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FOOD AND DRUG ADMINISTRATION (FDA)

DEVELOPMENT OF NEW TUBERCULOSIS DRUG REGIMENS-
SCIENTIFIC AND CLINICAL DESIGN CONSIDERATIONS
PUBLIC WORKSHOP

Wednesday, July 19, 2017

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<p style="text-align: right;">Page 6</p> <p>1 PROCEEDINGS</p> <p>2 DR. COX: I wanted to welcome everybody today</p> <p>3 to our TB drug development workshop. We will be</p> <p>4 talking a lot about a regimen development and having</p> <p>5 some discussions around all that. I really do</p> <p>6 appreciate everybody making the time to join us here</p> <p>7 today.</p> <p>8 And, first, let me just start off with some</p> <p>9 logistics, just so we can plan ahead a little bit. You</p> <p>10 may have noticed as you walked in, there is a window</p> <p>11 just beyond these large rooms and it is where lunch is</p> <p>12 served. And so, if you can order ahead of time, so if</p> <p>13 we can get your orders in, say, by about 10:30 in the</p> <p>14 morning, that can help a little bit with the lunchtime</p> <p>15 crunch, because then they're all prepared for serving</p> <p>16 the individuals. So, it's always important to make</p> <p>17 sure that everybody gets fed during lunchtime, so just</p> <p>18 check with that window, if you can. Hopefully, we'll</p> <p>19 be able to do that during the break. The folks over</p> <p>20 there should be expecting people to come out.</p> <p>21 Now, moving on to the topic for today. I</p> <p>22 mean, as folks know here, probably better than I, the</p>	<p style="text-align: right;">Page 8</p> <p>1 And lots of credit goes to the TB community, including</p> <p>2 the drug developers, the philanthropists, scientists</p> <p>3 from all sectors, patient advocacy groups, folks in</p> <p>4 government, both here in the US and abroad, and</p> <p>5 nongovernmental organizations that remain dedicated to</p> <p>6 the work of developing new therapies for TB and caring</p> <p>7 for patients with TB.</p> <p>8 And, at least in my view, as I reflect on the</p> <p>9 area, I think one of the things that has made things so</p> <p>10 successful in this area is really the attention to</p> <p>11 sound scientific principles and the dedication to work</p> <p>12 in this field. We all recognize that this is an area</p> <p>13 where there are unmet needs and that we can exercise</p> <p>14 flexibility and balance benefits and risks. But I</p> <p>15 think what allows us to do that is that underlying this</p> <p>16 foundation of flexibility is the sound science that is</p> <p>17 going on in the field, and that's great.</p> <p>18 If we can think back to TB therapies, the last</p> <p>19 new TB drug approval here in the US was bedaquiline for</p> <p>20 MDR-TB that was approved in late 2012. But for those</p> <p>21 that follow the field, there has also been a lot of</p> <p>22 other important activity that has been going on out</p>
<p style="text-align: right;">Page 7</p> <p>1 TB issue with global burden of disease really is</p> <p>2 phenomenal, a tremendous cause of morbidity and</p> <p>3 mortality with 10.4 million new cases of TB reported</p> <p>4 worldwide by the WHO. With 2.2 million cases in</p> <p>5 patients living with HIV, and estimates of 480,000</p> <p>6 cases of MDR-TB in 2015. So, the burden of disease is</p> <p>7 tremendous.</p> <p>8 We also know, too, folks working this area</p> <p>9 know how particularly challenging it is to develop new</p> <p>10 therapies for TB, and the treatments are long, require</p> <p>11 multiple drug therapy. And it's really not an area</p> <p>12 that is economically attractive for drug development.</p> <p>13 While we know the burden of disease is large, the areas</p> <p>14 of the world where the burden of disease is largest are</p> <p>15 not ones that have resources. And typically, it's low</p> <p>16 and middle-income countries where there is limited</p> <p>17 resources to be able to afford treatment and access to</p> <p>18 care can oftentimes be challenging.</p> <p>19 But, really, despite these challenges, as I</p> <p>20 look around the room and think about the</p> <p>21 accomplishments of this group, the folks that have been</p> <p>22 involved in TB work, I mean, it really is remarkable.</p>	<p style="text-align: right;">Page 9</p> <p>1 there reported in journal articles and press releases,</p> <p>2 and such. And so, we thought it would be a good</p> <p>3 opportunity to get the field together to discuss some</p> <p>4 of the important progress that has been made in the</p> <p>5 field and share that more broadly. That's one of the</p> <p>6 reasons, too, why we'll talk some about regimen</p> <p>7 development.</p> <p>8 And we're grateful, too, for the field's</p> <p>9 general willingness to describe ongoing development</p> <p>10 programs and have the chance to hear from the groups</p> <p>11 that are involved in this work. We'll hear some</p> <p>12 preliminary results from clinical trials to date, and I</p> <p>13 think we'll all benefit by hearing and learning from</p> <p>14 their experiences.</p> <p>15 And then if you'll look at the agenda, too,</p> <p>16 today, you'll see that we're going to span a range of</p> <p>17 topics over a really fairly packed agenda. We'll start</p> <p>18 out with hearing some about the current TB landscape</p> <p>19 patient needs, and then move on to preclinical and</p> <p>20 clinical development with a focus on TB regimen</p> <p>21 development. And then to guide our discussion over the</p> <p>22 course of the day, following the talks in the morning</p>

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<p>1 and the talks in the afternoon, we have a series of 2 questions that we'll try and cover during panel 3 discussions, both in the morning and the afternoon. I 4 look forward to hearing those discussions, and I hope 5 everybody has a chance to engage in the panel 6 discussions.</p>	<p>1 I'm the deputy director for safety in the Division of 2 Anti-Infective Products at CDER, FDA. 3 DR. NAHID: Good morning. My name is Payam 4 Nahid. I'm at the University of California-San 5 Francisco. I am a TB clinical trialist working with 6 the CDC TB trials consortium.</p>
<p>7 Today is a workshop, which is different than 8 an advisory committee. It's an informal chance for 9 discussion; it's not a chance for formal advice to the 10 FDA. So, that lets you know that it's a little more 11 freefalling, a little more flexible, and we think 12 that's a good opportunity, a good way to talk about 13 where things are in TB drug development.</p>	<p>7 DR. GITTERMAN: Steve Gitterman. I'm with the 8 Division of Microbiology Devices in the Center for 9 Devices at FDA. 10 DR. SCHITO: Marco Schito, scientific director 11 at Critical Path TB Drug regimens, Critical Path 12 Institute in Tucson, Arizona.</p>
<p>14 So, thank you all again for your interest, 15 your dedication, your commitment to the field of TB 16 therapeutics and with the shared goal of focusing on 17 developing and improving treatments for patients with 18 tuberculosis.</p>	<p>13 DR. VERNON: Good morning. I'm Andy Vernon. 14 I'm chief of the clinical research branch in the 15 Division of TB Elimination at CDC, and my group 16 oversees the TB trials consortium. 17 DR. HANNA: Debra Hanna. I'm the executive 18 director of the Critical Path, the TB drug regimens 19 initiative at the Critical Path Institute, Tucson, AZ.</p>
<p>19 So, now at this point I'd like to ask the 20 panelists to introduce themselves. And if you can just 21 tell people who you are and also your affiliation. And 22 so, that folks know, too, in the meeting materials we</p>	<p>20 DR. BANSBACH: Good morning. I'm Cathy 21 Bansbach from the Bill & Melinda Gates Foundation. I 22 play a role of the portfolio and platform lead, which</p>
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<p>1 also have disclosures of conflicts of interest that are 2 available so that folks may, if you're interested in 3 peoples' affiliations and the works that they're 4 involved in, that will be in the printed materials. 5 So, maybe at this point I'll ask Dakshina Chilukuri to 6 start out with the introductions, and then we'll go 7 around the table this way. Dakshina?</p>	<p>1 basically means I work on product development with our 2 grantees and partners to try to have the greatest 3 impact we can. So, pleased to be here. Thank you. 4 DR. SPIGELMAN: Morning. My name is Mel 5 Spigelman and I'm from the Global Alliance for TB Drug 6 Development. 7 DR. NAMBIAR: Good morning. I'm Sumathi 8 Nambiar, director, Division of Anti-Infective Products, 9 CDER, FDA.</p>
<p>8 DR. CHILUKURI: Good morning. My name is 9 Dakshina Chilukuri. I'm a clinical pharmacology 10 reviewer at FDA.</p>	<p>10 DR. LOBUE: Good morning. I'm Phil LoBue. I'm 11 director of the Division of TB Elimination at CDC.</p>
<p>11 DR. PELOQUIN: I'm Chuck Peloquin. I'm the 12 director of the pharmacokinetics lab at the College of 13 Pharmacy at the University of Florida.</p>	<p>12 DR. FARLEY: Good morning. John Farley, 13 deputy director of the Office of Antimicrobial Products 14 at CDER, FDA.</p>
<p>14 DR. PATEL: Good morning. My name is Sheral 15 Patel. I'm a medical officer at FDA.</p>	<p>15 DR. LIENHARDT: Good morning. I'm Christian 16 Lienhardt. I'm working at the World Health 17 Organization in Geneva, where I'm leading a team on the 18 research for TB elimination, and that, among other 19 things, is doing guidelines for introduction of new 20 drugs and regimens for tuberculosis for countries, 21 member states of the World Health Organization.</p>
<p>16 DR. STARKE: Hi. I'm Jeff Starke. I'm a 17 pediatrician from Baylor College of medicine and run a 18 kids TB clinic.</p>	<p>22 DR. WELLS: Good morning. I'm Charles Wells.</p>
<p>19 DR. GEITER: Larry Geiter, vice president, 20 global clinical development for TB for Otsuka 21 Pharmaceuticals. 22 DR. TOERNER: Good morning. I'm Joe Toerner.</p>	

<p style="text-align: right;">Page 14</p> <p>1 I'm the head of development for the infectious disease 2 therapeutic area at Sanofi.</p> <p>3 DR. HUGHES: Good morning. David Hughes. I'm 4 the senior global program head responsible for anti- 5 infective development at Novartis.</p> <p>6 MS. HIGGINS: Hi. I'm Karen Higgins. I'm 7 the statistical team leader supporting the Division of 8 Anti-Infective Products at FDA.</p> <p>9 DR. PHILLIPS: Good morning. I'm Patrick 10 Phillips. I'm a statistician now at the University of 11 California-San Francisco.</p> <p>12 MS. LESSEM: Hi. I'm Erica Lessem. I'm the 13 director of the TB project at Treatment Action Group, a 14 science-based activist organization.</p> <p>15 DR. NUERMBERGER: Good morning. Eric 16 Nuermberger, Johns Hopkins University with research 17 interest in preclinical and translational TB drug 18 development.</p> <p>19 DR. YASINSKAYA: Good morning. My name is 20 Yuliya Yasinskaya, clinical team leader at the Division 21 of Anti-Infective Products, FDA.</p> <p>22 DR. IARIKOV: Good morning. Dmitri Iarikov.</p>	<p style="text-align: right;">Page 16</p> <p>1 as well as the associate director for science before 2 being appointed TB division director. So, Phil, thanks 3 very much for being here with us today.</p> <p>4 DR. LOBUE: Thank you very much for inviting 5 me. So, the outline of my talk, I'm going to briefly 6 talk about the TB burden in the United States and 7 globally, and current treatment regimens. And doing 8 this pretty quickly at a high level, as I expect the 9 vast majority of people in the room are familiar with a 10 lot of this information, but just for completeness, for 11 those who may not be as familiar. And then spend the 12 rest of the presentation talking about some of the 13 challenges, at least from the CDC perspective.</p> <p>14 So, for those of you who are not familiar with 15 kind of the standard abbreviations for drugs and some 16 of the other terms, I just wanted to lay those out 17 here. So, the international single letter 18 abbreviations for various drugs. H is isoniazid, R is 19 rifampin, P is rifapentine, E is ethambutol, Z is 20 pyrazinamide. I use FQN for fluoroquinolones, MDR for 21 multi-drug resistant TB, which is TB where the isolate 22 is resistant to isoniazid and rifampin. It could be</p>
<p style="text-align: right;">Page 15</p> <p>1 I'm acting deputy division director of the Division of 2 Anti-Infective Products, FDA.</p> <p>3 DR. COX: Thank you all. And I guess I didn't 4 introduce myself. I'm Ed Cox, director of the Office 5 of Antimicrobial Products. And just so folks know, 6 too, the meeting is being webcast and it's also -- 7 there will be a transcript that will be available on 8 the meeting webpage after they produce the transcript. 9 So, it will probably be a few weeks after, same place 10 where the materials are already posted.</p> <p>11 So, at this point, thank you again for 12 joining, and now I will turn the chairship over to John 13 Farley and Phil LoBue, who will guide us through the 14 morning session. John?</p> <p>15 DR. FARLEY: Thanks, Ed. So, Phil and I will 16 be taking us through the morning session, and the focus 17 of the morning session is Landscape and Preclinical 18 Approaches to Inform Clinical Candidates for TB 19 Combination Regimens. And Phil is our first speaker. 20 As he mentioned, he's director of the Division of TB 21 Elimination at CDC. He's been at CDC since 1999, and 22 has served as chief of the medical consultation team,</p>	<p style="text-align: right;">Page 17</p> <p>1 other drugs in addition to that. A subcategory of MDR 2 is extensively drug-resistant TB, or XDR, which is MDR 3 plus resistance to at least fluoroquinolones and 4 injectables. And then LTBI is latent tuberculosis 5 infection, which is a condition where a person tests 6 positive by a skin test or interferon-gamma release 7 assay but don't have any clinical evidence of disease 8 by x-ray or symptoms. But those people are at risk for 9 progressing to TB disease and getting sick.</p> <p>10 So, a brief overview of the burden of TB, both 11 in the United States and globally. United States is a 12 low incidence country and as you'll see on this slide, 13 we're talking about orders of magnitude difference in 14 terms of the US problem versus globally. So, starting 15 out with the number of new cases of disease, in the 16 United States we have a little over 9,000 cases, where 17 globally there are over 10 million each year. Those 18 translate into case rates for the US of 2.9 per 100,000 19 as opposed to 142 per 100,000 globally. In the US our 20 prevalence of MDR is fairly low at about 1%, so in 2015 21 it was 89 cases of MDR-TB as opposed to globally, 22 where, as Ed already mentioned, we're talking about</p>

<p style="text-align: right;">Page 18</p> <p>1 almost 500,000 cases each year.</p> <p>2 XDR in the US, usually we have between 0 and 6</p> <p>3 cases per year. We had one in 2015, the last year that</p> <p>4 we have our surveillance data for, and globally</p> <p>5 estimates of about 45,000. Also, obviously, the</p> <p>6 prevalence of HIV among persons with TB varies quite a</p> <p>7 bit from country-to-country. In the US, it's less than</p> <p>8 10%. We had 539 cases in 2016; globally there were 1.2</p> <p>9 million, but there are obviously parts of the world,</p> <p>10 such as Sub-Sahara in Africa, where the prevalence can</p> <p>11 be 50%, 60% or more of HIV among persons with TB. We</p> <p>12 have relatively few deaths at 493 as opposed to 1.8</p> <p>13 million worldwide.</p> <p>14 And then, finally, latent tuberculosis, which</p> <p>15 although it is an asymptomatic condition and doesn't</p> <p>16 cause any immediate issues and persons are not</p> <p>17 infectious, the problem is that these are people who</p> <p>18 are at risk for ultimately getting TB disease. In</p> <p>19 fact, in the US, that's where about 85% of our cases</p> <p>20 ultimately come from, and both in the US and globally</p> <p>21 recognize that if we're going to eliminate disease, we</p> <p>22 actually have to deal with this problem more</p>	<p style="text-align: right;">Page 20</p> <p>1 And the standard regimen both in the US and globally</p> <p>2 starts with the four drugs of isoniazid, rifampin,</p> <p>3 pyrazinamide and ethambutol for the intensive phase,</p> <p>4 and then isoniazid and rifampin for four months in the</p> <p>5 continuation phase. The dosing is daily recommended</p> <p>6 globally, and daily is the preferred dosing regime in</p> <p>7 the US. For directly observed therapy, which I'll talk</p> <p>8 a little bit about later, it actually is generally the</p> <p>9 recommended way of treating TB in the US, and the World</p> <p>10 Health Organization guidance says it may be offered.</p> <p>11 Moving on to multidrug-resistant TB. So, in</p> <p>12 the US, basically, we use regimens of four to six</p> <p>13 effective TB medicines, and those are based on the</p> <p>14 results of drug susceptibility testing. The</p> <p>15 conventional duration is 18 to 24 months. There is now</p> <p>16 a shorter duration of regimen recommended globally, and</p> <p>17 that's for people who are not previously treated with</p> <p>18 second-line drugs, and who -- resistance to</p> <p>19 fluoroquinolone and second-line injectable agents is</p> <p>20 excluded or considered highly unlikely. That regimen</p> <p>21 is not currently recommended in the US. However,</p> <p>22 globally, as you can see, that 9- to 12-month regimen</p>
<p style="text-align: right;">Page 19</p> <p>1 effectively. There have been multiple models that have</p> <p>2 shown that ultimately you cannot eliminate TB under</p> <p>3 current circumstances without effectively addressing</p> <p>4 LTBI.</p> <p>5 But disease burden is not kind of uniformly</p> <p>6 distributed. It tends to be concentrated globally.</p> <p>7 Sixty percent of TB cases occurred in just six</p> <p>8 countries, and I show them here. Not surprisingly,</p> <p>9 these are the most populous countries in the world,</p> <p>10 such as China or India, but other countries which are</p> <p>11 low income, such as Nigeria, Pakistan, have quite high</p> <p>12 TB rates and contribute substantially to the global TB</p> <p>13 burden.</p> <p>14 Analogously in the US, almost 60% of our TB</p> <p>15 cases occur in just six states. Not surprisingly,</p> <p>16 again, these are some of the more populous states,</p> <p>17 including California and Texas, New York, Florida,</p> <p>18 Illinois and Georgia.</p> <p>19 So, moving on to current TB regimens. So, for</p> <p>20 drug-susceptible TB disease we divide the regimen into</p> <p>21 an intensive phase, which is the first two months, then</p> <p>22 a continuation phase, which is the next four months.</p>	<p style="text-align: right;">Page 21</p> <p>1 may be used instead of the conventional regimen for</p> <p>2 patients who fit those categories. For those who</p> <p>3 don't, the recommendation globally is that there are at</p> <p>4 least five effective TB medicines during the intensive</p> <p>5 phase, which is the first eight months, and then 20-</p> <p>6 month total duration for conventional treatment is</p> <p>7 generally what is recommended for most patients.</p> <p>8 Moving on to latent tuberculosis, there are a</p> <p>9 number of regimens that are available. The oldest one</p> <p>10 is isoniazid alone, and both the US and WHO recommend</p> <p>11 that for 6 to 9 months daily. More recent regimens are</p> <p>12 isoniazid and rifapentine for 12 weekly doses;</p> <p>13 rifampin, which in the US is recommended for 4 months</p> <p>14 daily, globally 3 to 4 months daily, and then the</p> <p>15 combination of isoniazid and rifampin, which is not</p> <p>16 currently recommended in the US but is recommended</p> <p>17 globally for 3 to 4 months daily.</p> <p>18 So, I'm going to move on now to the challenges</p> <p>19 that we face with these current treatment regimens from</p> <p>20 the CDC's perspective.</p> <p>21 So, number one is duration, and Ed already</p> <p>22 mentioned that and I've already covered that basically</p>

<p style="text-align: right;">Page 22</p> <p>1 by going through each regimen duration, but you can see 2 that generally for TB disease we're dealing with at 3 least six months of treatment. For drug-resistant TB, 4 it can be two years or longer, so long regimens with 5 multiple drugs. That can engender substantial cost, as 6 I will talk about in subsequent slides. There is 7 substantial toxicity associated with a lot of these 8 drugs and regimens. There are issues with drug-drug 9 interactions with these long regimens, which are 10 multidrug and potential toxicity. We have issues with 11 adherence. And then, finally, obviously, outcomes, 12 what we're all about. We would like to cure pretty 13 much everyone, and with drug-resistant TB, that really 14 becomes a significant issue. 15 So, while I went through that list, I don't 16 think you can really talk about these challenges in 17 isolation because there are inter-relationships and 18 there is interplay between them. So, if you have an 19 increased duration of a regimen, that's going to 20 increase the cost, it's going to tend to decrease 21 adherence and increases the risk of toxicity, because 22 the longer, just by probability, longer a person's on a</p>	<p style="text-align: right;">Page 24</p> <p>1 slide, but in US, where other medical costs are high, 2 particularly when you factor in hospitalization costs 3 for average cost, the costs are substantial, so about 4 \$18,000 to treat TB disease in the US. But when you 5 start moving into the drug-resistant forms of TB, which 6 is shown in the panel on the right, we start off with 7 drug-susceptible, as I said, \$18,000 direct cost. If 8 you start factoring productivity and other indirect 9 costs, so societal costs, that can go up to \$45,000. 10 However, once you move to MDR-TB, where the treatment 11 is much longer and more toxic with more difficult to 12 manage drugs, the direct costs, where hospitalization 13 is also more, it can go up to \$154,000 with the 14 productivity costs almost \$300,000. And then moving to 15 XDR, the most resistant form of TB, the direct costs 16 are just under \$0.5 million, \$494,000, and then when 17 you add in the productivity losses and other societal 18 costs, we're coming close to \$700,000 per case. 19 As I said, those costs are not just the drugs; 20 there are many other costs that go into it. So, when 21 we look at just the cost of drugs in the US, for drug- 22 susceptible TB, it's about \$400 for just the drugs for</p>
<p style="text-align: right;">Page 23</p> <p>1 drug the more chance there is for toxicity. Toxicity 2 will increase costs and decrease adherence. Increased 3 costs will decrease adherence if people have to pay for 4 part, even part of their regimen, which is fairly 5 typical in many parts of the world and in the United 6 States. And then obviously if you don't have good 7 adherence you're going to get worse outcomes, and also 8 with worsening toxicity you're going to get worse 9 outcomes. I don't need to cover every permutation of 10 this, but just to make the point that these things are 11 highly interrelated and all of them pose a problem. 12 So, let's start talking with costs. So, if we 13 just look at the direct costs of treatment, globally 14 for drug-susceptible TB the estimates are that the 15 direct costs are between \$100 and \$1,000 for a course 16 of treatment. That goes up substantially with MDR-TB, 17 where the estimates are \$2,000 to \$20,000. In the US, 18 the costs are even more. For latent TB, the cost is 19 about \$500 to treat, for example, with 3HP. For 20 treating TB disease, the estimated average cost is 21 about \$18,000. Now, a lot of that is not related to 22 drugs. I'll show those specific drug costs in the next</p>	<p style="text-align: right;">Page 25</p> <p>1 drug-susceptible. The global, as you get drugs to the 2 global drug facility, it's about \$40 internationally. 3 When you start moving to MDR, the conventional regimen, 4 the drug costs in the US are about \$58,000. Global 5 drug facility internationally is \$2,000 to \$5,000. We 6 don't use the short course treatment in the US, but you 7 can decrease costs internationally to about \$1,000 if 8 you use the MDR short course. And then we have 9 estimated drug costs for the US for XDR at \$164,000. 10 So, you can see that with drug-resistant TB these costs 11 jump quite substantially and become really a burden on 12 patients and public health programs. 13 And then toxicity. I did not go through every 14 possible form of toxicity, but there are many, but just 15 wanted to illustrate a few points. When we deal with 16 drug-susceptible TB, there are obviously a number of 17 other toxicities associated with each of the individual 18 drugs. But primarily the ones that programs have the 19 most problem with is hepatotoxicity, especially since 20 you have multiple hepatotoxic drugs in that regimen 21 particularly isoniazid and pyrazinamide. 22 With drug-resistant TB, you really start</p>

<p style="text-align: right;">Page 26</p> <p>1 seeing multiple toxicities and severe ones from 2 hepatotoxicity -- kidney disease, ototoxicity, 3 psychosis, this whole list of individual toxicities 4 associated with the various drugs and many of which can 5 be very serious and often result in that individual 6 drug having to be stopped, and which obviously impacts 7 the ability to complete the regimen. 8 And then for LTBI, again, the two main ones 9 that we tend to see are hepatotoxicity, particularly 10 with isoniazid-containing regimens, and then 11 hypersensitivity reactions with rifamycin-containing 12 regimens. Again, those are not exhaustive lists, but I 13 think the major ones for these different forms of 14 disease. 15 And I mentioned drug-drug interactions, and 16 here I just used two examples, isoniazid and rifampin, 17 which obviously are very commonly used in the regimens. 18 And, as you can see, for both isoniazid and rifampin, 19 I'm not going to go through these whole lists, but you 20 can see there lots of drugs with interactions that 21 occur that really people have to be aware of. And they 22 have to at least alter dosing of either the TB drug or</p>	<p style="text-align: right;">Page 28</p> <p>1 And then there are other things that we try to 2 do to get patients through, what we call patient- 3 centered care. And so, incentives, which are 4 innovations that try to motivate the patient that are 5 tailored to individual patient desires and needs. And 6 they should be meaningful, things like gift cards and 7 food vouchers. And then the other thing that is used 8 are enablers, which are other interventions to assist 9 the patient in completing therapy. Really, it's more 10 about removing barriers, so making sure they can get to 11 clinic. They want to get clinic but they can't because 12 they don't have transportation or that clinic hours are 13 just inconvenient for their work schedule. So, things 14 that enable them and help them get through their 15 treatment. Again, these things cost money. 16 So, finally, outcomes. So, if we do 17 everything right, where do we went up? Well, I think 18 in general, other than drug-resistant TB, these are 19 fairly good. But obviously 100% would be -- or as 20 close as possible, 100% would be better. But we start 21 with latent TB, treatment efficacy for the regimen is 22 around 90%. The issue there is completion. Especially</p>
<p style="text-align: right;">Page 27</p> <p>1 the drug which it interacts with. And so, this is 2 another issue that has to be considered when you're 3 treating people with TB. 4 And adherence. So, if you're going to get a 5 cure, the person needs to be adherent to the regimen. 6 And this is where directly observed therapy comes in, 7 which is the practice of having patients swallow the 8 antituberculosis medicines. The point is, you don't 9 want people, one, not completing, but also taking 10 individual drugs at different times, which is one of 11 the ways that drug resistance develops. And so, to 12 prevent that from happening, having someone make sure 13 that the patient takes all their drugs all the time 14 through completion of therapy is a standard practice in 15 the US and in many places globally. But it is 16 resource-intensive and costly because the standard 17 practice has been actually to have some kind of trained 18 worker from the health program do this. Various areas 19 in the US and globally now looking at ways of using 20 different technology, video, electronics, smartphones, 21 to try to cut down some of those costs. And so, that 22 may help, but this still resource-intensive.</p>	<p style="text-align: right;">Page 29</p> <p>1 with a longer course regimen of nine months of 2 isoniazid, at best you might see 50%. There are many 3 studies which show completion much, much less than 4 that. We have found with the shorter regimens, such as 5 three months of isoniazid or rifapentine, now we can do 6 substantially better, somewhere around 80%. 7 With drug-susceptible TB, most of the clinical 8 trials show you reach about a 95% cure. When you 9 translate it in the programmatic setting it's not quite 10 as good, and that very much depends on how good the 11 program is. But generally, you're looking at 85% to 12 95% success measured by cure or completion. 13 With MDR, not as good. We were surprised to 14 find that actually in the US programmatic setting that 15 recent publication showed that we could get about 80%, 16 90% success. Overall, globally it's been closer to 17 50%, although there are definitely places that do 18 substantially better, and especially with the newer 19 short-course MDR therapy seeing higher success rates 20 than that 50%. 21 So, finally, again, from our perspective at 22 CDC and mainly focused domestically, what are the</p>

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<p>1 things that we're looking at and trying to improve, and 2 what has been our focus? Really, our focus has mainly 3 been on duration and shortening duration, because as I 4 showed earlier, duration affects so many other things - 5 - cost, toxicity, adherence. We know with current 6 treatment we can do pretty well and get pretty good 7 results, but it would really be better in terms of 8 resources if we could get this shorter and actually 9 potentially use some of the saved resources to expand 10 more into the LTBI realm.</p> <p>11 So, Andy Vernon is going to talk in more 12 detail about TBTC, but just to give you an idea, 13 overview of our focus, looking at trying to decrease 14 the duration of drug-susceptible TB to four months, for 15 example, or decrease the duration of treatment for LTBI 16 for four to six weeks. And globally there are many, 17 many other things that are being addressed, and so I 18 certainly -- this is not an exhaustive list, but just 19 for completion of talking about MDR-TB, again, in terms 20 of duration, people are aiming to get to more of the 21 six- to nine-month range, which is being addressed in 22 trials. And also with that shorter course, want to get</p>	<p>1 Being new to the field, I went to my first 2 union meeting in Liverpool last year, and I learned a 3 very sobering statistic, which is that someone dies of 4 TB every 18 seconds. That was a reminder of why we do 5 what we do.</p> <p>6 At the Gates Foundation, our goal is to try to 7 accelerate the decline in incidents by breaking 8 transmission. And in order to identify where we could 9 best place our investments to have the maximum impact, 10 we commissioned a Patient Pathway Analysis from 11 of 11 the highest prevalence countries and learned that in 12 the world overall, approximately 25% of people are 13 never even diagnosed with disease. Of those who are 14 diagnosed, approximately 12% never initiate treatment, 15 and of those who do start treatment, almost 20% don't 16 complete. This is an abysmal picture and something 17 that gives us a lot of opportunity for investment, but 18 there was no specific one place that we felt we should 19 place all of our bets. And so, the foundation's 20 approach has been to develop a portfolio of 21 interventions to try to close some of these gaps in the 22 care cascade. And the one we'll be focusing on today</p>
Page 31	Page 33
<p>1 to the 85% to 90% success as opposed to the overall 2 average of kind of 50% currently. So, I will conclude 3 there and thank you, and turn it back to my colleague, 4 John. So, I don't know about timing, whether we'll 5 have time for questions or whether we're going to hold 6 based on where we are?</p> <p>7 DR. FARLEY: Sure. Why don't we see how we do 8 after Cathy's talk?</p> <p>9 DR. LOBUE: Okay. Thank you.</p> <p>10 DR. FARLEY: Shall I introduce Cathy?</p> <p>11 DR. LOBUE: Yes.</p> <p>12 DR. FARLEY: So, Cathy Bansbach is portfolio 13 and platform lead for the Bill & Melinda Gates 14 Foundation, global health program strategy team for TB. 15 Their goal was to reduce the incidence of infection and 16 disease, and she has worked in this field for over 20 17 years. We look forward to hearing form her this 18 morning.</p> <p>19 DR. BANSBACH: Thank you. I'm relatively new 20 to the field of TB, only having joined the foundation 21 two years ago, but I do have quite a bit of experience 22 in drug development.</p>	<p>1 is the work that we're doing to support a shorter 2 universal drug regimen. But before going there, I just 3 wanted to review what's been on drug development in TB 4 over the past decade.</p> <p>5 There are five basic approaches. The first is 6 actually one that's borrowed somewhat from oncology, 7 where you take standard of care and you add on an 8 additional compound in the hopes of improving efficacy. 9 Although since it's an add-on, you really don't do 10 anything for the underlying safety issues with the 11 background therapy or the duration or the cost. In 12 fact, adding on will probably add cost. What you do 13 gain is faster development time. So, we consider this 14 a fast-to-market but unfortunately slow to impact, 15 because you're only affecting the MDR population.</p> <p>16 A slight variation on that model would be to 17 switch out one of the molecules in the optimized 18 background regimen and substitute it with a better 19 compound, again with the goal of increasing efficacy. 20 And you may, if you switch out a toxic element, 21 actually increase safety, but the question mark as to 22 whether you can affect duration, chances are the new</p>

<p style="text-align: right;">Page 34</p> <p>1 agent won't be in lower cost than the one you're 2 switching out but, again, you have a faster development 3 time. Both of these approaches, however, have a 4 liability that by adding into what could be a failing 5 regimen, you do carry the risk of resistance to the new 6 drug.</p> <p>7 Again, borrowing from our friends in oncology, 8 the TB Alliance has taken a very brave approach to 9 developing a brand-new regimen in the XDR and pre-MDR 10 - pre-XDR population, where they combine bedaquiline, 11 pretomanid and linezolid. And here they saw, as Mel, I 12 think, will tell you a little bit later, dramatic 13 efficacy, and improvement in safety compared to what 14 XDR patients are generally treated with, and a much, 15 much shorter duration -- six months as opposed to the 16 up to 20 months that we heard about just now. Cost 17 will not be lower. Development time was rather quick 18 considering, and the risk of resistance, because all of 19 the compounds in that regimen are new, should be 20 extremely low.</p> <p>21 Then if you move from the MDR-XDR patient 22 populations that can tolerate some risk given the</p>	<p style="text-align: right;">Page 36</p> <p>1 So, to expand a little bit on what the unified 2 development path looks like, it's pretty vanilla up 3 until you get through Phase 1. Then you would move 4 into a 14-day study in TB patients for the first time 5 to look at antibacterial activity, that's your 6 monotherapy EBA. Then you would open up a new study or 7 potentially amend -- carry on in your initial EBA with 8 combinations of various regimens that either 9 preclinical data or clinical information have given you 10 a sense would be good regimens, test a variety of them 11 in the rifampin-sensitive patients only, because if 12 there is a problem you have a salvage therapy in HRZE. 13 Then take that information and then study, rather than 14 for 14 days, look at the regimen for two months to get 15 additional safety. Now we move into both the rifampin- 16 resistant and rifampin-sensitive populations and we use 17 HRZE as a control for the drug-sensitive, the rifampin- 18 sensitive population, but we also have the rifampin- 19 resistant arm as an experimental.</p> <p>20 And then, finally, if we find a regimen that 21 meets all of our criteria, you would move into Phase 3. 22 You would be looking to demonstrate shortened</p>
<p style="text-align: right;">Page 35</p> <p>1 benefit and look at the rifampin-sensitive population, 2 there are two models. One was used in the REMox 3 studies, where you swap out one element, in this case 4 either the isoniazid or the ethambutol and replace it 5 with moxifloxacin. Here the goal was to shorten 6 treatment. As we all know, that didn't work. The 7 regimen was effective, but no more effective than HRZE 8 itself.</p> <p>9 And then, finally, the pathway that the 10 foundation is currently supporting, which is our 11 unified development regimen, which enrolls patients 12 both rifampin-sensitive and rifampin-resistant. And 13 the idea here is, at least in the rifampin-resistant, 14 to improve efficacy. I don't know that we can actually 15 demonstrate improved efficacy over 90%, 95%, which we 16 see in clinical trials for the rifampin-sensitive 17 population, but we should see better safety, better 18 convenience and duration. Cost will probably not be 19 lower, but it will take more time. Development time is 20 the cost you pay for having a greater impact by being 21 able to address all of the patients in the TB 22 population and not specific subsets.</p>	<p style="text-align: right;">Page 37</p> <p>1 treatment. Four month is the current model, but we 2 hope at some point we'll be able to make that even 3 shorter. And here we're looking for noninferiority in 4 the rifampin-sensitive population and hopefully 5 increased efficacy in rifampin-resistant.</p> <p>6 So, what can we do with this drug development 7 pathway to accelerate? When I first looked at the 8 pathway, I said to myself, 14 days in healthy 9 volunteers, then 14 days in patients; can't we do both 10 of those studies in patients? And the reason I asked 11 that question was, my background in hepatitis C 12 research, where we have a very good, real-time 13 biomarker in viral load, and we were able to enroll 14 patients in Phase 1, the multiple ascending dose study, 15 which was probably more important in hep-C than in most 16 therapeutic areas because we don't have an animal model 17 that we can trust in hepatitis C. So, getting the 18 answers about activity in the patients as soon as 19 possible was very important.</p> <p>20 And during that program we went through three 21 lead compounds, very rapid succession. The third 22 compound had the potency that we were looking for, but</p>

