a

227

symptom questionnaire that measure these concepts, and of course using good measurement principles, which I'll describe later in a few slides, as well as within regulatory standards.

The study endpoint could possibly be the change in the questionnaire score during the clinical study, which would assess the amount of symptom improvement.

One key consideration is that there are many things that are important to patients that are going to be discussed in patient-focused drug development meetings, as well as in one-on-one interviews and focus groups.

However, not all of these things lend themselves to be measured in clinical study studies as they may not be impacted by treatment, making it difficult to interpret as results.

Here, at the FDA, we focus on efficacy and safety. For example, financial well-being may be important to patients. However, it may be minimally impacted or maybe not at all impacted by treatment in a clinical study setting. So we

228

encourage drug sponsors to consider selecting important concepts that can also be impacted by treatment as key study endpoints.

Financial well-being and other important concepts that are unrelated to treatment can still very well be measured but perhaps may be for exploratory purposes.

For non-tuberculous mycobacterial lung infections, study endpoints that include patient questionnaires will be helpful to provide additional evidence of clinical benefit. Often, cultures are considered for primary endpoints in these studies. However, cultures do not directly tell us how patients feel and function.

The information generation from these patient questionnaires in combination with culture and other diagnostic endpoints provides a fuller picture of clinical benefit.

At the FDA, we have to uphold laws and regulations. Within these regulations, there are regulatory standards for assessments, like patient questionnaires, that require methods of assessment

229

as subjects' response to be well-defined and reliable.

Thus, when we describe findings from these assessments and labeling, we can make sure that the statements are not particularly false or misleading.

Not only do we recommend drug sponsors to engage with patients on developing these questionnaires using qualitative research, we also recommend them to perform appropriate quantitative research or statistical testing to show that the questionnaire is well-defined and reliable.

Both qualitative and quantitative research can tell us whether the patients can understand and report as intended on the questionnaire. Additionally, these tests can provide an estimate of a meaningful change or improvement on the questionnaire. Patient involvement is also extremely important in telling us what that meaningful change means to them.

We do recommend that drug sponsors seek input from FDA as early and often as possible in

230

their drug development programs. In some cases, if a patient questionnaire does not exist, then an existing questionnaire may be modified or a new one developed.

It is important for drug sponsors to start the process of selecting or developing these questionnaires early and using them early and often in their clinical programs to gain experience with them before using them in phase 3 studies to confirm clinical benefit.

At this time, we do not know the patient questionnaire that is ready for use in clinical studies for non-tuberculous mycobacterial lung infections. However, you will be hearing from Dr. Quittner who will be presenting some preliminary work on a patient questionnaire, which we are very excited to see.

I do want to note that the FDA is not endorsing any questionnaire over another at this time but are encouraging drug sponsors or questionnaire developers to start early discussions with us so we can help guide them to

231

ensure that the questionnaire meets regulatory standards.

There are two pathways to provide advice to those who are interested in developing patient questionnaires or any other clinical outcome assessments in clinical trials. The first pathway is within an individual drug development program.

We encourage drug sponsors to begin these discussions as early as pre-IND stage so that if there is work that needs to be done on the questionnaire, they can get this done before their phase 3 studies.

The second pathway is outside of the individual drug development program. This is through our Drug Development Tool or DDT qualification program. In this program, we work with questionnaire developers to develop and qualify questionnaires for use across multiple drug development programs.

We work with many stakeholders, including consortia, patient groups, individual academic investigators, as well as drug developers

232

within this program to develop and qualify publicly available outcome assessment tools.

I want to leave you with a few key takeaways. Patient-focused drug development meetings are merely a starting point to the road for developing patient-focused outcome measures and endpoints. And these meetings will support and guide FDA risk benefit assessments and drug reviews.

Ultimately, the patient's input will help determine what is measured to provide evidence of treatment benefit, how best to measure concepts in a clinical study, and what a meaningful improvement is in treatment benefit.

That concludes my presentation, and I will now turn it over to Dr. Quittner.

DR. FARLEY: It's my pleasure to introduce Dr. Quittner. She's a professor of psychology in pediatrics at the University of Miami. I got to know her around the review of Cayston for cystic fibrosis. One of her instruments was actually an endpoint in some of

233

those clinical trials.

She worked in this area a very long time, and I was very excited to learn recently that she's begun working in the NTM arena. So I'm anxious to hear how things are going. Presentation - Alexandra Quittner

DR. QUITTNER: I'm really delighted and honored to be here today. As Dr. Farley mentioned, some of my research really focuses on developing patient-reported outcomes. Although he mentioned the process is very difficult to actually use them as an endpoint for approval, I have to say that the CFQ-R improvement in respiratory symptoms was the primary endpoint that led to the approval of Cayston for patients with cystic fibrosis. I want you to know that there's hope out there that this is a possible endpoint.

I wanted to first thank some of the people who've really worked hard on this work. Insmed has funded the work that I'm going to present for you today. I want to acknowledge many of the people in this room who've helped me to get

234

to this point, helping me collect data, serving in focus groups and stakeholder expert panels: Ken Olivier, Kevin Winthrop, Matthias Salathe, Dr. Wallace and Anne O'Donnell, and many others here. So lots of people have already put work into this effort. That's my acknowledgement slide.

Our objectives are pretty clear today. We know that NTM is a substantial cause of pulmonary infections and affects those with chronic respiratory diseases such as cystic fibrosis and bronchiectasis. It's rare, poorly understood, and difficult to treat as we have been talking about today.

We are developing a patient-reported outcome that identifies the key symptoms that can track progression of disease, show symptom improvement, and potentially serve as an endpoint in a clinical trial of new therapies.

The aim of this study, I'll present to you today, was to develop an instrument for NTM symptoms in particular. The key thing here is it would be a module attached to the very well-

235

validated CFQ-R in cystic fibrosis, which has a very good respiratory symptom scale, which, as I just mentioned, was used in the approval of Cayston; or it can be used with a QOL-B, which is the PRO that is very well-validated and published in several papers in thorax and chest for patients with bronchiectasis.

So as I present our development of this particular symptom module, you'll notice that there's less of a focus on respiratory symptoms because we checked all of those in our development of the two other PROs.

We did follow the steps that are laid out in the very clear and well-defined FDA Guidance on patient-reported outcomes, which came out 2009. As a first step, we reviewed all the literature on NTM to identify relevant, critical symptoms and the challenges of living with NTM.

I have to say, this morning, I took copious notes, and much of it is reflected, I hope, in some of what I'll say today.

We did focus groups moderated by a

236

psychologist, either myself or my post-doc with adults with NTM and bronchiectasis at two sites, and that included 31 patients. We also did a consensus panel at ATS with 9 pulmonologists who were all the who's who experts in NTM, many of them are in this room today, talking about how they see NTM impacting their patients and how those treatments affect their patients.

We then went on to open-ended interviews with 13 patients. This is the qualitative phase that Selena described so well, asking them very long and detailed questions: how does NTM affect your life, your daily functioning, getting to work, what symptoms are frequent for you, difficult for you, what are your effects not just on your respiratory symptom but on your physical functioning, your emotional and social functioning? Actually, social functioning came up a lot today in the discussions.

Patients then completed -- these were patients with bronchiectasis -- the QOL-B, and we also coded all of these transcripts in Atlas.ti.

237

We then did a draft instrument based on all of this work of the NTM module and did cognitive testing, which is also required in the FDA Guidance using a standard "think aloud" procedure with 53 adults.

Given the variety of symptoms we're hearing about today, I'm really glad we oversampled in many ways. We tested this in 53 adults, and I have to give a huge thank you to Katie Keating and her support group who really helped to make a lot of that process possible. They gave us input on the preliminary items and the rating scale options.

Finally, we completed our initial -- I'm most excited about this -- psychometric validation of the module in 148 patients. In a rare disease, I think you know that that's pretty tough. Again, this required help from lots of the pulmonologists that are in the room today who helped me collect data.

So this is just laying out this pathway, and this really is what I think the FDA means by

developing a patient-reported outcome: focus groups with both stakeholders like physicians, patients with the disease, the qualitative phase and try to identify key symptoms and impacts, interviews that are coded systematically, draft instrument, cognitive testing to make sure all of you are comfortable feeling out the questionnaire, understand the items, can use the rating scales effectively, and finally what we would say is the quantitative side, the psychometric analysis of the items.

All of these have to work. All of these are sequential processes that hopefully lead to psychometrically sound tool.

I wanted to just you the demographics of the patients participating in those different studies, and you can see primarily female, and I think that follows the epidemiologic data, mostly Caucasian although I live in Miami and Dr. Matthias Salathe helped me recruit patients, so do we have some Hispanic patients. And you can see the range of age here. The means are in the 60s.

So I think these data show that we collected fairly representative samples of people with NTM.

Here are some of the main themes that I've just wanted to show you from the focus groups: pain, that's something I've heard today -- pressure in the chest, a metal or metallic taste in the mouth, fever, lack of sleep, difficulties getting to sleep; some of the main themes in the open-ended interviews, of course, fatigue, we've heard about this overwhelming amount of fatigue; sensitivity to smell; cold -- I've been cold in this room myself; hot flashes and feeling sweaty at night; and then some other themes coming from the physicians and patients as well: memory loss and body image issues; side effects of the medications including GI problems, and weight loss as the disease progresses.

The focus groups and open-ended interviews also identified eating issues, sleep quality, fever chills, and body image. The NTM module consists of eight unique symptoms, and we administered them to 148 patients.

The alpha was 0.73, which indicates very good reliability. All of these items hung together as the 148 patients with NTM filled out the symptom module, so there was very good reliability.

Just a couple of sample items for you:

bothered by cold weather and have you experienced problems with memory? These were highly endorsed symptoms.

The really interesting part about this is if you have cystic fibrosis, all of these sort of body image, eating problems, digestive symptoms actually go along with that disease. Separately, I've already developed all of those scales that are particular to patients with CF.

In this project with NTM and those who have bronchiectasis, patients with bronchiectasis did not endorse a lot of digestive symptoms, eating problems, or body image. In fact, they tend to be a little bit more on the overweight side.

What was very interesting to me is if

you have bronchiectasis plus NTM, you then experience these kinds of issues: body image, losing weight, not feeling like you have a good appetite -- we actually heard that this morning very beautifully confirming that -- and digestive symptoms.

What's fascinating is that the CFQ-R got all of that, and we just add the NTM module. But the QOL-B will not have those, and we developed then the body image, eating, and digestive symptoms that go along NTM plus bronchiectasis.

You can see the alphas on these; these are all highly internally consistent. The quantitative data on these scales worked out very well also.

I wanted to just show you this because this is for patients, and there are a lot of people tuning in. You can see these are just the individual item loadings. The higher the loading, the more that it was endorsed and linked to that underlying construct of the module.

Look at these really high ones, bad

242

taste in the mouth, memory problems, bothered by cold weather, pain, lots other things we talked -- fevers, chills, lots of the things that have been mentioned today actually loaded really nicely in this module.

This is the algorithm. I know it looks really scary and confusing but actually, I'm just explaining to you that if you have NTM and bronchiectasis, you need the QOL-B plus our digestive kind of eating scales and the NTM module. If you have CF, you need just the CFQ-R plus the NTM module because those were all covered.

Summary and future directions, cognitive testing actually indicated the draft items were relevant, clear, easy to understand, very strong reliability. I've explained how you might use the module depending on whether you have cystic fibrosis or you have bronchiectasis, and next steps would include additional psychometric testing.