<p style="text-align: right;">Page 38</p> <p>1 we noticed that after four days we could see resistance 2 emerging in the population. So, we amended the 3 protocol and did a combination study in the MAD study, 4 where we added interferon, which is part of the 5 standard of care. And now, to our surprise, not only 6 did we see greater antiviral activity right from day 7 one, but we were able to overcome the resistance 8 problem. So, here very quickly we were able to get a 9 lot of information about how our drugs were performing 10 in the population of interest, not the least of which 11 is we get to understand the safety in what can be a 12 more sensitive patient population. So, that's one 13 thing. Let's combine the MAD and EBA. 14 There is no reason not to link the combination 15 and monotherapy parts of the EBA study, provided you 16 have the underlying preclinical toxicology to support 17 that. And one of the things that you could gain from 18 that is if you have a compound like bedaquiline that 19 doesn't have particularly strong activity in a 14-day 20 EBA, by then very quickly getting information of what 21 happens when you put it into a potential regimen can 22 really accelerate development.</p>	<p style="text-align: right;">Page 40</p> <p>1 see four months or less. 2 Simplr. One of the great notions behind the 3 universal, or pan-TB regimen, is that when a patient 4 walks into the clinic and receives a diagnosis of 5 tuberculosis, you could initiate therapy right then and 6 there. You don't need to know if they're rifampin- 7 sensitive or resistant to isoniazid, sensitive or 8 resistant, because the regimen won't contain any of the 9 compounds for which there is pre-existing resistance in 10 the population. We're hoping that the regimen will be 11 all-oral, so it's easier to take. Of course, we will 12 be considering, as they are developed, whether long- 13 acting injectables can play a role here. And, of 14 course, in order to help prevent cross-resistance of 15 compounds, it would be great to have fixed dose 16 combinations, where that is possible. 17 As far as safety, I know it's aspirational, 18 but we would like to have no laboratory or clinical 19 monitoring, because the reality in the field is that 20 even if the drugs are labeled for monitoring, it's not 21 getting done. And so, if you can build inherent safety 22 into the regimen by choosing the right individual</p>
<p style="text-align: right;">Page 39</p> <p>1 And while we're on the topic, why stop there? 2 Why not combine option 1 and option 2, so that you use 3 patients in your MAD study and you go right into a 4 combination study. 5 And then, finally, once we have our hands on a 6 real-time biomarker, it would be fantastic if we could 7 do adaptive Phase 2/3 designs, where you take a number 8 of promising regimens into your Phase 2 part of the 9 study, very quickly identify which ones are potentially 10 better, and then carry out the full Phase 3 six-month 11 cure with those regimens. 12 So, that's where we're thinking of going. I'm 13 hoping that we can have a nice panel discussion around 14 what sorts of nonclinical and other information you 15 would want to have in order to try some of these 16 options in the field. 17 So, we mentioned the universal regimen. What 18 I've done here is basically summarized a lot of work 19 that was done with Chris John and the members of the 20 WHO task force to talk about what would be the regimen 21 profile. And here we're looking for shorter regimens. 22 I have six months there, but I think we'd all like to</p>	<p style="text-align: right;">Page 41</p> <p>1 compounds, you should be able to address this. Again, 2 if we're going to be using FDCs, we can't have a lot of 3 dose adjustments, so we need to have compounds that 4 don't need to be weight-banded or don't have other 5 liabilities like that. And obviously, because of the 6 co-epidemics of HIV and diabetes, we have to be very 7 thoughtful about the potential DDI liabilities. And 8 all, of course, at affordable cost. 9 So, where is the chemical matter coming from 10 to build these fabulous new regimens? This is a page 11 from the Working Group for New Drugs that shows what is 12 currently in late-stage preclinical and through Phase 13 3. I've squared in red the compounds in which the 14 foundation is currently investing either through grants 15 to the TB Alliance or our work with Lausanne on PBTZ, 16 and we are in discussions currently with Otsuka about 17 supporting their work in this area. 18 So, in summary, what are the challenges of 19 this brave new world that we're about to enter into? 20 We finally have a pipeline, which is very exciting but 21 is also very challenging. How do you choose the best 22 combinations of drugs out of this rich diversity? And</p>

Page 42	<p>1 so, Debra Hanna will be telling us a little bit about</p> <p>2 the work that is going on at CPTR to try to develop a</p> <p>3 holistic view, bringing together the data from in</p> <p>4 vitro, in vivo and clinical information to try to give</p> <p>5 us some better sense of how to find the best</p> <p>6 combinations. By looking at two-month data and</p> <p>7 extrapolating to what might happen after six months of</p> <p>8 treatment or even six months' follow-up, we do wind up</p> <p>9 carrying a lot of risk into our Phase 3 studies, and I</p> <p>10 think that that's something that the field needs to</p> <p>11 think about. How can we better utilize data from 14-</p> <p>12 day or two-month studies to help increase our</p> <p>13 probability of success of cure?</p> <p>14 I've said before, if we finally had a</p> <p>15 treatment response biomarker what I couldn't do, and so</p> <p>16 the field is looking at a variety of opportunities,</p> <p>17 sputum and non-sputum assays, between Otsuka and CPTR,</p> <p>18 we're in the midst of trying to qualify a lamb sputum</p> <p>19 assay. Cliff Barry and his group are doing a lot of</p> <p>20 work with PET-CT imaging to see if that can be used as</p> <p>21 an early indicator of activity, and there is a lot of</p> <p>22 work going on in immune response markers, be they</p>	Page 44	<p>1 thanking the FDA for hosting this important workshop,</p> <p>2 and for allowing a member of civil society such an</p> <p>3 early slot on the agenda today. It's very appreciated.</p> <p>4 It's not that common, and just one of the many examples</p> <p>5 of how FDA's Office of Antimicrobial Products under Dr.</p> <p>6 Cox's leadership really tries to meaningfully engage</p> <p>7 with the community. So, I just wanted to acknowledge</p> <p>8 that. And I wanted to thank all of you for being here,</p> <p>9 because I think it's clear that even though we might</p> <p>10 have some differences of opinions about the best way to</p> <p>11 proceed, all of us really are trying to do better for</p> <p>12 people who are affected by TB. And I think what we've</p> <p>13 seen from the earlier presentations is that what's</p> <p>14 really most important for patients is how we can get</p> <p>15 safer, easier, and in the case of drug-resistant TB,</p> <p>16 more effective treatment.</p> <p>17 So, why do we need new treatments? I think</p> <p>18 Dr. LoBue and Dr. Bansbach presented it very nicely,</p> <p>19 but here's another way of looking at it. This is from</p> <p>20 an activist poster at the Union Conference in 2014.</p> <p>21 It's just not good enough. We wouldn't accept these</p> <p>22 kind of side effects in almost any other disease area,</p>
Page 43	<p>1 genetic or otherwise.</p> <p>2 Two questions I'd like to leave you with, for</p> <p>3 the panel to discuss later, and that is, we all know we</p> <p>4 have to do regimen development. Resistance is real.</p> <p>5 What kind of preclinical safety information do we</p> <p>6 really need in order to study combinations in the</p> <p>7 clinic? Do we need to do nonclinical combination</p> <p>8 safety studies? Are they really helpful or is</p> <p>9 understanding the liabilities of each of the individual</p> <p>10 components and knowing what to monitor for, when we get</p> <p>11 to the clinic, sufficient? And, again, the continuing</p> <p>12 question of how do we find the best regimens, and what</p> <p>13 is best? Thank you. Ten million people waiting for</p> <p>14 us.</p> <p>15 DR. LOBUE: Thank you. Our next speaker will</p> <p>16 be Erica Lessem. Erica is director of TB-HIV at the</p> <p>17 Treatment Action Group; an independent research and</p> <p>18 policy think tank. Erica oversees TAG's activism for</p> <p>19 research and access to improve tools and services to</p> <p>20 prevent, diagnose and treat TB and TB-HIV. Thank you,</p> <p>21 Erica.</p> <p>22 MS. LESSEM: Thank you. I'd like to start by</p>	Page 45	<p>1 and we certainly shouldn't in TB, since we've been</p> <p>2 treating it for so many decades.</p> <p>3 We have made a lot of progress in recent</p> <p>4 years, but TB has been operating from a position of</p> <p>5 scarcity, and that doesn't poise us well to do better.</p> <p>6 And I think we need to really think about taking a more</p> <p>7 bold approach and asking for more for patients, and</p> <p>8 building that, really, into the research and regulatory</p> <p>9 pathways. We all here are very well aware of the</p> <p>10 critical funding gaps, and given the short time frame</p> <p>11 for the talk today, I'll leave the questions of</p> <p>12 investments for another day and just kind of focus on</p> <p>13 the research and regulatory considerations that those</p> <p>14 of us in the room can influence, and how we can best</p> <p>15 employ the resources that we have.</p> <p>16 So, I think there are several overarching</p> <p>17 questions that I and some of the other community groups</p> <p>18 that we work with have been thinking about. I hope you</p> <p>19 can see the text. I might have had some Mac-to-PC</p> <p>20 conversion issues here. So, there are a lot of</p> <p>21 questions. When is it -- when do we have enough</p> <p>22 information to go into Phase 3? How can we balance the</p>

<p style="text-align: right;">Page 46</p> <p>1 need for really wanting to accelerate research with 2 making sure we have all of our ducks in a row; to make 3 sure that we're being ethical in terms of moving 4 forward when we really know enough about safety and 5 efficacy to open up a trial and to start going for 6 regulatory approval? When, if ever, is it appropriate 7 to forego a control or to forego randomization? This 8 is a real problem in drug-resistant TB, as all of you 9 know, since we don't have a great, validated standard 10 of care.</p> <p>11 How can trials generally be conducted 12 ethically in a way that we get information about a drug 13 or regimen while standards of care are changing? And 14 how can adopting new treatments that we have some 15 evidence, especially from kind of routine programmatic 16 use, and we want to do the best things for patients, 17 how can we balance that with being able to make sure we 18 can still collect enough data and not inhibiting data 19 collection?</p> <p>20 How can we avoid perpetuating the current 21 state that we're in, where we're using drugs and 22 regimens because it's the best thing that we have, but</p>	<p style="text-align: right;">Page 48</p> <p>1 because TB has been the victim of decades of 2 underinvestment and we still don't have an optimal 3 standard of care for MDR-TB, that puts us in a 4 difficult position to say what the ideal trial design 5 should be.</p> <p>6 And so, we have a lot of TB-specific issues, 7 but more broadly there is a climate of pushing for 8 increasing regulatory laxity from the 21st Century 9 Cures bill that was approved in the end of last year to 10 the Right to Try Movement, which is really pushing for 11 much earlier preapproval access. And some parties are 12 vilifying the important role that regulatory 13 authorities play and they are over-simplifying the 14 complex challenges of bringing a [product to market]. 15 It's much easier to say, oh, it's the government that 16 is being too slow. Well, we know that that's not true. 17 And I think if these pushes are successful, we're 18 really in danger of being in a pre-FDA era, and that's 19 not going to be good for any of us, either for 20 patients, for the broader community, or even for the 21 sponsors, who would then really be on the hook for 22 this.</p>
<p style="text-align: right;">Page 47</p> <p>1 we still don't have the complete evidence that we would 2 want to to support their safety and efficacy and 3 optimal use? And how can we balance the urgency of the 4 immediate access needs that we see for patients around 5 the world with the importance of really knowing the 6 full profiles of the drugs or regimens that we're 7 using?</p> <p>8 And another thing that I want to ask, since 9 we're here at FDA is, how can FDA be empowered to hold 10 sponsors accountable for delivering on conditions of 11 approval? How can we better position FDA to really ask 12 for what's needed in this field? And I think it's 13 important to point out the broader regulatory climate 14 here.</p> <p>15 There is a misconception, I think, among some 16 policymakers that patient groups only want faster 17 access to treatment, and that's not true. Patients 18 want access to safe and effective treatment that has 19 been studied. And TAG, where I work, was founded by 20 people with HIV, who really wanted more research and 21 more data to know whether the treatments that were 22 being given actually worked and were safe. And I think</p>	<p style="text-align: right;">Page 49</p> <p>1 In our experience, FDA has been highly 2 transparent and timely in its reviews. Already has a 3 lot of useful pathways for guaranteeing preapproval 4 access and for accelerated approval, and has several 5 incentives for drug development. So, that's why we 6 sent FDA a valentine last February. But since a lot of 7 us are really focused on TB, I just want to kind of 8 frame this in the bigger picture that TAG is really 9 concerned about, about jeopardizing the very strong and 10 transparent regulatory authority that we have here in 11 the US.</p> <p>12 So, going back kind of more specifically to 13 TB, some of the things that we've been thinking about 14 as a community are approaches to finding this balance 15 between getting the answers and moving trials 16 efficiently and having access in the meantime. So, 17 a lot of these things need to be considered on a case- 18 by-case basis. But I think we're already learning a 19 lot from the experience that we've had in the past 20 decade or so of some revitalization of clinical 21 research for TB treatment.</p> <p>22 So, just to point out a few of these kind of</p>

<p style="text-align: right;">Page 50</p> <p>1 options and things that we want you to think about and 2 I hope will solve all of this today. Seamless designs 3 would be -- are really useful, I think, for maximizing 4 efficiency. They allow the most advantageous arms to 5 move forward, but also really cut down on the delays 6 that might happen for having to go through regulatory 7 approval in multiple countries for multiple sites. 8 We're also very supportive of Phase 2c designs, to 9 gather more evidence about our regimen before moving to 10 Phase 3, as well as to validate endpoints. As we heard 11 from Cathy's talk, we really need some better endpoints 12 and biomarkers in TB. 13 And speaking of endpoints, I'd like to 14 encourage the group here to consider endpoints that 15 might be an alternative to kind of standard relapse- 16 free care, especially if we're thinking about pre-XDR, 17 XDR. It might be useful to think about adverse event- 18 free, relapse-free care as an outcome. That could help 19 reduce sample size as well as give a lot of information 20 that is very relevant to patients and providers, and we 21 could kind of build some of the safety considerations 22 into the outcome itself and allow for superiority</p>	<p style="text-align: right;">Page 52</p> <p>1 And then there's the question of a control, 2 and I didn't put bullets under this because it's really 3 hard to summarize. But I think the main point here is 4 we really want to move the field out of the dark that 5 we're in right now of not knowing how regimens perform 6 in clinical trial settings or compared to each other. 7 And we acknowledge the limitations of the existing 8 feasible controls for M/XDR TB particularly. But we 9 hope that if the regimens that are in development now 10 continue to perform well, we can have a new standard of 11 care that would set a higher bar for a control and can 12 obviate some of these questions. 13 And I just wanted to flag, too, with the 14 question of controls, because we've heard this as we 15 reviewed some protocols that a regulator might have 16 approved a study design. But I wanted to flag to you 17 that for studies proceeding without a comparator, 18 normative guidance can still be very challenging to 19 formulate, as can garnering community practitioner and 20 programmatic support. 21 So, one question is the regulatory piece, but 22 that's not really the only approval that would need to</p>
<p style="text-align: right;">Page 51</p> <p>1 studies to happen in that way even when a regimen is 2 not expected to increase efficacy. So, I'm just 3 thinking, if the regimen that is being studied in the 4 NIX trial, the BPaL regimen winds up continuing to look 5 as good as we're all hoping it does, then what's next? 6 That would potentially set a higher bar for efficacy. 7 We might not want to be focusing on increasing the 8 efficacy in terms of superiority, but certainly we 9 would want to reduce the linezolid toxicity. And so, 10 can we think of other endpoints that really capture 11 what's important to patients and to programs and to 12 providers in that? 13 And thinking also about this, we have some 14 concerns that noninferiority studies may be setting the 15 bar too low in some cases, especially when margins 16 allow for potentially even worse performance than the 17 comparators. So, I think if we can think of innovative 18 endpoints, we might be able to think more about doing 19 superiority studies rather than noninferiority studies 20 for some conditions which really don't help us kind of 21 move the forward bar forward or raise the bar for 22 patients.</p>	<p style="text-align: right;">Page 53</p> <p>1 be in place to actually get regimens to patients. And 2 so, I would encourage everybody in the room to be 3 thinking about what does it really take to get a drug 4 or a regimen into bodies, and how can we set up for 5 research in a way that would have the most efficient 6 pathway to get there? 7 Something else to flag, and I see that we'll 8 discuss some of it later in the panel discussions, but 9 inclusion of vulnerable populations. There is 10 systematic exclusion of pregnant women and of 11 adolescents and children from research, and this is not 12 ethical and it's not scientifically sound. 13 There was a recent paper from community 14 representatives including my colleague, Lindsay McKenna 15 in CID, and I think this is a really powerful quote. 16 "In the absence of research, each pregnant woman 17 treated for TB becomes an individual experiment." 18 Pregnant women will get TB, people with TB will get 19 pregnant, and we need to know how drugs and regimens 20 will work in them. A lot of drugs could potentially be 21 safe in pregnant women, but there's a lot of fear 22 around including pregnant women in trials due to</p>

<p style="text-align: right;">Page 54</p> <p>1 concerns about liability, getting insurance, getting 2 through ethics boards. Same for adolescents. 3 There is real consensus now that adolescents 4 metabolize drugs similarly to adults. There was a 5 consensus statement coming out of an NIH workshop 6 several years ago, that adolescents should be included 7 in later stage trials along with adults. And we also 8 need pediatrics-focused research, to make sure that in 9 children who do metabolize drugs differently or might 10 present disease differently that we know what the best 11 regimens and drugs to use are in them and the best 12 dosing for doing so. 13 Unfortunately, there is what's intended to be 14 an incentive for developing orphan drugs actually 15 perversely disincentivizes research in children. There 16 is a regulation here in the US that drugs must be 17 studied in children, there must be a pediatric plan, 18 but the Orphan Drug Act actually allows an exemption 19 for that. So, in children with TB, who are probably 20 one of the populations in most need of research, we're 21 actually trying to incentivize drug development by 22 saying that you don't have to study TB in this</p>	<p style="text-align: right;">Page 56</p> <p>1 people to kind of have a separate clinical trial of a 2 certain product in pregnant women. 3 And then just to flag, there are other special 4 populations that are often excluded from studies 5 because we don't want to have the "noise" that might 6 detract from finding the efficacy and safety that we're 7 hoping to see in the broader population. But we see it 8 reflected a lot in the guidelines because people 9 haven't been included in the research. So, we need 10 some additional research in a lot of special 11 populations, including people of advanced age. In a 12 lot of countries, the majority of TB is happening in 13 people who are over 65. We need people with very low 14 CD4 counts. They're at the highest risk of dying, but 15 for a lot of reasons they're excluded from clinical 16 trials, so we don't know really what the best options 17 for them are. 18 And then also people who use drugs or alcohol 19 or opioid substitution therapy, where there might be 20 extra concerns about toxicity and about drug 21 interaction. 22 So, there are a lot of issues to consider, and</p>
<p style="text-align: right;">Page 55</p> <p>1 population. And so, I think we really need to think of 2 regulatory solutions and legislative solutions to get 3 us out of that hole. And from TAG's perspective, the 4 default really should be to include pregnant women and 5 adolescents in research unless there is a rationale for 6 opting out. So, the current approach is opt-in, and 7 almost nobody is doing that. But I will give credit to 8 some of the studies, including from TBTC and ACTT, that 9 are trying to go down to age 12 or 15, in some cases. 10 But I think we need to reframe our thinking in that the 11 default must be to include these populations in 12 research unless there is a specific reason to take them 13 out, as well as to have a really robust pediatric 14 research plan in parallel to whatever is happening with 15 adults. 16 Another thing that would be really useful in 17 TB is a registry for pregnant women and seeing what 18 drugs they're on and note some of the outcomes. That 19 has been really helpful in the HIV field and it has 20 been expanded to hepatitis B as well. It would be 21 really useful to have this kind of registry in pregnant 22 women since it's unlikely that there would be enough</p>	<p style="text-align: right;">Page 57</p> <p>1 just to note that we're here to help. TAG and the 2 community groups that we work with, in particular, the 3 Global TB Community Advisory Board and the Community 4 Research Advisors Group have a lot of experience 5 reviewing protocols and study concepts and are 6 available to do this for any sponsor that wants to 7 share with us, and we encourage everybody to do so. 8 And we've been able to review almost all of the late- 9 stage MDR-TB trials in the last six years. We haven't 10 been able to review the Otsuka protocols, but other than 11 that, I think it's been pretty much everything late in 12 the pipeline and most of the late-stage prevention and 13 drug-susceptible TB trials, pivotal ones that are 14 happening. 15 And there is a nice publication about -- or 16 presentation about what we've kind of found across 17 this, and it's just something to think about as you're 18 developing your research plans. But what can be 19 included upfront, more information about results 20 dissemination, plans for post-trial access. Again, 21 this issue of the control arm, what the composition of 22 it is, or whether it even exists. Using</p>

<p style="text-align: right;">Page 58</p> <p>1 nonstigmatizing language in study documents, so we 2 facilitate participation, and appropriate inclusion of 3 key affected populations, like I mentioned on the last 4 slide. So, feel free to email me if you want us to 5 take a look at anything you're working on. We'd be 6 very happy to.</p> <p>7 One more thing on kind of the R&D side is 8 thinking about what we need to do with some of these 9 older drugs that are being repurposed for TB, or maybe 10 have been used for a long time for TB but don't have an 11 official TB indication. And two that I think are on 12 our minds and probably a lot of yours are clofazimine 13 and linezolid. And we need to think about how to 14 balance, again, the urgent access needs for these drugs 15 that we have a lot of evidence from routine use work 16 quite well, but we don't have a lot of great evidence 17 from clinical trials in the case of clofazimine.</p> <p>18 So, how can we ethically gather the data that 19 are still missing for optimal use of the drug when it's 20 now part of a standard of care? What would a control 21 look like if there was going to be one, and how can we 22 kind of ethically do that? And then how can we also</p>	<p style="text-align: right;">Page 60</p> <p>1 Just looking into the access front, 2 preapproval access plans, as mentioned before, really 3 should be built into the research plan. There is a 4 movement in the US to try and push for what's called 5 the Right to Try, which is preapproval access as early 6 as Phase 1. We think that this could do a lot of harm 7 without addressing some of the barriers. In our 8 experience and I think data go to show that preapproval 9 access options under expanded access in the US are 10 really functional, they're working well. This is just 11 an excerpt from the paper that shows that nearly all 12 applications are accepted and very few wind up 13 affecting clinical holds or the product development 14 pathway. So, we're very happy with the expanded 15 pathway in the US and don't want to jeopardize the 16 stringency that FDA has right now.</p> <p>17 But we do think that preapproval access is 18 really important and globally that there needs to be a 19 lot more of it. It's important for patients who are in 20 urgent need and it also allows for more experience and 21 familiarity with the product. This isn't why it 22 exists, but it really helps programs gain more</p>
<p style="text-align: right;">Page 59</p> <p>1 balance the urgent access needs? In the US, there has 2 to be an individual IND submitted for each patient who 3 wants to get clofazimine, and it's really unsustainable 4 and not feasible from a patient or provider 5 perspective. So, we know that the FDA is thinking 6 about these issues and we really encourage finding ways 7 to balance the immediate access needs with also still 8 finding ways forward for requiring some more data to 9 inform the optimal use.</p> <p>10 In kind of a different situation we have 11 linezolid, which is -- we do have some clinical trial 12 information about efficacy of the drug. We know it's 13 not optimal in terms of safety, but side effects can be 14 manageable and are certainly, in some cases, preferable 15 to going deaf or to dying from TB. But there is not a 16 clear regulatory pathway for the pediatric formulation, 17 and this is something that we really need to think 18 about is how we're disincentivizing future product 19 development, especially for populations, and can we 20 think of some kinds of flexibilities that might allow a 21 path forward to get new products, especially for the 22 populations in most need.</p>	<p style="text-align: right;">Page 61</p> <p>1 familiarity with a drug and gain some real-world use 2 with it, to then be able to roll out if the regimen 3 does wind up kind of being successful in trials and 4 approved.</p> <p>5 So, one thing that we're thinking about is 6 there are several barriers to compassionate use or to 7 preapproval access, and can we find -- can we build 8 some kind of more unified platform and approach to this 9 where we manage some of the risk on the developer side? 10 Do we set more clear criteria for when it's appropriate 11 to start compassionate use, and also provide some more 12 support for getting through some of the importation and 13 regulatory hurdles. And helping countries harmonize 14 their approach to preapproval access to make it easier 15 on the sponsors, and also easier on providers and 16 patients so they don't have to individually apply to 17 each sponsor for potential access.</p> <p>18 So, that is something to look out for. We'll 19 be putting out a concept note about that soon, and just 20 wanted to flag that. I think this is a really 21 important area where we want to maintain the current 22 levels of stringency in the US, but try to enable</p>

Page 62	<p>1 access in other countries and also support sponsors to</p> <p>2 provide access earlier and in a more efficient way.</p> <p>3 On the access side, here in the US we also</p> <p>4 have a lot of problems that are very related, price</p> <p>5 hikes and drug shortages. And this is an example. The</p> <p>6 top is a table. It's probably hard to read, but just</p> <p>7 to show you that between 2011 and 2013, several TB</p> <p>8 drugs were in shortage here in the US. At the same</p> <p>9 time, a few years ago there was a huge price hike for</p> <p>10 cycloserine that wound up being resolved, but it jumped</p> <p>11 from \$480 for a month's supply to \$10,000. And these</p> <p>12 are really two sides of the same coin, because we have</p> <p>13 this low incidence paradox here. I think this is a</p> <p>14 term coined by the CDC. But we're very vulnerable here</p> <p>15 in the US because we have actually a relatively few</p> <p>16 number of cases.</p> <p>17 So, it's not a particularly attractive market</p> <p>18 when we're thinking about the active TB market. And</p> <p>19 the underlying causes for both the drug shortages and</p> <p>20 the price hikes are unaddressed, so we haven't seen one</p> <p>21 of these in the past year or so. But we're always in</p> <p>22 danger of this, and it's because it's very hard to</p>	Page 64	<p>1 something like a list of essential medicines or a</p> <p>2 formulary so that if there were a shortage or a supply</p> <p>3 issue, there might be some recourse for either trying</p> <p>4 to import a drug that was quality-assured from</p> <p>5 elsewhere or really signaling to manufacturers that</p> <p>6 these are priorities to invest in. And certainly, TB</p> <p>7 as a communicable disease, I think products would</p> <p>8 feature heavily on whatever list or formulary could be</p> <p>9 developed.</p> <p>10 We have a lot more information about this. I</p> <p>11 have the links at the bottom of the slide. But I</p> <p>12 wanted to just end by trying to summarize as much as</p> <p>13 possible the various issues here.</p> <p>14 I'll close with remarks from Mark Harrington,</p> <p>15 my boss, which was made up hearing about the</p> <p>16 bedaquiline for its approval several years ago, and he</p> <p>17 encouraged us to be bold and to make history, but to do</p> <p>18 it stringently. And I think that this still holds true</p> <p>19 today and really underpins the balance that we want to</p> <p>20 see in access promoting innovation and providing</p> <p>21 accountability for evidence.</p> <p>22 So, just to close, our regulatory and research</p>
Page 63	<p>1 attract and keep manufacturers invested in the US TB</p> <p>2 market. It would be great if we could harmonize the</p> <p>3 domestic drug supply with the global drug supply and</p> <p>4 think of ways to do that. And I think it would address</p> <p>5 what Dr. LoBue raised earlier, which is the wide</p> <p>6 disparity in prices in the US and the global market.</p> <p>7 But also, it could be really helpful to have a lot more</p> <p>8 of the products in the global market kind of go through</p> <p>9 the FDA review, especially now that WHO</p> <p>10 prequalification fees are getting implemented. We</p> <p>11 might want to have some of those products be registered</p> <p>12 here with FDA, and they could also access the global</p> <p>13 market through that stringent regulatory authority</p> <p>14 approval.</p> <p>15 So, I think one thing I'd like to flag here is</p> <p>16 that it would be great to have more support for the FDA</p> <p>17 to be able to facilitate importation of global quality-</p> <p>18 assured medicines to help harmonize the market and</p> <p>19 create a more stable supply here so the US market can</p> <p>20 kind of benefit from the bigger demand globally. Also,</p> <p>21 it would be great if FDA could be more empowered to</p> <p>22 enforce reporting of drug shortages and even to create</p>	Page 65	<p>1 environments I think are really in jeopardy, and I</p> <p>2 encourage all of you to take action as you are able to.</p> <p>3 And TAG is creating a kind of list of how we can better</p> <p>4 engage various partners, from researchers to clinicians</p> <p>5 to policymakers. So, you can sign up on our website to</p> <p>6 get kind of alerts about actions that you can take</p> <p>7 either in your individual or organizational capacity.</p> <p>8 And I've also included my email address, so anybody can</p> <p>9 feel free to reach out with questions or comments, or</p> <p>10 to have us review a protocol. Thank you.</p> <p>11 DR. FARLEY: Thanks very much, Erica. Our next</p> <p>12 speaker is Eric Nuermberger from Johns Hopkins, where</p> <p>13 he is a professor of medicine, and he's been primarily</p> <p>14 engaged through his career in preclinical TB drug</p> <p>15 development, research using both animal and in vitro</p> <p>16 models. He has been a big part of the TB work at the</p> <p>17 ACTG as well as a core science group of the CDC TB</p> <p>18 Trials Consortium. So, thanks for being here.</p> <p>19 DR. NUERMBERGER: Thank you. So, thanks very</p> <p>20 much for the invitation to come and speak. It's always</p> <p>21 a pleasure, and I think this is a very important reason</p> <p>22 to be getting together and talking. So, at the risk of</p>

Page 66	<p>1 beginning with a clichéd quote, I thought that in the 2 limited time that we have it would be reasonable, a 3 reasonable way to frame the comments and perspectives 4 that I'd like to add today. And this is, I think, too 5 often, in thinking about preclinical drug development, 6 we get caught up in how well a given model, whether in 7 vitro or in vivo, mimics a particular disease state in 8 tuberculosis patients, or mimics a particular 9 subpopulation of persisters, and think less about 10 whether the data that are being provided by the model 11 are useful in some way, and whether they have to be 12 useful in a comprehensive way or useful in a 13 complementary way. And so, I'd like to provide the 14 perspective that I think we are better served by 15 thinking about how models can be used in a 16 complementary to provide useful data.</p> <p>17 But that then introduces the idea that we also 18 need to know how to use these data effectively. And so 19 there is whether the model provides useful data and 20 whether we have useful ways of using the data that are 21 provided that really go into this question. And so, 22 these are a few things that I'd like to hit on some</p>	Page 68	<p>1 untenable in in vitro systems and certainly untenable 2 in patients, altered dosing schedules for long 3 monotherapy, etc., etc. And there is the opportunity 4 to precisely measure the concentrations that the 5 organisms are being exposed to at the effective site of 6 infection, something that is challenging to do in in 7 vitro tuberculosis models.</p> <p>8 And, lastly, one of the cardinal advantages is 9 the opportunity to serially sample the organisms from a 10 single cartridge, in the case of the hollow fiber 11 system, which lends a great deal of advantage in terms 12 of statistical analysis. So, of course, the downside 13 is that you don't have the opportunity to introduce the 14 influence of the host into this system, and so one can 15 manipulate the environment to try and create 16 nonreplicating organisms, or organisms that may be, you 17 think, are mimicking certain niches within the infected 18 host. But one can certainly not get the kind of 19 spatial alignment or arrangement of organisms inside of 20 lesions that are seen in the host, effects of the host 21 immune response on the organisms in the system, and 22 other aspects. So, one really has to go into in vitro</p>
Page 67	<p>1 today.</p> <p>2 So, I've been asked to talk about both in 3 vitro and in vivo models. And again I'm going to focus 4 on some of the models that are a bit further along the 5 path, if you will, in drug discovery and in 6 development, and talk really from an in vitro 7 perspective only about a model such as the in vitro 8 hollow fiber system model, which provides an 9 opportunity to expose the bacteria to dynamic or 10 fluctuating concentrations of drug over time, as I 11 think that that has a greatest degree of applicability 12 to the kinds of questions that we're talking about 13 today.</p> <p>14 But these in vitro models, like the hollow 15 fiber system model, have a number of real advantages. 16 Most importantly you can expose the organism to drug 17 under very well controlled conditions. Manipulating 18 media conditions, manipulating the various populations 19 of bacteria susceptible in drug resistance, if you 20 would like, and a variety of other conditions.</p> <p>21 One can also obviously expose the organisms to 22 a wide range of drug doses and exposures that are</p>	Page 69	<p>1 models to be able to incorporate that in a 2 comprehensive way and really look at that in a dynamic 3 system.</p> <p>4 The other value, I think, of looking in in 5 vitro models is, of course, you have a mixture of 6 various subpopulations, if you will. Depending on how 7 the model is set up, those subpopulations may be 8 present in different proportions, and at least in some 9 of those cases you would hope that some of these 10 proportions are actively multiplying and nonmultiplying 11 and slowly multiplying and persisting and dormant are 12 present in some sort of clinically-relevant proportion. 13 So, that potential is there.</p> <p>14 The cons, of course, are many of the things 15 that are advantages to the in vitro systems. There are 16 limitations to the schedule. It's often difficult to 17 mimic the human PK very precisely, and any given in 18 vitro model may not represent all of the various 19 disease presentations or lesions types that are found 20 in patients.</p> <p>21 So, I want to, rather than pitting these two 22 types of models against each other, of course, we want</p>

<p style="text-align: right;">Page 70</p> <p>1 to get to -- you know, emphasize that I think these are 2 models that should be used in a complementary fashion 3 that really amplifies their -- each unique advantages. 4 And so, we, in collaboration with Debra and 5 the team at the CPTR, embarked on a landscape analysis 6 of preclinical models. This is now maybe five years 7 ago, maybe more, and really tried to survey what was 8 out there in terms of preclinical models and what 9 evidence there was to support their utility in the drug 10 development process. And we quickly identified the 11 hollow fiber system as a system for which there had 12 been enough data and the right kinds of data, meaning 13 quantitative data that had been used to try and address 14 key PK/PD-related questions related to the development 15 of TB drugs that would make that model suitable for an 16 evidence-based analysis of its utility to inform key 17 drug development decisions. And, again, most of these 18 related to PK/PD-based decisions. And so, this work 19 was largely done with Tawanda Gumbo and his team and 20 facilitated by the folks at CPTR. Pulled together data 21 both sort of retrospective and prospective for this 22 hollow fiber system and eventually wound up presenting</p>	<p style="text-align: right;">Page 72</p> <p>1 to say there is not a great deal of combination data on 2 a variety of common issues. (Sounding of alarm.) Is 3 that an offensive statement? 4 DR. COX: Okay. So, we'll exit and we'll 5 reconvene, we hope, after this. 6 Welcome back, everybody. 7 DR. NUERMBERGER: All right. Well, evidently 8 a hot topic, as someone said. So, I think we were in 9 the midst of talking about this hollow fiber model of 10 tuberculosis. And I think really the point that I 11 wanted to leave you with there is that this does appear 12 to be a promising model for sorting out PK/PD-related 13 questions. I think when it comes to regimen 14 development that obviously can inform dose 15 optimization, that can inform regimen selection to some 16 extent, then you may be able to down-select regimens in 17 which drugs don't appear to have a complementary or 18 additive effects, although that remains somewhat 19 preliminary. And so, it has real potential there. It 20 also has potential to limit the numbers of animal study 21 arms and doses and things that have to be tested and 22 then validated in in vivo situations. So, that's</p>
<p style="text-align: right;">Page 71</p> <p>1 the data package here at FDA, also at EMA. And at EMA 2 this presentation ultimately ended in this 3 qualification opinion for the hollow fiber system. And 4 I present this only to say that, one, this is evidence 5 of one approach that can be done to take an evidence- 6 based approach to demonstrating the utility of a tool 7 that is not meant to be a be-all, end-all tool to tell 8 you what to do with a drug or a regimen, but to 9 complement decisions. To show that this has value in 10 informing regulatory submissions, there was, again, the 11 statement included a statement that this was qualified 12 for use in regulatory submissions. And provided some 13 core areas in which -- in core questions in which this 14 model could be used in this capacity, where it was 15 qualified for this purpose. Now, most of these relate 16 to, again, PK/PD decision points looking at individual 17 drugs, identifying PK/PD drivers and targets and 18 susceptibility breakpoints that then ought to be 19 verified in further studies. 20 And also, stated here is the ability to 21 provide proof of -- preliminary proof of concept for 22 developing a specific drug or combinations. Suffice it</p>	<p style="text-align: right;">Page 73</p> <p>1 another aspect, I think, of the potential 2 complementarity of this model. 3 There remain some important questions that 4 have to be addressed, and I think this is still a model 5 that has been used largely at two research 6 laboratories. There are important questions about 7 reproducibility, about transferability or 8 transportability of the model to other sites. It is 9 important to note that this model has been in use for 10 other infectious organisms and used very effectively in 11 the pharmaceutical industry. And so, it's not that 12 there's not a wide range of experience in use of 13 systems like this, but with respect to TB and some of 14 the unique challenges with TB, the experience is 15 relatively limited. Now, that is being addressed in 16 some ongoing programs that I think Debra will probably 17 want to talk about further. 18 I think another key question, especially as we 19 think about bedaquilines and the clofazimines of the 20 world, drugs that have very high protein binding, are 21 very lipophilic, distribute very differently through 22 different tissues. One really important question is</p>

<p style="text-align: right;">Page 74</p> <p>1 how do you begin to estimate the drug exposures at the 2 site of infection that you should be simulating in 3 systems like this. And I think the experience for 4 those types of drugs is very limited to date, and these 5 are important questions. 6 Predictive accuracy as well. Getting into the 7 regimen questions, there are novel regimens now being 8 studied in these systems to try and address, again, 9 questions about their ability to rank order, the 10 efficacy of novel regimens in comparison to standard of 11 care. And even to begin to think about estimates of 12 treatment duration that may come from such studies, but 13 to date I think this process is early. 14 And, lastly, the way to different actively 15 growing and persisting subpopulations are modeled and 16 these systems are indistinct, experiments in distinct 17 cartridges, and so how do you begin to merge the data 18 coming from those different populations into a 19 synthetic whole that is predictive of overall drug 20 efficacy in a patient? 21 And this model, in addition to being qualified 22 by EMA, also was endorsed by FDA in a nice editorial</p>	<p style="text-align: right;">Page 76</p> <p>1 primary endpoints that are looked at are lung CFU 2 counts over time at different time points. Resistant 3 subpopulations can be quantified as well during that 4 time by plating on drug-containing agar. And then 5 because we often with many regimens, we'll get to a 6 point in time where we're not able to cultivate any 7 organisms from the lung at the time the treatment ends, 8 but yet holding mice for additional periods of three or 9 six months will eventually result in resumed culture- 10 positive status. We put a lot of stock in this 11 assessment of relapse-free cure. So, holding mice 12 after different durations of treatment for an 13 additional three to six months without treatment to 14 assess whether they remain culture-negative when we 15 grind up the entire lung and plate it in its entirety 16 on the organ. So, this obviously has some similarities 17 to the kind of Phase 3 relapse assessments that are 18 done for novel regimens that lend some extra interest 19 in this endpoint. But it also accommodates some of the 20 issues pertaining to drug persistence in the lungs at 21 the time the treatment ends. And as we've observed 22 with clofazimine and bedaquiline, drug activity can</p>
<p style="text-align: right;">Page 75</p> <p>1 that accompanied the papers describing the 2 qualification approach. But despite the promise of the 3 model, of course, there is, again, this emphasis that 4 this model could not be expected to be used in 5 isolation certainly at this point in its development. 6 And there will probably always be reasons that the 7 hypotheses generated in this model need to be validated 8 in in vivo systems. 9 And so, the in vivo systems that have been 10 used most extensively and thoroughly in these 11 preclinical studies, especially in recent decades, have 12 been murine models of tuberculosis. I'm presenting 13 here sort of a general schematic to make sure we're all 14 on the same page about some of the readouts that are 15 generally look at here. So, this describes an 16 experimental setup that we tend to use in our 17 combination development program that we collaborate on 18 with the TB Alliance. 19 So, mice are infected by an aerosol route and 20 at day zero they start with a very large bacterial 21 population bordering on 10 to the 8th, or sometimes 22 exceeding 10 to the 8th organisms in the lung. And the</p>	<p style="text-align: right;">Page 77</p> <p>1 continue beyond the end of treatment and could lead to 2 additional cure that happens despite the fact that the 3 mice are not still being treated on a daily basis. 4 Now, this also, being able to stop the 5 treatment at various time points and look at cure 6 allows for an opportunity to ask what is the effect 7 size of a novel regimen? What is the treatment 8 shortening potential if you compare it to the standard 9 of care, which is typically a five- or six-month cure 10 in these? How much shorter can you go with a novel 11 regimen without resulting in excessive numbers of 12 relapses, or higher numbers of relapses? 13 So, the way that this model is often used in 14 the context of drug development -- again, this is drawn 15 largely from our experience with the TB Alliance, is to 16 derive or confirm PK/PD relationships that help to 17 select the optimal dose of component drugs, to rank 18 order, drug -- novel drug combinations in terms of 19 efficacy. And this is often initially done on the 20 basis of serial CFU counts from the lungs, but 21 eventually for selected regimens on the basis of 22 treatment-shortening potential relative to standard of</p>

<p style="text-align: right;">Page 78</p> <p>1 care; to estimate the treatment-shortening potential in 2 the way that I just mentioned. 3 And then more recently now, efforts to 4 incorporate this so-called Kramnik mouse strain that 5 I'll talk about in a moment, to try and assess the 6 impact of caseous pathology on the efficacy of drugs 7 and regimens. And the implication here, the BALB/c 8 mice and other mice that have been traditionally used 9 in this capacity, don't develop caseating necrotic 10 lesions that better resemble caseating lesions in TB 11 patients. And so there has always been some concern 12 that the intracellular bacterial populations in these 13 mouse lesions and these lesions themselves likely don't 14 fully represent the bacterial phenotypes present in 15 caseating lesions, likely don't represent the need for 16 drugs to distribute through the caseous portions of 17 lesions to reach extracellular bacilli in that space. 18 And so, we'll speak some more to this in a moment. 19 And then, again, something that has not had as 20 much prominence as I think it perhaps should is the use 21 of experimental systems like this, if we're really 22 seeking to develop novel regimens, I don't think we</p>	<p style="text-align: right;">Page 80</p> <p>1 more novel regimens that have progressed to the clinic 2 with some basis, evidence base in these high-dose 3 aerosol BALB/c mouse models. I think the one that has 4 obviously attracted most attention is the substitution 5 of moxifloxacin into the standard of care, because 6 that's a regimen for which there are now Phase 3 data. 7 And certainly, a lot has been said about whether the 8 mouse or early clinical endpoints predicted the 9 outcomes of this Phase 3 trial or not. But an exercise 10 that we've gone through for this regimen and are now 11 going through for other regimens that are either in or 12 moving through clinical trials is to go back and 13 aggregate the mouse data, to really look as carefully 14 as we can at the treatment shortening effect that was 15 demonstrated in mouse studies, and to try and relate 16 that to clinical observations. And I think as we'll 17 hear again more later, this is an ongoing project that 18 is supported by the CPTR program, the PCS working group 19 of that. 20 And so, I'm just showing you here in this 21 table an example where there are novel regimens that 22 are either in or planning to progress to Phase 3.</p>
<p style="text-align: right;">Page 79</p> <p>1 should be complacent that simply putting three or four 2 drugs together is -- of uncertain efficacy is going to 3 automatically result in restriction of drug-resistant 4 mutant selection. And I think there are key questions 5 for novel regimens related to how stringently they will 6 suppress the emergence of resistance. That really 7 ought to be explored in preclinical models. 8 So, I don't want to spend a lot of time, but I 9 think, again, to get back to this idea of what is the 10 evidence base and how can we demonstrate utility of the 11 models? And certainly, the best case for the mouse 12 model was made by the fact that there were -- it was 13 studies in the mouse model that really first 14 demonstrated the treatment-shortening potential of 15 rifampin and pyrazinamide, the only two drugs that we 16 recognize at this point to be clinically validated 17 treatment-shortening drugs. And on the flip side, 18 every other drug that has been in existence up until 19 the last decade or so does not have that treatment- 20 shortening potential in mouse models or in clinical 21 trials, as far as we know. 22 Now, in addition, there have been a number of</p>	<p style="text-align: right;">Page 81</p> <p>1 We'll have relapse endpoints and have been subjected to 2 this analysis where there have been at least two 3 relapse studies that have been examined. And so, one 4 looks, and when you really aggregate these data for the 5 REMox regimens, there is not a compelling case for a 6 two-month, an absolute two-month shortening effect of 7 the moxifloxacin in the mice. And in that sense these 8 data are not inconsistent with what was observed 9 clinically in these trials. 10 And, indeed, there are, as has been alluded 11 to, some emerging data with a BPAL regimen, which do 12 support this thus far. Very preliminarily, of course, 13 as a six-month regimen that is effective within a six- 14 month time frame. And so, relative to RHC, that's been 15 an effect comparable to what was seen in these mouse 16 studies. 17 So, the real game-changer in the mouse studies 18 has been the combinations that include bedaquiline and 19 pyrazinamide. And those comprise a component of 20 regimens that we don't really have -- won't have 21 relapse data for soon, but will, again, provide an 22 important test for the mouse model as we expand the</p>

<p style="text-align: right;">Page 82</p> <p>1 number of regimens for which we can reflect on, on the 2 relationship between treatment-shortening effects in 3 mice and treatment-shortening effects in patients. 4 One aspect, obviously, again, in these 5 preclinical models is the opportunity to deconstruct 6 regimens and to look at the contribution of component 7 drugs. I'm showing here as an example from the, again, 8 work we've done with the TB Alliance, looking at 9 bedaquiline, pretomanid, moxi and PZA as a four-drug 10 regimen here in blue. And then looking at each of the 11 three drug components and asking does every drug 12 contribute to the activity of this regimen? And so, 13 one can see here the four-month -- I'm sorry, the four- 14 drug regimen is here and it's actually overlapping in 15 CFU counts with the same combination but minus 16 moxifloxacin. So, in this particular experiment, 17 moxifloxacin really didn't contribute much in the way 18 of bactericidal effect. But when one looks at the 19 relapse rates, there was a significantly lower relapse 20 rate after 1.5 months of treatment with this regimen if 21 moxifloxacin was in the regimen. And in subsequent 22 experiments we've seen a small effect on CFU counts as</p>	<p style="text-align: right;">Page 84</p> <p>1 mice as the predominant lesion, it's a non-necrotizing 2 lesion in which the pink acid-fast bacilli are found 3 here inside of cells virtually uniformly. Inside of 4 cells where they are still pretty well linked to a 5 blood supply is only part of the story in the Kramnik 6 mice, in humans, and lots of other larger mammalian 7 species. 8 So, in these caseating granulomas, which are 9 really the hallmark of adult tuberculosis, one finds 10 not only these cellular populations around the rim of 11 these caseating lesions, but also extracellular 12 populations inside the caseum, whether it's a closed 13 lesion or an open lesion or cavitory lesion where the 14 caseum has largely been expectorated and there is just 15 a thin rim of caseum surrounding. And it's in these 16 environments where there is less impact of the host 17 immune response, the organisms are felt to be more 18 likely to be actively replicating. Organisms are also 19 extracellular as opposed to intracellular, and so this 20 may have a variety of effects on drug effect. And that 21 may pertain to differences in Mtb growth rate; that may 22 pertain to intracellular or extracellular residence and</p>
<p style="text-align: right;">Page 83</p> <p>1 well as reproduced this sterilizing effect. 2 And so, one can do these kinds of experiments 3 and ask not only does each drug contribute, so there is 4 evidence presented here that each drug does contribute 5 to that combination, although the contribution of 6 pretomanid is not shown here. That's been shown in a 7 different study. One can also gauge the level or the 8 extent to which that drug contributes and see which 9 drugs tend to anchor the activity of the regimen based 10 on the effect of removing that drug from the regimen. 11 Obviously, one can also look at the impact of 12 drugs on prevention or killing of spontaneously 13 resistant -- drug-resistant mutants that are present at 14 the beginning of treatment, and also look at different 15 durations of treatment for different components of the 16 drugs. And just allows a lot of flexibility that 17 really can't be done for very long periods in patients. 18 So, I've already alluded to one, I think, of 19 the key challenges in trying to translate data from 20 these traditional so-called sterilizing mouse models to 21 human trials, and that is the issue of the caseous 22 lesion. And here, as opposed to what is seen in BALB/c</p>	<p style="text-align: right;">Page 85</p> <p>1 drug distribution either into cells or into the caseum, 2 where the extracellular organisms are, as well as 3 different aspects of the lesion microenvironment. So, 4 the areas of these caseating lesions tend to be more 5 hypoxic. In the case of the Kramnik mouse are 6 relatively neutral in pH as opposed to the acidic 7 compartments inside the cells of activated macrophages. 8 And these may all have important effects on the readout 9 of drug efficacy in animal models. 10 And so, we've been -- we and others have been 11 pursuing studies to try and better understand how well 12 these Kramnik mice may contribute information to drug 13 and regimen development. And what stands out already 14 are several examples where drug activity is represented 15 differently in these Kramnik mice as opposed to BALB/c 16 mice. 17 And one case in point is pyrazinamide, a drug 18 that appears to have limited bactericidal effect within 19 mice, Kramnik mice that have large caseating lesions, 20 where again the caseum has been shown to have a 21 relatively neutral pH and is thought to be, then, 22 conducive to PZA activity, which requires more acidic</p>

<p style="text-align: right;">Page 86</p> <p>1 pH. And this is not to invalidate the model, because 2 we do know that PZA works on some subset of organisms 3 within these mice. Because PZA is capable of 4 shortening the treatment duration when it's added to a 5 first-line drug combination in this strain of mice. 6 And so, looking at monotherapy over four weeks in mice 7 with large caseous lesions is not the only way to look 8 at the contribution of a drug to a regimen. And so, 9 longer studies of drugs in combination may be necessary 10 to better reveal the drug's effect against the 11 important subpopulations within a heterogeneously- 12 involved lung. 13 So, clofazimine is another example of a drug 14 that as the monotherapy over four to eight weeks 15 doesn't show very pronounced bactericidal effect in 16 Kramnik mice, and very much in contrast to its efficacy 17 over the same time frame in BALB/c mice. And there may 18 be a number of issues here. The drug does not 19 distribute well into caseous lesions. It accumulates 20 to a great extent inside cells but doesn't distribute 21 well through caseum, and so that may be one reason that 22 it's being overly represented in terms of activity in</p>	<p style="text-align: right;">Page 88</p> <p>1 have to go into studying these. But if we want to ask, 2 is there an evidence base on which to support the use 3 of these models for regimen development, then that 4 evidence base at this point is modest. And this is an 5 admittedly somewhat cursory look at the literature, but 6 the amount of evidence that would support their use is 7 extremely limited. 8 Now, again, thinking about complementarity of 9 models, how well could we use PK/PD-based approaches to 10 understand the impact of caseous disease and think 11 about how to integrate that with BALB/c mouse models, 12 for example? There certainly are some very important 13 tools, I think, being generated by Veronique Dartois 14 and her group at Rutgers. I think many of you are 15 familiar with these techniques. This MALDI-MSI 16 technique, which provides semi-quantitative assessment 17 of drug concentrations that yield these heat maps. So, 18 these are maps rendered over TB lesions, caseating 19 lesions here, and the heat map, the red is a higher 20 drug concentration, the blue is a lower drug 21 concentration. And what's encircled here are the 22 caseous parts of the lesions. These studies are always</p>
<p style="text-align: right;">Page 87</p> <p>1 BALB/c mice and perhaps underrepresented in Kramnik 2 mice. But there are also issues with respect to a 3 neutral pH, which may affect clofazimine activity 4 adversely, and hypoxia, which may also to some extent 5 compromise the activity if clofazimine. 6 And bedaquiline may be in a similar can to the 7 extent that it also does not appear to, again, because 8 of physical chemical characteristics, to diffuse quite 9 as well through caseous lesions as some of the other 10 drugs that we use. Although the diminishment of its 11 activity seems to be less pronounced than that of 12 pyrazinamide or clofazimine. 13 So, this also, this argument about using 14 caseous disease models for drug development has been 15 certainly part of the rationale for looking at larger 16 animal models in the context of drug development. 17 Guinea pigs, rabbits, nonhuman primates all develop 18 these caseating lesions. And so, what I have here is 19 not meant to in any way disparage these models. I 20 think these models certainly could have substantial 21 utility. You know, one of the most prominent issues, 22 of course, is the cost and the amount of resources that</p>	<p style="text-align: right;">Page 89</p> <p>1 done with the neck section going for histopathology. 2 And so, one can really try to orient now drug exposure 3 with the lesion. And they are also paired with in 4 vitro macrophage uptake studies. And so, one sees with 5 this panel of drugs that were assessed here, very 6 pronounced differences in how they distribute through 7 lesions. Some that distribute -- the smaller 8 hydrophilic compounds tend to distribute very well 9 through the caseum, and as they do in the cells lining 10 the caseum, whereas, as you go down the list and 11 molecules become more lipophilic, they tend to 12 accumulate in the cellular regions around the lesions 13 but not to diffuse as well into the caseum. And so, 14 one could certainly imagine that these may have 15 important effects on drug exposure and efficacy in 16 these caseous lesions. 17 But these are semi-quantitative assessments, 18 and what would be much more valuable is to have real 19 quantitative assessments. And her group has now 20 published on an even more exciting tool, I think, that 21 couple's laser capture or microdissection and 22 dissecting out small portions in various places on this</p>

<p style="text-align: right;">Page 90</p> <p>1 lesion section and quantifying drug concentrations by 2 LC-MS. And so, one is now getting absolute 3 quantification from various sections of the TB lesions 4 that would allow a more precise and geographically 5 relevant estimation of drug exposures at the site of 6 infection.</p> <p>7 Now, there are a number of other issues that 8 come up in terms of translating preclinical data to 9 clinical data, not the least of which is interspecies 10 differences in drug PK. But, of course, many of these 11 studies are done in inbred mice with a single 12 laboratory TB strain, a single aerosol dose, and very 13 limited, if not single range of drug doses. And so, 14 when you think about the vast heterogeneity in human 15 populations and TB patients, how could we really expect 16 that any one of these experiments would map directly 17 onto patient treatment? So, how do we begin to account 18 for PK variability in patients over population? So, 19 very different levels of severity of disease, different 20 degrees of immune status, different degrees of 21 adherence to treatment, and then various distributions 22 of drug susceptibility among TB populations that are</p>	<p style="text-align: right;">Page 92</p> <p>1 case from a clinical trial study, 2929X, about the 2 impact of cavitory disease on the dose or exposure 3 response relationship defining rifapentine's efficacy 4 and incorporated that into the model. As well as study 5 data from Veronique's study showing that rifampin can 6 be retained and concentrated in caseum with repeated 7 dosing.</p> <p>8 And so, then we performed some clinical trial 9 simulations to look at sputum culture status to 10 estimate or predict sputum culture status at eight 11 weeks and relapse status after one year of treatment 12 for regimens that had gone on and been studied in the 13 clinic. And so, again, it's a very preliminary, sort 14 of first iteration of this type of model that is really 15 just based on the rifamycins and moxifloxacin, but 16 shown with -- you know, in the bars here are the 17 simulated 95% confidence intervals for the predicted 18 relapse-free, proportion of relapse-free patients. And 19 then in green are the point estimates from the clinical 20 trials.</p> <p>21 And so, this was the four-month regimen 22 replacing ethambutol with moxifloxacin, where we</p>
<p style="text-align: right;">Page 91</p> <p>1 bound out in the world.</p> <p>2 And so, for a number of these I really think 3 to really try and make the most confident or predictive 4 translation from preclinical to clinical systems, we 5 really need a quantitative PK/PD-based translational 6 mathematical model to help translate results. And 7 we've, in collaboration with Rada Savic and her team at 8 UCSF have started down this path to try and build a 9 model that relies on mouse PK and efficacy data perhaps 10 informed by early PK data from humans to try and make 11 predictions, develop models that can then simulate 12 clinical trials to better inform a regimen's potential 13 for treatment shortening. And so, this early iteration 14 of the model includes PK data and PD data in terms of 15 CFU counts from the mice. So, again dispensing with 16 relapse in this particular setup. Human PK data that 17 includes things like food effect that is known in the 18 case of rifapentine and rifamycin, moxifloxacin drug- 19 drug interaction. We derived an immune effect 20 parameter that was based on comparisons of 21 immunocompromised nude mice and BALB/c mice. And we 22 took some information that had been learned in this</p>	<p style="text-align: right;">Page 93</p> <p>1 somewhat underpredicted the activity of the regimen but 2 was still pretty close. And then again from the 3 RIFAQUIN study, the four-month arm that had a twice- 4 weekly rifapentine continuation phase regimen and a 5 six-month once weekly rifapentine/moxi-containing 6 regimen. And, again, some underestimation of the 7 activity of the regimens, but in both cases identified 8 the four-month regimens as potentially less effective 9 than the standard of care. Have also looked at the 10 PanACEA trial data with increasing rifamycin exposures.</p> <p>11 So, in our view, for first go, this model 12 performed quite well. This is now in press. We're 13 really trying to improve on this by incorporating 14 individual PK/PD relationships for all the drugs in the 15 regimen, as well as interrelationships. We have also 16 simulated Study 31 and some other upcoming studies, but 17 we are now I think in collaboration with the Alliance, 18 hoping to move into some of the more novel regimens 19 containing bedaquiline and pretomanid and to use a 20 similar approach. And our ultimate goal is to try and 21 merge this with some more mechanistic models that Rada 22 has been working on to try and develop a really more</p>

<p style="text-align: right;">Page 94</p> <p>1 unified modeling platform in which, again, mouse and 2 maybe early human PK data, as well as some patient 3 clinical characteristics could be built in to try and 4 better predict regimen efficacy. 5 I'm just going to skip over this in the 6 interest of time. So, I think with respect to these -- 7 the take-home points, the emphasis is that models that 8 we have available today, I think, have complementary 9 roles to play. The in vitro hollow fiber system, 10 although there is still work to be done, especially 11 with respect to evaluating drug regimens, I think has 12 real potential in the PK/PD space, in dose 13 optimization, and even potentially minimizing the 14 number of animals that need to be studied in 15 preclinical studies. 16 The mouse models do have an established track 17 record, admittedly, though, with a very limited number 18 of drugs and regimens, and there is really an important 19 opportunity here with the newer drugs that are being 20 studied in newer regimens. There are, I think, 21 important variables that may impact the way that models 22 like the BALB/c mouse model predict human trials. And</p> <p style="text-align: right;">Page 95</p> <p>1 I think this is, again, especially important for drugs 2 that may partition very differently into caseous 3 lesions, the clofazimines, bedaquilines of the world, 4 in particular. 5 And then just to emphasize this role, I think, 6 for a more integrated platform in which we can further 7 enhance our predictions using quantitative mathematical 8 models. So, with that I'll stop. I've got a lot of 9 people to thank, lots of collaborators and funders over 10 the years, and appreciate the opportunity. 11 DR. FARLEY: Thanks very much. We apologize 12 for the interruption earlier. We're going to take a 13 15-minute break at this point and remind you that this 14 could be an opportunity for you to order lunch at the 15 window. We are going to keep to time, meaning that 16 we're planning on having lunch at about 12:35, and 17 we're going to take the talks in the order of the 18 program. So, we'll start with Chuck right after the 19 break. So, if we could ask everybody to come back 20 right at 11:05. Thanks. 21 [Break] 22 DR. LOBUE: I'd like to introduce Chuck</p>	<p style="text-align: right;">Page 96</p> <p>1 Peloquin, who is the professor of pharmacy and medicine 2 at the University of Florida in Gainesville, where the 3 University of Florida Infectious Disease 4 Pharmacokinetics Laboratory is located. Dr. Peloquin 5 and his lab are part of the University of Florida 6 Emerging Pathogens Institute. His laboratory serves as 7 a national reference center for the determination of 8 serum concentrations for antimicrobial, antifungal, 9 anti-HIV drugs, as well as beta-lactams and linezolid. 10 Dr. Peloquin? 11 DR. PELOQUIN: Thank you for this opportunity 12 to speak, and if Dr. Nuermberger can cause a fire 13 alarm, who knows what I can cause. Is there a fault 14 line near the building? Just asking. Now, I don't 15 have any industry conflicts of interest to disclose. 16 My laboratory, as mentioned, does do some therapeutic 17 drug monitoring. The laboratory is not-for-profit and 18 the clinical laboratory does not pay my salary. 19 So, I'm going to spend a minute on this slide, 20 because I think it's essential and it speaks to 21 everything that will follow. And I'm rapidly 22 approaching 30 years as a tuberculosis clinician and a</p> <p style="text-align: right;">Page 97</p> <p>1 tuberculosis researcher, and I'm impressed in the 2 meetings that I've gone to and presented at that 3 clinicians generally do not think in these terms. They 4 generally don't think about what's happening to the 5 drug after it's swallowed. They're interested in 6 making a diagnosis and in giving the dose, right? But 7 if we stop and think about it, the drug has to be 8 absorbed from -- it dissolves in the stomach, it goes 9 through the intestines, into the liver, from there to 10 the right side of the heart, to the lungs, back to the 11 left side of the heart, and then throughout the entire 12 body. And then you have a gradient of distributions of 13 drug. Some of the drug reaches where the TB lesions 14 are, some of the drug from that portion gets to the 15 bugs. Some of that portion gets into the bugs, and in 16 a small fraction still actually binds to the target, 17 typically a protein inside of the organism, and causes 18 its effect. So, from the pharmacological standpoint, 19 giving the dose is really just the kickoff of the 20 football game and then things happen. All of what I 21 just described are the pharmacokinetics of the drug, so 22 if you don't have good PK, you don't get good</p>
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<p style="text-align: right;">Page 98</p> <p>1 pharmacodynamics, or PD.</p> <p>2 So, where are we now? I'll spend a few</p> <p>3 minutes talking about the RIPE -- rifampin, isoniazid,</p> <p>4 pyrazinamide and ethambutol regimen. So, a lot of</p> <p>5 clinicians think in terms of, well, I thought we just</p> <p>6 gave the dose. And the dose implies that every patient</p> <p>7 is the patient, in other words, they're clonal. And</p> <p>8 while in a mouse model they're inbred, typically humans</p> <p>9 are outbred, and therefore there is no average Joe.</p> <p>10 There is a wide variety that you're going to have to</p> <p>11 deal with, and all of the clinical trials clearly show</p> <p>12 a lot of inter-individual variability in the PK. So,</p> <p>13 why do we keep giving the dose? Well, it's tradition,</p> <p>14 right? Some of you are old enough to remember the</p> <p>15 Talking Heads and "same as it ever was."</p> <p>16 So, here's June's issue of Pharmacotherapy,</p> <p>17 and there is an article on Personalized Medicine in the</p> <p>18 Management of Diabetes. There is another article on</p> <p>19 Driving Towards Precision Medicine -- the other term</p> <p>20 for that -- in Leukemias: Are we there yet? As there</p> <p>21 is an expectation that we're somehow late and we should</p> <p>22 be further along. Meanwhile, we have standardized</p>	<p style="text-align: right;">Page 100</p> <p>1 to get approximately 40% less killing.</p> <p>2 So, if your patient happens to be this size</p> <p>3 compared to what was originally studied, you've given</p> <p>4 the full dose. But if your patients are my size,</p> <p>5 you're really giving a lot less drug than that. Or, if</p> <p>6 you like other pictures, if your patient looks like a</p> <p>7 Mini Cooper, you've probably filled them up; but if</p> <p>8 your patient looks like a Chevy Avalanche, you have not</p> <p>9 filled them up with enough drug to get the kinds of</p> <p>10 effects that were shown in those studies.</p> <p>11 But here is the number one reason why people</p> <p>12 don't like to change. They say TB treatment is only</p> <p>13 six months long and it's 95% effective. Now, this is</p> <p>14 TB dogma. If you look at a review article or a chapter</p> <p>15 in a book, you're going to see this, and it is true</p> <p>16 that the British Medical Research Council showed using</p> <p>17 per protocol analyses that you could get those kind of</p> <p>18 responses. However, if you look at those papers, the</p> <p>19 numbers vary from paper-to-paper, but on average about</p> <p>20 10% of the patients evaluated were not included into</p> <p>21 the study, and another 10%, approximately, dropped out</p> <p>22 during the study. So, they really analyzed about 80%</p>
<p style="text-align: right;">Page 99</p> <p>1 doses of the TB drugs. So, always remember that you</p> <p>2 are unique, just like everybody else.</p> <p>3 So, here's the regimen developed in the 1970s</p> <p>4 by the British Medical Research Council, and we have a</p> <p>5 fixed dose of rifampin at 600 mg, which Denny Mitchison</p> <p>6 called the minimally effective dose of rifampin. We</p> <p>7 have a fixed dose if isoniazid at 300, and they looked</p> <p>8 at these milligram-per-kilogram doses for pyrazinamide</p> <p>9 at 35 and ethambutol at 25 mg/kg. So, this is the</p> <p>10 regimen they gave us the idea that we have a six-month</p> <p>11 regimen that is 95% effective. But the way we actually</p> <p>12 do it today, if you have someone who is my size -- yes,</p> <p>13 I weigh 80 kilograms, but I don't consider myself a</p> <p>14 giant person. I'm fairly typical for an American male.</p> <p>15 So, we're actually giving me 60% of the drug exposure</p> <p>16 that was given in the clinical trial. And likewise,</p> <p>17 we're giving me 60% of the drug exposure for isoniazid</p> <p>18 in those clinical trials. And arbitrarily in the US</p> <p>19 we've dropped the dose of PZA down to 20 to 25 mg/kg,</p> <p>20 and ethambutol to 15 mg/kg. So, all of these drugs</p> <p>21 show concentration-dependent killing. More drug, more</p> <p>22 killing. If you cut their doses by 40%, you're going</p>	<p style="text-align: right;">Page 101</p> <p>1 of the original people that they were looking at, which</p> <p>2 is still really good. Most clinical trials today have</p> <p>3 lower capture rates. But you might expect 76% efficacy</p> <p>4 in your clinic at six months, if this map is correct,</p> <p>5 right? That's wrong.</p> <p>6 So, every year the CDC compiles the data from</p> <p>7 across the United States and they analyze it, and of</p> <p>8 course it takes a little while to do that. And then</p> <p>9 they publish a slide set every year, and I strongly</p> <p>10 recommend that you go their webpage and look at all the</p> <p>11 information that they have. And on approximately slide</p> <p>12 30, and this is from the 2015 slide set, it shows</p> <p>13 completion of treatment. Now, we don't have cure as an</p> <p>14 endpoint in the public domain; we have completion of</p> <p>15 the scheduled doses. And so, we have completion of</p> <p>16 treatment, and this is ending in year 2013, at one</p> <p>17 year. Now, back in '93, at one year it was only about</p> <p>18 64%, so there has been steady progress and it has kind</p> <p>19 of plateaued over here in the last five years. So, the</p> <p>20 natural question is, well, if this is at one year, what</p> <p>21 happened between six months and 12 months? And this is</p> <p>22 what happened.</p>

<p style="text-align: right;">Page 102</p> <p>1 At six months, 18% of the patients in the 2 United States in 2013 had completed treatment. At 3 seven months, which you might say is a more fair 4 measure, because patients might be diagnosed in the 5 hospital and have to transfer to public healthcare, so 6 it's 45%, 46% at seven months. And here is the 89.6 7 shown on the prior slide. And it does get to 95, but 8 it gets so at 19 months. Now, remember, the CDC is 9 compiling the data, all right? So, they're your 10 friends, they're making this data available. If you 11 don't like the results, send your cards and letters to 12 the individuals who treating TB. But, actually, nobody 13 is doing anything wrong, all right? This is the 14 reality of treating tuberculosis with the regimen that 15 we've reduced the area under the curve, if you will, by 16 40% across a population giving standardized doses. 17 This is what you're going to get. So, that's the TB 18 dogma. This is what Phil Hopewell had to say about 19 dogma: "There is a fine line between dogma and dog 20 manure." 21 So, for the current regimen, and this is my 22 point. It's not to criticize the current regimen or</p>	<p style="text-align: right;">Page 104</p> <p>1 at 100%-time above MIC, you can't really capture that, 2 and the trough concentration, or C minimum, does a 3 better job because it's a continuous variable. So, 4 once you know what it is you're trying to optimize, 5 then you can go about finding a dose and a frequency 6 that actually allows you to optimize it. 7 Now, the PD linked, or pharmacodynamically- 8 linked parameter, is conserved for each drug in 9 organism pair. So, what you discover in the hollow 10 fiber model is going to be true in the mouse model, in 11 the mechanic model, and in the human model of the 12 disease, because these are one-trick ponies, basically, 13 or maybe they have two tricks. But the drugs only have 14 so many things that they can do to a mycobacterium, and 15 once you determine how to optimize what they do to a 16 mycobacterium, that's what you focus on. 17 Now, I'll point up that the PD driver, because 18 TB has different phases of growth, at least as we 19 understand it, the driver for cell kill does not have 20 to be identical to the driver for suppression of 21 resistance. 22 So, what does this look like when you try to</p>
<p style="text-align: right;">Page 103</p> <p>1 what anybody is really doing with it, but what we 2 should do is just tell it like it is. And the current 3 regimen in the United States, RIPE, is about 90% 4 effective at 12 months, and it's only about 20% 5 effective at six months, and 46% effective at seven 6 months. That's what we can compare any new regimen to. 7 So, where are we going? And I've been asked a 8 similar number of questions as Eric was addressing, and 9 I'll bring those back and look at them from a slightly 10 different perspective, I hope. So, how do we bridge 11 preclinical data to clinical data? And what you really 12 want to do, as Eric was pointing out, is find the 13 pharmacodynamic index, or the pharmacodynamically 14 linked parameter. Typically, it's going to be the free 15 drug, that's what the "F" stands for -- free drug AUC, 16 or area under the curve, divided by the minimal 17 inhibitory concentration, or MIC. For most TB drugs, 18 this is the most closely linked parameter to efficacy. 19 Sometimes it's the peak concentration, sometimes it's 20 the trough concentration. An alternative is time above 21 MIC, but percent time above MIC caps at 100%. So, if 22 you have continuing improvement in efficacy and you're</p>	<p style="text-align: right;">Page 105</p> <p>1 look at it? So, these are data that we acquired in a 2 study with the CDC in an MDR-TB outbreak in Micronesia 3 and the Marshall Islands. And just sort of cutting to 4 the chase for this study, and you'll have the reference 5 for each of these so you can look them up later if you 6 wish. This was the parameter we chose to optimize, and 7 we chose to optimize this ratio at four possible values 8 based on the fact that there were no clear data for TB 9 and, depending on Gram-positive or Gram-negative 10 infections, different target values were proposed for 11 this ratio. We have the target attainment on the y- 12 axis and minimal inhibitory concentration on the x- 13 axis. And with the smallest dose, you have very poor 14 target attainment regardless of which of the targets 15 you're trying to hit. And as we go from 5 to 10 to 15 16 to 20 mg/kg, you see that if you're shooting for a low 17 target, the 40 target, and your MIC is low, with the 18 highest dose you have a very high probability of 19 hitting that target. But if your MIC is high and 20 you're not giving -- and you're aiming for this highest 21 target, you're probably not going to get it. 22 So, if it turns out that 125 is what you need</p>