Dr. Daley is kind enough to now begin to

243

include the QOL-B and the NTM module in his clinic routinely, and I know he sees lots of patients in Denver, and so hopefully, we'll gather additional data. And the other step we need to conduct -- and Selena mentioned this -- is identifying what is a meaningful change on the score for patients like yourselves with NTM, and that piece we have yet to do. So with that, I thank you.

(Applause.)

DR. FARLEY: Great. And to just got us ready for panel discussion, Dr. O'Donnell, who is professor and chief in the Division of Pulmonary Critical Care and Sleep Medicine at Georgetown is -- I've given her the hard job of actually summarizing the challenges in the design of clinical trials particularly that we face to date.

Presentation - Anne O'Donnell

DR. O'DONNELL: All right. Thank you, John. And thank you for the invitation to be here. Thanks to everybody for participating in this.

I just want to give my disclosures here.

244

We are part of the Insmed liposomal amikacin trial. We're also a site for the bronchiectasis and NTM registry that's sponsored by the COPD Foundation. And I've done a little consulting with another company regarding this.

We all realize here that in a perfect world, we give an antibiotic to the patient with NTM and they would get better, they would feel better, patient would feel better, the infection would be cured, and the damage to the lung would be reversed, i.e., antibiotic for pneumonia.

But this is not pneumonia. This is also not Pseudomonas bronchiectasis. This is not necessarily CF NTM disease. It's really its own disease. Just like Dave said, this is not TB. This is also not Pseudomonas in bronchiectasis.

The regimens for therapy are much more complex. The side effects are very potentially troublesome. As you've already heard, we really don't know the best definition for defining response to therapy.

Is it microbiology? Is it lung function

245

improvement? Is it radiologic improvement? And of course, patient symptoms, which hearing everybody talk today, clearly, what patients want is to feel better, and that's what we want for the patients. But we have to come up with some scientifically rigorous endpoints in order to make all these assessments so that we can actually prove that these drugs, which as you know are potentially toxic, do have benefits for the patients.

Like I said, I think the big four things that we can look at for endpoints are number one, microbiology; number two, imaging change; three, change in lung function; and four, of course, patient-reported outcomes.

Let's talk about the microbiology. You've already heard this is difficult because we don't eradicate the bugs in most patients, at least over the long term as best we know. Things that we can look at, our reduction in organism counts, obviously eradication of the organism in some patients, the duration of response of that

246

eradication, and that's already been alluded to, and then of course the presence or development of resistance.

What is the current microbiologic "gold standard" in NTM lung disease? Really looking at the literature on this, it's basically 12 months of negative cultures while receiving therapy. I think everybody alluded to this, that the follow-on after therapy is much more difficult to assess.

Other problems we have -- and this isn't so much for clinical trials but this is clinical practice. And I know many in the audience have experience the foibles of dealing with clinical microbiology labs in terms of actually even diagnosing NTM or speciating the organisms or defining resistance.

I think for clinical trial purposes, we're definitely going to need standardized lab microbiology. The current trial is using Richard and David's lab in Tyler. They published on using semi-quantitative cultures for monitoring patients on therapy.

247

We also know that they are kind of the leaders in looking at amikacin resistance and in genotyping, as Richard already alluded to. I think one thing is that in clinical trials and hopefully for better patient care ultimately, we need very standardized microbiology.

One other appeal I would make to the FDA because you're one of the people responsible, one of the organizations responsible for clinical laboratory management in the U.S. is that we need to come to some clinical consensus on this ultimately about how mycobacteria is handled in clinical labs.

Let me just talk about a couple of papers that you've already heard about, Richard and David and colleagues' paper from Tyler that was published last year in Chest, where patients -- and again these are nodular bronchiectatic patients which are most of you in the audience -- who had 82 percent culture conversion to negative. But as was alluded to earlier, 14 percent recurrence of organism while on therapy of which

248

73 percent were thought to be reinfection and 27 percent true relapse, and then about half the patients had positive cultures after the conclusion of therapy.

Obviously, this makes it difficult for microbiology to be the sole endpoint for these clinical trials.

I think we've already heard about similar studies from South Korea. The South Koreans in this paper that was published in the Blue Journal this year did not tell us what happened post therapy.

Again, we haven't really focused too much on cavitary disease today except for a couple of mentions this afternoon, and there are a substantial number of patients who have cavitary mycobacterial disease, and the culture conversion rated there is much -- it leaves much to be desired, I would say, and we have to factor that in when we're designing these trials.

We have a couple of small papers published recently about salvage therapies. As

249

was discussed, this is one way to approach these patients, the patients who have failed standard therapy:

bedaquiline, a TB drug, has some potential for non- tuberculous mycobacterium, and Julie Philley from the Tyler Group has published a small series on that.

Finally, the liposomal amikacin trials, what's been presented in abstract form so far show some, but clearly not 100 percent culture conversion with the addition of liposomal amikacin to standard therapy.

Why do we need a microbiologic endpoint? For one thing, it's one of the easier things to measure if we do it correctly in the correct laboratory environment. It's clearly reproducible again in the right hands, I would say.

The problem is, you know, what's success? What's microbiologic success? Really, I'm going to leave that to the panel to tell us after I finish my talk and we have our break because, honestly, I don't know the answer to

this, and I don't think any of us do and know how to really handle this.

Three negative cultures while on therapy, does that constitute success? If you have one positive culture and all the rest are negative as our colleagues from Tyler put out there, is that still success? What about after the conclusion of therapy?

In clinical trials, do we need to monitor the patients for three months post therapy, six months post therapy, 10 years post therapy? How are we going to handle that in the context of a clinical trial to get drug approval? I'm anxious for the panel to tell us when we're done.

I'm going to briefly touch on what I think are a few other potential endpoints but probably not primary endpoints when looking at antibiotic treatment for this disease.

Imaging, a couple of patients mentioned, hey, my CT scan got better. We all know that that's not the be all and end all of treating NTM

disease. One of the major features of NTM radiology, if you will, is that we often see a waxing and waning of the findings on the CT scan.

So I think it will be very hard to quantitate CT or use CT as a primary endpoint in this disease. I think there is a role, but we need more information. We need some standardized scores for looking at CT scans in order to use this, and we also have to be concerned about the radiation exposure with too much imaging for patients who have already probably had a fair number of scans.

There are a couple of trials that have looked at serial imaging that report improvement, but again, I think we have a ways to go, and this would not be, what I would think, a primary endpoint in monitoring antibiotic response.

What about lung function testing? The pulmonary world loves the 6-minute walk test. I tell you, I hate the 6-minute walk test. And Michelle Cooney, my research coordinator, can vouch for how much we love doing those tests in

our hallway.

I think a lot of studies now have 6-minute walks as part of the protocol. I think it's a pretty soft endpoint. It is reproducible. There is data on that, but it's not, to me, in my mind, the best marker of disease progression or disease correction when you're giving an antibiotic in a very complex disease where the infection is not the whole story for the patient.

I think we need this. I think we need pulmonary function tests as part of clinical trials but mainly to monitor for adverse effects from the drugs, particularly the inhaled drugs. But I think we all recognize that FEV1 change is probably not an outcome that's going to help us very much in these antibiotic trials complex disease.

It's clear -- I mean Alexandra just did a great presentation. She's done so much fantastic work on translating what you all said this morning into some scientifically validated way for us to incorporate your symptoms into

clinical trial work. It's just vitally important.

Now, Ken published a paper looking at basically the things that are listed here: cough, fatigue, hemoptysis, that can be incorporated into a validated tool and clearly is vitally important.

Whether that can be the primary endpoint, I think we could debate, but having your symptoms translated into something that we can use in a clinical trial by monitoring it serially while you're on therapy is very, very important. I think we need to probably incorporate this trial, as was said about Chuck, into our clinical practice.

All right. What about looking at patient-reported outcomes? I think Ken, in his paper where a small number of patients were reported who received inhaled amikacin off label for a refractory NTM treatment, there was some benefit in the symptom score that was administered during that trial. Alexandra just showed us the work that was presented at the ERS meeting last month about this.

254

I think to kind of summarize it, you know, we have these four things: microbiology, imaging, lung function, and patient-reported outcomes. But I think we also, when we're designing clinical trials, we have to think of a few other things about this disease because it's very heterogeneous.

We have to decide I think as we launch more trials, are we going to include all NTM species in these trials or should we segregate MAC and M. abscessus when we design these clinical trials? Should we separate or stratify, in some way, patients with nodular bronchiectasis versus cavitary disease?

I think we heard today from what Ken is saying with some data forthcoming that that probably would be a good idea to look at that as a way in the trial to stratify because the outcomes are quite different.

We really have to decide about the chicken and the egg issue, right? Is the NTM causing the bronchiectasis or is the NTM

255

superimposed on chronic fibrotic disease or emphysema?

It's a different ball of wax when you have patients who have a lot of underlying structural lung disease and get this infection versus getting the infection and then developing nodular bronchiectasis.

I think another thing that patients brought up today, which I find to be a really important issue in assessing patients with NTM, is patients with NTM who also have other bacteria.

If you have Pseudomonas, if you have Staph, and you have NTM, it's a different situation. Patients have more exacerbations whereas pure NTM patients tend not to have exacerbations and hence I don't think exacerbations are going to be an appropriate endpoint to monitor here.

But patients who are co-infected with Pseudomonas, or with Staph, or Nocardia, or Aspergillus, we have to somehow figure out a way to make the clinical trials responsive to those

256

different types of organisms because, obviously, there's also some overlap.

For example, with inhaled amikacin. It takes care, to some extent, of the Pseudomonas as well, and so that complicates matters. And just to show you a few images, I mean this is a male patient of mine with both MAC and Pseudomonas. I mean he's had it for years. He really functions quite well, doesn't have a lot of -- he has symptoms but he doesn't have frequent exacerbations.

This is a patient with cavitary MAC. As you can imagine from looking at these images, she's quite symptomatic all the time and this has been a very difficult disease to get under control. But then we have the patients who are positive on their sputum cultures for 10 years but have non- progressive disease. How do we put those kind of patients into clinical trials?

As was said by Dave earlier, he's followed his 75-year-old patient for 15 years and she hasn't changed, but it might change at some

257

point. So that has to be factored in as well.

And finally, looking at the abscessus patients.

Again, I think I tried to make four points, four potential endpoints that we've already heard about today. I think imaging is something we have to have, but it's not something I would consider to be a primary endpoint.

I think pulmonary function testing is useful in inhaled antibiotic trials for monitoring for any adverse effects from the inhalation but are is not a helpful primary endpoint. And six-minute walk, I think is of mixed value.

I think it's clear that a patient-reported outcome is vital here because again, we face, again, positive microbiologic patients who are symptomatically better with therapy and vice versa.

I think we're kind of stuck right now with a microbiologic endpoint, but we have to consider stratifying patients in clinical trials based on their organism. I think we also need to know more about these organisms, avium versus

intracellulare, not something our clinical labs differentiate, but the patients probably have different prognoses.

What about the abscessus, the true abscessus-abscessus patients who have macrolide resistance versus other M. abscessus complex patients? We probably need to separate in clinical trials nodular versus cavitary patients and also evaluate the impact of the co-infecting organisms.

Finally, I think we need to come to some consensus about combining a longer term microbiologic endpoint with patient-reported outcomes.

One last thing I would throw out there -- and I know there's not much on this, but whether there's any role for serologic monitoring of these patients. I know there are a couple of posters presented on this at the ERS meeting last month. This is all coming from Japan.

I know I've had some side conversations kind of saying, poo-pooing this, but whether this

is some as an exploratory endpoint might have some value to look at IgA antibodies in MAC patients and see if the IgA antibodies go down with therapy.

Again, that's something I see as a primary endpoint but something that might be of value that we in the U.S. really have not used at all in either clinical trials or in clinical practice.