<p style="text-align: right;">Page 106</p> <p>1 for TB, even 20 mg/kg for levofloxacin, if the MID is 2 1, levofloxacin is not going to be really good in that 3 situation. 4 So, how to fine-tune in patients. Well, no 5 matter how good your stethoscope is, you can put it on 6 the antecubital fossa but you cannot hear the drug 7 going by, and you certainly can't quantitate it. So, 8 if you want to know what's going on in your patient, 9 you're going to have to draw a couple of blood samples. 10 Now, for TB drugs it's basically the same as getting a 11 chem panel, it's just the red top tube. And currently 12 we can, and other labs, can measure all of the drugs 13 with about 5 mL of blood, or 2.5 mL of serum, right? 14 Do TB patients metabolize drugs differently? No, but 15 they're much more variable than you would see in 16 healthy volunteers. 17 Discuss PK variability and considerations 18 across populations. Well, there is no single predictor 19 of poor drug absorption, so, again, if you don't absorb 20 the drug, it's never going to get to the lesion and 21 it's not going to work. And there are different 22 studies that have shown different populations with</p>	<p style="text-align: right;">Page 108</p> <p>1 hour sample. So, this is not a PK analysis; this is 2 just a QA analysis, or quality assurance. But you can 3 see that it ranged from 0, which is clearly not 4 therapeutic, up to 45 mcg/mL with this pattern on the 5 histogram. And if we look at the distribution of the 6 doses, we had some pediatric patients, so that's why 7 some of the doses are very small. We have the 450-mg 8 dose that used to be recommended for people who were 9 under 45 kg. I personally would not recommend that. 10 The standard 600 mg dose, where most of the density of 11 the data are. But you'll see there is a real 12 distribution across the doses, and I'll point up the 13 guys who got 1800 mg, they didn't have very high 14 concentrations despite an 1800 mg dose. They were 15 profound malabsorbers of rifampin, and you will see 16 this in your population. 17 So, over time people have either been fans of 18 or enemies of therapeutic drug monitoring in TB, and 19 you can decide for yourself how you choose to look at 20 it. But the decision to do TDM is really the same as 21 the decision to get any other test, whether it's 22 complete blood count, CAT scan or MRI. None of these</p>
<p style="text-align: right;">Page 107</p> <p>1 malabsorption including the ones shown here, HIV/AIDS, 2 diabetes, acutely ill or cachectic patients, but from 3 study-to-study you see a lot of variability, and that's 4 just unfortunately the fact of the matter. There is no 5 one predictor for this. 6 Now, this is a study we did with David Perlman 7 in an AIDS clinical trial group in Study 309, and I'll 8 focus on rifampin, which is arguably the most important 9 drug. So, in the light blue, those are healthy 10 volunteers that were extensively sampled; in the dark 11 blue, those are TB patients who were extensively 12 sampled; in the purple, those are TB patients who only 13 had two blood draws at two and six hours. So, it was 14 pretty close to the pattern seen with the other two 15 groups. And in the yellow, those are the AIDS 16 patients. So, clearly, these patients have delayed 17 absorption, they have malabsorption, and the 600-mg 18 dose in this population, in this study, clearly was not 19 the optimal dose. 20 This is a snapshot of quality control data 21 from our clinical laboratory for 2016, and this is well 22 over 800 rifampin samples, and just looking at the two-</p>	<p style="text-align: right;">Page 109</p> <p>1 guarantees the outcome of treatment. If you want a 2 guarantee, buy a fridge. For three years, anything 3 goes wrong, you get a new fridge. But in the clinic, 4 there is nothing like that, and you have to deal with 5 the uncertainty, but all of these tests allow you to 6 make an informed decision, and in this case an informed 7 decision about dose for an individual patient. So, if 8 you want the long-play version, this was published in 9 Microbiology Spectrum in the end of 2016. 10 So, why use TDM? In the end, knowing is 11 better than guessing. So, I would propose it's best, 12 if possible, to get individual MIC data to know just 13 how susceptible a patient's bug is, individual PK, and 14 then you can optimize those parameters that I just 15 showed you. So, you want to use smart bombs and not 16 use dumb bombs, right? 17 How does PK change in TB patients over the 18 course of the months? Well, clearly, the rifamycin 19 have autoinduction, so their concentrations actually 20 get lower from the first dose out to the seventh or 21 fourteenth daily dose. Some patients take a full month 22 to come to full autoinduction, but most of it happens</p>

<p style="text-align: right;">Page 110</p> <p>1 in the first seven days or so.</p> <p>2 Isoniazid absorption can improve once the</p> <p>3 patient starts getting better. And so, we have</p> <p>4 patients who will have very, very low doses or rather</p> <p>5 concentrations of isoniazid, and we'll crank their dose</p> <p>6 from 300 to 600 mg daily. And then after about a</p> <p>7 month, if they're rechecked, they're in the normal</p> <p>8 range, and then after another month they might be at</p> <p>9 the upper end of the normal range and we can reduce the</p> <p>10 dose again. So, isoniazid is the one drug that clearly</p> <p>11 will show a rebound. For other drugs that depend on</p> <p>12 renal clearance, like ethambutol, levofloxacin and</p> <p>13 cycloserine, if you have a chance in your patient's</p> <p>14 renal function, you're going to have to change the</p> <p>15 dose.</p> <p>16 What about the epithelial lining fluid, or ELF</p> <p>17 data? So, I asked the Keebler elf, but the Keebler elf</p> <p>18 had no data on this, nor do I. You could argue that</p> <p>19 the drug has to get into this fluid before it gets into</p> <p>20 the lesion, but that's not absolutely proven for TB.</p> <p>21 So, we await further study on this. There are data,</p> <p>22 including the data that Veronique Dartois has produced,</p>	<p style="text-align: right;">Page 112</p> <p>1 mentioned. So, this is a study we participated in.</p> <p>2 This was the Tuberculosis Trials Consortium Study 22,</p> <p>3 which in in the continuation phase, after the first two</p> <p>4 months gave once-weekly INH and once-weekly</p> <p>5 rifapentine. And the patients who malabsorbed their</p> <p>6 isoniazid were essentially getting rifapentine</p> <p>7 monotherapy, and we selected for acquired drug</p> <p>8 resistance.</p> <p>9 Continuing in this school of hard knocks, this</p> <p>10 was thrice weekly rifabutin and isoniazid in the</p> <p>11 continuation phase. There was concern that we would</p> <p>12 overdose people on rifabutin because of drug-drug</p> <p>13 interactions with protease inhibitors. The problem is,</p> <p>14 in some cases we underdosed them, and there was no</p> <p>15 mechanism in the trial to adjust doses based on the</p> <p>16 concentration. So, all of these data are post hoc</p> <p>17 data. But the patients with the low exposures to</p> <p>18 rifabutin had failure, relapse, and acquired rifamycin</p> <p>19 resistance, which is essentially MDR-TB. And the odds</p> <p>20 ratio for the rifabutin AUC being the driver for that</p> <p>21 was 23, which may be in the odds ratio hall of fame.</p> <p>22 And why is that important? Well, Dr. LoBue</p>
<p style="text-align: right;">Page 111</p> <p>1 and Eric showed you that, about cavitory lesions.</p> <p>2 There is also another approach that we've taken. This</p> <p>3 is with Russell Kempker and the folks at Emory, and our</p> <p>4 colleagues in the Republic of Georgia, in Tbilisi,</p> <p>5 where we use microdialysis. So, this is a probe that</p> <p>6 actually measures the free drug concentration, and we</p> <p>7 put it in the center of a TB lesion that has just been</p> <p>8 removed from a patient who was going to surgery</p> <p>9 otherwise.</p> <p>10 And one example, this is levofloxacin. You</p> <p>11 can get a series of serum concentrations, including a</p> <p>12 concurrent concentration in the serum; you can get</p> <p>13 cavitory concentrations. And then from that you can</p> <p>14 get a ratio. So, in this particular case the median</p> <p>15 ratio shows that there is more drug in the lesion for</p> <p>16 levo, a free drug in the center of the cavity, than was</p> <p>17 found simultaneously in the serum. So, that's kind of</p> <p>18 good news. You could argue that this number might vary</p> <p>19 depending on when you sample after the dose.</p> <p>20 Are there PK-specific predictors of drug</p> <p>21 dosages from previous trials? Yes, including PK data</p> <p>22 that speaks to some of the issues that I just</p>	<p style="text-align: right;">Page 113</p> <p>1 was pointing up some of the costs of treatment, and</p> <p>2 this is a nice study from Suzanne Marks and the TB</p> <p>3 Epidemiology Studies Consortium looking at how much it</p> <p>4 costs. So, these are slightly older data than what</p> <p>5 Phil presented. At the time, it was about \$17,000, but</p> <p>6 if you, in the course of treatment, select for MDR-TB,</p> <p>7 not only have you eaten that \$17,000, but now you have</p> <p>8 to pony up an additional \$134,000, which is</p> <p>9 approximately 250 times the cost of therapeutic drug</p> <p>10 monitoring.</p> <p>11 This is a prospective study on high-dose</p> <p>12 rifampin by Martin Boeree and company with the PanACEA</p> <p>13 Consortium, and in this publication, they went up to 35</p> <p>14 mg/kg, but currently they are up to 50 mg/kg. So, in</p> <p>15 that study they are at 2,400 mg, but now they're up to</p> <p>16 basically 4,000 mg, a piperacillin-like dose of</p> <p>17 rifampin. And there are more than proportional</p> <p>18 concentrations. As you increase the dose of rifampin</p> <p>19 you get a larger than expected increase in Cmax and</p> <p>20 AUC. So, that's like a BOGO, you know, buy one, get</p> <p>21 one free. And what they showed is, like I've shown you</p> <p>22 in my clinical data, high interindividual variability.</p>

<p style="text-align: right;">Page 114</p> <p>1 So, even though the patient got the high dose, they 2 don't necessarily get a high exposure of drug. And the 3 patients who did get the greatest reduction in the 4 sputum colony counts had the highest exposures. 5 Same thing was seen in the study by Susan 6 Dorman and the TBTC with high-dose rifapentine. 7 Knowing the dose, whether it was 600, 900 or 1,200, did 8 not tell you how people were going to do. Knowing the 9 exposures, which were highly variable, did tell you how 10 people were going to do. So, again, it was the drug 11 exposure that was the driver of efficacy in the studies 12 that I just presented. 13 Now, TDM does allow you individualized therapy 14 and it allows you to optimize the PD variables that I 15 was talking about. The most popular argument against 16 it is that it's expensive. So, we just round off the 17 number of patients in the United States to 10,000, and 18 if you did two and six-hour concentrations for RIP and 19 E, that would set you back about \$560 per patient, for 20 a total of \$5.6 million. So, that's a lot of money. 21 But if you say it's a lot, you have to say compared to 22 what? So, I'll compare it to the University of Florida</p>	<p style="text-align: right;">Page 116</p> <p>1 the United States and in Vietnam. 2 DR. NAHID: That is a tough act to follow, 3 Chuck. Let me start by echoing Erica's thanks to the 4 FDA for organizing and hosting this workshop on 5 tuberculosis. It's a disease that is often ignored, 6 it's a disease of the poor, and that should not allow 7 it to have such little attention given to it. So, I 8 appreciate the FDA bringing this forward. 9 Several of the speakers this morning have 10 alluded to somewhat strongly the need for biomarkers to 11 move our decision-making forward around which regimens 12 and drugs to move forward in the pipeline. And I must 13 say I feel under a great deal of stress and pressure 14 with my talk. 15 Here, I just have a couple of disclosures that 16 I'm federally funded through the CDC contract, TB 17 Trials Consortium and some NIH funding. 18 So, the overview of my talk will be, first, I 19 just want to quickly review the current laboratory 20 methods for TB drug testing. Second, I want to speak 21 to you a bit about the challenge of culture-based 22 systems. I think this is important to reflect on,</p>
<p style="text-align: right;">Page 115</p> <p>1 athletic budget, which this year is \$128 million, and 2 the increase, just the increase, is \$6 million, right? 3 Our football team is going to cost \$25.5 million, but I 4 would argue that's less than the cost of the Alabama 5 team. I'm just saying, right? 6 So, there is nothing wrong with this; I enjoy 7 athletics. But as a nation we spend billions of 8 dollars on sports and entertainment. Wouldn't it be 9 nice to spend comparable or even a fraction of that 10 money on an airborne communicable disease? 11 So, I'd like to thank our top team of 12 researchers in my lab. As I get older, everybody in my 13 lab looks like this. So, do your assay and then clean 14 your room, right? I'd like to thank TJ, <p style="text-align: center;">Kyung Mee,</p> 15 Emily, Yas and Stacy, who are the employees of the lab, 16 and my students, Wael, Mohammad, Yang, Toni, Carlos and 17 Maggie. Thank you very much. 18 DR. FARLEY: Thanks, Chuck. I think we got 19 the message. We're going to turn our attention to TB 20 biomarkers and hear from Payam Nahid, who is a 21 professor at the University of California-San Francisco 22 School of Medicine, and focuses his TB research both in</p>	<p style="text-align: right;">Page 117</p> <p>1 because there is virtually no other infectious disease 2 entity that I'm aware of that has the complexities that 3 we face with sputum and in a way, we do with the 4 pathogen. I'm going to then talk to you a little bit 5 about the microbiology we've undertaken in Study 6 31, and then close with some novel biomarkers on the 7 horizon. I'll only be able to speak about a couple of 8 them, but I've listed a handful here that seem to be 9 emerging as interesting. So, let's just start first 10 with current laboratory methods and the importance of 11 microbiology in Phase 2 and Phase 3. Oops, this 12 is the wrong slide set. The one I just sent this 13 morning hasn't been replaced. 14 Well, while the correct slide set is found, I 15 don't want to use this one because I would be -- yeah, 16 that's the one; thank you. Perfect. Thanks very much. 17 So, these are the phases that you heard 18 presented by Cathy earlier in the morning. On the 19 bottom, you have the EBA studies, then Phase 2, and 20 then on the top Phase 3. The endpoints vary according 21 to these different phases, obviously. So, Phase 3 22 we're looking for disease-free survival at 12 months.</p>

<p style="text-align: right;">Page 118</p> <p>1 And, in fact, what we're really seeking for from our 2 biomarkers is some high sensitivity and specificity in 3 that follow-up period after treatment end to capture 4 people who are relapsing.</p> <p>5 In Phase 2, the classical endpoints that are 6 used include the culture negative status at eight weeks 7 on solid and liquid media separately, time to culture 8 conversion, and some information on speed of decline of 9 viable bacilli in liquid media is also being evaluated.</p> <p>10 In EBA it gets even more complicated. It's 11 logarithms of daily CFU counts per mL of sputum, 12 usually over a 14-day period. And I don't think people 13 quite appreciate the complexities of these assays. EBA 14 endpoint studies required tenfold dilutions, quadruple 15 cultures for each dilution. These are very burdensome 16 assays. But the one thing that they all have in common 17 is they all rely on culture. And in the Phase 3 18 setting we are really using it essentially as a 19 diagnostic, if you will, liquid or solid culture. 20 We're diagnosing patients as having relapsed during 21 their follow-up, and that then leads -- provides 22 isolates which we can use for genomic sequencing and</p>	<p style="text-align: right;">Page 120</p> <p>1 drug regimen, even if you extend it out to 28 days, you 2 do see some difference there from a regimen that 3 doesn't have rifamycins, but it's a modest difference, 4 and while -- I guess you could ask whether that really 5 does represent sterilizing or not.</p> <p>6 The other part that bothers me about EBA is 7 there are drugs that we know do have clinical efficacy. 8 We use them in clinics. The linezolid that is used in 9 the Nix-TB regimen that surely is contributing 10 significantly at 600 mg twice daily here is showing 11 modest to no EBA effect. So, EBA wouldn't have told us 12 whether linezolid should be moved forward or not. The 13 same is true for pyrazinamide in Amina Jindani's early 14 work, showing that pyrazinamide that we know is 15 critical for TB regimens, has poor EBA or minimal EBA.</p> <p>16 So, then we move to two-month culture, and I 17 think in the long view the two-month culture must be 18 our best way of assessing sterilizing capability. And 19 this is on an individual level prediction analysis. 20 This is a meta-analysis forest plot showing to you that 21 the sensitivity and specificity of culture status at 22 two months is unacceptable for individual level</p>
<p style="text-align: right;">Page 119</p> <p>1 determining whether or not a reinfection is occurring 2 or a relapse.</p> <p>3 The other Phase 2 endpoints, also liquid and 4 solid culture at various time points, and in the EBA 5 there is a very complex daily solid culture system that 6 enumerates CFU. All rely on culture.</p> <p>7 What can we say, then, about these culture- 8 based systems? And there are some uncertainties around 9 the prediction and surrogacy of these culture-based 10 systems, and I'll go over them. And there is also 11 technical and specimen-related issues.</p> <p>12 Number one, EBA. It's well known, I think, 13 and accepted that EBA is not predictive of the 14 sterilizing activity or long-term outcomes. So, here 15 is a cutout from a letter that Bob Wallace submitted to 16 Lancet that shows you on the left here several 17 groupings of drugs -- isoniazid alone, with a multi- 18 drug regimen, and you can see at 14 days the essential 19 EBA effect of a regimen that we know can treat TB for 20 six months, and one we know that can't is about the 21 same. So, there is no distinction there. And a 22 similar point is illustrated here, that with a multi-</p>	<p style="text-align: right;">Page 121</p> <p>1 prediction. Sensitivity is in the 50%, specificity is 2 modestly in the 80% range. So, on an individual level 3 prediction, it doesn't seem to perform well and 4 decisions based on it are hard to make.</p> <p>5 On a surrogate level, which I think is 6 something we really often have to remind ourselves as 7 biomarker researchers, there is a distinction between 8 prediction and surrogacy. This is work that Patrick 9 Phillips conducted using 37 treatment comparisons from 10 49 British Medical Research Council trials. And using 11 appropriate statistical techniques that involve trial 12 surrogacy comparisons, the month 1 culture, the month 2 13 culture, and the month 3 culture. And the 14 corresponding effect it has on log odds ratios of a 15 poor outcome. You can see these squares are really 16 dismal. So, R squares of the one-month culture of 17 0.36, 0.36 at two months, and modestly improved to 0.69 18 at three months. Yet we focused a lot of our intention 19 on the month 2-time point. And I think this 20 illustrates first the prediction versus surrogacy 21 distinction, but also that there is uncertainty about 22 what these time points are really telling us.</p>

<p style="text-align: right;">Page 122</p> <p>1 So, add to that the REMox trial, which you've 2 heard about earlier this morning, were found that the 3 two 4-month experimental regimens did not meet 4 noninferiority, yet in their own data culture 5 conversion was faster in the experimental regimens with 6 moxifloxacin substituted. So, within this setting we 7 also didn't -- whereas, we saw improved culture 8 conversion, that didn't translate to treatment 9 shortening at four months.</p> <p>10 I think another interesting thing about this 11 study in subsequent analyses that Patrick Phillips did 12 is that not -- in a nonsignificant proportion of 13 patients in REMox converted very quickly and yet still 14 relapsed. So, that was also challenging. I think that 15 leads to this issue of level of detection. So, we have 16 our solid media that has a certain level of detection; 17 we have our liquid media that maybe has slightly better 18 level of detection; but after some point we no longer 19 know what's going on. They are undetectable based on 20 our culture systems.</p> <p>21 Despite these significant, I think, issues, 22 there are some newer ways of modeling this -- the data</p>	<p style="text-align: right;">Page 124</p> <p>1 Powers, have pointed out there's a lot of places this 2 can go wrong. The intervention -- first of all, the 3 surrogate endpoint might not even be in the causal 4 pathway to the true clinical outcome. The intervention 5 that you use may affect the surrogate endpoint, but 6 there's other causal pathways where it doesn't have an 7 effect, and so on. It gets more complicated.</p> <p>8 But the point is that that classical 9 intervention impacts the surrogate, which then leads in 10 the causal pathway to the endpoint of interest isn't 11 the case, in my opinion, for culture.</p> <p>12 Let's move to the technical and specimen- 13 related issues. It's plausible that we actually are 14 working with the most informative surrogate marker 15 available to us already. But could our technical 16 methods be imperfect and need improving? There are 17 technical challenges with sputum as a sample time that, 18 as I would say, probably there is no other sample type 19 that I can think of other than stool, that would be as 20 complex. But we're dealing with Mtb in sputum, and in 21 stool studies they are often looking at other markers. 22 So, we really do face a big challenge technically here</p>
<p style="text-align: right;">Page 123</p> <p>1 that I've shown you and some more data that Bob Wallace 2 has conducted and his colleagues. And he'll probably 3 speak to this a bit more later today, wherein, you can 4 essentially look at both the duration of the regimen 5 and the culture conversion at two months and model some 6 ability to predict the likelihood of that regimen 7 succeeding. And I think what I would draw your 8 attention to here is that really where a regimen is 9 likely to reach an acceptable efficacy to meet 10 noninferiority is on the range of having essentially 11 99% culture conversion at eight weeks. And this is 12 where a four-month regimen in pink starts to get to 13 recurrence of proportions that are, I guess, somewhat 14 in the realm of acceptable. So, really, an almost near 15 100% conversion at eight weeks is what's needed.</p> <p>16 So, going back to the surrogate endpoint 17 issue, because this is obviously very important for 18 regulatory agencies and well known to you. This is the 19 classical definition to remind people that it has to -- 20 changes induced by therapy on the surrogate endpoint 21 are expected to reflect changes in the clinically 22 meaningful endpoint. And Dr. Fleming and others, Dr.</p>	<p style="text-align: right;">Page 125</p> <p>1 with sample type, the need for culture, the requirement 2 of training of laboratory staff and maintaining 3 proficiency. This is not a minor issue, especially 4 when one considers an international trials network that 5 has variability in the way they collect specimens, 6 transport specimens, process specimens. And there is 7 frankly a lack of standardization in these methods 8 across trial networks, trial sites internationally.</p> <p>9 TB trials also occur where TB is, which is in 10 resource-limited settings. And so, these are not 11 state-of-the-art labs, as you might think of in other 12 disease entities. Furthermore, drug TB trials are 13 sponsored by not-for-profit networks with limited 14 resources, and sometimes they are in settings in which 15 there are a limited number of laboratories with 16 expertise for culture. And in one case, in Kenya, 17 currently there is only one laboratory in the entire 18 country that is certified to do this kind of work for 19 trials activities.</p> <p>20 I'm going to give you a real-life example 21 here. Here is a comparison of what -- hypothetically 22 an identical specimen at baseline. Lab A has a one-</p>

<p style="text-align: right;">Page 126</p> <p>1 hour transport, 4 degrees' transport temperature. You 2 see it's decontamination proportion used here. And it 3 gives you a baseline TTP of seven days. Great, TB 4 diagnosed.</p> <p>5 Lab B, three days' transport time. It takes a 6 long while to get to that Kenya lab. It's got 21 7 degrees' exposure during transport. It has a different 8 decontamination for the sodium hydroxide used and 9 slightly different methods. It gives you a TTP of 12 10 days. Great, TB diagnosed. That's fine for diagnosis. 11 However, when you're looking at TB trials and you're 12 looking at time to positivity as a marker or biomarker 13 of interest, these details matter.</p> <p>14 So, this is the same specimen now looked at 15 eight weeks. At eight weeks, Lab A using these 16 techniques and methodologies gives you a TTP of 21 17 days. And then you can use this for modeling work, 18 PK/PD modeling work, and so on and so forth.</p> <p>19 This identical sample will be negative culture 20 because of these, if you will, aberrancies or 21 differences in methodology. So, this sort of 22 underscores why this is (a) it's a complex --</p>	<p style="text-align: right;">Page 128</p> <p>1 standard. We try to get two culture media to prevent 2 complete loss of a specimen due to contamination, 3 wherein -- like if your culture has no results, that 4 would be devastating. The whole patient contribution 5 will be essentially lost to some degree.</p> <p>6 We're using solid media -- the solid media 7 types vary by labs and, to be frank, I was asked to 8 address this. The solid media that is best for 9 clinical trials remains uncertain, and it probably is 10 still a scenario wherein a media type is best suited 11 for a particular lab. And then it is also important 12 that this contamination issue is worse during treatment 13 as the sputum quality itself reduces weeks into 14 therapy.</p> <p>15 So, this is some of the activities we've done 16 to address these issues, to try to mitigate them. Just 17 to remind people, Study 31/A5349 is a large, 2,500- 18 patient FDA registered trial comparison two 4-month 19 daily high dose rifapentine-based regimens to a 20 standard six-month regimen.</p> <p>21 In this study, we have pursued what we're 22 calling key elements. These are essentially attempts</p>
<p style="text-align: right;">Page 127</p> <p>1 technically, it's complex specimen type. These details 2 matter and they vary across sites worldwide.</p> <p>3 So, is it challenging to standardize? Yes. 4 However, and the however is in relation to what we're 5 at least trying to do in Study 31, so please bear with 6 me. But for one, the specimen is not sterile at 7 collection. It has contaminants that will affect 8 culture results. The specimen, unlike probably any 9 other specimen, with the exception of stool, has to be 10 manipulated, extensively processed, decontaminated, and 11 these are tedious methods. It takes 1.5 hours to 12 decontaminate a sputum specimen, and there are critical 13 steps that I just showed you in terms of 14 centrifugation, resuspension, and any lack of precision 15 will affect your recovery and cause variability in the 16 results. Further, we have to use harsh chemicals to 17 reduce the likely of contaminants, and these will also 18 destroy Mtb and reduce culture yield.</p> <p>19 So, with those, I guess, playing cards, we've 20 come up with some basic ways to come to a compromise. 21 We expect a rate of contamination for cultures, 2.2% to 22 5% for solid media; 5% to 10% for liquid media is</p>	<p style="text-align: right;">Page 129</p> <p>1 to harmonize across trial networks, the TBTC and the 2 AIDS Clinical Trials Group, 20 key steps in TB methods 3 focusing on those that are most likely to impact 4 endpoints and measures. This required a significant 5 within-lab validation at some sites prior to the 6 adoption of key elements. When you tell a lab, you've 7 got change your concentration of your sodium hydroxide, 8 their response is usually no, and we have to validate 9 it. So, this took quite a lot of effort, but it has 10 paid off, I believe.</p> <p>11 In addition, thanks to systems that have been 12 established with the data center at TBTC, we're doing 13 real-time monitoring for deviations from standard 14 methodology and reporting to assure quality data are 15 collected real time. Why does that matter? The trial 16 is 2,500 patients; it's going to take years to finish. 17 We don't want to find out in 18 months that there's 18 errors here or deviations from the methodologies 19 recommended. And really what we want to do is maintain 20 the QA continuously so that we can lock the database 21 within a few weeks or a couple of months of the trial 22 ending.</p>

<p style="text-align: right;">Page 130</p> <p>1 And we've also tried to collect the data in a 2 CDISC-compliant manner so they can be pooled and 3 transferability is possible with pooled analyses. 4 In terms of the cultures, we decided to use 5 both liquid and solid media for Study 31. We used -- 6 we are using MGIT 960, an automated system by all, 7 except one site that currently uses manual MGIT. The 8 use of MGIT and automated systems reduces variability, 9 it uses a standard commercial media, it automates the 10 time to detection. So, there's lots of advantages 11 there, and Debra will likely speak to this. 12 We could not prescribe a particular solid 13 type, as I told you. It's not clear that one media 14 fits all labs, and so we'll be able to compare this, 15 but so far, I was told that 75% of our specimens are 16 being cultured on LJ, 74% on 7H11S, and 1% on 7H10. 17 One of the things that I want to call out and 18 is essential for trials networks I think going forward 19 is that I was impressed by the TBTC and ACTG 20 leadership, for their strong support of this technical 21 training for laboratorians, as well as lab focused site 22 visits. And there is a lot you learn when you actually</p>	<p style="text-align: right;">Page 132</p> <p>1 on liquid media as a way to replace classical EBA 2 studies, which I told you have these very complex 3 systems, 10 dilutions quadruple cultures for each 4 dilution. 5 And this is work that is done by Andreas 6 Diacon and colleagues. There has been other work done 7 at other centers. But it essentially shows across 8 5,700 sputum samples from about 500 patients using sort 9 of a formula here, there is the ability to convert the 10 time to positivity to be at least highly correlated 11 with the CFU, and this obviously has a spread to it. 12 But this line would be a -- this solid line would be a 13 perfect association or correlation, and it shows some 14 promise there but needs further development. 15 I want to tell you about a new project that is 16 embedded into Study 31 that is called Sputum 17 Transcriptomic Expression Profiling. This is Study 31A 18 of the clinical trial I just presented. And why I find 19 this particular project exciting is that it's really, 20 to my knowledge, for the first time really looking to 21 alternatives to enumeration. Everything I've told you 22 about has been about enumeration -- enumeration of</p>
<p style="text-align: right;">Page 131</p> <p>1 go in the lab and process samples with these 2 technicians. And the labs have been welcoming. That 3 would be the other part of the story is that they have 4 not felt it as a threat but as a partnership and 5 collaborative approach that has been wonderful. 6 This is the 20 key elements, just a snapshot, 7 to show you there is everything from the transport -- 8 sputum collection and transport features in terms of 9 the temperature, the processing of the sodium hydroxide 10 concentrations, and so on and so forth. But this has 11 been essentially presented; sites have been trained. 12 Before a site can open they must prove they can do all 13 20 key elements and sign off on them, and that has 14 caused delays for several of our sites from opening 15 because their labs are still in the process of 16 validation. So, this is an example of how we can try 17 to harmonize and standardize and address those 18 differences. 19 Lastly, I'm going to close with what I hope to 20 be some positive and encouraging biomarker 21 opportunities. One of the areas that I think is 22 exciting is the potential to look at time to positivity</p>	<p style="text-align: right;">Page 133</p> <p>1 cycle thresholds, enumeration of CFU, the time to 2 conversion. This is really looking at the Mtb 3 physiologic state, because we know the physiologic 4 state, as has been presented by Eric and others, is 5 dynamic. We know that it is adapted to immunity and 6 tissue microenvironments, and we know that this affects 7 drug effectiveness. And we also know that it differs 8 in vitro and in humans. We heard about various in 9 vitro systems and whether or not these in vitro systems 10 recapitulate what happens in humans has quite a lot of 11 uncertainty to it. 12 So, this study is in humans, and what we're 13 using is a nested qRT-PCR assay of 2,400 Mtb mRNA 14 transcripts that covers about 60% of the genome. So, 15 it was developed by Gary Schoolnik and Greg Dolganov at 16 Stanford. And it essentially gives us the 17 transcriptome of TB. This is not host transcriptomics; 18 this is bacterial transcriptomics. Because mRNA half- 19 life is minutes long, we think this gives us a 20 biological snapshot of the Mtb population in sputum, 21 the physiologic state. And what's been found is really 22 fascinating.</p>

<p style="text-align: right;">Page 134</p> <p>1 First, there is the usual enumeration findings 2 that I'm showing you here. DNA is slow to decline but 3 it does decline over 60 days of treatment, but RNA has 4 a very rapid drop. What was very exciting and 5 interesting to see was that you can detect Mtb mRNA in 6 100% of patients at day 56, even those that are 7 culture-negative. We achieved culture negativity in 8 maybe 80% of patients. We can still detect 9 mycobacterial mRNA, and that suggested there is viable 10 mycobacteria present at that time point, even though 11 we're not culturing it.</p> <p>12 In regard to the actual physiology, this is 13 also interesting. So, first of all, I acknowledge that 14 there is massive alteration of the Mtb transcriptome 15 within days of receiving anti-TB-type therapy, and at 16 least 20% of the genes are differentially expressed 17 each day. When you categorize these in sort of -- 18 classify them into groupings, you can see that there 19 are reductions in massive down-regulation. So, this is 20 day 2, day 4 of treatment, day 7, day 14. In relation 21 to baseline there is massive down-regulation of 22 metabolism pathways, Mtb. So, it is adapting in</p>	<p style="text-align: right;">Page 136</p> <p>1 biobank accelerating development of new TB cures by 2 validating biomarkers of response for TB drug 3 treatments. The goal is to have about 1,000 patients 4 with longitudinally collected samples. There are seven 5 scheduled time points which samples are collected, a 6 whole array of samples collected. This work, this bank 7 would not be in existence were it not first for FDA to 8 recognize its need and fund it as a first federal 9 source of funding.</p> <p>10 But you can see it's a partnership now with 11 NIAID, Bill & Melinda Gates Foundation, and the 12 patients are being enrolled at TB Alliance sites, ACTG 13 sites and TBTC sites. And we've had several founts of 14 application proposals and have had 11 submissions. And 15 please distribute this information to as many people as 16 possible, because it's a good resource for people 17 exploring TB biomarkers of treatment effect.</p> <p>18 So, in summary, all phases of TB drug 19 development rely on culture. Sensitivity appears to be 20 somewhat of a priority in Phase 3, but, really, 21 accuracy and precision in enumeration are paramount for 22 EBA in Phase 2. There are uncertainties still about</p>
<p style="text-align: right;">Page 135</p> <p>1 treatment, shutting systems down, and dealing with the 2 physiologic stresses of the drugs in the immune system.</p> <p>3 So, there is reduced energy metabolism; there 4 is educed protein translation; there is reduced DNA 5 synthesis; there is reduced lipid synthesis. These are 6 all down-regulation pathways. Reduced expression of 7 ESAT-6 genes. And then there's transcriptional 8 regulation that seems to be increased oxidative stress 9 response, increased translational regulators, increased 10 transcriptional initiation factors, and increased 11 stress signature. There's even findings that I think 12 could potentially hold promise for finding new targets, 13 drug targets. These are two efflux pumps that show up- 14 regulation, significant up-regulation on treatment. 15 And these are two efflux pumps that are involved with 16 isoniazid and rifampin. So, if we could target which 17 of these efflux pumps are being turned on in response 18 to drug therapy, we would be able to potentially find 19 new targets for action.</p> <p>20 In closing, I wanted to tell you about a 21 terrific resource. It is the Consortium for TB 22 Biomarkers Biorepository CTB2. It's a collaborative</p>	<p style="text-align: right;">Page 137</p> <p>1 the prediction and surrogacy of these culture-based 2 systems, because, frankly, mechanisms of relapse exist 3 that are not fully captured by the culture-based 4 intermediate markers because there are non-culturable 5 bacilli present as the mRNA data showed you.</p> <p>6 Standardization of methods is feasible 7 Standardization of methods is feasible and essential. 8 I didn't write it in this slide, but I would say it's 9 not done enough and requires more attention. These 10 standards will assuredly reduce noise, increase 11 precision, accuracy and sensitivity, classical things 12 in research -- in the conduct of rigorous research. 13 And I think more investment should be put into the 14 standardization methods in the labs. And support for 15 the labs, frankly. A lot of the labs are public labs 16 that are contributing to trial network data. 17 Harmonization across networks and sites is also 18 essential. This will allow us to do multi-site, multi- 19 trial pooled analyses.</p> <p>20 And then biomarkers that move the field beyond 21 the simple enumeration, at least in my mind -- and 22 imaging is another one, by the way, that was mentioned</p>

<p style="text-align: right;">Page 138</p> <p>1 earlier -- holds some promise. I think the work that I 2 showed you provide insights into the physiologic 3 adaptations of TB in response to drugs, and they may 4 vary by the drugs used, so this could be a potential 5 EBA alternative in accessing new therapies. And then 6 potentially we could identify the mechanisms of 7 persistence that are indeed in the causal pathway to 8 relapse, how TB is modifying its physiology to survive.</p> <p>9 I just want to acknowledge the protocol team 10 for Study 31. The data center at TBTC has been 11 immensely helpful and supporting embedding biomarker 12 studies in this trial. I want to call out Anne 13 Purfield, who helped with feedback and input into this 14 talk, as well as Andy Vernon. And this is the Express 15 31 transcriptional profiling collective. Thank you.</p> <p>16 DR. LOBUE: Thank you, Payam. Next speaker, 17 moving on to diagnostics, is Marco Schito, who is 18 scientific director of the Critical Path to TB Drug 19 Regimens. He leads several work groups to facilitate 20 the development of novel TB drug diagnostics for wide 21 collaboration between basic science approaches to 22 better understand mechanisms of resistance, molecular</p>	<p style="text-align: right;">Page 140</p> <p>1 the right, you can see over the past 10 years there 2 have been a number of advances in those diagnostic 3 tools that have been made. And even if you go further 4 to the right, some additional ones, including the PET- 5 CT scan that others have talked about as well.</p> <p>6 But, really, TB, I'm not going to go into the 7 background to it, but I would like to mention that it 8 is a spectrum of diseases. It's not just you have TB 9 or you don't have TB; it is a wide spectrum of disease. 10 And the problem is that most of the diagnostic tests, 11 at least the TST/IGRA, as you can see on the bottom of 12 this, really span a wide variety and range of that 13 spectrum. Whereas, the smear, microscopy, the culture 14 and the molecular assays are really more towards the 15 right-hand side, where it is looking more at active 16 disease. So, to be able to identify what distinguishes 17 individuals to move into these various different 18 categories is really unknown, and we really don't 19 understand why individuals progress to those various 20 areas, whereas, those can remain latent for oftentimes 21 decades.</p> <p>22 And I'm not going to talk too much about the</p>
<p style="text-align: right;">Page 139</p> <p>1 surveillance, drug resistance database efforts, and in 2 vitro diagnostic assay developers. And prior to 3 joining Critical Path Institute, he spent nine years in 4 TB as HIV clinical research branch at Division of AIDS 5 at NIH.</p> <p>6 DR. SCHITO: Thank you very much. I would 7 also like to echo some of the comments with regards to 8 having the FDA produce this and have this type of 9 meeting, especially for TB. And also for including TB 10 diagnostics. Oftentimes that's left out. I'm going to 11 provide a little bit of an overview, and it really is 12 quite a big overview as opposed to going into a lot of 13 details, especially for the culture and the molecular 14 tools that are currently available. But I will be 15 spending a little bit more time on sequencing-based 16 assays, as well as those applications for clinical 17 trials.</p> <p>18 And just to begin, there have been a large 19 number of classical ways in which diagnostics have been 20 done not only in the US but, more importantly, outside 21 in high burden countries, and those are represented on 22 the left-hand side of the slide. And as you move to</p>	<p style="text-align: right;">Page 141</p> <p>1 gold standard, because other have already talked about 2 this, and talking about the sample type primarily being 3 sputum. But there are obviously some pathogens, 4 specific challenges about TB growing slowly, 5 contamination issues, laboratory delays. And that's 6 just enabled to actually be able to identify TB, 7 getting TB in culture.</p> <p>8 But then there are phenotypic DST delays after 9 that, which requires additional time for first-line, 10 second-line, and obviously limited capacity in 11 countries that have that capacity to do those.</p> <p>12 And then there are some established 13 challenges, obviously. There have been huge 14 investments that have been made in the past decade. A 15 lot of technical capacity has been gone on, 16 infrastructure, a lot of the quality issues that Payam 17 and others have talked about, contamination rates as 18 well. But there are emerging challenges as well. The 19 maintenance of equipment in labs; the infrastructure to 20 get samples to those labs; the capacity of those labs; 21 appropriate infection control measures; and programs 22 for staff screening. And then there are additional new</p>

<p style="text-align: right;">Page 142</p> <p>1 costs more recently on legislation and international 2 transfer. And all of this really culminates in the 3 need for rapid and affordable point-of-care diagnostic 4 tests. And over the past seven or eight years that's 5 really been something that has been driven primarily as 6 a result of the Xpert MTB/RIF assay that was WHO- 7 endorsed back in 2010. And since then there really has 8 been almost an explosion of different types of genomic 9 tests that can be done at point-of-care. And this has 10 gone throughout the different healthcare systems, going 11 all the way up to the reference labs, where you have 12 large companies, like Becton Dickinson, Abbott, as well 13 as Roche, providing these types of diagnostic tests and 14 reference labs, all the way down even to the microscopy 15 center.</p> <p>16 And then there are also other technologies 17 other than molecular types of technologies that are in 18 development including phage-based breath detection, 19 which nobody has mentioned yet; biomarkers again come 20 up as well. But even though you have commercially 21 available diagnostics at the bottom at 2012, 2013 and 22 2014, many of those actually don't get WHO-endorsed</p>	<p style="text-align: right;">Page 144</p> <p>1 countries? And here is a trial that was recently 2 published out of the ieDEA program. This is an NIH- 3 funded epidemiology cohort looking at HIV/TB-infected 4 individuals. And just to note that although HIV 5 individuals should be tested with TB, only about three- 6 quarters of this in a programmatic setting that is well 7 funded were actually tested with TB. And out of those, 8 it was only 80% -- actually, 80% were tested for AFB 9 smear microscopy, and shockingly only 5% actually were 10 tested with GeneXpert, even though the majority of the 11 sites had access to the test.</p> <p>12 This isn't just a one-off type of observation; 13 there is also a number of work that's in press now from 14 Madhukar Pai's group, and the purpose of this slide 15 here on the right is that he's looking at the number of 16 smears that were done in country versus the number of 17 Xpert cartridges that were procured in that country for 18 that year. And this just gives you a very rough, crude 19 estimation on how much GeneXpert was actually done 20 within countries, and the countries are listed on the 21 left-hand side, although you can't see them. What's 22 important to see is that in the bar graph on the very</p>
<p style="text-align: right;">Page 143</p> <p>1 until much later. Just the process in that is very 2 extensive. And then there are others, like Alere q, 3 that have dropped out of the market as well. So, there 4 are challenges there.</p> <p>5 But looking at probe-based GeneXpert assay, it 6 was FDA cleared in 2013. So, a few years later FDA was 7 able to get that cleared. It provides results in 8 sputum, as you know, in two hours. It identifies TB 9 and determines resistance to rifampin. But more 10 recently the ultra-cartridge has just been released. 11 It is as sensitive as culture but there is a downside 12 to this and it has a slightly lower specificity, and I 13 can talk specifically about that a little later. There 14 is a new Omni form factor that will probably be coming 15 out next year for point-of-care applications, and 16 that's what it looks like. So, you can use a cell 17 phone to operate that. And the year after they're 18 hoping a new XDR cartridge will expand the drug menu, 19 so that you can start looking at fluoroquinolone as 20 well as aminoglycoside resistance.</p> <p>21 But the question that came to me early on is 22 how well are these tools actually being utilized in</p>	<p style="text-align: right;">Page 145</p> <p>1 right-hand side, closer to the left, the lower the 2 ratio the more Xpert that is being used. And the only 3 country that really is replacing smear microscopy with 4 Xpert is South Africa. Almost all the other countries 5 are using this as a research type of tool.</p> <p>6 And why is that? That's a good question. I 7 think a lot of it has to do with cost; a lot of it has 8 to do with political will. But there are also other 9 concerns, such as discordance and concordance assays 10 between these various different ones. This is a paper 11 that was published a few years ago, but it does provide 12 an example of how discordant some of these different 13 assays, whether they be liquid culture, solid culture, 14 GeneXpert, other molecular-based tests, or even some 15 laboratory assays.</p> <p>16 So, why the discrepancies? Well, there are 17 some phenotypic issues known for some drugs, especially 18 for ethambutol and pyrazinamide. There are unknown 19 rare or unique single nucleotide polymorphisms, or 20 mutations, that can be picked up in one assay but not 21 in the other. The critical concentrations are often 22 poorly characterized, and we really don't have a good</p>

<p style="text-align: right;">Page 146</p> <p>1 idea of the epidemiological cutoffs for MIC detection 2 as well. And there is low-level mixed population in 3 many of these circumstances which result in 4 heteroresistance, and I'll get back to heteroresistance 5 in a little while. But first I want to talk a little 6 bit about next-generation sequencing, which is where I 7 want to spend most of my time, because this really is 8 an all-in-one type of tool. We can identify TB, drug 9 resistance, virulence determinants, and because of the 10 way TB is transmitted in a population, it is oftentimes 11 clonal. So, it's really important from an 12 epidemiological standpoint to understand the 13 genotyping, evolution, population structure as well as 14 the phylogenetics. And all of this can be done with 15 next-generation sequencing. 16 And when we talk about next-generation 17 sequencing, oftentimes we're talking about whole genome 18 sequencing. It's one of the most comprehensive ways in 19 which NGS, or next-generation sequencing can be done. 20 However, it is culture-dependent. As a result of that, 21 it's slow, still fairly expensive, because you're using 22 both culture and molecular at the same time. And</p>	<p style="text-align: right;">Page 148</p> <p>1 differentiating ourselves from other databases that are 2 already out there. So, we have predefined a number of 3 different criteria where we take a look at a very basic 4 statistical approach to the data, looking at p-values, 5 likelihood ratios, looking at homoplasy as a next step 6 to determine lineage markers, ensuring those are not 7 included in this analysis. 8 And then there's a number of expert rules, 9 where we take a look at each individual mutation and 10 determine whether that mutation is associated with 11 increase in the minimum inhibitory concentrations, 12 whether that's also associated with an adverse clinical 13 outcome, and then go back and look at some functional 14 genetics to confirm that those observations are also 15 true. 16 So, sequencing has been done in clinical 17 trials. This has been shown by a number of different 18 speakers. Looking at transmission of multidrug 19 resistance, looking at relapse versus reinfection, drug 20 resistance. But I do want to spend a little bit of 21 time on heteroresistance. And, again, 22 heteroresistance, really what this means is a presence</p>
<p style="text-align: right;">Page 147</p> <p>1 because it is so comprehensive, it's a huge amount of 2 bioinformatics that need to go in with that. 3 More recently a lot of people have been 4 turning to targeted amplicon sequencing primarily 5 because you can sequence the sample directly, so you 6 don't have to rely on culture and, as a result, 7 simpler, it's a lot faster. You can actually do much 8 deeper sequencing and you can do several hundred 9 different loci at the same time. The weakness, of 10 course, it's not as comprehensive and you have to have 11 prior knowledge of the targets that you're going to be 12 looking at. And, finally, you do need some additional 13 optimization. It's not a really well characterized 14 assay as of yet. 15 So, as a result we need for a comprehensive, 16 standardized database to provide a priori information 17 regarding these drug-resistant loci and mutations that 18 are associated with drug resistance, and that's really 19 the remit of ReSeqTB. And it's not just finding out 20 what these mutations are, but it's the interpretation 21 of these mutations that is really holding a lot of the 22 field back. And this is where we think that we're</p>	<p style="text-align: right;">Page 149</p> <p>1 of a small number of organisms that are resistant to an 2 antimicrobial drug within a population that is 3 susceptible to that drug. And this actually may 4 explain why we're seeing some failure to eradicate an 5 infection in some patients that seem to be actually 6 treated with appropriate antibiotic drugs. And the 7 reason for this may be that the sensitivity of 8 detecting heteroresistance is different for the 9 different assays. 10 So, Sanger sequencing, line probe assays, it's 11 around 30% to 50%. Whole genome sequencing can go a 12 little bit lower, 5% to 10%. Culture, which is our 13 standard, standard methodology, typically 1%, but often 14 -- actually, it can go down as low as 1%, but typically 15 3% to 5%. And targeted sequencing actually can get 16 much lower than that at 0.01%. 17 Targeted amplicon sequencing, and the one that 18 I'm going to be mentioning is a single molecule 19 overlapping read or the SMOR assay, can reduce 20 sequencing error rate and that's how they're able to 21 get down to that low amount. And this also has the 22 potential to identify populations of resistant bacteria</p>

<p style="text-align: right;">Page 150</p> <p>1 with sensitivity that exceeds the current gold 2 standard, and that's almost a problem when we're 3 looking at clinical trials. So, is that a false 4 positive? And so, the only way to really take a look 5 at this is to take a look at serial samples of an 6 individual that is under treatment, and this is a 7 published -- a study that's recently been published by 8 John Metcalfe and Rob Warren. This is a patient out of 9 Moldova who is MDR-positive. And what they've done is 10 tested, taken some samples throughout a period of about 11 four years. They have tested amikacin DST both 12 phenotypically and genotypically, and then did their 13 SMOR assay. And the bottom line to this is that you 14 can actually detect very small numbers on the first 15 2011 time point in the SMOR assay, that it's less than 16 1%, but it's susceptible for the DST assays. And then 17 obviously, it becomes positive once those numbers 18 increase above 10%.</p> <p>19 So, I really concentrated mainly on the 20 pathogen side of the equation, but there is the host 21 side as well, and so can NGS be used to assist host 22 pharmacogenomics? And the answer is yes, it can.</p>	<p style="text-align: right;">Page 152</p> <p>1 So, in conclusion, culture remains a 2 challenge. I think it's still a very important tool to 3 keep in mind that is within our armament, but we need 4 to start optimizing other tools that are much faster 5 and quicker to get that type of information to patients 6 much better. And we need to be able to optimize those 7 tools. From a clinical trial perspective, sequencing 8 assays, I think, are a couple of things that we can do. 9 One for the pathogen side is resistance prediction, and 10 one from the host side is predicting adverse events.</p> <p>11 There are a number of biomarker assay tools 12 that are still in development. I'm not going to go 13 through these in the interest of time, but I will 14 mention that the treatment-monitoring assay, the 15 prediction of cure versus relapse, and the biomarker 16 LAM tool is something that my colleague, Debra Hanna, 17 will present next.</p> <p>18 I'd just like to acknowledge members of -- my 19 colleagues at Critical Path Institute, as well as our 20 partners, and they're listed on this slide. Thank you 21 very much.</p> <p>22 DR. FARLEY: Thanks very much. We're going to</p>
<p style="text-align: right;">Page 151</p> <p>1 There's a number of genetic variations for specific 2 targeted human genes that can be associated with drug- 3 induced liver injury or with, on the other hand, on the 4 right-hand side, greater drug exposure. And the result 5 of this, if you can start doing a systematic review and 6 start taking a look at what's available in the 7 literature, and this is by no means comprehensive, but 8 you can start seeing that there are a number of genes 9 that are associated with having a number of different 10 SNPs. And those SNP frequencies oftentimes population- 11 dependent, but they do have an effect on adverse 12 reactions.</p> <p>13 So, if you increase levels of the drug, 14 obviously, you approach maximum tolerated dose, 15 accumulation of toxic metabolites and adverse events. 16 So, you can probably predict some of those. If the 17 levels decrease, however, you could reduce treatment 18 efficacy, incomplete eradication of bacteria, prolonged 19 treatment, and potentially relapse. Alternatively, you 20 can actually increase the chance of developing drug 21 resistance. So, this may be some mechanisms that could 22 be more characterized better in clinical trials.</p>	<p style="text-align: right;">Page 153</p> <p>1 hear next from Debra Hanna, who is the executive 2 director of the Critical Path to TB Drug Regimens 3 initiative led by the Critical Path Institute and 4 funded by the Gates Foundation.</p> <p>5 DR. HANNA: Wonderful. So, thank you to FDA 6 for the opportunity to speak today on the role of the 7 Critical Path to TB Drug Regimen initiative in 8 facilitating drug development for TB. I was asked to 9 make up a little bit of our time today and fortunately 10 that is very doable, because you've heard from many of 11 our critical experts and partners who contribute to the 12 CPTR program, Eric, Payam, and others today. So, if I 13 skip over a few slides, I'm happy to answer any 14 questions you might have during the discussion session 15 about those particular projects.</p> <p>16 So, for those of you who aren't familiar with 17 the CPTR initiative, we are a public private 18 partnership that was launched about seven years ago, 19 now with the focus of the remit to accelerate the 20 development of entirely novel regimens for TB. So, 21 specifically we're interested in helping our partners 22 move forward the combination of multiple new agents</p>

<p style="text-align: right;">Page 154</p> <p>1 that haven't been individually approved.</p> <p>2 The areas of focus, primarily focus for CPTR</p> <p>3 really are around the advancement of new drug</p> <p>4 development tools, which include biomarkers. I'm going</p> <p>5 to talk about one exciting program today. And the way</p> <p>6 that we do this is really taking an evidence-based</p> <p>7 approach so that we're ensuring that we're applying the</p> <p>8 most robust scientific framework around evaluation of</p> <p>9 these model systems.</p> <p>10 We're really at an important part in our</p> <p>11 lifecycle as a CPTR program, so we're in the midst of</p> <p>12 evaluating the work we've done over the past six years</p> <p>13 and applying for a new award with the Gates Foundation.</p> <p>14 And through those discussions and through discussions</p> <p>15 with our partners we've really decided that we're going</p> <p>16 to hone in and refine our work specifically on</p> <p>17 advancement of these preclinical methods, drug</p> <p>18 development tools, which also include modeling and</p> <p>19 simulation components. A big part of the theme of my</p> <p>20 talk today will be the importance of collecting,</p> <p>21 curating, aggregating data across multiple different</p> <p>22 sectors and contributors within our program. I'll talk</p>	<p style="text-align: right;">Page 156</p> <p>1 important for advancing our projects.</p> <p>2 So, I talk a lot about the evidence-based</p> <p>3 evaluation of methodologies. And the reason that we</p> <p>4 use that terminology is that in the CPTR program, and</p> <p>5 really in this community here in the room, we're very</p> <p>6 focused on how you apply these different methodologies</p> <p>7 for making drug development decisions. There's a lot</p> <p>8 of important and wonderful work that are done in these</p> <p>9 model systems to drive future research and scientific</p> <p>10 hypothesis, but we care specifically about applying the</p> <p>11 rigor to give developers confidence that they can use</p> <p>12 these data to make robust decisions about derisking</p> <p>13 compounds.</p> <p>14 So, this is just a quick slide to tell you</p> <p>15 about the framework that we use, which is called the</p> <p>16 Qualification Pathway. Both FDA and EMA have a</p> <p>17 strategy for the qualification of novel drug</p> <p>18 development tools, and two points that I want to make</p> <p>19 on this slide is that you begin all of these projects,</p> <p>20 including hollow fibers, sterilizing mouse model, LAM</p> <p>21 biomarker work, that I'll talk about, with a definition</p> <p>22 of a context of use statement. And what that really</p>
<p style="text-align: right;">Page 155</p> <p>1 about how we do that in a moment. And really focusing</p> <p>2 on developing pathways for new treatment regimens that</p> <p>3 include drugs that are not yet individually approved.</p> <p>4 We have a large number of members and partners</p> <p>5 that participate in our organization. I've described</p> <p>6 it here at the bottom of this slide. In this graphical</p> <p>7 depiction, what I'm showing you on the outer side of</p> <p>8 this circle is all of the different sectors that do</p> <p>9 participate in the work of CPTR. So, we have large</p> <p>10 pharma, biotech companies, small pharmaceutical</p> <p>11 organizations; we have academia, government</p> <p>12 institutions, patient advocacy groups. And,</p> <p>13 importantly, this infrastructure supports the work that</p> <p>14 we do because we provide a neutral ground for data</p> <p>15 collaboration, again, which is underpinning for all of</p> <p>16 the model and methods work that we do. We provide a</p> <p>17 legal infrastructure that allows for the safe sharing</p> <p>18 of those data. But as importantly, it's a neutral</p> <p>19 opportunity for the members of our consortia to</p> <p>20 interface with regulatory agencies, which for our</p> <p>21 programs include both FDA and EMA, and I'll talk about</p> <p>22 a couple of projects where that has been critically</p>	<p style="text-align: right;">Page 157</p> <p>1 means is that we're making a very clear statement about</p> <p>2 how a particular method should be used to make a</p> <p>3 particular decision in the drug development pathway.</p> <p>4 And that's a lot harder than it sounds.</p> <p>5 And depending on the context of use statement,</p> <p>6 that will drive how much data is required to prove that</p> <p>7 context of use is true and applicable. And so, this is</p> <p>8 the approach whether we pursue formal qualification or</p> <p>9 not that we use to assess methodologies in the program.</p> <p>10 So, I'll skip a couple of slides here. I do</p> <p>11 want to mention very briefly the importance of data</p> <p>12 collaboration within the context of this consortia.</p> <p>13 So, one of the very first deliverables of the CPTR</p> <p>14 program was to develop with our partner at CDISC a TB</p> <p>15 therapeutic area data standard which allows us to</p> <p>16 aggregate clinical trial data across multiple sources.</p> <p>17 And for those of you who are moving forward with new</p> <p>18 drugs that you hope to register, you know now that you</p> <p>19 have to collect all your clinical trial data using that</p> <p>20 standard to submit to FDA. And so we as a consortia</p> <p>21 develop that standard. We implement it within the</p> <p>22 course of our consortia, and this allows us to evaluate</p>

<p style="text-align: right;">Page 158</p> <p>1 preclinical data that is shared by many of the 2 collaboratives in the room with clinical outcome data 3 to really assess productivity. Marco has already told 4 you about our ReSeqTB data platform, and I do want to 5 briefly mention another partnership between CPTR and 6 WHO, where we have -- and TB Alliance, where we have 7 aggregated the Phase 3 quinolone-containing trials and 8 made those fully publicly accessible to everybody in 9 the room and researchers across the globe to ask 10 important questions about those data sets.</p> <p>11 So, this is really a great summary slide, if I 12 needed to just, in one slide, describe to you what 13 we're doing in CPTR now. So, our original remit from 14 the Gates Foundation was to assess in this drug 15 development paradigm gaps in our understanding of 16 either how to choose the right drug to put in earl 17 combination studies, how to choose the right dose, or 18 translatability among steps. And we found a couple of 19 big gap areas that will not be a surprise to any of 20 you. We have focused a lot of our efforts in 21 preclinical methodologies, as you've heard about today, 22 because we think it's critically important for these</p>	<p style="text-align: right;">Page 160</p> <p>1 and a very expensive leap and time-consuming leap 2 between Phase 2b studies and Phase 3, and so we're 3 doing a lot of mathematical simulation work around 4 understanding quantitative assessment of time to 5 positivity, as Payam mentioned earlier. Chuck talked 6 about the importance of population PK. He's leading a 7 project with CPTR to develop that model and make it 8 accessible.</p> <p>9 We're doing a lot of work with Rada Savic's 10 lab at UCSF and Eric Nuermberger to understand 11 mechanism-based implications in developing new drugs 12 and drug combinations. Happy to talk about any of 13 those in detail during the discussion.</p> <p>14 So, this is a dangerous slide, as we found out 15 earlier this morning, but the good news is I don't need 16 to spend a lot of time on it. Just simply want to say 17 that, yes, we did a robust assessment of the in vitro 18 hollow fiber system and for a couple of reasons. One, 19 we know that we needed to improve that PK/PD 20 understanding, and this was one methodology that was 21 going to generate intensive quantitative information in 22 that space. But as Eric had mentioned, this model has</p>
<p style="text-align: right;">Page 159</p> <p>1 new drugs moving forward that we understand very 2 crisply as much as possible about the PK/PD 3 relationship that individual drugs will have and also 4 how those will behave in combinations.</p> <p>5 So, we turned our focus first to the hollow 6 fiber system. We're now working on a similar 7 assessment of the sterilizing mouse model. I will say 8 in this critical preclinical to early clinical study 9 transition phase we have hit another important 10 milestone, which is the development of physiologically- 11 based PK model to help describe potential drug 12 penetration in the granuloma of adult patients. This 13 is based off the South African population. This model 14 is fully developed. It was developed based on the data 15 repository that we have in hand, including preclinical 16 data from Veronique Dartois, the hollow fiber system 17 data, the Baylor labs. Also, Eric Nuermberger's data. 18 This model is publicly accessible. We can provide it, 19 we can also provide training to any developers 20 interested in applying the model. But very important 21 to understanding translation from preclinical space 22 into early clinical studies. There is also a big gap</p>	<p style="text-align: right;">Page 161</p> <p>1 been used for the past decade in lots of different 2 anti-infective programs, as well as TB, but really as a 3 research tool. And so, we had a lot of work to do 4 assess predictive accuracy. He told you about the 5 outcome of that work, but what I do want to mention is 6 he mentioned two important points. Questions remaining 7 around reproducibility of the model and the ability of 8 other laboratories to take up this technology. So, 20 9 months after -- for the 20 months following the 10 qualification with EMA of this methodology, we did 11 intensive studies around -- in trying interlab 12 reproducibility for the hollow fiber system. And we 13 will be publishing on that soon. We're so confident 14 with that work that several of our pharma partners are 15 now working with us for the industrialized application 16 of their new chemical entities in combination going 17 into filings.</p> <p>18 In terms of uptake into other laboratories, 19 we've also developed a laboratory manual with several 20 experts. That laboratory manual will be fully 21 accessible for those who want to start up systems like 22 this in their own facilities and want to reproduce</p>

<p style="text-align: right;">Page 162</p> <p>1 studies.</p> <p>2 So, I'm not going to spend a lot of time on</p> <p>3 the sterilizing mouse model work, but to simply say</p> <p>4 that we're applying the same kind of approach. So, I</p> <p>5 think that there is a false assumption that because</p> <p>6 there is so much data in the sterilizing mouse system</p> <p>7 because it has been such a pivotal methodology in drug</p> <p>8 development decision-making in TB, that we may have had</p> <p>9 more standardized data, or more standardized systems,</p> <p>10 or had done this predictivity analysis with a mouse</p> <p>11 model as we did with hollow fiber system, but that's</p> <p>12 not true. And so, we are at the point where we've</p> <p>13 collected all of the important data that we think we</p> <p>14 need in order to do that predictivity analysis and</p> <p>15 literally within the next month we'll kick off that</p> <p>16 statistical analysis plan.</p> <p>17 So, I do want to spend the last few minutes of</p> <p>18 my talk specifically focused on the LAM pharmacodynamic</p> <p>19 biomarker program. This was alluded to in a couple of</p> <p>20 different talks earlier this morning and really is one</p> <p>21 of the areas of most energy CPTR right now, and I think</p> <p>22 for really just cause. We've talked in several</p>	<p style="text-align: right;">Page 164</p> <p>1 contamination, and then the time to grow up cultures</p> <p>2 from sputum.</p> <p>3 So, through our partnership with Otsuka and</p> <p>4 through CPTR, the LAM biomarker has come forward. We</p> <p>5 know that lipoarabinomanna is a major cell wall</p> <p>6 component and may have developed a new immunoassay,</p> <p>7 which is an ELISA-based methodology that measures LAM</p> <p>8 in sputum. The good news is that very specific for LAM</p> <p>9 from Mtb and doesn't have cross-contamination with</p> <p>10 other oral bacteria. And there is strong correlation</p> <p>11 between sputum LAM and colony-forming units, as well as</p> <p>12 TTD. Two wonderful qualities of this is that the data</p> <p>13 to date say that it's not affected by contamination or</p> <p>14 drug carryover, and it offers much quicker testing,</p> <p>15 approximately five hours, which we can agree is better</p> <p>16 than six to eight weeks.</p> <p>17 So, we are taking the qualification approach</p> <p>18 with FDA on this specific pharmacodynamic biomarker,</p> <p>19 and I've talked to you about the importance of defining</p> <p>20 a context of use statement. So, we have done that and</p> <p>21 we have actually submitted a full letter of intent with</p> <p>22 all of the data that are available to date on this</p>
<p style="text-align: right;">Page 163</p> <p>1 presentations today about the high-unmet need for real</p> <p>2 time assessment of efficacy in TB drug development</p> <p>3 trials. We really do require a tool that can assess</p> <p>4 early bactericidal activity and sputum culture</p> <p>5 conversion endpoints, which we know are recommended by</p> <p>6 regulators in real time or as close to real time as</p> <p>7 possible, allowing for quick decision-making.</p> <p>8 There are lots of bonuses that come along with</p> <p>9 that, like reduced cost and reduced time for trials.</p> <p>10 We've heard from Payam, we've also just heard from</p> <p>11 Marco, that we need to be able to have methodologies</p> <p>12 that are easily implemented in laboratories where these</p> <p>13 clinical trials are run. And if at all possible,</p> <p>14 methodologies that aren't affected by contamination for</p> <p>15 measuring burden sputum or impacted by drug carryover</p> <p>16 effect.</p> <p>17 We've talked about the potential value of EBA.</p> <p>18 We know sputum culture conversion is very important,</p> <p>19 but there are a lot of issues with these, including the</p> <p>20 number of different laboratories, which is very, very</p> <p>21 minimal, that can do -- or trial sites that can do EBA</p> <p>22 studies. And there's lots of problems with</p>	<p style="text-align: right;">Page 165</p> <p>1 specific pharmacodynamic biomarker, and submitted that</p> <p>2 letter of intent on June 9th of this year to FDA, and</p> <p>3 we are continuing conversation with them.</p> <p>4 Context of use, incredibly important. So,</p> <p>5 this one I'm going to read, right, because we choose</p> <p>6 our words carefully. LAM is a pharmacodynamic</p> <p>7 biomarker for quantitative measurement of bacterial</p> <p>8 load in sputum. A decrease in LAM sputum likely</p> <p>9 affects the reduction of bacterial load in the lung.</p> <p>10 This pharmacodynamic biomarkers should be considered</p> <p>11 with other microbiological measurements, such as</p> <p>12 culture, as a real-time evaluation of treatment</p> <p>13 response in clinical trials that patients with</p> <p>14 pulmonary TB and positive smears and cultures, such as</p> <p>15 14-day EBA trials, clinical trials of pulmonary TB up</p> <p>16 to 56 days, or clinical trials to provide evidence for</p> <p>17 early decision-making in adaptive trial designs. And</p> <p>18 so now it's our job to coordinate all the data that</p> <p>19 supports this context of use statement and execute the</p> <p>20 statistical analysis plan, which will result in the</p> <p>21 submission of a briefing book to both FDA and</p> <p>22 potentially over time, EMA.</p>

<p style="text-align: right;">Page 166</p> <p>1 So, the envisioned impact, which is really the 2 punchline of this presentation and I think what many 3 alluded to as an important pivotal game-changer within 4 the TB regimen development space is what a real-time 5 pharmacodynamic biomarker could do for this field. So, 6 again, we are not proposing this as a surrogate 7 biomarker for culture, but now we can get a real-time 8 assessment that with confidence we know can measure the 9 decrease of bacterial load in sputum in patients within 10 the course of clinical trials? 11 So, you've heard about the length of clinical 12 trials in that the typical strategy is regimen EBA 13 trials followed by a Phase 2b study, which is most 14 likely two-month sputum culture conversion, and then 15 moving on to the very labor-intensive Phase 3 pivotal 16 endpoint studies. And between each of those phases 17 there is a 12 to 18, 18 to 24-month delay in working 18 with regulators in countries where these clinical 19 trials were designed. So, that is a huge time sync for 20 these different programs. And also, you're losing the 21 understanding that you have within individual patients 22 across the course of a clinical trial. And so, Patrick</p>	<p style="text-align: right;">Page 168</p> <p>1 DR. FARLEY: Thanks, Debra. Robert Wallis, 2 you are invited to come right up to the podium. In the 3 Federal Register notice for this meeting, we invited 4 folks who wanted to, to provide some very brief formal 5 comments, and Bob took us up on that. So, he has about 6 a five-minute, five-slide presentation. We'll hear 7 from him right now. 8 DR. WALLIS: Thank you very much. I'm 9 delighted, actually, to take up some comments from 10 Payam and to talk about this question of moving from 11 Phase 2 to Phase 3 more efficiently. I think all of 12 you are familiar with this work that we did while I was 13 still at Pfizer, looking at results from 24 trials from 14 20 to 40 years ago, of 58 regimens, almost 8,000 15 patients, in which we identified month 2 culture status 16 and treatment duration as predictors of relapse. There 17 was a rather simple mathematical equation. What was 18 interesting about it is our ability to then go ahead 19 and subsequently validate this, using independent data 20 from six studies, 12 regimens, involving another 4,000 21 patients, and that's what I want to talk about here. 22 So, the way I'm showing these data, the</p>
<p style="text-align: right;">Page 167</p> <p>1 Phillips has done and proposed some work on potential 2 seamless adaptive trial designs that could be 3 implemented should a qualified pharmacodynamic 4 biomarker that gives you a real time assessment could 5 be implemented within the course of these trials. 6 So, one of the aspirational goals we heard 7 about earlier in Erica's presentation was a more 8 seamless trial design, where you could have a single 9 program and continual enrollment, and that's the 10 aspiration of the application for a biomarker such as 11 LAM, should the data warrant that type of qualification 12 decision. We at CPTR work together with Patrick and 13 others in the room to do a landscape analysis and 14 actual mathematical simulation of the impact and 15 implementation of a biomarker like LAM if qualified, 16 and that work will become one of the core projects of 17 CPTR going forward. 18 So, with that thought I will just end with a 19 thank you to all of our partners and collaborators, and 20 just continue to put in a strong pitch for data 21 collaboration and top partnership, because that's what 22 makes CPTR possible. Thank you.</p>	<p style="text-align: right;">Page 169</p> <p>1 observed relapse -- the observed recurrence rate on 2 this axis, the predicted recurrence rate on the 3 vertical axis, this scale is Logit transformation, 4 which takes a proportion that can range from 0 to 1, 5 and stretches it out from negative infinity to positive 6 infinity. It's a very useful transformation for this 7 type of analysis but it's not very intuitive. So, for 8 each of the corresponding values I have the percentage 9 here represented in the inset. And obviously, a 10 perfect prediction is this 45-degree dotted line here. 11 And then here at 10%, this is my personal threshold for 12 the limit of acceptability for relapse rate. We can 13 argue about whether it should be higher or lower. It's 14 a reasonable guess. 15 So, what we first looked at was for the three 16 fluoroquinolone trials. We wanted to predict the 17 results of the four arms, experimental arms, from five 18 Phase 2 trials of six fluoroquinolone regimens, and 19 this is the prediction, exactly on target. 20 The relapse rates in all eight arms of these 21 trials were then predicted based on the month 2 culture 22 results and the duration of each arm, and I'm showing</p>