I would conclude by saying -- we have a break, I guess. I'm leaving all these questions to this very august group here. I think we've heard a lot of great things about the patient-reported outcomes. We need to really understand what we're going to do with the microbiologic endpoints and particularly the duration of response.

Again, I thank everybody for being here, particularly the patients, and just acknowledge the NTM advocacy group and our bronchiectasis registry, and the FDA, of course, for bringing us together. Thank you very much.

(Applause.)

DR. FARLEY: Thanks very much, Dr. O'Donnell.

We will have some time for questions during the panel discussion. At this point, I'm mindful of the time, so we're going to take a 15-minute break. And we're going to begin again promptly at 3:15. Thanks.

(Whereupon, at 3:02 p.m., a recess was taken.)

DR. FARLEY: Could we ask everyone on the panel to please take their seats up front, and we'll get started? Great. I'm going to turn the gavel over to Dr. Nambiar who is the division director for the Division of Anti-Infective Products.

She trained at Children's Hospital in Pediatric Infectious Disease, and for quite some time actually was part of running a joint fellowship program we have in Infectious Disease between Children's and the FDA. She took over as division director about two years ago now, I

think. Thanks, Sumathi. Panel Discussion

DR. NAMBIAR: Thanks, John.

Before we go into the actual panel discussion, I would like to extend my sincere thanks as well to patients and patient representatives for participating in this morning's discussion. Hearing from all of you about issues that matter most to you are a tremendous value to us as we move forward in finding safe and effective treatment for this condition.

We've heard from experts in the field this afternoon who provided an overview of NTM lung infections and set the stage for the next discussion. Dr. O'Donnell's talk has made my task a lot easier because I think a lot of the points I wanted to raise have already been brought up.

We only have about 90 minutes to go through a lot of topics, so we'll try and focus on four key issues. The first three really relate to trial design. We'll talk about the appropriate trial population, the endpoints, and choice of

262

appropriate controls for the trials. And then the fourth topic, which is just as important, is regarding practical considerations in conducting these trials, and as briefly mentioned this morning, did not come up much in presentations this afternoon, but I think it's an important point to discuss as these trials are certainly of long duration; treatment regimens are very complicated and the frequency of visits can be quite challenging.

With that, I thought the first topic that we can talk about would be the populations and how might we streamline our trials, and who would be appropriate to enroll.

In terms of the populations to study -- and I think Dr. O'Donnell laid this all out very clearly -- is it all right to limit it to only NTM patients who have underlying bronchiectasis; is it okay to also include patients with cystic fibrosis in the same trial, if so do we stratify them?

We've heard in the discussions today that these two populations can be fairly different

263

in terms of the outcomes. The frequency of the pathogens might be different between these two sets of patients. And there might be differences in other risk factors such as steroid use and macrolide use as well.

So that would be one question that we would really appreciate the input from the panel. The second key area would be differentiating between those who are treatment-experienced versus treatment-nais it okay to combine them again in one study or should they be studied separately? Potentially, one can have different trial designs depending on whether it's a napopulation or an experienced population.

Would we consider different endpoints? Again, if their treatment-naversus treatment-experienced, what might be the treatment benefit? Would there be a difference if this a treatment-experienced patient versus being a treatment-na patient?

Again, Dr. O'Donnell has addressed this; whether MAC patients and non-MAC patients should

264

be in the same study; if so, should they be stratified? Are they different enough that they should be kept separately, patients with nodular disease versus patients with fibrocavitary disease?

I think they are all -- I think the bottom line, as we've heard today, is that this is a very heterogeneous disease and what might be the best way to study it in terms of the patient population.

So I pause here. I welcome input from the panel members, and then we move on to the next topic. Any takers?

DR. DALEY: Okay. I'm going to answer all of these -- no, just kidding. First of all, thank you to the FDA for convening this incredibly important meeting. I'll just start with that because this is extremely important for our patients, for us as clinicians. I thank everyone who is here for their input.

I'm just going to run down that list really quick. CF versus non-CF. I believe that

265

this is a need for both populations, that it's a significant health issue for both populations. And yes, they're different but, in my mind, they should be included in trials.

If you marshal the resources to put on one of these trials, why would you exclude a population of need? If you recall, we did that with HIV and TB for way too long. And now, all TB trials include HIV as well. Yes, they're different. We can deal with that in the design and the analysis. So I think yes.

Naive versus experienced. This is a practical issue. Most of the napeople are the ones who haven't been treated or out in primary care offices and pulmonary offices, they're very hard to find.

From a practical standpoint, you know, if you really want to get a lot of patients, they're going to be coming to the reference centers that we keep hear getting mentioned today. I think just think from a practical standpoint, leaving them out is really problematic in terms of

266

being able to find patients to treat.
MAC versus non-MAC, that depends on the MIC. That decision, science should drive whether you include MAC and abscessus. Not all drugs that work for one work for the other. I think if they work for both, same argument. To me, as with the CF question, they should both be included if the drug works for both.
The most important thing -- and this really wasn't, I don't think, highlighted well enough, that really what matters is the precise speciation of the organism.
Anne mentioned this issue, but really it's about speciation. And that means it needs to go to the right laboratory so that it can be speciated, or how do you interpret the outcome of someone who's treated with abscessus versus massiliense, as Anne said, where one does really well and the other doesn't, but most labs don't distinguish the two.
The final thing here is there are so many confounders here that I want to propose this

267

idea and I want to hear from industry. They won't like it. We can't tell who's going to progress on day 1; it's not possible.
But we do have a little better idea at about six months. In South Korea -- and they published this approach -- when they see someone, they follow them for six months, collect additional sputum, re-image at six months. And now, at least, they've had six months to say, this is a progressor; this patient is not a progressor.
I think it helps you find the right people to be enrolled in a trial. Otherwise at six months, many of these are going to be stable. Those are not the people you want to enroll in a trial. You want to enroll the progressors to be able to understand, did the treatment have an impact on any of the outcomes which we'll subsequently measure?
DR. WINTHROP: Are we done with that question?
DR. NAMBIAR: No, no, no.
(Laughter)

268

That is just the beginning.
DR. WINTHROP: Okay. That's just the start. We were just in San Diego, some of us. I was there last time. I'm sure I'll hear about it. But we spent five hours talking about just one question for the new guidelines of meeting, so this -- maybe we should move to the next question.
But I want to echo Chuck's comments and thank everyone for doing this and for putting this disease on the map. I think the last few years, we've gained a lot of momentum, and a lot of that has to do with the patients here and the patient advocacy groups, as well as the FDA, and industry and the academics. We're all in this together and we're all trying to accomplish the same thing. I'm very happy to see movement in the last few years.
I liked all of Chuck's answers, so I'm not going to weigh in and disagree. In fact, we just submitted a grant today that took the approach that Chuck just mentioned. I guess we're going to get to the comparison groups later.

269

But I think the idea that everyone needs to be treated right away is obviously not true. And we know that. It's in our guidelines that we support watching people who clinically can be watched.
At some point, I feel that most people do need to be treated or they'll want to be treated. Exactly when that happens, of course, is a spectrum and it's a case by case thing. It's different for everyone.
I do think that the answers Chuck provided, I would just say I'd agree with them. I don't like excluding groups up front. I'm an epidemiologist. I like to handle it in the analysis. And as long as you can construct a big enough trial -- and I know this gets challenging because it becomes more costly. But it's really silly to exclude people up front if you don't have to. And it's better to sort out who responded later in your analysis in looking at subgroups and things like that. So I think as much as possible, we should try to be inclusive.

DR. WALLACE: I'd like to make a comment that it depends on whether the trial is primarily the safety -- that is the drug has never been used in any of these populations -- or as we are with Arikace, we've already been through one trial; now, you're probably more interested in efficacy and safety is much less of an issue.

So if it's a safety issue, the more patients you put in the trial, the more you may be able to answer that question. But an efficacy trial, it may also be helpful to put them altogether if you can divide them all out.

I talked earlier about the design trial of having patients come every month and dealing with a patient population that averages 75 years of age. It is not a possible trial. We lost so many patients.

We did a trial just with inhaled amikacin and got two-thirds of the patients because they were unable to find a way to get there to do that. So if there's anything to emphasize, it would be that.

Again, some difference based on whether it's safety or efficacy, and that would, I guess, be whether this is the first trial or the second trial.

I agree with Chuck about CF. As long as we're going to do them, you can always split them out. The clinics are often together, fairly close together. I mean I think we could be able to do that.

I think M. abscessus, as Chuck alluded to, the difference between the islets that are macrolide-susceptible and the macrolide-resistant on the basis of the ERM gene is enormous. Obviously, there's only been maybe one trial, but none of us were surprised by the results.

Again, I don't know if you have to separate them out but you have to identify them. We have to know which ones are macrolide-susceptible, which ones are massiliense, so you can separate them out when you get there.

I think with the recently completed Arikace trial that had both abscessus and MAC, for

safety reasons, I think that was fine. Now, if you want to do an efficacy trial, you might not make them same. I don't know we've thought about that in terms of what -- I mean the next trial is going to look at just one of them, but they may not be treated the same. They may not respond the same.

And I actually don't know that, I mean in the sense that you had one group that responded better than the other, but I don't know if it was study design. Should you have gone longer before you assessed them or not? Six months isn't very long for M. abscessus.

I pretty much agree with Chuck. The one other thought is if the endpoint is primarily or exclusively microbiologic, it doesn't really matter to me how sick the patient is. The endpoint is fairly objective. You can either make the cultures negative or -- I mean, they need to be treated or you decide, but I wouldn't -- 99 percent of our patients come to us because they're symptomatic.

Somebody has referred them to us, primary care, a pulmonologist, or why did they have the test done in the first place? They had some kind of symptom, so most of them are usually willing to enter the trial at that point.

So I don't know about the six months if the endpoint is primarily microbiologic. Patient-reported outcomes, it is tougher if the patient doesn't have a lot of symptoms. I mean if that's very important, then you may want to separate them out so that the ones that are the sickest, you can really use patient-reported outcomes as an outcome as compared to some patients who are -- they don't feel well but they're not going to give you a lot -- they're not really sick in the way that you could probably measure that very objectively.

DR. EAGLE: I would just like to add that like when you're actually sitting down to put these clinical trial designs together, you think you've got it, and then you pressure test it, and you wonder whether you are doing the right thing when you're going to put so many patients through

274

the trial and resources.
One of the things I want to highlight that hasn't actually been spoken about is the timing of the endpoint, not just the endpoint. Right now, we have the microbiological endpoint, which is the gold standard.
Whether that is the right thing, it's clearly a biomarker, a surrogate, and we do need correlated patient endpoints, whether they're functional or whether they are patient-reported outcomes. We welcome a patient, a PRO, for these trials because it seems like if it's one that's properly validated and works, it will solve a lot of our problems. We don't have it at this moment, unfortunately.
But when we looked at -- in our experience when we looked at our trial, we did have non-CF, and we had CF patients, and we had abscessus, and we had MAC. And when you look at what happened, they behaved differently.
So when we're trying to put another trial together, we do want to include all the

275

patients. The question for us became, do we include them all in the one trial or do we actually have separate trials for them because we believe of these -- if you believe that all of these patients could benefit from your drug, then you have to actually do clinical trials and include all the patients.
The question isn't do we need to do clinical trials in all the patients? The question is how do we design a trial so that we capture whether the drug works or not?
When we looked at our trial, the non-CF MAC population appeared to respond in terms of their cultures much, much faster. The clinical trial was it wasn't long. It was three months, double-blind, then another three months, open label.
In that time, if you really dig down and look at it, I can say that some of the M. abscessus patients look like if we gave them enough time, we may have seen something that we didn't. So the subpopulation that really stuck

276

out and seem to do really well was the non-CF MAC population.
When you're pioneering trials in this area like we are without -- it is a paucity of perspective controlled clinical trials. It's very difficult to draw your assumptions. And without assumptions, you're literally just stabbing in the dark.
We have some assumptions, and that's why the current study that we're doing is a much narrower population. We'd love to do more studies and hopefully have the PROs ready to go when that happens.
Also, we now experience with the narrower, the non-CF MAC, we didn't know what outcomes we were going to expect, that we're actually going to show something. And it happened to be that the 6-minute walk test that was in this trial, and we don't really know what that means at this moment other than we do have a separation. We did see a separation in the non-CF MAC patients. They seem to do much better.