<p style="text-align: right;">Page 170</p> <p>1 these results here. So, in green are the six-month 2 arms, and in pink are the four-month arms, and this was 3 published in 2015.</p> <p>4 We have two new studies to add. One is the 5 TBRU treatment shortening trial. This study took 390 6 HIV-negative patients with noncavetary disease at 7 baseline and negative culture at month 2, and randomly 8 assigned them to six or four months of treatment. From 9 my perspective, this study succeeded, actually, in 10 showing that low relapse rates in this population were 11 consistent with what we thought in advance. So, 1.6%, 12 this is the six-month arm, and 7% in the four-month 13 arm. So, a 7% relapse rate in a four-month regimen 14 actually is pretty good, but unfortunately the study 15 failed by finding that duration was a predictor of 16 relapse, which for reasons known only to the 17 investigator was contrary to the study's hypothesis. 18 In any case, the predictions were quite in line with 19 what they should have been.</p> <p>20 And then, lastly, two additional studies of a 21 single arm, open label studies of the Bangladesh 22 regimen in Niger and Cameroon. The month 2 positive</p>	<p style="text-align: right;">Page 172</p> <p>1 So, the conclusion, the model is accurate, R- 2 square value of greater than 0.9 in this independent 3 dataset, and it's generalizable. And by that, I mean 4 it remained accurate under previously untested 5 conditions. So, the fluoroquinolone results were 6 predicted without fluoroquinolone data. The TBRU study 7 results were predicted without any information about 8 host data, and the MDR results were predicted without 9 any MDR or clofazimine data. Does this mean that it 10 will continue to be similarly useful in all studies in 11 the future? I don't know, but this is a reasonably 12 impressive track record.</p> <p>13 None of the studies in the training dataset 14 and very few in the validation dataset excluded 15 recurrent disease due to reinfection. And this 16 presumably introduced noise into the predictions, and 17 you would think that accuracy would be increased if we 18 had had the ability to look at true relapse.</p> <p>19 The data right now are insufficient to create 20 a similar model using time to culture conversion and 21 liquid medium or one including baseline parameters, and 22 I think collecting those sorts of data and</p>
<p style="text-align: right;">Page 171</p> <p>1 proportions were 6% and 13%, and they followed about 2 150 patients in total for one year, and no relapses 3 were detected. And these show up over here in blue. 4 These were assigned a value of 0.5% relapse rate 5 because values of zero are not permitted, and we had 6 originally used this method for small studies with 7 either relapse rates or culture-positive rates of zero 8 in the original publication. But these -- this 9 estimate, there is some uncertainty, could be further 10 in this direction, further in that direction; we'll 11 have to wait for larger trials. But in any case, this 12 overall result I think is quite impressive.</p> <p>13 This is what the database looks like now. 14 Seventy regimens, a distribution of less than six 15 months, six months, and more than six months, and a 16 distribution of African studies and global studies.</p> <p>17 And these are the p-values for the parameters 18 for the equation. And I want to point out, this is 10 19 to the minus fourth to 10 to the minus fifth. This is 20 very striking. And if anyone wants to play with a 21 simplified version of the calculator, it's online here 22 at my website.</p>	<p style="text-align: right;">Page 173</p> <p>1 incorporating into this sort of model should be a 2 research priority. And I would be particularly 3 interested in incorporating the sputum LAM assay into 4 this sort of model. I think that would give you an 5 outstanding approach to informing the required duration 6 of new, potentially shorter regimens, and that's my 7 five minutes. Thank you.</p> <p>8 DR. FARLEY: Thanks very much. We absolutely 9 promise that you will get to eat lunch soon. But we 10 wanted to turn our attention, to have a short panel 11 discussion and opportunity for some questions and 12 answers and interactions. And as folks think about 13 question they want to follow up with the speakers, 14 we've heard a lot of good information this morning, as 15 well as discussion points they would like to bring up, 16 I'd kind of like to remind the panel that our focus 17 today is development of drug regimens. And what you'll 18 hear this afternoon is that evaluation of those 19 regimens, once we move into efficacy studies, the 20 benefit of each of the components of those regimens has 21 already been understood. And part of that has been 22 through in vitro and animal work as well as PK, and so</p>

<p style="text-align: right;">Page 174</p> <p>1 we invite you to focus discussion around lessons 2 learned and approaches going forward, and things that 3 developers ought to keep in mind, based on our 4 experience, to help move the field forward. So, we 5 invite the panel to open the discussion, and then if 6 the audience wishes to participate, you just need to 7 stand at that microphone and we'll see you. Thanks. 8 DR. COX: So, Eric, you talked some about the 9 animal models and the animal models are sometimes 10 helpful but not always correct. As far as TB regimens, 11 a whole new regimen somebody is constructing, how 12 confident do you feel from the data that you might get 13 from animal models that you're able to select a good 14 regimen to effectively treat patients with TB? Your 15 thoughts? 16 DR. NUERMBERGER: Well, I think it really gets 17 to the justification for doing the kinds of evidence- 18 based assessments of these methodologies so you can 19 understand exactly how much confidence that you can 20 have in these tools. So, I don't think we're at the 21 point where we could say with supreme confidence that 22 we can adequately predict a contribution of each agent.</p>	<p style="text-align: right;">Page 176</p> <p>1 information we get from it, or are there inherent 2 limits in what the mice can tell us? 3 DR. NUERMBERGER: Yeah, I mean, it's a model, 4 but I think that if we -- if we really look objectively 5 at what we know on either side of the equation, what 6 the mouse model has yielded and what the clinical 7 trials have yielded. I think it's difficult to argue 8 that the mouse has provided false or misleading 9 information. 10 I think the key issue is how we interpret 11 results that come from the model. And if you look at 12 these REMox regimens as an example, there were 13 increased bactericidal effect in mouse models, there 14 was a relatively small effect on the treatment 15 duration, and I think that was wholly consistent with 16 the REMox result in the sense that there was 17 demonstrated increase in bactericidal effect. But 18 whatever effect size there may have been on treatment 19 shortening, it was not a two-month effect. And so, I 20 don't think the mouse gave us bad data; I think it's -- 21 we were -- we as a group, in moving forward with a 22 trial like that, we're perhaps in hindsight overly</p>
<p style="text-align: right;">Page 175</p> <p>1 Certainly, within the preclinical setting it's 2 relatively straightforward to demonstrate the 3 contribution of an individual drug with the kind of 4 factorial designs that are quite amenable. And the 5 better one can demonstrate that with -- by showing dose 6 response and efficacy at exposures that we could 7 justify as being clinically achievable the more 8 powerful that is. 9 I think an important question is when -- we 10 look at a variety of different endpoints, and I would, 11 again, generally have the most confidence in looking at 12 -- in proclaiming a contribution if we can show that 13 the component contributes to bactericidal effect, 14 contributes to sterilizing effect, contributes to 15 suppression of resistant mutants that are resistant to 16 other companion drugs in the regimen. So, the more 17 preclinical endpoints one can bring to bear and 18 demonstrate activity or contribution, the better. So, 19 I think that's an important aspect of it. 20 DR. COX: Do you think the mouse model, with 21 further research, can it be pushed so that we can 22 squeeze more water from the stone, as far as</p>	<p style="text-align: right;">Page 177</p> <p>1 optimistic, but that was based on some of these, you 2 know, at the time, recognition that many patients do 3 well with four months of standard therapy. And there 4 were other rationales for moving forward with a Phase 3 5 trial at that point, building capacity and, you know, 6 and there weren't a lot of other regimens to push 7 forward at that time. So, I think obviously, the mouse 8 model was also not the only reason that that trial went 9 forward, so we have to think about the decision-making 10 in that context. 11 DR. SPIGELMAN: You know, a common theme to 12 me, and it applies here and it applies to a lot of 13 other areas, and I'll get into it maybe in the 14 afternoon a little bit, is distinguishing between what 15 we can learn qualitatively and what we can learn 16 quantitatively. And I think that's basically what Eric 17 has been saying. 18 And if we look for over-interpret -- if we 19 look for having to derive truly strict quantitative 20 data from a lot of these, we're going to be 21 disappointed and, to a certain extent, throw out the 22 baby with the bathwater. If we realize that</p>

<p style="text-align: right;">Page 178</p> <p>1 directionally or qualitatively there is a huge amount 2 that can be learned, then I think it can inform steps 3 moving forward. But I think we have to be careful in 4 terms of what the expectations are in terms of 5 quantitative relationships.</p> <p>6 DR. HANNA: I would just add, to underscore a 7 point that Eric made during his presentation, I don't 8 think we've ever said there is going to be one single 9 model that gives us all the answers that we need. And 10 I think this is where we think pairing the quantitative 11 system in the in vitro PK/PD model with more 12 qualitative data that is assessed in the appropriate 13 mouse model, those two pieces of information together 14 will be important.</p> <p>15 DR. NUERMBERGER: And I certainly wouldn't 16 have wanted my comments to suggest that I think the 17 mouse model is a be all, end all. I think it's just as 18 suggested. And I think there are plenty of 19 opportunities to continue to improve. And, again, 20 incorporating information that may come from Kramnik 21 mice or marmosets or other caseous models with respect 22 to how well drugs are partitioning into various</p>	<p style="text-align: right;">Page 180</p> <p>1 feedback and that database will grow over time to 2 further increase the understanding of what can be 3 concluded from those various different preclinical 4 models.</p> <p>5 DR. NUERMBERGER: That's absolutely right. If 6 we're not asking these questions and thinking about how 7 we want to answer these questions right now, then we 8 won't be in a position to capitalize on these kinds of 9 opportunities. And it's critical because a lot of the 10 new drugs coming forward now are different in the sense 11 of their physical chemistry, their PK characteristics, 12 and they don't necessarily act like the isoniazids and 13 the pyrazinamides. And so, it's a really important 14 stress test for the preclinical models.</p> <p>15 DR. COX: Chuck, can I ask you, you seem to be 16 hinting at TDM. Do you want to say anything more about 17 that?</p> <p>18 DR. PELOQUIN: I appreciate the fact that you 19 picked up on that.</p> <p>20 DR. COX: And how would that work? I'm just 21 sort of curious, your vision on this?</p> <p>22 DR. PELOQUIN: So, if you get on an airplane,</p>
<p style="text-align: right;">Page 179</p> <p>1 important places. I think there is very good 2 rationale, at least, to believe and certainly 3 opportunity to demonstrate in these types of models 4 that there may be compartmentalization of certain drug 5 effects. And maybe there is a rationale for putting a 6 drug in a combination just because it's only one of two 7 or three instead of all four of the drugs that really 8 achieve the kind of concentrations that you think you 9 need in the caseous portion of a lesion.</p> <p>10 And so, I think there are ways to build on 11 that and certainly ways to continue to try and enhance 12 our quantitative understanding. I think it sounds pie 13 in the sky at the moment, but I think there is no 14 reason to think that we can't continue to build and 15 move closer and closer to quantitative appraisals of 16 what various preclinical models can tell us in an 17 integrated and comprehensive way. But that work has 18 got to start somewhere.</p> <p>19 DR. COX: And I guess one more part of this, 20 too, is that to the extent the animal models and the 21 other tools are used to inform choices that then go 22 forward in clinical trials, you'll be able to have that</p>	<p style="text-align: right;">Page 181</p> <p>1 someone is flying the airplane, typically, right? Or 2 if you get on a bus, somebody is driving the bus. And 3 if you're giving drug therapy and you're not going to 4 do surgery, then you want to get the most out of that 5 drug therapy. So, either you're controlling the 6 therapy or its controlling you. So, if you give 7 standardized doses, which is generally what's done, 8 that broad spectrum -- I gave the example of rifampin 9 from 0 to 45, that's what you're going to get. Now, it 10 would be convenient of that wasn't the case, but 11 unfortunately it is. And we have similar data for all 12 the different drugs.</p> <p>13 So, if you wish to -- and I would suggest 14 doing it early, before you select for drug resistance, 15 if that's going to happen. If you can get even just 16 two blood samples in an individual patient for the 17 drugs that you're using, you have a snapshot of what's 18 going on. If you have the MIC, you might be lucky, and 19 their organism is very, very susceptible, and you might 20 not need to push the drug really hard. On the other 21 hand, the patient's isolate might have an MIC that goes 22 right up to the epidemiological breakpoint that we use</p>

<p style="text-align: right;">Page 182</p> <p>1 clinically and in which case you might have to push 2 harder. And if you know that, then you have a good 3 idea of how hard you're going to have to push and how 4 much toxicity you might be expected or willing to 5 tolerate in that situation. 6 DR. COX: So, it seems there are two laudable 7 goals that we heard about. One is you want to get the 8 dose right, you want to get to an exposure that's 9 actually going to be able to treat the patient. And 10 the other is the idea of sort of a pan-TB regimen, in 11 essence, something that is simple that you could 12 administer to patients that doesn't -- you know, 13 ideally not have to do testing for either drug toxicity 14 and all. So, it sounds like what you're describing 15 would be something where you did some testing early on 16 to see how you're doing with dosing, maybe adjust it 17 once, do one more test, and then hope at that point 18 that you're on autopilot for the dosing and you're 19 going to achieve exposures that would remain constant 20 throughout. Fair or -- 21 DR. PELOQUIN: Well, hope is not a strategy. 22 What I would say is that if we have drugs that are</p>	<p style="text-align: right;">Page 184</p> <p>1 US that can do this, and there are several labs in 2 Europe that can do this. So, it's not impossible to do 3 it. That's all I can say. 4 DR. COX: So, one other thing, and just so 5 folks sort of have a feel. So, what we're going to try 6 to do is we're going to break for lunch at 12:55. So, 7 we'll do about five more minutes with the panel this 8 morning and then we'll -- that way we can start the 9 afternoon session on time, and we can finish on time, 10 which I think will be really important. So, if anyone 11 has any burning issues they want to surface for the 12 morning, please do so now. Mel, please. 13 DR. SPIGELMAN: Chuck, only because I know you 14 so well. More is always better and apple pie is great. 15 Have you come up with a clinical trial design that 16 would actually test what is the obvious, you know, true 17 hypothesis that therapeutic drug testing really does 18 yield better clinical results, more cross-detective 19 results, etc. in TB? Because I think as a next step to 20 actually ever get to the point of implementation is 21 frankly having clinical trial robust, prospective data 22 that quantifies to a certain extent the benefit.</p>
<p style="text-align: right;">Page 183</p> <p>1 immensely potent relative to how much is required in a 2 patient. So, if your AUC to MIC is in the thousands, 3 because you have an incredibly potent drug, then you 4 probably don't need therapeutic drug monitoring, 5 because you're way, way above it. But that's not true 6 of virtually any of the drugs that are being looked at 7 right now as experimental drugs or the drugs that are 8 in clinic. And we're really much more in a situation 9 that, for example, our lab does TDM for patients with 10 fungal infections, and fungi can't even make up their 11 mind what they are, they're a yeast, they're a hypha, 12 or whatever. Yet if you're treating a transplant 13 patient, they get TDM for all their immunosuppressants 14 and their antifungals. And now in our intensive care 15 units we're measuring beta-lactams because the MICs are 16 getting higher and higher and the concentrations are 17 all over the place with all the things we do to 18 patients in the ICU. So, TB is not quite as extreme as 19 those cases, but there is still a lot of variability, 20 and up until now we generally don't control it. 21 About 200 different centers around the country 22 send samples to my lab. There are several labs in the</p>	<p style="text-align: right;">Page 185</p> <p>1 DR. PELOQUIN: The closing number of studies 2 that I showed, showed the consequences of low exposure 3 of the drug, and the last two, the high rifamycin 4 studies, showed the advantages of high exposures of the 5 drug. So, I think actually the data are there in 6 clinical situation. Now, as far as testing, TDM versus 7 not TDM, could it be done? Yes, it could be done, but 8 that's a little bit more challenging. But I think from 9 the clinical trial data, it's pretty clear that, again, 10 unless you're going to do surgery, you're relying on 11 the drugs. And what the drugs work through is a 12 pharmacodynamic parameter, and you can identify that 13 preclinically and then you can optimize it. So, in a 14 clinical trial you could get early concentrations and 15 feedback. 16 So, it's just like flying a plane -- you 17 direct the plane where you want it to go and then you 18 get feedback of whether, as you turn the plane, if it 19 actually went where you wanted it to go. You can get 20 that information with serum concentrations, adjust the 21 dose even in a clinical trial. I'm not saying it's 22 easy; you'd have to have the assays probably close to</p>

<p style="text-align: right;">Page 186</p> <p>1 the different centers, but you could do it. HPLC is 2 not a new tool. I was using it as an undergrad, and 3 that's a long time ago.</p> <p>4 DR. SPIGELMAN: Yeah, but I think, again, not 5 meaning to belabor the point, there is a difference 6 between frankly retrospective cherry-picking with data 7 to show what could be considered obvious if somebody 8 malabsorbs and doesn't get the drug, they're probably 9 not going to do as well, to prospectively actually 10 quantifying basically almost even cross-benefit. Do 11 you do it for everybody? Do you wait until somebody 12 doesn't respond? If you do it for everybody, with 13 which drugs? How do you intervene in terms of the 14 changing? What difference does that make ultimately? 15 So, I do think if you want to change policy and 16 ultimately really impact systems, it's just necessary 17 to go that next step.</p> <p>18 DR. PELOQUIN: Well, I'm open to doing that. 19 As far as the studies, obviously, I had a finite time 20 to present, so I don't really think that they're 21 cherry-picked, per se. I think the most recent 22 rifampin and rifapentine studies really encourage</p>	<p style="text-align: right;">Page 188</p> <p>1 to the development of drug resistance, that would make 2 up for the cost, but in fact we really don't see a lot 3 of acquired drug resistance in programs that really 4 start patients on the right regimen at the right time 5 and do good directives or therapy.</p> <p>6 DR. PELOQUIN: What you say is true. I think 7 where you could see an advantage would be the duration 8 of the treatment. So, if you optimized early, you 9 might be able to get back to more what was seen in the 10 BMRC trials, whereas, you hit them hard, you hit them 11 early, which is really the mantra in HIV. Hit hard, 12 hit early. And that's not really what's done in TB. 13 We just sort of use the standard regimen, and that 14 regimen by itself is not really optimized. It was sort 15 of, this was good enough at the time, and decisions 16 were made. You know, the BMRC was not highly funded 17 and they had only so many things that they could do.</p> <p>18 So, again, I think however we approach this, 19 the PK and the PD are essential components, because 20 that's how drugs operate. And if we have the 21 opportunity clinically to optimize it individually, 22 that would be fantastic. And that's really what we do</p>
<p style="text-align: right;">Page 187</p> <p>1 people to look at those in great detail, because it's 2 telling us that without good PK you don't get PD. But, 3 conversely, with good PK you get excellent PD. So, 4 again, I refer you to those papers.</p> <p>5 DR. COX: And it sounds like, Mel, maybe what 6 you're suggesting would be a randomized trial where one 7 arm got TDM and the other did not, and then the 8 question is, are the outcomes different between the two 9 groups, yeah.</p> <p>10 DR. SPIGELMAN: Yeah, I mean, that's the most 11 obvious, sort of off-the-hand clinical trial design, 12 but I'm sure when people would sit around and think 13 about it, you might be able to come up with something 14 better, but that sort of data, to me, would almost be 15 the next step.</p> <p>16 DR. LOBUE: I mean, I think the issue from a 17 program standpoint is ideal versus good enough, and we 18 might need those level of data to make those type of 19 programmatic changes. Because unlike the University of 20 Alabama football program, TB -- even in this country, 21 TB programs are not that well resourced or funded. And 22 while you made the point, well, if they're contributing</p>	<p style="text-align: right;">Page 189</p> <p>1 with other disease states. With diabetes, we don't 2 give everybody 10 units of regular insulin three times 3 a day regardless of the glucose being 300 or 30, and we 4 don't give standardized doses of warfarin. And you can 5 go down the list, so we don't give standardized doses. 6 TB is one of the exceptions where we do.</p> <p>7 DR. FARLEY: Great. Well, we're going to 8 break at this point and we promise to get to you this 9 afternoon first thing. So, we're going to try to 10 resume at 1:35. That will be Dr. Higgins' talk, the 11 FDA talk. You don't want to miss that. And we'll see 12 you all in about 40 minutes. So, thanks very much and 13 we'll have more time for talking this afternoon.</p> <p>14 [Lunch break.]</p> <p>15 DR. SPIGELMAN: I'd like to initially, for the 16 first talk this afternoon, introduce Karen Higgins. 17 Karen, as I think most of us know, is the statistical 18 team leader that supports the division of anti- 19 infective products at the FDA and has clearly been 20 involved in so many of the programs that have come 21 before the FDA. Karen, thank you.</p> <p>22 DR. HIGGINS: Thanks, Mel. So, I'm going to</p>

<p style="text-align: right;">Page 190</p> <p>1 go over some regulatory issues to think about when 2 designing your adequate and well-controlled trial for 3 TB regimen development. There is a lot to talk about, 4 so I'm going to kind of briefly talk about a lot of 5 things. My main point, and it's something I'm 6 hopefully going to repeat a lot, is every TB 7 development program is different, so I highly recommend 8 that you come into FDA and talk about your specific 9 program, because there are going to be a lot of 10 nuances.</p> <p>11 But I'm going to talk about some regulatory 12 requirements, including substantial evidence, 13 accelerated approval, and added contribution of 14 components of the TB regimen. And then I'll go into 15 some of the clinical trial design things to think 16 about, including patient population, control, endpoints 17 and statistical analysis. My focus is really going to 18 be on efficacy.</p> <p>19 So, the FDA has required since 1962 to have 20 substantial evidence of effectiveness to approve a 21 drug. That is outlined in the Code of Federal 22 Regulations, and it discusses adequate and well-</p>	<p style="text-align: right;">Page 192</p> <p>1 regimen. This allows for earlier approval of drugs 2 that treat serious conditions that provide meaningful 3 therapeutic benefit over existing therapies. So, it 4 uses an accelerated approval endpoint that is 5 reasonably likely to predict clinical benefit, but in 6 itself not a measure of clinical benefit. And, of 7 course, the whole point of the accelerated approval 8 program is it can considerably shorten the time 9 required prior to receiving FDA approval.</p> <p>10 A sponsor would then be required to conduct a 11 post-marketing study to confirm the anticipated 12 clinical benefit. If it's confirmed, then they would 13 get full approval; if not, it potentially could remove 14 the drug from the market.</p> <p>15 So, some things to think about regarding 16 accelerated versus standard approval for TB regimens. 17 I kind of have a couple of thoughts on this slide. One 18 thing we should think about as kind of the impact of 19 the regimen is it's a high impact regimen. And, if so, 20 you would tend to think more towards accelerated 21 approval, and that would certainly be the case for MDR 22 treatment regimen that is more effective or less toxic,</p>
<p style="text-align: right;">Page 191</p> <p>1 controlled trials, which you probably all heard, since 2 it's plural, it's been meant to mean two or more 3 trials. However, in 1998, the Clinical Effectiveness 4 Guidance came out as part of the FDA Modernization Act, 5 and in that it kind of opened the door a little bit 6 more and gave situations where one adequate and well- 7 controlled trial would be sufficient, along with 8 independent substantiation of the findings. And in TB 9 we often find that that would be the case where we 10 would have one adequate and well-controlled trial plus 11 a large amount of information from EBA trials, and plus 12 studies in animal and in vitro.</p> <p>13 But keep in mind the importance of adequate 14 comparative safety information. So, sometimes one 15 trial might be appropriate for efficacy but it wouldn't 16 lead you to quite enough adequate safety information. 17 So, that is always something to keep in mind. 18 Sometimes, if there is not a large enough safety 19 database it could lead to some kind of a limited use 20 indication.</p> <p>21 So, the accelerated approval program is 22 something important to think about when developing a TB</p>	<p style="text-align: right;">Page 193</p> <p>1 or an XDR regimen that has fairly good efficacy.</p> <p>2 But an additional thing to think about, not 3 only is the regimen high impact but, kind of, how much 4 complete information do we need? And the more complete 5 information you need, the more maybe you'd think 6 towards standard approval. And something I would think 7 about would be for a drug-sensitive regimen we really 8 may need information on the final long-term outcome 9 before switching patients from a highly effective 10 standard regimen of the HRZE. So, in that case, even 11 though a new drug-sensitive regimen with a totally new 12 treatment regime would certainly be high impact, it 13 might not be appropriate for accelerated approval 14 because we would really want information on that long- 15 term endpoint.</p> <p>16 For an MDR regimen, if the test regimen has a 17 markedly shorter duration, it's quite likely that we'll 18 want to have an endpoint past the end of treatment. 19 So, again, that would give us some estimate of relapse 20 rate to make sure patients wouldn't be at a high risk 21 of relapse if they were on this markedly shorter MDR 22 regimen. And once you have that information, that in</p>

<p style="text-align: right;">Page 194</p> <p>1 fact might be evidence of clinical benefit, so that 2 might just automatically lead you more towards standard 3 approval. But this just kind of underscores, again, 4 the need to come in early and kind of talk about your 5 program and your drug, what you're going to be studying 6 and maybe what the best plan for approval would be. 7 So, an example of accelerated approval is 8 bedaquiline. It was approved in 2012 for the treatment 9 of adults with MDR pulmonary tuberculosis. It was an 10 add-on trial where patients were randomized to 11 bedaquiline or placebo for 24 weeks. Patients received 12 best available therapies for 18 to 24 months. The 13 accelerated approval was based on time to sputum 14 culture conversion, where there was a superior effect 15 over placebo. But due to limited safety and an 16 increased mortality on bedaquiline, it received a 17 limited use statement saying to reserve use when an 18 effective treatment regimen cannot otherwise be 19 provided. And, again, the sponsor would need to 20 conduct a confirmatory trial assessing patient 21 survival, clinical resolution of tuberculosis, and rate 22 of relapse at a later endpoint after patients have</p>	<p style="text-align: right;">Page 196</p> <p>1 preferred, but that in some cases it may not be 2 possible. And in those cases, which TB is likely one, 3 because you wouldn't want to give patients a regimen 4 that is not fully effective. That perhaps information 5 on the added contribution of the components could come 6 from in vitro and in vivo animal models, Phase 1 or 7 early studies, where the clinical study would assess 8 the full regimen. So, in many cases this might be what 9 we can do with TB development. 10 So, just to keep in mind, you could develop a 11 TB regimen as a fixed dose combination, where all the 12 components of the regimen are formulated together into, 13 say, one tablet. It could be co-packaged in, say, a 14 blister pack, or they could be individually packaged 15 but labeled to be used in combination. And I just 16 wanted to let you know that pretty much the efficacy 17 and safety requirements will be similar for those three 18 situations. 19 So, some things to consider for designing the 20 TB efficacy trial. The main one is what is that TB 21 regimen you're looking at, and is it a new, completely 22 new regimen or is it really a new drug kind of being</p>
<p style="text-align: right;">Page 195</p> <p>1 completed TB therapy. 2 So, something to consider and that we've 3 discussed today already is this combination rule, since 4 we have a multiple drug regimen. So, the combination 5 rule as stated in the Code of Federal Regulations 6 states that two or more drugs may be combined into a 7 single dosage form when each component makes a 8 contribution to the claimed effect. So, you need to 9 know that if you're going to give patients an 10 additional drug that that drug is actually adding 11 efficacy and not just potentially adding toxicity. 12 That's been interpreted to mean a factorial design 13 trial, which can be -- grow huge if you have multi-drug 14 regimens. So, just in this little example of a two- 15 component regimen, you'd need at least a three-arm 16 trial, and you need to show the superiority of the 17 combination to each of the individual components. So, 18 that could be a high hurdle. 19 So, in 2013, the guidance on co-development of 20 two more new investigational drugs for use in 21 combination talked about that, and talked about how a 22 factorial designed clinical study is certainly</p>	<p style="text-align: right;">Page 197</p> <p>1 added to a regimen that's already out there? So, for 2 example, if it's a new regimen, if it's a high impact 3 new regimen, for example, three or four new drugs with 4 new mechanisms of action to treat TB in four to six 5 months; that would be a high-impact brand-new regimen. 6 Or, similarly, two new drugs with new mechanisms of 7 action possibly paired with an older drug. If the 8 contribution of the effect of the components could come 9 from an earlier phase of development, such as EBA 10 trials in animal models. Then the clinical trial could 11 assess the efficacy of the regimen as a whole. 12 But on the other extreme, let's say it's a new 13 drug being developed, for example, a new drug to treat 14 MDR-TB given on top of the best available therapy, or a 15 new drug to replace one drug in the standard drug- 16 sensitive regimen, then it's more of the development of 17 a single drug, and the efficacy of that single drug we 18 will likely need to know from a clinical trial. And 19 just an example, bedaquiline was that case. Of course, 20 these are kind of two extremes of the spectrum. You 21 could fall somewhere in between there, so, again, 22 coming into discuss it with the division early on would</p>

<p style="text-align: right;">Page 198</p> <p>1 be helpful.</p> <p>2 So, the patient population of your clinical</p> <p>3 trial could be drug-sensitive TB, MDR-TB, XDR-TB, or</p> <p>4 any combination or all combined. And, as mentioned</p> <p>5 earlier, different patient populations might lead to</p> <p>6 different routes of approval. So, the expectation is</p> <p>7 that you would conduct a randomized, controlled,</p> <p>8 blinded trial. There are some cases where blinding is</p> <p>9 just not feasible, so the trial should really be then</p> <p>10 conducted in a blinded manner however possible.</p> <p>11 The control treatment would really depend on</p> <p>12 the patient population and the regimen. So, for</p> <p>13 example, if it was a drug-sensitive TB trial you were</p> <p>14 conducting, we would expect that standard six-month</p> <p>15 HRZE regimen is the control. For MDR-TB, it would</p> <p>16 really depend on the resistant patterns and the</p> <p>17 location where it was studied. For XDR-TB, given the</p> <p>18 poor outcome and long duration of treatment, it might</p> <p>19 be possible for a drug with great effect to have it be</p> <p>20 assessed in a single-arm trial with an historical</p> <p>21 control group. I worry about mentioning historical</p> <p>22 control groups because they are the weakest of the</p>	<p style="text-align: right;">Page 200</p> <p>1 adequate.</p> <p>2 The late endpoint is the one we consider kind</p> <p>3 of the final or the ultimate endpoint in measuring TB</p> <p>4 efficacy. Sustained culture conversion 6 to 12 months</p> <p>5 after treatment ends. I'd say the timing of the</p> <p>6 endpoint really should be based on time from</p> <p>7 randomization and it should be the same for the two</p> <p>8 treatment arms. So, even though I'm referring to it as</p> <p>9 it is approximately measured at 6 to 12 months after</p> <p>10 the end of treatment, that should then be defined in</p> <p>11 the protocol as a time from randomization.</p> <p>12 And you should capture the reason for failure,</p> <p>13 as in treatment failure, relapse, reinfection, if</p> <p>14 you're able to differentiate the two, and if you've</p> <p>15 lost the patient.</p> <p>16 And then the last point I want to talk about</p> <p>17 is just the analysis of the clinical trial. Obviously,</p> <p>18 it depends on the specific clinical trial in your</p> <p>19 hypothesis, so you could assess it using a superiority</p> <p>20 analysis or noninferiority analysis. You all pretty</p> <p>21 much understand superiority analysis, but it helps to</p> <p>22 then go on to explain noninferiority once I've walked</p>
<p style="text-align: right;">Page 199</p> <p>1 controls. It's nonconcurrent and it's very difficult</p> <p>2 to have a confidence that the patients in the</p> <p>3 historical control are comparable to the patients in</p> <p>4 the trial that would have XDR patients. So, again, I'd</p> <p>5 come in early and we'd talk about how best to come up</p> <p>6 with an adequate historical control for that.</p> <p>7 And I just want to mention briefly, again,</p> <p>8 like was done for bedaquiline, for a single new drug</p> <p>9 for MDR/XDR, you might use an add-on design where</p> <p>10 patients are randomized to either an optimized</p> <p>11 background regimen plus the new drug versus optimized</p> <p>12 background regimen plus placebo. And this is really a</p> <p>13 placebo-controlled trial. I know over time this is</p> <p>14 likely going to be getting more and more difficult to</p> <p>15 conduct as therapies for MDR-TB improve, but I just</p> <p>16 wanted to point that out.</p> <p>17 So, we've talked about endpoints already this</p> <p>18 morning, but there are early endpoints that people</p> <p>19 would measure -- sputum culture conversion at two or</p> <p>20 six months, say; time to sputum culture conversion.</p> <p>21 But keep in mind these early endpoints really don't</p> <p>22 test whether the planned duration of the regimen is</p>	<p style="text-align: right;">Page 201</p> <p>1 through this a little bit.</p> <p>2 So, superiority is really the gold standard of</p> <p>3 assessing efficacy. It's determined by showing the</p> <p>4 test arm is better than the control. And really since</p> <p>5 an add-on design is a placebo-controlled trial, it</p> <p>6 would be an automatic analysis for an add-on design.</p> <p>7 And here is just a figure to represent the</p> <p>8 superiority design, where I have a number line which</p> <p>9 captures the treatment difference between test and</p> <p>10 control. On the left, it's in favor of control drug;</p> <p>11 on the right it's in favor of the test drug. The</p> <p>12 diamonds, the point estimate from the trial, and the</p> <p>13 parentheses capture the 95% confidence interval. So,</p> <p>14 in this case for superiority, that confidence interval</p> <p>15 would have to be completely to the right of zero,</p> <p>16 demonstrating that the test is superior to control.</p> <p>17 Now, moving on to noninferiority, efficacy is</p> <p>18 now determined by showing that efficacy of the test arm</p> <p>19 is close enough to a known effective control. So, two</p> <p>20 key points in that sentence are close enough, how close</p> <p>21 it has to be, and to a known effective control. So,</p> <p>22 how close it needs to be is the noninferiority margin,</p>

<p style="text-align: right;">Page 202</p> <p>1 which is labeled as M here. And this is all greatly 2 detailed in the FDA Guidance on Noninferiority Trials. 3 So, this margin, M, depends on two pieces of 4 information. One is how effective is that control, and 5 that's called M1, and the other is just based on 6 clinical judgment, and that's how much efficacy we 7 would be willing to lose. And the margin can't be 8 greater than either of those two numbers. 9 So, in this case it's the same number line, 10 where on the left is still in favor of the active 11 control, and right is favor of placebo. But now that 12 confidence interval doesn't need to be completely to 13 the right of zero; it's a more relaxed test. And 14 you're actually -- it can go down to up against that 15 margin, which is the limit of how much the new test 16 regimen can be worse than the active control. And 17 coming up with that margin for TB can be very 18 difficult. 19 So, it depends on the specific trial design, 20 including the patient population, timing and definition 21 of endpoint. And it really depends on what that active 22 control is. So, in the situation that I mentioned</p>	<p style="text-align: right;">Page 204</p> <p>1 of this high impact regimen, which might be better in 2 terms of treatment duration or sputum culture 3 conversion or toxicity, but we'll still want to make 4 sure that you're not losing too much on that final 5 clinical endpoint, which is why we're assessing it for 6 noninferiority. 7 When you assess noninferiority of a test drug 8 to a control drug, it's much more complicated. Because 9 you have a multi-drug regimen, the efficacy of any one 10 of those particular drugs in that regimen is going to 11 be fairly modest compared to the efficacy of the whole 12 regimen. So, in this case it's going to be much harder 13 to conduct the trial. 14 An example would be, let's say you'll have a 15 new drug and you want to replace ethambutol in the 16 drug-sensitive TB regimen. So, you're going to 17 randomize subjects to HRZX as the new drug versus HRZE. 18 In order to determine that FX has efficacy, you need to 19 understand how efficacious ethambutol is in that drug- 20 sensitive TB regimen, and that is going to be very hard 21 to estimate from the literature. 22 Another option would be, let's say a new drug</p>
<p style="text-align: right;">Page 203</p> <p>1 earlier, if it's a test regimen, if you're going to 2 test the efficacy of your complete test regimen to the 3 complete control regimen, and that means you kind of 4 determine the added contribution of the effects from 5 previous Phase I or animal studies. Then you need to 6 understand that the effect of the whole control 7 regimen, which is highly effective in TB. So, that M1 8 that we've estimated would be really very large and 9 should be fairly easy to estimate. 10 So, for instance, in the drug-sensitive TB 11 study, HRZE versus no treatment is going to be very 12 large for patients. Similarly, for MDR-TB, best 13 available therapy for MDR-TB is going to be really 14 quite large compared to no treatment. So, when it 15 comes to estimating a noninferiority margin for testing 16 a test regimen to a control regimen, it's going to 17 really hinge on that clinical judgment of how much 18 efficacy you're willing to lose. It still might wind 19 up being a small number, but at least it's -- there is 20 no data, you are able to come up with a number and then 21 you conduct your study. 22 And just keep in mind, this is often for kind</p>	<p style="text-align: right;">Page 205</p> <p>1 added to drug-sensitive TB regimen, but the regimen is 2 shortened by two months. In that case, it's a little 3 bit easier because your drug would kind of be replacing 4 the last two months of therapy in a drug-sensitive TB 5 regimen. And there is some data to show that that has 6 a fairly large effect. And that's actually in the TB, 7 the draft TB guidance. It's in the appendix, a 8 justification for how you would do that. 9 So, just in conclusion, adequate and well- 10 controlled trials are required to determine the 11 efficacy for TB regimens or drugs, and you really need 12 to put together good evidence on the contribution of 13 each drug in a regimen. 14 The pathway for approval depends on the impact 15 of the regimen. Accelerated approval is possible. 16 It's also possible it could lead to a limited 17 indication if you have limited safety data. 18 Development of a single drug will lead to a different 19 study design than development of a full regimen, 20 especially with high impact. And it's important to 21 discuss development program with FDA as early as you 22 can. Thank you.</p>

<p style="text-align: right;">Page 206</p> <p>1 DR. NAMBIAR: I think we have a couple of 2 minutes, if there are any clarifying questions for 3 Karen.</p> <p>4 DR. LIENHARDT: Yes, thank you very much. A 5 very, very short question, please, Karen. For the 6 early endpoints, sputum culture conversion, you 7 mentioned that you would like to see sputum culture 8 conversion at two or six months. What is this or? Can 9 you please tell us? What does it depend upon?</p> <p>10 DR. HIGGINS: The or was just listing some 11 possible early endpoints. So, I think that would also 12 be something to discuss with us in the development of 13 your program.</p> <p>14 DR. LIENHARDT: Okay, there was nothing really 15 due to the fact that you want two-month culture 16 conversion if it is drug-susceptible TB and six months 17 if it is MDR, or was it really more on type of 18 appreciation of the investigation arm and what the 19 regimen might be?</p> <p>20 DR. HIGGINS: Exactly.</p> <p>21 DR. LIENHARDT: Thank you.</p> <p>22 DR. NAMBIAR: So, we move on to our next</p>	<p style="text-align: right;">Page 208</p> <p>1 people come from. But a common anchor of what we've 2 always believed and frankly I think may be the 3 situation in all other diseases around the world, and 4 therefore I've labeled this as being an approach that 5 has existed in the past, although more so recently, in 6 the present, and I think will continue even more so to 7 be important in the future. It starts out with maybe 8 what could be viewed as a truism, and that is that we 9 have to ensure explicit clarity on exactly the problem 10 that we're trying to fix with the development program. 11 And it has to provide very practical, cost-effective, 12 and implementable solutions for the identified problem.</p> <p>13 And one of the subsets of this is especially 14 where it deviates a little bit from something like an 15 FDA charge, getting regulatory approval is necessary 16 but not sufficient in order to justify a TB drug 17 development program. Now, that doesn't mean that the 18 solutions have to be optimized, but they do have to 19 have a net compelling benefit to patients, to payers, 20 and to healthcare systems. Now, I would say that this 21 is really important in developed countries that are 22 resource-starved, but I think for any of us who follow</p>
<p style="text-align: right;">Page 207</p> <p>1 topic, which will be New Approaches to TB Drug 2 Development. We hear both from a developer and some of 3 you are presenting industry. So, it is my pleasure to 4 introduce Mel Spigelman, who is the president and chief 5 executive officer of the Global Alliance for TB Drug 6 Development. And prior to joining TB Alliance, Dr. 7 Spigelman was at Knoll Pharmaceuticals, which is a 8 division of BASF Pharma. Thanks.</p> <p>9 DR. SPIGELMAN: Thank you very much, and 10 definitely thank the FDA for convening this meeting. 11 It really is fantastic to see the attention being given 12 to TB. So, the first thing that I've done is change 13 the topic of my talk a little bit from new approaches 14 to TB drug development to the past, present, and I 15 should say potential future approaches. So, I took 16 that liberty first, and I think you'll see why.</p> <p>17 Disclosures, I work for the TB Alliance. And 18 now let me first start with what, from my perspective, 19 as being with an organization that is responsible for 20 developing new therapies for TB, the approaches that we 21 see as being relevant, if not mandatory. And this may 22 be different depending on organizations and where</p>	<p style="text-align: right;">Page 209</p> <p>1 or are involved in what's going on even in the United 2 States, this is certainly true here in the US, too. 3 Not from an FDA perspective of approving something, but 4 for having it actually do something in the real world. 5 Let me give a couple of concrete examples that might 6 raise a little more clarity on what I'm trying to say 7 here.</p> <p>8 The first one is an example, and that's 9 actually a real-life example, that if -- you know, 10 would one substitute a drug in first-line therapy but 11 not shorten the duration or increase or decrease the 12 side effects?</p> <p>13 Now, it's interesting, about 10 years ago, or 14 something like that. It was a while ago, Mark 15 Goldberger, who, you know, Ed's predecessor at the FDA, 16 we were in the first meeting I had with the FDA and we 17 were presenting, actually, in a four-month regimen. 18 And he asked, well, why don't you just study a six- 19 month regimen with a drug substitution, you know, and 20 if it works, if it's safe, if it's effective, etc., 21 etc., you can get the drug approved. And I was sort of 22 dumbfounded from even having been in the TB world for a</p>

<p style="text-align: right;">Page 210</p> <p>1 while, because I said why would we do that? It would, 2 you know -- yeah, you would get the drug approved, but 3 why would we do it? He said -- obviously, if anybody 4 who knows Mark, he was trying to be helpful, you know. 5 The goal was to get the drug approved in TB. 6 Now, so that may not be that controversial, 7 but the second example, which I think could be more 8 controversial for discussion at some point is, does 9 adding an additional drug to poor second-line regimens 10 with the only obvious advantage being getting higher 11 sputum conversion rates but no other advantages, does 12 that offer a net benefit? 13 You can get the drugs approved. We've seen 14 two drugs globally get approved on that basis. Does it 15 offer truly a net benefit, if you really consider all 16 of the sort of accompaniments that would go along with 17 that type of development program? So, that is past, 18 present and future. Let me now get down to the real 19 present of what are we really doing in terms of the 20 development programs that we have, at least the TB 21 Alliance. I want to just present two programs, or two 22 approaches that we currently use, one of which has</p>	<p style="text-align: right;">Page 212</p> <p>1 1 type of work. And if a drug could pass Phase 1 work, 2 then it would go into a straightforward two-week -- 3 and, again, I don't like the term EBA. We try to get 4 away from that early bactericidal activity, because, 5 frankly, the real benefit as we see in two-week studies 6 of single drugs is dose ranging. Because there's 7 almost no other chance from a practical point of view 8 to do much in the way of dose ranging for TB drugs. 9 And obviously, it's critical to figure out what dose do 10 you want to work with and -- as opposed to almost every 11 other disease. We can't do dose ranging from a 12 practical point of view when we get into late stage 13 Phase 2s or Phase 3s, not to any appreciable extent. 14 Now, the fact that it has to kill bugs in 15 human beings is clearly critical, but it's not the old 16 days of a two-day EBA to click off yes, no, does the 17 drug kill bugs in people; it's really to try to figure 18 out what's the dose that we want to bring forward that 19 we can at least convince ourselves a little bit that it 20 is the optimized dose. 21 Then the -- what we designed then was saying, 22 okay, before we go much further, we want to take two</p>
<p style="text-align: right;">Page 211</p> <p>1 already been gone into -- both of them have already 2 been mentioned. 3 So, these are specific -- right now, not new 4 approaches, but things that we do. The first one, and 5 Cathy put this slide up earlier, I think, as part of 6 her presentation, is an approach that we really 7 designed -- I think it's now about seven years ago -- 8 when we really were looking for what we called a 9 unified pathway for moving really -- and at that point 10 we were thinking of pretty much of a straightforward 11 start at the beginning, go to the end process. We 12 started it with a pretty intricate preclinical program 13 that defined preclinically -- and Eric can speak to 14 this because he was involved from the beginning -- that 15 we had at that point in time a basket of about 10 16 different drugs. And we said, look -- and they were 17 either in late development or late preclinical or 18 approved drugs seven. And we said, if we took all 19 combinations and permutations that made sense, which 20 regimens would surface to the top as being the most 21 effective or the most promising? 22 That was done in parallel with standard Phase</p>	<p style="text-align: right;">Page 213</p> <p>1 weeks and look at a two-week combination program, and 2 this is all intertwined with the preclinical work and 3 with the Phase 1 work. So, clearly, this has to be 4 done not just based on a single go/no-go criterion, but 5 really on the total profile. If you have two or three 6 drugs with similar toxicologic issues, you know, that's 7 tough to think you're going to push those forward, etc. 8 And similarly, is the benefit -- is there any evidence 9 of synergy preclinically, etc., and then moving into a 10 two-month regimen and then moving into a three-month 11 regimen -- or into a definitive Phase 3 trial. 12 So, this approach, and also the advantage here 13 of what we tried to integrate, and this is another 14 important piece of it is, we were looking for regimens 15 that could cross over between drug-sensitive and 16 conventionally what was called MDR-TB. At least MDR- 17 TB, so we were looking at novel regimens that one could 18 obliterate this distinction. And that raises all sorts 19 of difficulties of how to design those trials when you 20 get especially into the later stages. How do you fit - 21 - you can't randomize MDR patients, for example, to 22 HRZE as the control group?</p>

<p style="text-align: right;">Page 214</p> <p>1 So, without going into all the details of how 2 we finally decided to move this whole paradigm forward, 3 we figured out a way that made sense that if the MDR 4 patients do just as well as the DS patients for all 5 intents and purposes, that would be convincing -- with 6 the same regimen -- that would be convincing and enough 7 proof that it was valid in both.</p> <p>8 Now, it's been raised by other regulatory 9 authorities, also, on the issue of do you really need 10 that or do you simply have a regimen that says you want 11 to use it in patients who are sensitive to the known 12 entities in the regimen, but it's irrelevant what their 13 resistant to. So, again, that's a nuance that went 14 into the whole consideration of designing this path 15 forward for developing regimens.</p> <p>16 Now, about three years ago, four years ago at 17 the most, we started thinking about, well, could we do 18 it a little differently? Because by now we had at 19 least two totally novel drugs that we had access to, 20 and a third one that wasn't totally novel but for which 21 there was almost no preexisting resistance, and said 22 could we sort of skip all of this stuff and kind of</p>	<p style="text-align: right;">Page 216</p> <p>1 this in a well-controlled clinical trial in the sense 2 of the oversight but not in the sense of a control 3 group in the clinical trial. And, frankly, not look at 4 any surrogate endpoints. Look at two-month, actually, 5 at the end of the day cure rates in these patients, 6 understanding full well that this trial could have 7 blown up in the first 10 patients by virtue of either 8 toxicity or lack of efficacy, or anything. And we said 9 let's try this as a different approach, and that's what 10 I think people have heard about now in the Nix trial.</p> <p>11 So, if we look at what are the present 12 approaches that we see in terms of developing new 13 therapies, new regimens in TB, I think for us, at 14 least, we can either kind of move forward with the 15 approach that I showed initially, or in a sense move 16 backward. Because the next step actually with Nix is 17 now that we think we see compelling evidence that those 18 three drugs work in the XDR-TB population, obviously, 19 we're still doing that trial, but we are already 20 starting an optimization trial of that regimen to move 21 backwards. And by that, I mean it would be difficult, 22 although not impossible, certainly, to use the regimen</p>
<p style="text-align: right;">Page 215</p> <p>1 just go to the end and potentially then move backwards? 2 And that was really the genesis of the Nix trial, where 3 we said, okay, you know, have access to bedaquiline, 4 we've got pretomanid, we've got really good early data 5 on those two. We've even used those two a little 6 together. We knew from other people's work that 7 linezolid certainly appeared to have activity in TB, 8 although it had some side effects.</p> <p>9 Now, note that these three drugs had never 10 been used together in a single patient, to our 11 knowledge, and I'm pretty much 100% sure, and we said, 12 look, in the XDR-TB population, we can go right not to 13 a two-month sputum conversion or to have a regimen that 14 may have efficacy, but we can't really even tell people 15 how to definitively use the regimen. But based on the 16 mouse data that Eric had generated with us, and based 17 on other data, we really said let's be a little 18 conservative in the sense of maybe this regimen can 19 cure in four months, but that's maybe going a little 20 too far. And we frankly arbitrarily said let's treat 21 patients for six months, XDR-TB patients for whom the 22 risk-benefits seem to be justified. And obviously do</p>	<p style="text-align: right;">Page 217</p> <p>1 in MDR-TB patients. I would say it would not at all be 2 justified to even consider that regimen because of the 3 linezolid in DS patients. But if we can optimize the 4 regimen in terms of safety, especially, then one could 5 move backwards, so-to-speak, and move it into MDR and 6 move it into drug-sensitive patients, and have that as 7 the path, development path to get one regimen that 8 would suffice for all patients.</p> <p>9 So, I think both of these approaches are 10 viable. I think we've already moved regimens forward 11 and backwards now with both of these approaches. So, 12 with that, let me now move to the next question is, 13 what's the story with new approaches? Because 14 everything I've talked about so far, to me, at least, 15 are what I would call old or present approaches.</p> <p>16 So, I don't have to spend a lot of time on 17 this, because I think we've really been talking about 18 it for most of the morning. Clearly, the lack of the 19 instantaneous readout of response severely limits the 20 implementation, at least in my opinion, of different 21 types of adaptive designs that could be put into drug 22 development.</p>

<p style="text-align: right;">Page 218</p> <p>1 Now, clearly, we've heard about the LAM assay, 2 which could serve a tremendous purpose in that regard 3 if it truly were -- you know, if all the data falls in 4 place and it's scalable, etc. But right now, we still 5 don't have that instantaneous readout that could give 6 us the ability to really pivot very quickly from Phase 7 2 to Phase 3, etc.</p> <p>8 The other point that really is a problem, and 9 I think I tried to bring this up a little bit in the 10 morning discussion is, we don't have a predictive 11 quantitative relationship between Phase 2 readouts and 12 Phase 3 readouts. So, when we look at culture 13 conversion and we really try to then design Phase 3 14 trials and ask the specific questions of, okay, well, 15 what are really the specifics? Are we going to do a 16 four-month experimental arm, a five month, a three 17 month, three-and-a-half months? We don't have the data 18 preclinically that give us a huge amount of comfort 19 that we're picking the one point. And that, I think, 20 is still a limiting factor. But I think we have to be 21 careful not to, you know, as the saying goes, throw the 22 baby out with the bathwater. Because, again, I tried</p>	<p style="text-align: right;">Page 220</p> <p>1 this morning. So, I do think we can learn a huge 2 amount from the preclinical models; obviously, never 3 enough.</p> <p>4 So, that brings us, really, to the next 5 question of, okay, speculating now on what are 6 potential future or new approaches that could be used 7 in TB drug development? And I really put these out as 8 really just sort of very abstract thinking at this 9 point. Because I have to tell you, there's not a huge 10 amount of real thoughtfulness or real concrete 11 proposals behind them, but just to throw out a couple 12 of ideas. Oh, and also, before that, I really want to 13 add, because I think we're all aware of this, is that 14 approaches to TB drug development are going to be 15 highly dependent on any advance we make. So, an 16 approach, for example, like Nix could totally go away 17 almost if we're successful in XDR-TB patients. When we 18 have a four-month regimen, if TBTC and ACTG trial, for 19 example, works and our new standard becomes four 20 months, we've got a whole new ballgame, then, in terms 21 of how to predict for a three-month or a two-month, 22 etc.</p>
<p style="text-align: right;">Page 219</p> <p>1 to mention this morning, preclinical models are 2 predictive; they're just not quantitatively predictive 3 the way it would ideally be desirable to have them. 4 And what do I mean by that? This is a slide that Eric 5 showed, so I'm not going to go into it in terms of if 6 we look at mouse relapse experiment data and then we 7 apply that to a variety of regimens that have been 8 studied in the clinic -- and, again, the slide that 9 Eric showed this morning from his data. Whereas, I 10 don't believe, and I'm sure Eric doesn't believe it, if 11 a regimen cures in a mouse in four months, will it cure 12 in four months in man? That still is a bit of a leap 13 of faith, in my opinion, whether it's four-and-a-half, 14 five, etc. But what really is convincing in terms of 15 the preclinical data is the rank order of the duration, 16 so that in fact from everything we've seen, if the 17 preclinical mouse model, and we still have yet to be 18 able to add on to this hollow fiber and other 19 modalities in terms of preclinical data. But the rank 20 order of efficacy and of predictiveness in man really 21 appears to hold up, at least in this five regimens that 22 are on this page, for which Eric also showed the data</p>	<p style="text-align: right;">Page 221</p> <p>1 But having said that, and absent either having 2 new technological advances or having new breakthroughs 3 with new approvals for different regimens for either 4 DS, MDR or XDR, there are two ideas that I just wanted 5 to float by everyone and obviously for discussion as we 6 see fit. One is the concept of large, simplified 7 clinical trials. These are -- for those of you who are 8 old enough, like me, to remember the concept of large, 9 simplified clinical trials was in vogue really around 10 the '80s and '90s in terms of, you know, the issues 11 around the cost of clinical trials, the complexity of 12 clinical trials, and could they be made somewhat bigger 13 but with less data collection and all of that? And I'm 14 not sure that we can't do something along those lines 15 in TB.</p> <p>16 I think -- you know, I won't do it justice -- 17 you know, Payam brought up the fantastic point this 18 morning that just going through the culture issues in 19 Phase 3 clinical trials is a bear. I mean, it is a 20 nightmare and fully agree with everything that Payam 21 talked about and give credit to what TBTC and ACTG have 22 done in terms of trying to standardize them. But then</p>

<p style="text-align: right;">Page 222</p> <p>1 I raise the issue that if we really had big enough 2 studies, do we have to do culture, or can we live with 3 very few cultures at the end of therapy, for example? 4 Even with different labs doing them somewhat 5 differently but with larger numbers that truly would 6 separate out something that work from something that 7 doesn't. 8 And this goes all the way along the lines, for 9 those of us who have the 100-page case report forms and 10 all the ancillary tests, etc., etc., that really eats 11 into a huge amount of resources, is that could we be 12 thinking about larger but simplified clinical trials 13 that could even be done in some of the better TB 14 programs that exist around the world, etc.? So, that's 15 just one idea to float. 16 And the other idea that I wanted to float by 17 is, should we be thinking about in a Phase 3 type of 18 design, looking at multiple arms, and we could talk 19 about having large, relatively large or noninferiority 20 margins that look at multiple time points for cure. 21 So, that if we had a -- and then, in doing that, we 22 could potentially look at the shape of that cure curve</p>	<p style="text-align: right;">Page 224</p> <p>1 feel comfortable with that after we've proven that it's 2 either a four- or a five-month regimen. 3 So, this would take a much more sophisticated 4 statistical expertise than certainly I have, but to be 5 thinking about would such a design be feasible and 6 practical in terms of dealing with the problems that we 7 have and the limitations that we have as of today? 8 So, anyhow, that's -- thank you very much for 9 the opportunity, and hopefully at least generate some 10 feedback later on this afternoon. 11 DR. NAMBIAR: Thanks, Mel. Our next speaker 12 is Charles Wells, who is an associate vice president 13 and head of development for infectious diseases 14 therapeutic area at Sanofi. And prior to joining 15 Sanofi he was at Otsuka, and before that spent a few 16 years in the CDC. Thanks, Charles. 17 DR. WELLS: Good afternoon, everyone. Can you 18 hear me okay? It's a great pleasure to be here this 19 afternoon to speak with you about perhaps a little bit 20 different perspective on drug development for TB from 21 industry. And as was mentioned, my disclosure is that 22 I work for Sanofi. And I was asked to speak about</p>
<p style="text-align: right;">Page 223</p> <p>1 and not just each one arm by itself in terms of 2 generating more data. 3 So, if we did trials, for example, with a 4 three, four, five -- and I'm just arbitrarily picking 5 these numbers out there. You know, if we did a trial 6 that had a three-month arm in it, a four-month arm, a 7 five-month, and a six-month, even, or not -- if we get 8 a six-month, and obviously a control arm, could we 9 potentially, in a study like that, deal with the issue 10 that we don't have the translational power to know that 11 this will be a four-month regimen, this is a five-month 12 regimen, this is a three-month regimen? And we put all 13 of our eggs into that one basket when we roll the dice 14 on designing that clinical trial, knowing that if we 15 get conservative, like I said on the earliest example, 16 we go with a six-month arm and almost know for sure 17 that we'll get the drug approved, but that's worthless. 18 On the other hand, if we get a drug approved, 19 or a regimen approved for a five-month or a four-month, 20 but, you know, it really could be a three-month 21 regimen, that would be a shame, because that's another 22 five to seven years of a clinical trial to actually</p>	<p style="text-align: right;">Page 225</p> <p>1 these points in thinking about my talk. In particular, 2 approaches taken from industry-based development 3 programs. And as you'll see in my talk, I kind of look 4 at it from the period before 2005, building up to when 5 the new drugs went into development at that time point. 6 And then up until -- okay, sorry, this is always a 7 problem, logistics, for people who are 6.5 feet tall. 8 At any rate, I will talk about this sort of breakdown 9 of periods for development, especially focusing on the 10 two new agents that were approved three or four years 11 ago, the regimens that were studied and why; the trial 12 design endpoints; nuances of combination development 13 from the perspective of taking single agents through 14 development; challenges and barriers in development 15 programs; and then kind of moving forward to 16 registration and beyond. And I think many things that 17 went on during that period apply to what we're looking 18 at today. 19 So, the first really important point to make 20 about industry's perspective is expediency. The clock 21 is ticking. There's -- time-limited patent protection 22 for molecules in development for TB takes 10 to 12</p>

<p style="text-align: right;">Page 226</p> <p>1 years, so there's a rush ahead to try to get something 2 through the development pipeline. And also, too, 3 because of competing resources internally, you really 4 have to give a reason to believe to the key stakeholder 5 to make decisions about appropriation of resources for 6 projects. And so, you really need a quick path to and 7 through proof-of-concept and then bold and grand plans 8 for later-stage development to keep people engaged and 9 committed.</p> <p>10 Unfortunately, the biology of tuberculosis, as 11 we've heard all day today, works against expediency. 12 It's anything but that, and if you think about 13 previously with TB trials coming up to the time that 14 the new agents were developed, treatment at six months, 15 two years of follow-up to chart relapse made a lot of 16 sense from a public health perspective and for 17 patients, but it's a huge challenge for developers. 18 Animal models and early bactericidal activity studies 19 are great early tools but they have limitations, as 20 we've heard again and again today.</p> <p>21 And then sputum culture conversion as a 22 surrogate marker, which I'll talk a little bit more</p>	<p style="text-align: right;">Page 228</p> <p>1 So, just briefly, this is a very simplified, 2 scaled-down TPP, but you're looking for, if it's a new 3 drug or new regimens, novel mechanism of action that's 4 active against resistant strains that are in 5 circulation. In terms of target patient population, at 6 a minimum it should be good for multidrug and 7 extensively drug-resistant TB patients, but as a base, 8 then also good for drug-susceptible TB patients as 9 well.</p> <p>10 Skipping down to efficacy, where M and XDR-TB 11 are concerned, the new agent added to or the new 12 regimens should be superior to the existing treatment 13 that can be achieved. And then also because of the 14 degree of toxicity for treating MDR and XDR-TB, it 15 should be safer.</p> <p>16 So, a little bit more focused now on M and 17 XDR-TB, and it's interesting, because XDR-TB wasn't 18 even defined until 2006 or '07 -- 2006, I believe. So, 19 looking at them collectively as an opportunity for 20 development, it is clear there is an unmet medical need 21 for better efficacy, and shorter, easier and safer 22 regimens. And the idea in the mid-2000s, that this</p>
<p style="text-align: right;">Page 227</p> <p>1 about. Important help in moving the new agents that 2 came through ahead faster, further and faster. And 3 there is no doubt, earlier sputum culture conversion 4 means something clinically for the patients' overall 5 trajectory if they're treated long enough and, of 6 course, it's important for public health. But when? 7 Two months? Three months? Four months? Six months? 8 Even now, 10, 12 years later, there is still some 9 debate about when is the much meaningful time point?</p> <p>10 And then most importantly, as was said again 11 and again today, practical considerations of using that 12 for trials slow contamination capacity for laboratories 13 to support trials.</p> <p>14 So, the other important thing in industry, at 15 least from my experience, is all roads lead to the 16 target product profile and what your label will look 17 like at the end of development. And so, that serves as 18 the blueprint for development throughout the process, 19 and so you should really have a very good idea of where 20 you're headed at the very beginning of the process, and 21 you will be held very accountable to that throughout 22 the process.</p>	<p style="text-align: right;">Page 229</p> <p>1 population could be a great entry point for development 2 was really laid out very nicely in a paper by Dr. Sacks 3 in 2008, where I quote, "Exploring efficacy in the 4 setting of drug-resistant disease may present a certain 5 opportunity," and, "The possibility of accelerated 6 approval based on the surrogate endpoint might be 7 feasible." So, that really set the stage on how to 8 approach development for the new agents that were 9 coming through the pipeline at the time. And this, 10 ironically, could actually confer efficiency for 11 development and hasten the arrival of new drugs to 12 patients who really needed them. Yes, faster to 13 market, but even more importantly, faster access for 14 patients.</p> <p>15 But now to -- so, it's one thing to sort of 16 have the sort of blueprint and the pathway forward, but 17 it's another thing to execute it. And so, I really 18 want to highlight what was going on at the time that 19 the development programs were going on and getting 20 launched for the new drugs, because I think it's really 21 important to keep these things in mind and think into 22 the future for development.</p>

<p style="text-align: right;">Page 230</p> <p>1 So, what had been identified in the late '90s 2 and early 2000s that drug-resistant tuberculosis was 3 going to undo all the great progress that was being 4 made for global TB control. And within the auspices of 5 the Stop TB Partnership, the Green Light Committee 6 mechanism was established to help the rollout and 7 expansion of treatment for MDR-TB in helping programs 8 build better services and support for treating patients 9 reliable drug supply, quality drugs, and as 10 importantly, laboratory services to support their 11 treatment and care. And as you can see, a whole list 12 of things were going on -- limited diagnostic capacity. 13 There were a large reservoir of chronic patients, those 14 that had already been treated with some combination of 15 second-line treatment after several cycles of TB. 16 Weaker second-line drugs were available, like 17 ciprofloxacin. And as the initiative got underway and 18 progress was made, by about 2005, in total globally 19 there were about 20,000 patients that had been brought 20 onto good quality treatment that could even be accessed 21 for possible development. And also, of course, since 22 there had been no new drugs for TB in 40 years, no new</p>	<p style="text-align: right;">Page 232</p> <p>1 bedaquiline in the US and Europe, and delamanid in 2 Europe, it really did stand to test that the Green 3 Light Committee site served as a great network and had 4 the laboratory support to lead to the development of 5 the agents. And I think in a paper by Carol Milnick 6 that suggested this idea of using these sites, that 7 they could be a great platform for development, really 8 held true. 9 At the same time, there were stringent 10 definitions that WHO released requiring multiple 11 cultures to confirm sputum culture conversion and cure. 12 And as you can see, the basic design of the trials was, 13 as has been discussed, an optimized background regimen 14 plus a test agent versus the optimized background 15 regimen. This was actually outlined in Dr. Sacks' 16 paper in suggesting that we follow what had been done 17 in the HIV development community. 18 And looking at the effects on sputum culture 19 conversion for the six months, the way that the trial 20 was designed for bedaquiline, you can see the 21 differences there. And then for delamanid on the two- 22 month sputum culture conversion endpoint. And, of</p>
<p style="text-align: right;">Page 231</p> <p>1 or novel drugs, there was limited experience for doing 2 clinical trials and most definitely with GCP. 3 So, in these earlier years, after the Green 4 Light Committee was launched, some of the earlier 5 programs, the best rates that you could see two months' 6 sputum culture conversion of 30% cure, and the best 7 prevalence was about 60% to 65% with some exceptions, 8 and mortality was about 10% to 20%. So, this was the 9 backdrop for the new agents. 10 I want to highlight here from one of those 11 programs, data from Latvia. These survival curves 12 indicate sort of the heterogeneity of patient 13 populations, and I think it's very informative now, 14 looking forward to the future, some of these breakdowns 15 of patients. And in this analysis, you see that for 16 patients who have never been treated for TB before and 17 are started on MDR-TB treatment, the respond fairly 18 well and fairly quickly compared to those who have had 19 previous treatment with second-line drugs, which is the 20 top dotted line curve. 21 So, leading into the 10 years that it took for 22 bedaquiline and delamanid to be developed and approved,</p>	<p style="text-align: right;">Page 233</p> <p>1 course, because of the accelerated approval, processes 2 for these drugs, they had limited datasets and so they 3 wound up with restricted labels in very specific 4 patient populations for which they could be used. The 5 irony in all this is that they were putting 6 combinations with drugs that had never been formally 7 evaluated for MDR-TB. But I don't think their approval 8 was the end of the story; I actually think that was the 9 beginning of the story. Because what has followed 10 since is that those drugs have actually gone on to be 11 included in drug-drug interaction studies that would 12 evaluate their use together. And then they've been 13 incorporated in treatment optimization trials that I'll 14 talk a little bit about later. So, in fact, that's the 15 beginning of the odyssey and perhaps even the 16 experience with the bedaquiline trial informed to some 17 degree the Nix trial. 18 So, where are we now versus 10 years ago, or 19 12 years ago? So, treatment capacity has expanded. 20 There are a lot more opportunities for patients now. 21 More than 100,000 come onto treatment annually. This 22 is woefully short of the 400,000 or 500,000 that should</p>

<p style="text-align: right;">Page 234</p> <p>1 be on treatment, but it is much improved from earlier 2 in the story. There are also a decreased population of 3 chronic patients now. Those that have gone through 4 iterative rounds of treatment, there are not as many of 5 those patients most likely now as there were before. 6 Better diagnosis. We can go for months now 7 down to days to know that we have a drug-resistant TB 8 patient, and that has had a huge impact independent of 9 the drugs being better available. And then now we have 10 better drugs. Moxifloxacin and linezolid and 11 clofazimine from the existing catalog, and then the new 12 agents themselves. There is also some very good 13 experience looking at MDR-TB patients without previous 14 second-line treatment who can be treated with a shorter 15 course regimen for MDR-TB that was tested out initially 16 in Bangladesh with cure rates of 88%. 17 And so, I definitely think, when you think 18 about where we are in patient populations for 19 development, the WHO report does state that 52% 20 treatment success is what's been achieved overall 21 annually. But that doesn't tell the whole story about 22 the treatment programs that have been well established</p>	<p style="text-align: right;">Page 236</p> <p>1 programs, very high cure, 83%, versus those sites that 2 did not go under the same sort of development, 59.8%. 3 The same for the labs. Labs that had more capacity to 4 do second-line drug susceptibility testing had higher 5 performance than those that had labs with less 6 capacity. And then lastly you see the breakdown there 7 of outcomes for patients based on previous treatment 8 history. 9 Also, too, another great publication from 10 Korea, which shows, in addition to programs, what the 11 newer drugs or the repurposed drugs could do. Shows in 12 this nice study that over the course of three different 13 cohorts evaluated, the treatment success went up from 14 54% up to 84%. And improved outcomes were mostly 15 associated with the frequent use of later-generation 16 fluoroquinolone and linezolid in the third cohort. And 17 linezolid in particular was used for those patients who 18 were refractory to treatment at three to six months. 19 And about one-fifth of those patients were XDR-TB 20 patients. 21 And even where XDR-TB is concerned, things 22 have gotten better. They are still woefully away from</p>
<p style="text-align: right;">Page 235</p> <p>1 and are doing great work in taking care of patients. 2 And so now I'll call your attention to a publication 3 shortly, but in fact, some of these more mature 4 programs can achieve treatment success of greater than 5 80%, and even for XDR-TB patients, greater than 60%. 6 I want to highlight this study from Peter 7 Cegielski and a whole sea of colleagues called the 8 Preserving Effect of TB Treatment Study published last 9 year. This is a multinational perspective cohort 10 study, over 1,000 patients, nine countries and 26 11 sites, and basically all of these sites receiving 12 essentially the same treatment regimen. But what this 13 study was designed to do was to ask the question, did 14 the Green Light Committee mechanism essentially prevent 15 the emergence of additional resistance to second-line 16 drugs? And the answer from the publications is yes, 17 but what it also gave us an opportunity is to really 18 look at treatment in a prospective way and what can be 19 achieved by better programs and better lab services. 20 So, if you look at the top there, you can see 21 that in sites in this stud that received Green Light 22 Committee approval and went through the effort to build</p>	<p style="text-align: right;">Page 237</p> <p>1 where the need to be, but this gives you an idea that 2 things are changing. And I call your attention to the 3 top study there. Sorry for the busy slide. But this 4 is from colleagues in Korea in collaboration with NIH, 5 who did a nice controlled study looking at the benefit 6 of linezolid, basically as monotherapy for chronic XDR- 7 TB patients. And in that study, they achieved six- 8 month sputum culture conversion at 87%, and cure rate 9 of about 71%, with about 11% having -- developed 10 resistance. 11 Equally of interest in Peru, in the lower 12 left-hand corner, our colleagues there building a 13 strong program over the years, showed that for XDR-TB 14 patients who had good laboratory services and access to 15 the drugs, they could actually do quite well with those 16 patients. 17 And then lastly, the trial that was used for 18 the registration of delamanid, about 15% of the 19 patients in that study were XDR-TB, and as you can see, 20 there was an improvement of sputum culture conversion 21 at two months and mortality at the end of 24 months of 22 treatment.</p>

<p style="text-align: right;">Page 238</p> <p>1 So, looking to the future in terms of where 2 we're headed, I think it's very encouraging what we've 3 heard this morning, that advances in the nonclinical 4 realm to improve translational accuracy for the 5 selection of the development of new regimens is very 6 encouraging. It looks like advances have been made 7 with models in the Kramnik mice model, marmosets. A 8 lot of encouraging data coming out of that that could 9 help early on know if we have something or not. And 10 these models are hopefully going to provide better 11 details on drug synergy, antagonism, cross-resistance 12 and whatnot. 13 So, just kind of taking what I took -- what I 14 presented about the period of development for the two 15 new agents, how do we look at patient populations now 16 moving forward? So, clearly, there is still a lot of 17 room for pre-XDR and XDR-TB patients to do superiority 18 trials, but what are the appropriate comparators now? 19 We have regimens with linezolid -- or should we have 20 regimens with linezolid, bedaquiline, delamanid and/or 21 clofazimine? For MDR-TB patients that don't have 22 resistance to fluoroquinolones and injectables, maybe</p>	<p style="text-align: right;">Page 240</p> <p>1 qualification process. 2 So, now a little bit more about trial design. 3 It's been talked about a lot already, so I'll only be 4 adding very little to some really great points made 5 earlier. But just, again, keeping in mind that with 6 conventional design it can take up to 10 years, and you 7 have your standard Phase 1 program, your sort of proof- 8 of-concept, which is a combination of EBA studies and 9 the two-month combination studies. And then onto your 10 Phase 3 program with fixed, balanced randomization. 11 Very, very slow, steady progress of development. But 12 maybe now is the time to investigate adaptive trial 13 design, and some really innovative things are already 14 going on in terms of either using Bayesian adaptive 15 design as is being used in the endTB trial, or the 16 multi-arm, multi-stage design MAMS that's been used by 17 the PanACEA consortium for evaluating high-dose 18 rifamycins for revisiting treatment. 19 Both use information, sputum culture 20 conversion during the course of the trial to adapt the 21 trial, and Bayesian perhaps has more efficiency if you 22 have more than one regimen in the mix that you're</p>
<p style="text-align: right;">Page 239</p> <p>1 now the standard should be the nine-month regimen, and 2 so on. 3 And, again, I really don't have to go through 4 all the details of this slide. It's the challenges of 5 culture-based assessments for endpoints for trials in 6 assessing treatment effect. So, I won't, in the 7 interest of time, I'll skip over this, because it's 8 already been stated this morning. 9 So, bottom line is, we need new tools. And I 10 think there is some very encouraging developments that 11 have been talked about today, which I think makes the 12 future look a bit brighter for expediency and 13 efficiency in getting new regimens developed, the 14 PET/CT imaging holds great promise. And then very, 15 very exciting today, what was presented this morning 16 and then at a webcast with Resist-TB about a month ago, 17 on sputum LAM. And if it holds that it's a 18 quantitative marker that can show potential 19 pharmacodynamic trends, if this assay holds up, this 20 could really revolutionize things for the future. And 21 there I've cited the trials that are ongoing in 22 evaluating this, and it's going through the</p>	<p style="text-align: right;">Page 241</p> <p>1 evaluating, that you're trying to move forward, 2 whereas, MAMS may be more efficient if only one regimen 3 is going to make it through. But both have more 4 efficiency that conventional design. 5 And just a little bit more in thinking about 6 adaptive trial design and the endTB trial. Again, I 7 mentioned that the two new drugs were evaluated as a 8 single agent added to an existing regimen, but then -- 9 and the story really didn't stop there. And I think 10 this is a very exciting indicator that in fact the 11 story was just starting. Once the benefit-risk profile 12 of these new drugs had some degree of establishment, 13 then they could move into these trials to be evaluated 14 I combination with other agents. And as you've seen 15 here in the table, the various agents include 16 bedaquiline, delamanid, clofazimine, linezolid, 17 fluoroquinolones and pyrazinamide. And in this Phase 3 18 study they're examining these five new regimens 19 compared to the WHO control regimen, which is following 20 the guidelines for treatment that WHO has. And here at 21 the bottom you can see the efficiencies that some 22 simulations attached to that trial have suggested it</p>