277

Furthermore, we actually saw when we actually looked at the data even more that the converters amongst that sub-group drove that result. That's what we're left with now to actually put it in the next trial, and we hope to see that result to be reproduced.
But that's really the difficulty, is the timing of the endpoint because you can cut the data -- I mean you can analyze it, you can stratify patients, and you can analyze it a number of different ways. But if your endpoint is at 6 months and your M. abscessus patients are going to convert or improve in their PRO at 8 months or 9 months, you've missed it. And that's the danger, and that's what we were afraid to allow to happen.
DR. OLIVIER: I would just bring up the issue of numbers and practicality of accrual. I think we are very early on in development of clinical trials from this. If we get too narrow and too focused too early on, we're not going to get clues about how these different subpopulations may or may not respond to a drug.

278

The tremendous successes that cystic fibrosis has had in terms of clinical trials, I think in large part, is related to the easy accessibility of those patients with them aggregated into clinical care centers and the willingness of the patients to participate, but that comes on the backs of what we see now of years of building excitement in that disease.

We don't have all of the patients aggregated into geographically dispersed centers throughout the U.S. And again, we're very early on in development of trials. So trying to get that excitement to build, trying to get patients encouraged to participate to where we can get the types of timely accrual that we need, I think is an issue.

When you're looking at things like MAC versus M. abscessus, there may be differences in right or wrong the perceived need of new drugs. I think many of us would agree that M. abscessus has a pressing need for something more effective to develop.

279

When we actually sit down and look at the numbers that we have access to, if you say that these organisms are more important than the setting of cystic fibrosis, we can calculate fairly quickly, and I think fairly accurately, how many CF patients in the U.S. have these infections, and it's not very many.

If you were going to try to design a trial of a drug to look at M. abscessus in cystic fibrosis, I think even in that disease where it's relatively easy to accrue, you're going to have problems, whereas MAC, I think that there may be more patients, especially non-CF patients, that have it. Finding those patients and getting them to participate may be a problem.

When it comes to treatment-naversus treatment-experienced, I think it depends, again, the sort of stage that you're developing the drug in and what you're looking to show. If you're trying to introduce a novel drug into treatment-na MAC patients as part of a multidrug regimen, as David and Richard have discussed, the proportion

280

of patients that will respond to the standard of treatment is pretty high, and it's going to be difficult to get numbers that will show a benefit of adding or substituting a new drug in for those patients.

On the other hand, if you take a patient population like we started with, with the Insmed trial that we had some documentation of their refractoriness to their sort of optimized background regimen, I think from a number standpoint, it becomes easier to introduce a new drug and if that drug has effectiveness, to be able to see that in the context of what people would consider standard of care.

So we'll talk about study designs next, and there may be other ways of getting around that. But I think those are considerations that need to be kept in mind when you're talking about the dichotomies that we're discussing in this section.

DR. HUGHES: Again, as the others have said, thank you to the FDA for convening this.

281

This is a critical need and great to have the input particularly that we had this morning from patients.

Chuck, yes, I like your idea actually, because we have to find some way of trying to predict or enrich the population and somehow to identify those who are likely to progress and that you can demonstrate the difference.

Because I think the challenge we will have is probably -- from my statistician friend, which is how do we handle then that data set, because we'll draw the line on time zero, and it will be finished 30 months later. We have to figure out how between that -- it's going to take some creativity, I believe, and really some novel thinking to find ways of assessing particular endpoints in ways that will allow a drug to be approved to the point where we believe there is a good benefit risk of that product. It's really quite a challenge.

Also, last week in San Diego, call from the podium, which is we're having to do the wrong

282

trials in the wrong populations. The path to registration for new antibiotics now is in skin infections or UTI.

It's not the challenge that we have, but because we have that path there, we're allowed to follow it because we know how to design the trials and select the populations because we've learnt from that. Now, we're sort of having to learn the difficult way of complex patients, very heterogeneous, heterogeneous rate of progression, and that really does challenge us.

So I think hopefully in the next little while, there'll actually be some more flexibility in terms of design for an area where there's such a big need and being a little bit more flexible up front in terms of what has to be prespecified because otherwise, the number of patients and the overall cost, the amount of microbiology testing you have to do, really is a barrier for good studies.

DR. GRIFFITH: I would like to just mildly dissent on a couple of points. In terms of

283

the 6-month waiting period, there are very clearly people who are symptomatic and have progressive disease at the time of their initial evaluation. And I think that there would be no benefit gained by asking those people to wait further for initiation of therapy. As a matter of fact, I think they'd go somewhere else.

But I mean the routine for me is -- at least half of the people I see, I don't start on therapy at the initial visit, but within two or three months, I've got a pretty idea about whether or not they need therapy

I just think 6 months is kind of rigid and a little bit long. Perhaps it could be -- I mean, maybe there's room to compromise in that.

The point though about MAC and abscessus, they're totally different. If you go into it knowing that you're going to post hoc separate the analysis, why wouldn't you do it initially?

I mean I understand that you have to have numbers. And that's really a lot of what

284

we've been discussing is patient accrual. Clearly, we're looking at multicenter trials. In anything that you talk about, you got to marshal all of the resources in the country to get the power to do statistical analysis. But there's no overlap in medicines between MAC and abscessus except perhaps the study medicine like Arikace.

I, personally, I think the way that Insmed has approached the second trial makes sense, but I wish they would do another trial for abscessus. I'm all for treating them all. Why don't include simiae? Simiae is such a difficult bug to treat. Why don't we try a few simiae patients?

Well, you're not going to lump them with MAC. But at any rate -- I'm sorry; that's just my thought on that. You know that you're going to separate them in your analysis regardless.

DR. O'DONNELL: I just want to address the getting more patients into trials and spreading out our network because, clearly, from hearing from everybody today, that sort of makes

285

me feel sad for our profession that patients aren't getting diagnosed in a timely fashion.

One thing we're trying to promote is this bronchiectasis research registry, which has an NTM component to it to try to get more patients involved, and actually a patient-powered network so patients themselves can register to potentially be in clinical trials.

We've got to get this word out better. We're not doing a very good job, I would say, in getting patients. Patients in the room, great, but there's tons of other patients out there that we're not getting into clinical trials.

The second thing I'd like to pick on a little bit is this treatment-naive patients because maybe we do need a trial in treatment-na patients.

My clinical experience -- and I bet many of the patients will say rifampin is the hard drug for many patients in the current regimen. Maybe we need a trial that looks at something other than those three and substitute something else for

286

rifampin in that head-to-head trial.
I know Dave is giving me the evil eye there, but I do think we're not -- we don't have the final answer for treatment-napatients either.
DR. GRIFFITH: We discussed it briefly at the meeting, where do you put your resources? What's the priority of your questions? I mean that's tough. Is that a question you want to take a sizeable number of people to enroll in a trial to answer when they might be in another trial? It's a tough call.
DR. EAGLE: First of all, I want to just reiterate that we actually do believe all these patients need to be studied, and we're committed to that.
Just with respect with the treatment-na patients, I'm wondering if this is a time to talk about separating that group into the cavitary lesions versus not having cavitary lesions. And the reason for that is because without cavitary lesions, the current standard of care has a high success rate, which makes the sample size that you

287

need for your trial in this disease almost impossible to achieve in a reasonable period of time.
DR. FARLEY: Just a few comments from somebody who sees development in a bunch of different drug areas, but doesn't know very much about NTM.
Just to underscore what Dr. O'Donnell said, it seemed to me that in the CF world that having that registry data is very, very helpful to trial designers in terms of understanding the optimal timing of endpoints with patients with certain characteristics, et cetera. Just to sort of underscore that that's a very important effort, I think, based on my own observation, it really helped them move forward.
I think one of the things just to point out is that if the patient population is heterogeneous enough that there are groups of patients where one expects the optimal timing of the endpoint to be better -- this is not an FDA opinion; it's just my personal opinion -- that one

288

might want to consider two trials with different patient populations with different timings of endpoints.
Karen Higgins, I invited on the panel, make sure I don't say something heretical.
(Laughter.)
DR. FARLEY: She's from the Office of Biostatistics. But I would think that if both of those trials were successful, they could support each other, and you then have a package of substantial efficacy.
I know that funding is limited, et cetera, but that's something that has been effective in other infectious disease areas as far as getting to approval.
DR. HIGGINS: Just very briefly, this could also be done, these two trials kind of under an umbrella protocol where the two trials are considered separate, but for logistical reasons, it would be easier to potentially enroll patients and put them in the trial that's best for them.
DR. DALEY: Can I just comment? We

289

don't have enough patients to do that, and the need is so great. You know how many examples in medicine where that's what the company said they were going to do, and they didn't do it. And it's left to the clinician to work off label with no data.
So when we have a chance to enroll patients who have a great need, we need to rethink that, I think. And it may not be perfect, but I still think it's a really important issue that we go and we study non-CF because there's more of them, and then we just don't study CF because it's approved and everyone says, now, CF Foundation, you go pay for that, or academia, you pay for that.
I think that they're all sitting in the same clinic, usually in the same hospitals, so there's a real strong argument mainly based on need to get them studied early, not later.
This 6-months is an example of trying to use some kind of marker of progression. It could be you use the previous 6 months, too, to be able

290

to identify progression. That's really all I was saying.

One thing that I think is another issue that's really important whether you decide to do a separate trial for abscessus or MAC, recognize that in our study of abscessus, 55 percent of the patients also had MAC concurrently or previously. This is a problem in terms of trying to figure out how to design a study to look for efficacy when there's so much recurrence and reinfection.

DR. WINTHROP: And also, I'll add a lot of them have Pseudomonas, and they have Aspergillus, and they have Stenotrophomonas and everything else growing in there, so it does get complicated.

DR. NAMBIAR: So I think we've heard quite different viewpoints on this issue. It hasn't made our life any easier, but I can see the merits of doing a study, which is sort of an all-comer population, so you haven't really restricted to one subgroup versus the other. I think that makes a lot of sense in terms of extrapolating to

291

the larger population. But from a practical standpoint, I think it does pose some challenges.

Dr. Wallace, I think you had a question earlier about whether the study was being done for safety or efficacy. I think the discussion here primarily is about assessing the efficacy and really deciding if a new therapy works or not.

Our focus here was more in the context of an efficacy trial, but I think your point is valid, not that it's not important but becomes less of an issue with safety studies.

We will get some safety obviously from these efficacy trials, but sometimes if the numbers end up being small, the treatment effect is large and the sample size may be smaller, then we might ask for a separate study primarily focused on safety. We'll collect some efficacy data, but it's not powered for any kind of efficiency assessment.

DR. WINTHROP: Can I just add one thing?

DR. NAMBIAR: Sure.

DR. WINTHROP: The only thing I'll add

292

is that I think it depends on what the question is a bit, right? And we're all kind of talking about the same thing, but no one is articulating the question.

If the question is, does the drug kill NTM, that's a different question than, does the drug make CF better; does the drug make non-CF bronchiectasis better? These are different questions, and so are going to potentially use different measurements of efficacy for those individual groups; you might study them different lengths. That's why we are tempted to segregate.

But again, if your question is, does the drug kill mycobacterium, it might kill it to a different extent or over different time periods in different subgroups of people. But if your ultimate questions is, does the drug kill mycobacterium in a human body, you can lump all those groups together.

Again, I'm just saying it depends on what the question is. I know we're getting to that next here, what is the endpoint that we're

293

actually trying to ascertain?

DR. NAMBIAR: I think the basic question is does it make the patient feel better? I think that's what we're trying to get to. Along the way, hopefully, it's also killing the NTM and then making the patient better. So it's more than just killing the organism. I think that's what we're trying to find out.

DR. WINTHROP: Then the next question is, is killing the organism a surrogate for actually feeling better and living longer?

DR. NAMBIAR: Right. So I think you --

DR. WINTHROP: And that's really what we cared about.

DR. NAMBIAR: So that's sort of the next question. Maybe that's a good way to start the discussion on the endpoint, I think Dr. O'Donnell.

DR. O'DONNELL: I think that's a good question for Alexandra, how can we correlate the PRO with organism-killing. Can we for the semi-quantitative cultures or something? Can we do something like --

294

DR. QUITTNER: You definitely can correlate them. In the CFQ-R studies I've worked on, we did that. We would correlate change in respiratory symptoms with changes in microbiology. The FDA, of course, isn't interested in the microbiology as the primary but it definitely correlated. So with greater killing, we saw better symptom improvement . You can also correlate it with the 6-minute walk. We've done those kinds of studies. Yes, if you have a good respiratory or symptom scale, you can do that.

DR. WALLACE: You know, I can't think of another disease in which we briefly talked about in which you have two diseases active on the same part of the body producing the same symptoms, and then you're trying to do a PRO.

I mean these are people with bronchiectasis. Even if they don't have another identified tough pathogen and you have an NTM, both functional, both inflammatory, both -- and going through the symptoms, if your bronchiectasis stays calm, the PRO for the NTM will probably be

295

great. But if they're having lots of trouble -- they grow Staph several times or in the middle of this stuff. And if you count it negatively against them because they didn't show a response when, in fact, the problem was bronchiectasis.

It's such an unusual circumstance. We just have to think about the PRO and how to make it work when you have two diseases that are active at the same time.

DR. WINTHROP: I agree with Richard. That's why I think killing NTM may be a surrogate for better living for some of these people, but it may not be for other people; not that it might be harmful but it just may not have the same effect.

DR. WALLACE: I mean, there are people who come in after you've eradicated their MAC at the end of the treatment course and say they feel worse. That's because they have another disease going on at the same -- now, that doesn't mean that if we did enough numbers or whatnot, that overall that they would look better.

DR. QUITTNER: Well, I think you're

296

raising just a really amazingly great point. One thing I'd been thinking about this whole day is one of the advantages that we actually might have -- and we would need to talk to our statisticians and things like that -- but we do have a very well- validated respiratory symptom scale that's particular to CF and has proven efficacy, as well as the respiratory scale on the QOL-B. They're different. They actually reflect the different respiratory symptoms of bronchiectasis versus CF.

One thing that would be interesting and perhaps an answer to this problem is to be examining both the respiratory symptom scale, which differ by disease, and the NTM module, which focuses in much more in what Kevin is saying.

That might enable us to see -- if the respiratory symptoms are going up, that might be a sense that they colonize with Pseudomonas. That might be one way we could actually get around that problem. And I agree with you, it's complex.

DR. GRIFFITH: I would just add in our paper on the semi-quantitative sputum cultures,

297

Kevin, the people who converted within 6 months, half of them had a bronchiectatic exacerbation during that 6-month period. For the people who took longer than 6 months, it was almost 80 or 90 percent.

There's no question that the bronchiectatic symptoms are going to complicate the deal. If you can separate them out, I mean that would be really helpful.

DR. WALLACE: I mean it's a cheap test. I mean, you know, we just have to fill out some forms or paperwork, and it'd be very informative. We haven't done it. We're assuming that it won't help, but I mean I'd rather do it than not do it.

These are great patients. I mean there are only a few things that keep them from saying -- they always want to be in trials. I mean virtually every one of them and it's only characteristics of travel or a little bit of reservations about being in the placebo side that keep them from being involved. I mean, I bet they'd fill out those forms in a second.

298

DR. GRIFFITH: I think another complication is the toxicity of the drug and how that complicates how the patient feels. If you just take the example of an inhaled drug that might have airway toxicity, that if the mycobacteria is killed, it may eventually make them feel better; it may increase their functional status; it may make them live longer in the long run, but during the period that they're inhaling the drug, they may cough more; they may wheeze more; they may feel more short of breath.

It becomes very difficult to tease out exactly what's causing that PRO when you throw that complicating factor into it as well. It can be any toxicity for any drug that might affect that particular part of the PRO.

DR. DANIELS: I agree. It's going to be hard to discern disease-related symptoms versus treatment-related symptoms, and that might be another module that needs to be added into a questionnaire to maybe try to get to that and tease that out.

299

DR. FARLEY: That's a good point. Just to bring up -- because I know you've been talking a lot about how these patients are complicated; they have a variety of risk factors; they're somewhat heterogeneous. But remember that randomization is a wonderful thing. And that if it works, the risk factors should be relatively even between the arms.

I think one of the things related to the Chuck -- we'll talk about the "Chuck Approach" -- is that it points out to me that -- if you are going to have a very heterogeneous trial, it might be important to stratify at enrollment so that you make sure that you've got your risk factors balanced between arms.

DR. DALEY: This brings up another reason to follow the "Chuck Approach." One of the things that we have noted at National Jewish -- and I'm sure all my colleagues have -- is that if someone comes in with bronchiectasis and mycobacterial infection, if we introduce airway clearance, their cough will improve within 2 weeks, 3 weeks, a month.

If this is a multicenter study, if that varies across centers, how aggressive you do airway clearance, which approach you use, do you prevent reflux from occurring, then that randomization may get screwed up because you can't randomize practice.

If you had a period where you started a certain protocol like a run-in airway clearance, check that PRO instrument to see how much better the symptoms got with that intervention before you started the antibiotics, it would clean it up. That's all I can tell you. It would clean up the ability to understand how symptoms change with antibiotic therapy.

DR. WALLACE: Couldn't you just try to standardize the pulmonary care that you gave them across -- I mean it clearly means something that your attention should be paid to it, and should not be left to just each institution to do it the same way.

I mean the only way it would work is if

300

301

-- now, admittedly, respiratory therapists are not the same, but you're making an effort to know they are at least using -- they're all using saline; they're all using, you know, whatever type of equipment and stuff you want to use.

DR. DALEY: But for trying to look the efficacy of an intervention on antibiotic and you want to know what that antibiotic contribute or that regimen, you can't do what you just said.

DR. WALLACE: That's true. We don't even -- maybe Anne can correct me. But I mean when it comes time to tell these patients what to do to treat their bronchiectasis and what makes them live longer and do better, we don't know the answer to that question either.

DR. O'DONNELL: I think --

DR. NAMBIAR: Dr. Eagle, I was wondering if in your experience how you'd been able to handle the other therapy.

DR. EAGLE: One of the things that I was going to mention is that this is a rare disease and we don't have that many patients. When you

302

start to put your pivotal trials together and you need to power them up with a sizeable number of patients, you're reaching out to a large number of sites.

We already heard today a number of times that once you start moving away from the experts in this room, it becomes very difficult to have the same type of care. You need to recruit your patients in a reasonable amount of time, and these are the real life challenges that we have, and they're very real.

DR. O'DONNELL: I think we saw today that when the room was surveyed, only 57 percent of people were using airway clearance in this room. But I think what Chuck proposes is possible, like a 2-week run-in, just use a device, not anything more complicated than that. That could be done. I think hypertonic saline and all that kind of thing is more complicated.

DR. EAGLE: I was going to bring up one more thing just as a difficulty because of the toxicities of the medications during the

303

treatment, and right now, following the guidelines, while the patient has a negative sputum, you still need to continue treating them. And it's for a long time. It's 12 months after you have that first negative culture.

So the best time is probably to look at a PRO or any other measure of function, once you have durability of that treatment success. But the challenge is, you're facing a trial that has an outcome like years from when you start.

In a disease area where you need to maybe fast track whether you know something is working or not, it just becomes very challenging to do that. Although, in our trial, we are looking at these. I mean we're looking at function, and we're looking at the sputum 3 months out from treatment success for that very reason.

DR. NAMBIAR: Dr. Quittner, would you have any thoughts on what might be the right time to use the PRO to make a final assessment if the patient is getting better or not? I think as Dr. Eagle said, usually treatment is long.

304

Do you do this on treatment? Do you take a break after treatment to make sure things have gotten better? We welcome your thoughts on that.

DR. QUITTNER: I mean, this is a very important point. I can tell you for antibiotics in cystic fibrosis quite well because I've worked on so many clinical trials in that area. One of the really important things we did in those studies, which I don't think would work here -- the run-in, I think, is a good idea and measure the PRO -- is that I told the various studies to be sure to measure, of course, baseline, but 2 weeks into the antibiotic, because we were fairly certain that it would have a lot of efficacy at a month.

These were shorter studies obviously. These are in the days when the CF studies were much shorter. But I told them measure at 2 weeks because my sense of doing other smaller studies was that the efficacy was really there at 2 weeks.

So we actually did baseline 2 weeks. In

305

every study that was approved and successful, they saw the improvement at 2 weeks. And then we measured it again in a month. And then if they were going to take them off the drug, we waited a month later.

This is obviously a different paradigm where it takes a lot longer, but what Chuck was suggesting was sort of a baseline run-in, 2-week or 1-month point. And then where is it that you really think these drugs -- which we haven't talked about which ones -- where do they have their maximum efficacy? Is that 6 months; is it a year? And you measure it at that point as well. And then if you're going to take them off or you're going to wait, you have a follow-on.

So what would that endpoint be? Where would you all, the practitioners, say is what you believe you get efficacy at that point?

DR. DALEY: Don't look at me.

(Laughter.)

DR. NAMBIAR: That takes us right into the timing of the endpoint. Maybe before we go

306

into timing, I was wondering if there are any more comments on the microbiologic endpoint, any other thoughts from the panel on the merits, demerits, the timing of the endpoint, whether it's one culture, two cultures, three cultures, what the interval must be between these various sputum cultures and also the merits of doing a culture a certain time point after treatment has stopped and how long that might be because 3 months has been chosen as fairly arbitrary. Is there any science behind it? We welcome any discussion on that topic as well.

DR. WALLACE: Let me divert a little bit. I mean I've listened to -- Hala and I discussed semi-quantitative sputum cultures and its dilemma. There still may be some in-between points that you might be able to analyze, for example, positive on solid in-broth media versus positive in broth-only. In a way, it's semi-quantitative, but not as we discussed.

I mean we find it useful because we usually can measure what's happening to the

307

patient, although we can't tell when they're going to convert or whatnot. But maybe that would be some sort of semi-quantitative --

It's better than broth-alone, which I found very distasteful because you have such a huge range of potential possibilities in terms of the number of the organisms that are growing. You can be 4 plus and still be 4 plus, or you can be 4 plus down to 5 colonies, which is an enormous response, and the report would still be the same, positive in broth.

DR. NAMBIAR: Are there any practical considerations in terms of all labs being able to do this kind of semi-quantitative testing? I understand that your group is very comfortable or has been doing it, but I don't get a sense that that's true across --

DR. WALLACE: But I think they all do. Virtually, all of them culture in an agar median broth. I mean that's the recommended standard in the U.S. Now, for the European studies, do they do it in agar broth too?

308

FEMALE SPEAKER: Yes.

DR. WALLACE: So you couldn't get counts but you could at least report it. That's our main issue, is in Europe where they do not. I guess in Australia too, they don't. They don't do counts so --

DR. EAGLE: They culture it in the two media, but they don't use the scale and define the steps the way that you have defined them. That's the only difference.

DR. WALLACE: And actually, many labs -- this is very interesting. Virtually, all labs do it, but virtually, all labs don't report it. I mean, it's the check for contamination; it's the check for mix cultures, so it has its values, but no one has recommended reporting it, so they don't do it. It's there; you just have to ask for it.

DR. NAMBIAR: Hala, you had a comment?

DR. SHAMSUDDIN: Other than semi-quantitative cultures, have you looked at time to positivity in broth?

DR. WALLACE: I don't know that we've

309

done it in the studies, but I do it all the time. If you have just one species there, MAC or rapagor [ph], where you can pretty well predict based on the cultures.

For example, almost all MAC in the broth medium we use are positive within 14 days. Almost all rapagor were positive in 7 days. If MAC takes 3 weeks to turn positive, you know there's hardly anything in there. You can bet money that the agar is going to be negative because you only have a few colonies that are in there.

But I don't know that we all use the same broth system, and I don't know whether you could actually relate one center to another. But I'm guessing that there would be some relationship, and that is an objective number that you could use.

DR. O'DONNELL: Aren't there issues, though, with the quality of the specimen and how it's collected? I mean there's just so many foibles in sputum.

DR. OLIVIER: I think along those lines,

310

I think one thing to keep in mind is sampling variability. There are a couple of issues on that. I think the confidence you can have in one negative culture is a lot less than you would have in, say, three consecutive negative cultures. That's why I think the sort of terminology even though it may not be definitively defined in terms of culture conversion is a bit more attractive.

The other thing to kind of get around that is the collection of multiple specimens, and that actually ended up working quite well in the Insmed trial in that for each time point, we had at least two, and in most cases, three cultures that were obtained either at the clinic or from home collection that allowed us to sort of compare the consistency of whatever finding we were having at that time point.

I think when we're building these studies, having some redundancy in that and having more confidence in whatever culture-based endpoint we're determining, I think, was very helpful.

DR. DALEY: I was going to say at

311

National Jewish, we do this same as Richard's lab in terms of the semi-quantitative. The issues here are just so basic. It's sample collection, but it's also processing, too, that's very important.

A lot of these patients have co-pathogens and require significant decontamination of the specimen. That greatly reduces the colony-forming units of the NTM, and that's going to vary. That's why it actually is different than TB in this regard.

Where in TB, we have really quite a lot of good data about the consistency of CFU over time; it's not that way in NTM. At least, it doesn't appear to be. Even though it sounds good, I think there are some really basic standardization that would have to occur across labs to get to the same place that TB is in terms of being able to use these cultures and try to quantify or semi-quantify the counts over time.

DR. O'DONNELL: We also don't know how it correlates with the extent of disease or --

312

DR. NAMBIAR: Right. That's the next --

DR. O'DONNELL: Yes, so it's kind of like either we're going to have to go with the positive/negative and then define the number, because we really don't have a correlation between quantitative cultures and disease state, I don't think. Maybe Dave and Richard do --

DR. GRIFFITH: I was going to say we did correlate -- they did predict sputum conversion, the improvement in semi-quantitative sputum scores. They also correlated with symptomatic improvement. Now, it was gross. We looked at better or worse, but there was a good correlation in semi- quantitative culture improvement and symptom improvement.

DR. DALEY: And I was just going to say I applaud them for doing this because actually, I think that study was extremely important to be able to do that. Now, the issue is, can it be done across multiple laboratories? Can they all get the same kind of results?

DR. OLIVIER: I think the other issue is

313

the species you're dealing for reasons that you raised for M. abscessus and the susceptibility, the decontamination process, having consistency in that semi-quantitation may be very different than what you see in MAC.

DR. WALLACE: We're just reminding ourselves that Australia, Europe, and the U.S., for the current trial, only has a single central lab so you don't have the issues of smaller labs, all of which are very experienced, long term doing these. You would be doing the best you could to minimize those issues that might occur if you used smaller labs or less experienced labs.

DR. NAMBIAR: So it totally sounds like there are some issues purely from a microbiology standpoint, some of then we could potentially address but some of them, we just have to live with and see how to work with the information available.

But I think the bigger and an important question is I think what Dr. Winthrop had brought up earlier is, how does a micro endpoint translate

314

to clinical outcome, whether it be a semi-quantitative -- and it's encouraging that we at least have data from one institution. Whether that may hold true in other institutions and other settings, it remains to be seen.

But if we do use microbiologic endpoint as a surrogate, we have to be at least comfortable to some degree that it reliably predicts clinical benefit. I mean, that's the basic definition of a surrogate endpoint as Dr. Shamsuddin had outlined in her presentation.

We welcome your thoughts on how you think there is correlation, whether we define it based on sputum culture conversion or whether it's a semi-quantitative measure or saying the bacterial load has decreased.

But if it does translate into clinical benefit, what might that clinical benefit look like? Is it a mortality benefit? Is it symptomatic benefit? I think that's a big question we have to deal with in terms of deciding whether it's a primary endpoint, an exploratory

315

endpoint, or a secondary endpoint. We welcome your thoughts on that topic.

DR. O'DONNELL: Insmed trial, don't you have culture and QOL-B?

DR. EAGLE: Yes. One of the things that I would say as the first statement would be it depends on the population and where that population is in terms of the progression of the disease. If somebody has severely progressive disease with very limited functional capacity, I'm not sure eradication of the organism is going to make that much difference to that, whereas your na patient who's just recently treated may actually get the most benefit from a PRO or from a functional. I mean, I would put that out there to everybody to address that question.

With respect to our experience in our trial, we actually enrolled a population of patients that had refractory disease in that they weren't responding to standard of care treatment, and many of those patients, up to half of them, had more than two years, much like the patients

316

here, have long periods of treatment.

Amongst those patients, the majority had fibrocavitary disease or at least the presence of cavitary lesions, so we were looking at a specific population. So in terms of separating out the things that I'm talking about, we were looking at one end of that spectrum.

DR. O'DONNELL: But don't you have the QOL-B and the cultures at the same time?

DR. EAGLE: We did do the QOL-B, and we did not see anything significant. It might have been a function of the time in which we were looking at that endpoint. There was some sort of a trend within the patients who received OAI for like activities and things like that. But I really wouldn't draw any conclusions.

We didn't have anything that we saw on these measures, so we couldn't correlate that with anything as a result. The study was a short study in terms of the double-blind phase, where you would like to assess the difference between active and placebo.

317

DR. OLIVIER: I mean, this is an area where despite and just like the 6-minute walk, I think having some functional assessment in there, I think, is very important. It can be very difficult to tease out, especially in the short term how the drug may make you feel better.

But if you can show that the drug increases your functional ability, that may have meaning that eventually, the symptoms would catch up from that. Again, it depends a lot on the toxicity of the drug.

DR. EAGLE: Because we did see a difference in the 6-minute walk test, we could correlate it, and it did correlate with the microbiological outcomes.

DR. NAMBIAR: Microbiologic endpoint itself might be problematic but if one could couple it with some kind of a clinical outcome --

DR. OLIVIER: Right. But we are dealing with antibiotics. And as a first step, if the drug doesn't kill the bug, unless it's got some magical properties like the macrolides do, it's

318

unlikely going to have a significant effect on the outcome of the disease.

DR. NAMBIAR: But if you do look at clinical outcome in the short term, and 6-minute walk test has come up as an example which, again, has some who like it and some who don't like. And we heard from patients this morning as well that their results on the 6-minute walk test could be highly variable depending on what day it's administered and how they were feeling on that particular day.

But again, we don't have a lot of good clinical outcome measures here. So maybe the 6-minute walk test is a starting point. We have to start somewhere and sort of build up on it.

We've heard about the use of FEV1, which might be more relevant in a CF population, but I think Dr. O'Donnell mentioned it may not be very helpful in a non-CF patient populations.

Are there any other clinical endpoints one could think of besides the 6-minute walk test or an FEV1, a pulmonary function test, which is

319

probably more helpful to CF population? Is there anything else, from a clinical standpoint, you have found helpful?

DR. WINTHROP: I don't know of anything else existing. I think there's a need to develop more combined disease activity measures, and that's something we should do as we go through all these trials together. So those would include objective things, as well as subjective measures.

DR. DALEY: I would say that in CF where we know the FEV1 is a very important marker to follow and -- but in NTM, even in CF, we don't know that if you treat them, you reserve that trend of downward with it. There are anecdotes, but in terms of -- even CF where FEV1 has been very useful. In non-CF bronchiectasis, I think FEV1 has not been very useful as a marker of -- I mean, people come in; the CT is better; the micro has been negative for a year, but their FEV1 is worse, and you're trying to figure out how does that -- it just doesn't correlate.

My personal clinical experience is that

320

FEV1 in non-CF bronchiectasis is not correlated well enough that I think it could be used in a trial, anything more than a secondary outcome.

DR. OLIVIER: I mean, in our recent look at sort of mortality predictors, it looked almost absolutely useless. We had patients who died with very well preserved FEV1s. Many of the patients came into the follow up period with very high FEV1s, and it didn't seem to correlate well with mortality at all.

It's not to exclude PFTs in general. I mean there may be other factors and maybe something like diffusing capacity that might reflect changes in pulmonary vascular involvement that may explain some of the reason why 6-minute walk may be responsive, may be important. But FEV1 in and of itself does not look like a very good predictor, at least not in our hands.

DR. WALLACE: I think we need to move on or we'll never eat dinner. Well, there are some other questions especially under the definition of the sputum conversion, all that kind of -- like we

321

said -- like Anne said, we haven't -- I mean, it might be we'd all agree on them, but we at least need to bring them up --

DR. NAMBIAR: Right. I think it might be more to we need to learn more about it when we have these trials; we use them as exploratory endpoints. That might be the best way to learn about them.

I think in the interest of time, we need to keep moving. If there are no other comments about endpoints, I thought we could spend a few minutes talking about -- I skipped number 2 because I think everyone was so eager to get the endpoint discussion, and so I jumped ahead. If we could talk about use of controls, if they have to be active control or is there any place for placebo-controlled trials.

I think that then ties us back to the patient population because it might be feasible in a certain subgroup of patients to do a placebo-controlled or a delayed therapy option. So I would welcome your thoughts on controlled --

DR. WINTHROP: Yes, I'm glad you went back to number 2 because I think it's really important, and I think it reflects how we'd answer number 3.

I might get yelled at by my colleagues. I know have been before. But I'm a big fan of placebo-controlled trials to show that your drug actually does something. While we've heard over and over again today that this is not TB, this is not TB, pretty much everything we've heard up here about trial design has been about TB, and we have approached it similarly.

I think TB is very different as well. I mean, we're all in agreement on that. You can't really do a monotherapy trial against placebo and TB. Obviously, you can't. Patients with TB have to be treated. It's a public health concern, and then there's also the patient concern.

A lot of people with NTM, as Chuck mentioned and Dave seconded and we've all talked about, don't need to be treated yet. You have this huge pool of NTM. I don't know what

proportion it is, but I would suggest it's the majority of patients, that when they are incubating their disease for years and years, it take so long to diagnose. If you we could diagnose it earlier, we'd find these people sooner.

But I mean there's a lot of people that don't need to be treated right away, and it's a unique group. It's a unique infection where you could actually do a placebo-controlled monotherapy trial, where you're taking your drug and you see if it does anything.

If it doesn't do anything, you don't probably need to study it further. It would obviate all of our discussions from 3, 4, and 5 because the drug doesn't in vivo activity, and it actually doesn't work. And if it does have activity, then you've move to number 3, 4 and 5 figure out how to design a trial and how to actually use the drug.

Anyway, I'm a big fan of that. You can't do that with TB. You can't do it with most

infectious diseases because there's an imperative to treat it right away.

DR. O'DONNELL: I thought you had the primate model that we could test this on.

DR. WINTHROP: We do, yes.

DR. O'DONNELL: Because I think you're right. I mean you hear about people being on quinolones, and you heard about linezolid. And we really don't have any data, right, very good data for stuff that's being done.

DR. WINTHROP: I agree. The other issue is why haven't we approached this like bronchiectasis? I mean, for at least a subgroup of people with non-CF bronchiectasis, why aren't we thinking about treating the disease, at least studying the therapies in a similar fashion? I mean those are all monotherapy trials.

You got people that are infected with something and you give them something to see what it does to them, or at least does to their bacterial burden. And then there's all the other things to measure.

Again, those are different diseases, but the point is, you have the luxury of doing it. You can't do that with TB. It's different for all the things that we've talked about. I put it forward for everyone to criticize, but I think that we should think about doing that with our new drugs as they come out. And I do think we should be doing animal models first. We need animal models. We have one. Other people here are working on them, so I do think it's important.

DR. NAMBIAR: Just a clarifying question, Dr. Winthrop, so when you said it's doing something, you mean in terms of microbiology? Was that the intent?

DR. WINTHROP: Yes.

DR. NAMBIAR: So were you planning to look at that at an early time point, so within, say, 4 weeks or 8 weeks of initiating treatment, or were you planning to do it much longer, if a placebo-controlled trial is the way you want to go?

DR. WINTHROP: I think it depends on how

326

the drug works, and I think it depends on the bug we're talking about. So just as everyone has mentioned, abscessus is probably different than MAI, et cetera, and certain drugs have different PK parameters, et cetera. So I think you'd have to design the trial with those things in mind.

DR. NAMBIAR: Just from a practical standpoint, would that be challenging, I mean to just put somebody on monotherapy for 6, 8 months and they have M. abscessus? I mean is that --

DR. WINTHROP: Let me clarify something. This is not for everybody.

DR. NAMBIAR: Okay. That's what I was wondering.

DR. WINTHROP: This is not for people with cavitary disease, people who are sick and need to be treated. It's probably not for M. abscessus unless they fit that patient that Dave showed, you know, no progression.

I have non-progressing abscessus patients that are always culture positive and they're non- progressive. I mean they don't feel

327

great, but they're non-progressive. So there are those people out there, but I think they're less frequent for abscessus.

DR. DALEY: Kevin, I think just for clarity, though, I think what you're talking about is an early phase study that would be of relatively short duration in a highly selective population. Right?

DR. WINTHROP: Yes.

DR. DALEY: Okay.

DR. NAMBIAR: It's something akin to the EBA studies one does for tuberculosis. I think that's what you had in mind.

DR. WINTHROP: I just didn't want to say that because I want it to be different than TB.

(Laughter.)

DR. WINTHROP: I really tried hard.

DR. GRIFFITH: But it's not an EBA study. No, I mean that's very important. This is not 2 weeks. It's 3 months or 4 months. You know, acquired mutational resistance is a phenomenon that we know occurs in a couple of

328

drugs but that's it.

I know there are a lot of unknowns here, but in my mind, this is one of those big areas where we're not talking about TB.

DR. OLIVIER: I would ask the question on the opposite end of the spectrum, also understanding all the virtues of placebo-controlled trials about whether a placebo control is always needed. And if you were starting out with patients with refractory disease, and especially now that we know something about what that target population looks like on placebo, is it mandatory to have a placebo in patients that there's no question that the disease needs to be treated, there's no question that they failed what they're on.

Especially in early phases of putting drugs first on target disease, could it be conceived that you would have a single-arm study looking at efficacy and sort of compare that to historical effects of the natural history of a similar length of time off drug?

329

DR. GRIFFITH: As Kevin alluded, I think it would be unethical to have a placebo arm in a cavitary patient.

DR. OLIVIER: That was one of the competing concerns about where to set the endpoint in a placebo-controlled trial, so you're competing against the ethical aspects of leaving someone on placebo where they definitely meet criteria to be treated versus having a long enough time to see a drug effect. Those two are very dichotomous in terms of where you set that endpoint.

DR. NAMBIAR: Okay. If there are no other thoughts on the control arm, just one question, in terms of the optimized background regimen. If one were to go with a trial design where you have a test drug; you add it to the standard of care, whatever one considers as standard of care, and you compare that with the standard of care, and you have to optimize the background regimen.

If you truly end up having a very heterogeneous mix of patients, wouldn't that pose

330

yet another challenge in terms of the background regimen? It would be quite different depending on whom you are treating. I think that was another reason why we had asked if it makes sense to separate out the patients. We would welcome your thoughts.

DR. OLIVIER: Well, failing a regimen is failing a regimen. So if the design is to add the drug onto their failing regimen, with the assumption that there are no other viable options to it -- again, it takes into account whether the drug biologically is thought to be active in the two groups that you're mixing. I'm not sure it makes that big of a difference.

DR. GRIFFITH: I think the cavitary patients also offer the opportunity of having higher bacterial, mycobacterial loads. It might be a little easier to evaluate efficacy of the drug microbiologically, particularly if you're using a semi-quantitative score.

DR. HUGHES: Yes, from the industry side, it's a little bit challenging because we

331

would end up having to provide perhaps three or four different drugs, none of which are approved. They would, therefore, all be experimental at that time. I think just leaving it as optimized background regimen, plus or minus the experimental, is a much more pragmatic way to go.

DR. EAGLE: And I would just add what Dr. Farley said earlier about the perils of randomization. And I think that -- I mean, that can sort it out to a degree.

DR. HUGHES: Or you stratify by site or collect cluster of sites.

DR. EAGLE: Yes, or I mean even stratify it by whether someone has interrupted treatment or not. What we find in the refractory population is that patients that are on treatment for a long time, and they do take holidays because of the toxicities and it's not working anyway. That's an area where you can potentially stratify as well.

DR. NAMBIAR: If there are no more comments about clinical trial design itself, I thought we could spend a few minutes just talking

332

about some practical difficulties. And I think it had come up for discussion this morning, and Dr. Wallace had made a point about how difficult it is for patients to travel 75, 50, 100 miles if they need to.

Maybe Dr. Eagle, you can provide your perspective as you're actually doing one of these trials.

DR. EAGLE: Yes. The feasibility of these trials, it's very challenging primarily because of the length of time you are expecting the patients to stay in the study. Retention is something that you need to work really hard on.

In order to meet the definition of a conversion as it is in the guidelines right now, you do have to have your patients produce sputum every month. Otherwise, how else do you define it? And it is arduous.

These centers are not everywhere, but the patients are everywhere, so you need to be able to understand and accommodate their travel. So it has a lot of challenges.

333

I think one of the things that we're been told particularly by the physicians that were in our last study is that these patients need to just be hand-held basically because it's a lot of -- it's arduous.

They've got their comorbidities; they've got underlying lung disease; they're on all these medications. I think what we need to do is actually just pay attention to all of that and just help them along.

DR. GRIFFITH: Dr. Daley asked me to say that monthly visits were not practical.

DR. OLIVIER: And I would just reiterate that and the fact that I don't think the visits need to be monthly. And again, patients can very easily be trained to do standardized collection of sputum and they have that sent directly from wherever they are to wherever the core lab is. So that takes care of your microbiologic outcome.

The PROs can be administered remotely. We're not talking about other measurements that are that difficult to do. Things like 6-minute

334

walk or PFTs are fairly standardized by guidelines.

I think if we can think outside the box instead of having everything tightly controlled in a relatively few research centers and space out the actual visits a bit, we could probably still maintain the frequency of data collection that we would need for the trial.

DR. WALLACE: You could also arrange to have blood drawn and sent to the centers. I mean I think you could do essentially -- and this is one place where doing a complete physical exam probably is not -- I mean it's -- we fill out the forms, but it really doesn't add much, and probably not totally essential that we do it if you really felt like it needed to be done.

DR. WINTHROP: Yes. I think taking more of a pragmatic trial approach in the future would be useful. I echo --

DR. WALLACE: You know, it takes them all day to come to clinic, prepare, come early, blood drawn, whatever needs to be down, sitting

335

there, they miss lunch, and they're exhausted when they get home. So by the time they've done that four or five times, they start thinking, well, gee, I don't want to go today.

I agree with Gina. It's very hard on them even though they want to be part of the study. It requires a whole day's worth of -- I mean, these are people, they're sick, so they get fatigued relatively easily, and they may be down for a week after they make the visit.

DR. NAMBIAR: Yes, there's an interesting comment from one of our patients this morning about how they spend six months in Florida and six months in another state. To be in a clinical trial and to be geographically that separate is really challenging.

It seems like it's a perfect setting where the PI and the local -- the primary care physician have to sort of collaborate and work hand-in-hand to make this work.

DR. EAGLE: Fortunately, the most common destination is where most of our centers are

336

because of those high evaporative pressures.

DR. NAMBIAR: Right.

DR. O'DONNELL: Could I ask one last question of the panel, the serology data that I showed, the IgE? Does anybody think that has any value as, say, some kind of marker in a trial?

DR. WINTHROP: No.

(Laughter.)

DR. OLIVIER: I think that this is a discussion that's been going on for many, many years of trying to find both a sero diagnosis and sero marker. I mean it may. It might be something interesting to put in as an exploratory variable.

DR. WINTHROP: I'm joking. I think you should look at it. But I think there probably are sero markers out there, but that's probably just not the most useful.

DR. NAMBIAR: If the panel doesn't mind, I just had one last question. I think we heard in a couple of presentations that the likelihood of reinfection is so high; 60, 70 percent of

337

patients, in fact, have reinfection. And the way we are looking to design to trials, we are requiring regular visits while on therapy, but certainly a visit, at some point, after treatment is complete. Again, as I said earlier, we picked three months, but it could be short; it could be longer.

It seems very important at that point one has to differentiate if it's truly a relapse of the infection that they started or if it's truly a reinfection, especially given the numbers are so high.

Any thoughts on how we might address that?

DR. OLIVIER: I think it's imperative that the islets be banked. I mean Richard will tell you that's really the only way you can tell, is to be able to compare those microbiologic recurrences off treatment to what they started with.

DR. NAMBIAR: Okay.

DR. WALLACE: In the last trial, the

338

broth bottles can be saved, so we saved every positive that the patient has. As we said, sometimes, there'll be a positive in the middle of five negatives, and you want to know if that's the same or not. If you don't have the bottle, then we got to turn it over to you, and you don't know what it is.

So banking those organism -- all of the islets, even the screen islets, turn out to be important sometimes when you want to go back and they have a late positive and you want to compare them. It's not difficult to do. You just have to be the mindset. You just set up to do it. And I'd like to think that one of these days, most labs will be doing it because for long term follow-up, these are long term patients.

It's not like they show up with an E. coli urinary infection, and you treat it, and you throw the organism away. These are often patients for life, and they're complicated, and being able to evaluate them, especially in the study --

Think of the studies, think of the --

339

the British Research Council did that M. kansasii study. They didn't save the islets, and they had a bunch of relapses, which could have easily have been new infections. But they didn't save the islets, so the study kind of went down in flames in the sense that we don't -- they were all about the 5 percent relapse rate. If you accept all those as being true relapses, it killed them.

DR. EAGLE: I think when we do see the -- we have a patient that's negative and then comes positive, pretty much parallels the numbers that you had with respect to which ones are new infections or which ones are relapse.

It is a very important question. The difference in the meaning of what each of those is, is huge. We did look at it in the last study, and we're definitely looking at it in the next study.

It's very important, but it needs to -- after the study, this is within a clinical trial, and it's well and good, but I think it needs to also be information that's available for

340

physicians treating patients in the clinic.

From what I understand, you can tell me -- you're in a great lab. But when we look at some of the patients coming in and they have their history, they have a history of MAC, but sometimes those labs don't even separate intracellulare from avium. Sometimes that's all you need if you're going to have a relapse. I mean at the very basic level, if you get a different species, you don't have to go any further but that's not even done.

DR. NAMBIAR: Okay. So I think we're running out of time. Dr. Farley has reminded me only three times that I need to stop talking. With that, I'll thank all the panel members. I think this was very helpful. And we'll have to take all this back and put our heads together and hopefully design better trials as we move forward.

With that, I'll turn it back to Dr. Farley. Open Public Comment Session

DR. FARLEY: This has been great. As with most federal meetings, we will invite a period of open public comment. If you signed up

341

for this earlier and you didn't actually know what you were signing, it's perfectly fine to pass.

I'm going to ask Meghana to help by using the hand mic. Open public comments, speaker number 1 is Dr. Renu Gupta. We would ask you to limit your comments to three minutes.

DR. GUPTA: Good afternoon. Thank you very much for giving me the opportunity to speak. My name is Renu Gupta. I am a physician, infectious diseases, and I am working as an independent consultant. I was formerly working with Insmed.

I just really have a couple of points to make. I would like to thank the agency for holding this forum today. And although NTM lung disease is an orphan disease, it today does not feel like a neglected disease. This momentum that we have started to gain with all our patients here, our clinicians and researchers and the agency needs to be sustained.

I have only a couple of points, which probably echo what has been discussed today,

342

nothing novel. One is the unmet need and the seriousness. We need a strengthening of our infrastructure within United States at a minimum. And by that, I mean if we can have increased outreach to primary care physicians and also pulmonology centers outside the Centers of Excellence, so that we can have increased awareness around diagnosis of the disease. This has been discussed for many years, but we now need to put a system in place, an infrastructure.

The CF Foundation's registry is a model and the TDN is a model. I only illustrate that because I've had the good fortune of working with their team and learning over time as to how successful that has been in terms of outreach for patients, and that clearly had an impact in drawing patients into clinical trials.

We have an NTM registry, which is a module of the bronchiectasis registry with 13 sites. I've been talking to stakeholders and making a plea for a stronger public and private sector partnership. I think this registry and the

343

benefits of a registry pre-approval and post-approval are immense.

The last thing that I would say is related directly to the drugs currently being used and the drugs in development, is that if we could come up with a model of cooperative groups like we have in oncology or we have in mycology with significant funding and backing from the NIH and some investment from the biopharmaceutical industry, that those cooperative groups could take on the mission of NTM- focused-related research agenda. I know the ADS has that in their mission as well. ADS cannot do it alone.

So that would also lend itself to looking at current regimens and evaluating -- and I believe there are ways one can do that in cooperative group studies.

Lastly, a plea for my colleagues in the biopharmaceutical industry to go to their management and ask for greater investment in both diagnostics and small molecules and biologics for treating the bacteria and also for improving the

344

underlying inflammatory cascade in the lungs of these patients. Thank you very much.

DR. FARLEY: Next, we have Ms. Mary Fisher. Could you identify yourself? It's right here.

MS. FISHER: I just want to make a comment regarding clofazimine. As I alluded to it when I was on the panel, I started clofazimine back in 2011. For those of you who don't know clofazimine, it was a medication that was used to treat Hansen's disease or leprosy.

It no longer is available commercially. When they prescribed it for me, my physician had to fill out reams of paper, jump through a thousand hoops just to get it approved. Once it was approved, then my physician had to order it from the pharmacy in Louisiana. It had to be delivered to the physician office, and then I had to drive an hour to go get it.

My concern is that medication is an old medication. I understand when they started using it, it was investigational. However, I have been

345

on it for four years, and I'm sure there's quite a few people in here that have probably been on it or are on it.

I don't have any side effects. The one side effect that is very common; that I would've loved to have had was the bronze skin. I'd love to have a tan year around but I never got it.

Anyway, what I am requesting is if we cannot streamline that process of getting that medication to us. I have to still call my physician's office, and then when they went to request it again this year, the process changed.

In January, they decided that they no longer were going to pay the postage, which I have no problem with. However, that was not communicated to my physician's office until April. When I went to get it renewed, they tried to reorder it the old way. They told them it wasn't the proper way.

The incompetence in the doctor's office didn't get it done, and I was a week without the medication after many, many phone calls to the

346

office to remind them to get the drug.
Now, I'm responsible for generating the postage. I'm responsible for sending the email with the postage, but it still goes to the doctor's office, and I have to go pick it up. I don't understand why that can't come directly to me. If I'm doing all the work, I'm doing all the generation, why is it that I have to still jump through the hoop? And I can guarantee you my physician doesn't even know when it arrives. It gets to the receptionist, they call me, I pick it up.
So I am just asking for them to look at that and see if that drug cannot come off that investigational and streamline the process for us to get that medication.
DR. FARLEY: Thanks. So people don't say something in a vacuum, so we might've talk to you on the phone a bunch of times because we actually have about three full time equivalents working on the clofazimine expanded access program. We have heard you loud and clear and

347

we're working very hard to streamline it.
Part of it is that because it's not marketed in the United States, it is only available through the single-patient IND program, and those regulations, unfortunately, require us to deliver it to the physician, not to the patient, even though the patient paid us to deliver it to the physician.
But we are working hard on streamlining it, and it's a priority here at the FDA to get that done. Be patient, and we appreciate your patience so far. Part of it is that through that that process, we actually have gotten to know a fair number of the patients.
We find that really helpful because we got to talk to you and we know kind of more of what your life is like and we're more connected to what you're going through. But there might be a better way to do that. We hear you.
Next is Marcy -- W-E-I-N-E? Weiner, sorry.
MS. WEINER: I have three things. The

348

first would be early diagnosis perhaps through a skin test such as they do for TB, and is that a possibility, and is anybody working on that? It seems to me it should be feasible. I just don't know.
The second issue is something that Dr. Gupta brought up, which is the inflammatory cascade. I'm very well aware of that, and oftentimes, when I try to bring in some sputum, I'm really getting what looks like to me to be inflammatory. It's white and cloudy, but it's just really inflammatory and not necessarily bacterial.
As a patient, I say, okay, maybe I should try antihistamines, this or that, what about low dose aspirin? But I don't hear anybody, really, as far as the medical and the pharmaceuticals, trying to deal with this cascade in the lungs, inflammatory in the lungs. I think that's very critical especially with us with bronchiectasis. I think it's perhaps the number one thing that we need to do for bronchiectasis

349

patients.
Third, I know it's an old one. I think it has some eucalyptus in it, which is a known antibacterial. It was used in the Vicks VapoRub. Those of us that are old enough remember our mothers putting this in a vaporizer, rubbing it on our chests. But it also helped to break things up and brought relief and perhaps in a more modern form in delivering and through either an inhaled or nebulized form, eucalyptus could be used.
I mean this has such strong antibacterial properties. I just can't believe that we're utilizing this in any fashion. Now, as a person who did microbiology so many years ago, I'm probably useless for you. But I just can't think -- it's a thought to spark some kind of look-into. It's very easily accessible. They have a lot of it in Australia -- I brought some back -- and in California. You go to a spa in Arizona, they're going to have little bottles of it.
For the ladies with bronchiectasis that

350

are told they cannot take showers but they have to take baths, put five or six drops, little drops, of that in and get the benefit of it. I mean I think for scientific purposes, it would be good to have something looked into.

DR. FARLEY: Ms. Deborah Schwartz.

MS. SCHWARTZ: Very quick question, I just wondered how many people here have cavitary disease, if anyone just had surgery and reoccurrence after surgery.

DR. FARLEY: Did you want folks to raise their hand?

DR. WALLACE: I can tell you it happens. Remember that surgery is a de-bulking procedure. It does not --

MS. SCHWARTZ: I had two surgeries [inaudible - off mic.]

DR. WALLACE: Did you have them on both sides or on the same side?

MS. SCHWARTZ: Upper right and middle left by Dr. Mitchell. For four years, I had negative sputums. I had one positive in February.

351

Dr. Daley and my doctors decide I should go back on medication, and I did, but I've never had another positive sputum, and they still want me to stay on it for 18 months.

I guess they're worried about cavitary disease again. I don't know. But anyway, I'm taking the medication. I'm doing okay. Inhaled amikacin, I like very much, but I only had one positive four years after surgery.

DR. WALLACE: I'll just say that our experience from fingerprinting is that people who have relapse with the same strain almost all do so within six months. I've never seen a relapse with the same strain after a year. So almost certainly, your islet is a different islet --

MS. SCHWARTZ: It is a different one. It's intracellulare.

DR. WALLACE: And so on the basis of a single -- I can understand why they're concerned, but the answer is we would not put you back on medicine for a single positive. We just collect samples and follow you. I mean I don't know that

352

there's a right answer here, but that would be my approach. Closing Remarks and Adjourn

DR. FARLEY: Okay, great. Thanks very much, everyone. Before I forget, I need to announce there is a shuttle bus -- Phil are you involved with the shuttle bus? You're not. Okay. But there is a shuttle bus that some of you came on. It's leaving from the circle out front at 5:15. We're around. If you have trouble finding the way you came back in, let us know, and we'll get you headed in the right direction.

I want to thank everyone, particularly the patients who I know have traveled. Many of you have traveled a very long way. I was told at lunch by the patient-focused drug development group that is one of the best meetings we've had in terms of the quality of feedback that we've gotten from patients. This has been extremely helpful to us.

I can tell you from early on in the HIV epidemic that the progress that got made, got made because patients and academics and developers of

353

drugs and regulators were talking on a regular basis and knew each other and working together. And I'm seeing that happening in NTM, and I'm very excited about that, and you've been a big part of that process.

I want to thank the panel in particular for taking time out of your schedule. This has been very valuable to the division as they begin to work on clinical trials.

I know that there are some companies here who are thinking of working in this area. And we want to encourage you, and we also want to remind you that the division is available to meet with you at any point in your program, particularly early under the pre-IND program and provide you regulatory advice. That's a fairly easy thing to access. If you don't know how, just look up Sumathi or I, and we'll get you pointed to the right person.

With that, I want to thank everybody for a great meeting, and we look forward to seeing many of you again soon and talking further as we

begin to make progress, continue to make progress in this area. Thanks very much and safe travels, everyone.

(Applause.)

(Whereupon, at 4:57 p.m., the meeting was adjourned.)

CERTIFICATE OF REPORTER

I, Janet Evans-Watkins, the officer before whom the foregoing proceedings were taken, do hereby certify that the proceedings were taken by me in stenotype and thereafter reduced to typewriting under my direction; that said proceedings are a true record; that I am neither counsel for, related to, nor employed by any of the parties to the action in these proceedings were taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

_____
JANET EVANS-WATKINS
Notary Public in and for the
State of Maryland

My commission expires: July 8, 2016