<p style="text-align: right;">Page 242</p> <p>1 might have.</p> <p>2 And so, taking all of this together, this</p> <p>3 slide was presented already this morning, so I don't</p> <p>4 need to go through the details. But something like</p> <p>5 this is really a game-changer at the point -- at the</p> <p>6 risk of being cliché, for the future of development,</p> <p>7 and regimen development in particular. And so, with</p> <p>8 LAM applied to an adaptive design approach can see the</p> <p>9 light of day, I think it could really change things for</p> <p>10 the future. So, I'm glad to reinforce the message from</p> <p>11 Debra earlier this morning.</p> <p>12 So, lastly, I can't stress this enough and</p> <p>13 it's been stated by Dr. Higgins. In looking to the</p> <p>14 future and working on your plan and your development</p> <p>15 strategy, early engagement of authorities is essential.</p> <p>16 Seek critical feedback on design of programs and trials</p> <p>17 in the face of a very steadily, rapidly evolving field,</p> <p>18 and pay attention to what they tell you. Really listen</p> <p>19 and work together. Questions about patient population,</p> <p>20 the comparator arm, endpoints, follow-up, trial design,</p> <p>21 combination rules, you know, are there efficiencies for</p> <p>22 that, that Dr. Higgins presented earlier. All of these</p>	<p style="text-align: right;">Page 244</p> <p>1 now. And it's ironic, too, when you think about it,</p> <p>2 that Jim O'Neill's report about AMR, one of the largest</p> <p>3 parts of the story that he tells in that report is</p> <p>4 drug-resistant tuberculosis. So, with that I'll end,</p> <p>5 and thank you very much for your time.</p> <p>6 DR. SPIGELMAN: Charles, thank you. I think</p> <p>7 because of the pressure of time, let's move on. Next</p> <p>8 speaker is Andy Vernon. Andy is the chief of the</p> <p>9 clinical research branch of the Division of Elimination</p> <p>10 at the US CDC, and has been involved in clinical trials</p> <p>11 for, oh, a couple of decades at least.</p> <p>12 DR. VERNON: Yes. Thank you very much. I'll</p> <p>13 echo the sentiments of others who have preceded me here</p> <p>14 at the podium in thanking FDA and encouraging their</p> <p>15 continued engagement in this domain. The opinions I'll</p> <p>16 express are those of myself and not of my agency, and</p> <p>17 my conflicts of interest are declared here.</p> <p>18 I'll move quickly through the overview of</p> <p>19 TBTC. I think most of you are familiar with us. I'll</p> <p>20 talk a bit about our approaches to research, talk about</p> <p>21 specific considerations on the role of individual</p> <p>22 drugs, where there's a couple of examples from our</p>
<p style="text-align: right;">Page 243</p> <p>1 conversations can help really, really improve the</p> <p>2 likelihood of success for getting things through</p> <p>3 development.</p> <p>4 And then just a couple of final two points</p> <p>5 here. It's very, very encouraging in thinking about</p> <p>6 taking your development program forward to multiple</p> <p>7 authorities for review and potential approval that the</p> <p>8 possibility that they're harmonized and that your</p> <p>9 program could fit the needs and requirements of various</p> <p>10 authorities is really important. And it's very</p> <p>11 encouraging, in fact, that the EMG, the PMDA and the</p> <p>12 FDA have been in dialogue and have reached an agreement</p> <p>13 to align certain data requirements to stimulate</p> <p>14 development to fight any microbial resistance, which TB</p> <p>15 would fall under that category, I hope, an protect</p> <p>16 global public health.</p> <p>17 And, finally, despite how it's categorized or</p> <p>18 what list it makes or doesn't make, TB is and should be</p> <p>19 a priority pathogen in the fight against AMR. And the</p> <p>20 pull and push mechanisms that are being entertained for</p> <p>21 AMR more broadly are the lifeblood to TB, and I hope</p> <p>22 that TB doesn't lose out in this juggernaut that is AMR</p>	<p style="text-align: right;">Page 245</p> <p>1 work, and end with some comments on our work with other</p> <p>2 networks as well.</p> <p>3 As you know, we were initially funded in the</p> <p>4 early '90s, reorganized and are housed in the Division</p> <p>5 of TB Elimination. And we've enrolled about 16,000</p> <p>6 patients in trials since '95. We are focused on</p> <p>7 regimens and research that is programmatically</p> <p>8 relevant, and we take that particular piece seriously,</p> <p>9 so there are elements of the areas we're talking about</p> <p>10 today that are not particularly applicable for our</p> <p>11 group. We began as a domestic consortium but have</p> <p>12 become international, as you are aware. And over the</p> <p>13 past 20 years we've conducted a number of studies in</p> <p>14 various domains including several Phase 3 studies,</p> <p>15 diagnostic studies, a number of mostly Phase 2b</p> <p>16 studies. We placed a large emphasis on pharmacokinetic</p> <p>17 work.</p> <p>18 We have been collaborating with others in our</p> <p>19 studies for 15 years or more now, and in particular</p> <p>20 have collaborated a good deal with the ACTG.</p> <p>21 These are studies we've engaged in over the</p> <p>22 past eight years, and our current group of studies are</p>

<p style="text-align: right;">Page 246</p> <p>1 shown here, an observational platform study that's 2 ongoing, a study of dose optimization for levofloxacin 3 in treatment of MDR, which is a collaboration, 4 actually, with NIH. And our current Study 31, which is 5 a collaboration with ACTG. We are hopeful to move 6 forward with a study of a new pediatric formulation for 7 rifapentine, and for a six-week LTBI regimen late this 8 year or early next year.</p> <p>9 As you know, we're organized like other 10 consortia. We have a number of working groups and a 11 core science group which bring forward concepts for 12 consideration by the group, and then adoption as full 13 protocols to move forward.</p> <p>14 We've undergone a couple of efforts to review 15 our programs. In 2007, a decade ago, we had a formal 16 external review, which -- whose members encouraged us 17 to continue in the path of doing targeted Phase 2 18 trials, leading the way to Phase 3 trials, and to 19 continue our efforts to collaborate with multiple 20 partners. A retreat in 2012 emphasized the importance 21 of treatment shortening in drug-sensitive TB, as well 22 as treatment shortening in treatment of LTBI. We have</p>	<p style="text-align: right;">Page 248</p> <p>1 As you know, considerations about the role of 2 individual drugs were based early on the population 3 hypothesis put forward by Professor Mitchison and 4 colleagues at the MRC initially. And he and they 5 proposed specific roles for the activity of anti-TB 6 drugs, focusing on bactericidal activity, sterilizing 7 activity, and drugs which were important in the 8 prevention of acquired drug resistance. And we have, 9 in the work that we and others continue to do, we have 10 more or less continued to focus on these important 11 elements.</p> <p>12 However, in recent years we've begun to 13 realize that it is considerably more complex than we 14 had initially thought. The work of Veronique Dartois 15 and others have emphasized that individual drugs might 16 penetrate, as Chuck and others have mentioned today, 17 into different compartments at different rates to 18 different degrees over different time frames and by 19 entry into different compartment components, all of 20 which makes it very increasingly difficult to predict 21 what will be the impact of individual agents or 22 regimens.</p>
<p style="text-align: right;">Page 247</p> <p>1 continued with interest in a variety of these other 2 domains, including drug-resistant TB, but our capacity 3 in this latter domain is a bit limited at the present 4 time.</p> <p>5 As I said, our studies are programmatically 6 relevant. They're expected to drive guidelines, to 7 have domestic as well as international relevance, and 8 to help establish clinical excellence in program 9 settings. Our core science chairs have repeatedly 10 emphasized the importance -- I had this conversation 11 with Payam in the past month -- the importance of a 12 robust Phase 2 engine to identify promising regimens. 13 Our Phase 2 working group called CRUSH TB addresses 14 this need, and we have worked with MRC statisticians 15 and others who emphasize the importance of Phase 2 now 16 with their proposal, as you know, Patrick's here, for 17 novel Phase 2c approaches.</p> <p>18 We pay very close attention to murine results. 19 Every TBTC meeting now, at least for the past decade, 20 has invited a report from the murine TBTC at Hopkins. 21 And so we consider this an important part of our 22 efforts.</p>	<p style="text-align: right;">Page 249</p> <p>1 I want to provide briefly two examples from 2 work we've been involved with in the effort to sort 3 some of this out. Over the past 20 years we have 4 worked intermittently but largely with, in particular, 5 with rifapentine, a long-acting rifamycin, as you know, 6 with -- shown here in the yellow, to illustrate its PK 7 curve difference from rifampin, shown in the bluish- 8 green.</p> <p>9 In Study 22, we found that relapse rates 10 varied substantially in patient subgroups, in patients 11 with both cavitation and positive sputum culture at two 12 months. Rates of relapse were 22% in the rifapentine 13 arm and 21% in the rifampin arm, and with neither the 14 rates were about 1.9% and 1.7%, a substantial 15 difference that influenced our 2003 guidelines 16 domestically.</p> <p>17 TBTC investigators 17 years ago, reasoned that 18 the group of patients who were cured with a 19 continuation phase of once-weekly INH/rifapentine were 20 paucibacillary, and thus similar to persons with LTBI. 21 Murine data available at the time supported this logic. 22 It was thought that LTBI patients were likely to have</p>

<p style="text-align: right;">Page 250</p> <p>1 even lower bacillary loads and that increasing the dose 2 of rifapentine from 600 to 900 would further strengthen 3 the combination against LTBI.</p> <p>4 British experience in the Uganda Preventive 5 Therapy Trial with three months of isoniazid and 6 rifampin suggested that the three-month, once-weekly 7 LTBI regimen was reasonable. And, as you all know, 8 that expectation was borne out and the results were 9 published in 2011, showing noninferiority and really 10 suggesting superiority of the 3HP once-weekly regimen. 11 But, of course, nothing was as simple as it seemed, and 12 one of the problems we encountered was this flu-like 13 and other systemic drug reactions among persons -- 14 about 4% or 5% of persons receiving this regimen.</p> <p>15 I was particularly concerned about this as we 16 issued guidelines for use of 3HP and wanted to be sure 17 that we had published, also, information about what to 18 expect and how it might be dealt with in this regard. 19 And I was one of those who was not very convinced that 20 there was much potential for INH to be playing a role 21 in this set of reactions since we knew that rifampin 22 had been associated with a similar problem when used</p>	<p style="text-align: right;">Page 252</p> <p>1 efforts to study the interaction between dolutegravir 2 and weekly isoniazid/rifapentine. That study was 3 stopped after four patients had been enrolled because 4 two of the patients had marked hypersensitivity 5 reactions. And so, I thought, well, we're seeing this 6 again.</p> <p>7 And then at the ACTG network meeting we were 8 informed that there is now evidence at least for a 9 possible for INH in this reaction -- in this study. 10 Because there was a closed meeting I can't say more 11 about that, but I'm sure it will be published -- 12 presented soon. But it was a reminder to not to leap 13 to conclusions as we try to think about the roles of 14 individual drugs and regimens, and that the complexity 15 of the roles of these drugs is not well appreciated.</p> <p>16 The next part of my talk I could begin by 17 quoting Jeremiah, "Oh, foolish people without 18 understanding, who have eyes and see not." I think 19 this has to do with the four-month regimens. I think 20 that the use of two-month culture as a surrogate began 21 with this publication from Professor Mitchison and 22 Professor Nunn, I think -- or, this was a letter just</p>
<p style="text-align: right;">Page 251</p> <p>1 intermittently previously. However, that publication 2 on hypersensitivity included this note: Given the 3 similarity of published reports of flu-like syndrome 4 associated with rifampin and the reactions seen in this 5 study, one might think rifapentine the more likely 6 cause of these symptoms than isoniazid. However, 7 rifapentine was better tolerated than isoniazid on 8 rechallenge, about tenfold better. In a recent 9 multicenter randomized clinical trial of intermittent 10 continuation phase therapy, participants received 900 11 mg of rifapentine twice weekly or 1200 once weekly, 12 both in combination with moxifloxacin, and there were 13 no reports of possible hypersensitivity or flu-like 14 syndrome. But it is possible that the lack of flu-like 15 syndrome was due to the regimens or the populations 16 being studied.</p> <p>17 Kelly Dooley pursued a couple of 18 pharmacokinetic studies in healthy volunteers using 19 intermittent rifapentine regimens in both and ran into 20 problems with participant reactions. Earlier this year 21 at CROI, Christina Brooks, Alice Pallen and colleagues 22 from the NIH, presented a poster on their initial</p>	<p style="text-align: right;">Page 253</p> <p>1 from Professor Mitchison, I think. "In conclusion, 2 there is good evidence that culture conversion at about 3 two months is a reliable measure of the sterilizing 4 activity of drugs and can be used, for instance, in the 5 development of new rifamycins as an indicator of 6 efficacy long before the ultimate relapse rates are 7 known." I note that he limited that to new rifamycins.</p> <p>8 When we looked at culture conversion rates as 9 we were preparing to think about treatment shortening 10 and looking at Phase 2, we initiated this assessment -- 11 Bill Burman led that effort -- to look at how much 12 treatment -- how much improvement in two-month culture 13 conversion meant something. And at the time we thought 14 that, well, there was a 13% increase overall in two- 15 month conversion when PZA was added to regimens. And 16 that was enough to shorten for three months, so we 17 thought a similar shortening might play a role in 18 shortening the current regimen by another 30%. 19 Sometime not long after that and as we were already 20 well into our Phase 2 work, Bob Wallace had published 21 his meta-regression model suggesting that it was going 22 to -- that the culture conversion rates were going to</p>

<p style="text-align: right;">Page 254</p> <p>1 have to be substantially better to achieve a four-month 2 regimen. As you know, several sets -- four different 3 trials were undertaken, two single site trials, which 4 showed about a 17%, 18% increase in two-month culture 5 conversion, and our two studies that showed very slight 6 or no increase in culture conversion at two months, 7 when moxi was substituted into the standard regimen. 8 And, of course, then the three large studies were 9 undertaken subsequently, which did not achieve a four- 10 month treatment-shortening outcome.</p> <p>11 I was interested that Jean-Philippe Lanoix and 12 Dick Chaisson and Eric had published a very nice piece 13 discussing that finding, and what we had perhaps 14 misunderstood in the efforts to look at moxi in this 15 way in CID in 2016. And they went about this by 16 dissecting out the different models that were used 17 according to the different infection models and the 18 different species that were used to predict this. And 19 very consistently showed that if you look individually 20 at each of these, they don't suggest that four months 21 was going to be achievable. They go on to say that we 22 share the views that further development and validation</p>	<p style="text-align: right;">Page 256</p> <p>1 combinations be more consistently studied across a 2 greater range of phase 2 endpoints.</p> <p>3 We attempted to do some of this with our Phase 4 2 work on rifapentine, our Studies 29 and 29X. We 5 discussed and decided to go first with a simpler model 6 of relatively lower dose of rifapentine, no food, no 7 weekend doses, and we failed completely to achieve an 8 improvement in culture conversion. And so, we 9 essentially pivoted without having to resubmit -- 10 without having to completely redesign our protocol 11 added a dose-ranging element and continued forward with 12 the same protocol to look at higher doses with weekend 13 dosing and food and, indeed, found much higher rates of 14 two-month conversion, which encouraged us to move 15 forward with a Phase 3 trial. I show here the, as 16 Chuck pointed out earlier, the issue is exposure and 17 not dose, so that you see that in the red box the 18 groups who had higher exposures achieved very high 19 culture conversion rates on both solid and liquid 20 culture, exceeding the rates in the liquid culture in 21 the standard regimen by 24% to 34%. So, we're now 22 doing this Phase 3 looking at four months of a high-</p>
<p style="text-align: right;">Page 255</p> <p>1 of more pathologically similar yet reproducible animal 2 models is warranted. We also agree that more 3 predictive biomarkers for Phase 2 trials should be 4 sought. However, the analyses of murine model data 5 presented here and the predictions from the model of 6 Wallis et al., suggest that the principal failure in 7 the development of these regimens was not misplaced 8 confidence in murine models and trials based on sputum 9 culture-based surrogate endpoints, but rather an overly 10 optimistic translation of the output of these studies 11 into expectations of a two-month treatment-shortening 12 effect.</p> <p>13 Gerry Davies' group have published in the past 14 couple of years a couple of meta-analysis basically 15 making some similar points about the importance of 16 looking at the Phase 2a and 2b data. The striking 17 feature of the available dataset that they looked at is 18 the variability of pooled estimates of effect for all 19 the endpoints examined. Our review shows that the 20 existing evidence base supporting phase 2 methodology 21 in tuberculosis is highly incomplete, and that it's 22 desirable that a broader range of drugs and</p>	<p style="text-align: right;">Page 257</p> <p>1 dose rifapentine-based regimen.</p> <p>2 We're also aware that working with Rada Savic 3 and others that there are pharmacokinetic, 4 pharmacodynamic data from our Phase 2 trials that raise 5 that same -- the question once again: Will we be able 6 to achieve culture conversion in the most severe 7 patients? And suggesting that indeed we should be 8 giving continued consideration to some modification of 9 regimens in the face of baseline predictors of 10 severity.</p> <p>11 The Nix TB trial of the TB Alliance was -- of 12 course has captured all our attention with very high 13 two-month conversion rates in a previously almost 14 untreatable disease, and high rates of relapse-free 15 cure. I was led to look back at the mouse data 16 supporting this regimen and wondering about the role in 17 particular of linezolid, and I show here the -- one of 18 the murine studies looking at three-month and four- 19 month culture conversion in the regimens of 20 bedaquiline, pretomanid with or without linezolid. And 21 you see this very marked difference in culture 22 conversion at three months, suggesting that linezolid</p>

<p style="text-align: right;">Page 258</p> <p>1 really is playing a very important role in this 2 regimen. Now, it begs the question of the role of the 3 other two drugs, because we don't really have the data 4 in this study to dissect that piece out, but it is 5 strongly suggestive of a critical role of linezolid. 6 And it's part of my point, that we really need to 7 seriously look at the data that we have already. 8 A similar point made here in the Phase 2 that 9 was presented by Rod Dawson, the bedaquiline, 10 pretomanid, moxi and PZA study that was presented also 11 at CROI as a poster. And I just note this really 12 important difference, which we've seen in the mouse 13 studies, also. When PZA is active as in the case of 14 PZA-sensitive patients versus when PZA is not active in 15 the PZA-resistant patients, and so the very important 16 role that PZA is playing in conjunction with 17 bedaquiline. 18 So, a few comments about other networks. As 19 you know, we've been partnering with ACTG on this very 20 large trial now. Dick Chaisson shared a couple of 21 slides on their activities. A very similar set of 22 priorities to those that TBTC have and that make us</p>	<p style="text-align: right;">Page 260</p> <p>1 efforts. A need for continued and increased 2 collaborations among the major trial funders and 3 networks. A useful step toward this goal might be the 4 consideration for creation of an annual or biannual 5 research conference focused in this area. And then 6 continued efforts by regulatory authorities, such as 7 FDA and international bodies to educate their 8 interested communities and improve the development 9 path. Workshops such as this are a promising step. 10 Thank you. 11 DR. NAMBIAR: Thank you, Dr. Vernon. Our next 12 speaker is Jeffrey Starke. Dr. Starke is a professor 13 of pediatrics at Baylor College of Medicine, and has 14 been the director of the Children's TB Clinic for over 15 three decades. Dr. Starke will be talking to us about 16 trial design considerations in the pediatric 17 populations. Thank you. 18 DR. STARKE: Thank you very much. It's a 19 pleasure to be here, and I really want to thank the FDA 20 and Sunita and the organizers and everybody for having 21 me here to talk about this subject. I am a member of 22 the Data Safety Monitoring Board for the PK studies of</p>
<p style="text-align: right;">Page 259</p> <p>1 good partners from a philosophical point of view. They 2 have a very impressive and very large set of trials 3 already completed or active in a very short period of 4 time. 5 This is a quote from Dick's slide, which he 6 presented to his external review group earlier this 7 year. "Partnerships are essential for conducting TB 8 clinical trials." I can remember 15 years ago, when it 9 was very difficult for us to find partners, because 10 everybody felt they would be able to do it when they 11 needed it without looking for additional partners. We 12 have a lot of work going on now. The clinical trials 13 landscape is very different from what it was 15 years 14 ago, and a number of fascinating efforts underway. 15 In conclusion, I just emphasize that we need 16 more and more consistent work in preclinical and in 17 Phase 1 and 2 evaluations of new agents and regimens. 18 And we need to pay attention to those results very 19 carefully. We need more strategically linked Phase 2b, 20 Phase 2c, Phase 3 efforts begun with a successful end 21 in mind and substantially simplifying the 22 administrative environment of major development</p>	<p style="text-align: right;">Page 261</p> <p>1 delamanid for my disclosure. And I want to thank Tony 2 Garcia-Prats in South Africa, and some folks in the TB 3 Alliance for some help in preparing this talk. 4 I have a feeling this talk is going to be 5 really different from other talks that you've heard so 6 far today. Ironically, just before Andy's talk I got a 7 phone call about a child that I'm helping out with 8 multidrug-resistant TB meningitis in Texas. And what I 9 came to realize is that we are completely making up how 10 we are treating, and to be perfectly blunt, that child 11 is benefiting from basically nothing that has been 12 talked about so far here today. And unfortunately, 13 that's part of our current state-of-the-art. Some of 14 it unavoidable, some of it avoidable. 15 So, how does childhood TB differ from adult 16 TB? It's a fundamentally different disease. It 17 develops much more rapidly after infection, 18 particularly in children less than two years of age. 19 It is a paucibacillary form, probably not as 20 paucibacillary as TB infection, but still 21 paucibacillary in the vast majority of children. And 22 only 30% of cases can be confirmed microbiologically.</p>

<p style="text-align: right;">Page 262</p> <p>1 There is a diagnostic tetrad that really involves 2 symptoms, radiology or physical examination, tests of 3 infection and epidemiology. And there are standardized 4 research definitions which are hopefully used now in 5 clinical trials for those 70% of kids that can't be 6 confirmed microbiologically, but clearly that's a huge 7 limiting factor in doing drug and efficacy studies. 8 I haven't heard really anybody talk about 9 extrapulmonary disease, and there's a greatly increased 10 propensity for extrathoracic disease in children, up to 11 30% of children get extrapulmonary disease, especially 12 meningeal and miliary TB. Relapse and failure are 13 obviously very difficult to define because we usually 14 can't define them microbiologically. 15 Children tolerate drugs better than adults do 16 in general, so that's a very good thing. And fewer 17 children have other significant medical problems, 18 hepatic, renal and cardiac, and so forth, that can 19 affect both pharmacokinetics and the ability to 20 tolerate the drugs. 21 The two target groups for pediatrics really 22 are kids less than two and adolescents, and you can see</p>	<p style="text-align: right;">Page 264</p> <p>1 The estimated mortality of 210,000, that would 2 be 21%. That's the actual measured mortality of 3 children from tuberculosis in the pre-chemotherapy era. 4 I'm going to let that one sink in a little bit. And, 5 of course, that's because we're not finding these kids, 6 diagnosing them and properly treating them. 7 The global burden of MDR-TB in children, 8 again, estimated 25,000 to 32,000 cases a year, but a 9 very small minority are identified and certainly are 10 not getting properly treated. And, of course, HIV 11 association with TB, even with ART, these kids still 12 tend to have worse outcomes. 13 LTBI, just to mention briefly, tens of 14 millions of children obviously with tuberculosis 15 infection, at least 2 million probably infected with 16 MDR-TB. Those are our cases of the future. And the 17 estimated child household contacts less than 5 eligible 18 for treatment globally is in the millions, yet this is 19 not being done at all in most of the high burden 20 countries. 21 Current TB regimens for children are pretty 22 much the same as they are in adults, and I'll be coming</p>
<p style="text-align: right;">Page 263</p> <p>1 this is based on the pre-chemotherapy era of up to 50% 2 of children less than a year of age who get TB 3 infection will go on to develop TB disease. And up to 4 25% of them will develop serious forms of disease, 5 particularly meningitis and miliary disease. One to 6 two years of age, 25% will develop disease, and then it 7 goes down, the so-called favored age of children in 8 elementary school. We don't know why that is, but it's 9 been observed in virtually every human population. And 10 then we start to see more cases in adolescent 11 population as well. So, the adolescents and the very 12 young kids are the two biggest groups. 13 The global burden of TB prior to 2012, there 14 were no global estimates of tuberculosis in children 15 given by WHO, because there was no methodology to 16 develop those estimates. Now there have been several 17 modeling studies, and it's estimated there are a 18 million cases of children, about 10% of the total 19 burden, but only a little over a third of those cases 20 are actually notified. We heard earlier, I think, 23% 21 of cases not reported in adults; well, over 60% of the 22 cases in children probably are never notified.</p>	<p style="text-align: right;">Page 265</p> <p>1 back to that point several times, so I'm not going to 2 spend a lot of time on this particular slide. 3 What are some of the current knowledge gaps in 4 the treatment of childhood TB right now? Well, PK and 5 adverse effect profiles for existing drugs, I have a 6 kid right now with a very difficult-to-treat infection 7 and I was considering putting him on clofazimine or 8 bedaquiline, and it involves the CNS. I could find 9 virtually nothing on clofazimine levels in the CSF, and 10 he's 5 years old, I have no idea what dose of 11 bedaquiline I would use in him. Even though that drug 12 has been licensed for years, there is zero 13 pharmacokinetic data for 5-year-olds on that particular 14 drug. Very frustrating. 15 The optimal duration in follow-up of TB 16 regimens for drug-susceptible and drug-resistant TB, we 17 have limited data. Adequate drug combinations in 18 relevant doses for many of the forms of extrapulmonary 19 TB that have been for the most part unstudied. Optimal 20 duration in combination of drugs for TB treatment in 21 children living with HIV, we're starting to get some 22 data, but we're behind in optimal drug combinations and</p>

<p style="text-align: right;">Page 266</p> <p>1 durations for MDR-TB in children, especially those with 2 so-called minimal disease. We know that regimens that 3 work in adults tend to work in children, but that 4 doesn't help us define actually if we need less drug or 5 fewer drugs, or for a shorter period of time in these 6 children with paucibacillary disease.</p> <p>7 So, there are some real barriers to the 8 inclusion of children in TB studies. Obviously, this 9 difficulty of microbiologic confirmation of disease 10 failure and relapse is a huge barrier, huge problem. 11 There is difficulty in performing PK sampling in 12 children, especially infants and toddlers, who are big 13 targets. And especially very important, the 14 developmental pharmacokinetics and pharmacodynamics of 15 young children, particularly in the very youngest age 16 groups, is very, very important.</p> <p>17 There is really complacency about the 18 effectiveness of existing regimens. Well, they work, 19 so what do we really need to do?</p> <p>20 Trial design issues, what are the proper 21 endpoints? What are the proper sample sizes for 22 children, especially when we start to break them down</p>	<p style="text-align: right;">Page 268</p> <p>1 together, and I have no idea about the pharmacokinetics 2 under those conditions, and I have no idea about the 3 safety profiles, especially when we get beyond the 4 first line drugs. I would argue that anybody in this 5 room treating an adult under those conditions would 6 almost consider it unethical, yet it's standard 7 operating procedure in pediatrics because of lack of 8 information. And that's one of our biggest problems.</p> <p>9 The next two slides I'm just throwing out to 10 show you. If I were to show you this slide in 2010, it 11 would in essence be empty, but there are -- and this is 12 the good news -- many, many trials going on now 13 involving children, looking at regimens for both 14 prevention of disease and also treatment of disease. 15 So, we are making progress in finally getting 16 information. Most of these actually are PK studies and 17 pharmacodynamic studies. There are not as much 18 efficacy studies because of the difficulty of doing 19 those studies in children.</p> <p>20 There have been several really nice papers 21 that have been published including children in 22 tuberculosis trials, at what stage is it appropriate</p>
<p style="text-align: right;">Page 267</p> <p>1 by different age groups?</p> <p>2 Capacity. We lack trial sites around the 3 United States, certainly, and around the world for 4 actually conducting good studies in children. There 5 has been very little capacity building until recently. 6 Complicated research oversight and some regulatory 7 concerns, which I'll come back to.</p> <p>8 And then we still hear this, that we can't do 9 studies in children because it will take funding away 10 from adults. I mean, we actually hear this. Reminding 11 you that children have more than 10% of the disease but 12 get less than 2% of the research funding by current 13 measurements.</p> <p>14 Regulatory issues are huge. So, the European 15 Union has a regulation that requires an early pediatric 16 investigation plan no later than the completion of PK 17 studies. The United States, orphan designation, we've 18 already heard this. So, let me tell you in practical 19 terms what this means. When I'm treating a child, even 20 with drug-susceptible TB, I'm taking pills that are 21 meant for adults, we crush them, we maybe put them in a 22 solution, we give them with food, we combine them</p>	<p style="text-align: right;">Page 269</p> <p>1 and when should things be done. And this is just an 2 algorithm from one of them about when is it reasonable 3 to introduce children, asking several questions. Is it 4 reasonable to assume that children, when compared with 5 adults, have a similar disease progression in response 6 to intervention? Yes/no. If it's yes, then is it 7 reasonable to assume a similar exposure response with 8 the drugs compared to adults? And so forth. I'm not 9 going to go through the whole algorithm, but the point 10 is, people have thought this out and in general, for 11 tuberculosis, the answer to most of these questions is 12 yes. Of course, there are some differences in disease 13 expression and other things, but in general, especially 14 when it comes to dealing with drugs and drug regimens, 15 the answer to most of these is yes, which leads to a 16 justification of earlier involvement of children in 17 trials.</p> <p>18 So, what are some of the lessons we've learned 19 over the years? Well, efficacy, again, difficult to 20 study regimens as opposed to individual drugs in 21 children because of problems with sample size, cost, 22 capacity, lack of microbiologic markers. We realize</p>

<p style="text-align: right;">Page 270</p> <p>1 that, but the truth is, almost everybody I know in 2 childhood tuberculosis is willing to accept the premise 3 that if it works in adults it will work in children. 4 And so, efficacy studies are not -- I don't want to say 5 they're not important, but they're probably not 6 necessary in order for us to accept that certain drugs 7 and certain regimens may be extremely useful and 8 helpful to use in children. We almost take that off 9 the table. 10 The aim is to match the PK and area under the 11 curve and other pharmacokinetic and -dynamic 12 measurements in children with those that are known in 13 adults to be both safe and effective, and that's really 14 the major goal of many of the pediatric studies. 15 We might need efficacy studies for children 16 for some forms of extrapulmonary tuberculosis, and also 17 when it comes to drugs and regimens for prevention, 18 treatment of infection or primary prevention, well, 19 then some pediatric efficacy very well may be important 20 as well. But remember that some children with milder 21 forms of disease may actually require fewer drugs for a 22 shorter period of time, so we agree that's what done</p>	<p style="text-align: right;">Page 272</p> <p>1 studies? Well, traditionally nothing was done until 2 after a drug was licensed, and I'm sorry to say, but 3 once a drug is licensed, the motivation is gone. And 4 we know this because drug after drug after drug after 5 drug after drug, we have no pediatric data for -- or 6 limited pediatric data. So, we already have proof-of- 7 concept that that simply doesn't work, and as Einstein 8 said about insanity, continuing to do the same thing 9 and expecting a different result pretty much means 10 you're crazy. 11 So, the consensus is that a pediatric study 12 should begin with safety and basic PK are established 13 in adults, which is usually somewhere between Phase 2a 14 and Phase 2b studies. We also feel strongly that 15 adolescents, and most people are using now 10 years of 16 age and older based on their PK and pharmacodynamics, 17 should be included in late phase adult studies and 18 later on. And you heard a little bit about this 19 earlier today about adolescents being included in adult 20 studies, and I think the pediatric community would be 21 completely behind that concept. And also, begin 22 development of pediatric dosage forms much earlier.</p>
<p style="text-align: right;">Page 271</p> <p>1 for adults will be efficacious. It's possible we could 2 do less for children and that also would be 3 efficacious, but difficult to figure that out and 4 certainly not when new regimens are introduced or 5 starting to be used. 6 The general consensus for us, it's okay to 7 enroll children in drug research after the following 8 things. There is a full range of nonclinical studies 9 in adult animals. Safety, pharmacology, genotoxicity 10 studies and appropriate juvenile animal studies do not 11 raise any alarms, any signals or cause for concern. 12 The animal and human studies have substantiated anti- 13 tuberculosis activity, no surprise there. The PK and 14 PD data from adults allow for selection of appropriate 15 PK targets for children where a safe dose has been 16 established, which is around Phase 2a or 2b. I'm 17 talking about drug approval phases now of the drug. 18 And it would be helpful, of course, if there was some 19 data on drug interactions with ARV drugs, since TB in 20 children living with HIV is such a huge problem in many 21 parts of the world. 22 So, when should we actually begin pediatric</p>	<p style="text-align: right;">Page 273</p> <p>1 Not after licensing, but during Phase 2a, so that 2 they're actually available at Phase 2 at or around 3 Phase 2b so, in fact, the pediatric studies can begin 4 immediately. We think this is an extraordinarily 5 important concept for new drug development. 6 Several papers have been published about 7 accelerating clinical drug development. This is one 8 for 2015, and I know it's hard to read things that are 9 like this. But this just talks about both 10 developmental strategy and then some of the challenges 11 that were historical, that are current and that are 12 proposed. So, if we look at developmental strategy, 13 historically there was no specific pediatric 14 development. Kids were given adult doses or adjusted 15 according to weight, but we know that that's an 16 incredibly simplistic way to do things. 17 Currently, pediatric development is generally 18 initiated once the drug or regimen is approved for 19 adults, starting with adolescents and then gradually 20 moving to children so-called dosage de-escalation. But 21 now what's really being proposed is single-dose PK 22 studies begin as soon as successful Phase 2 adult</p>

<p style="text-align: right;">Page 274</p> <p>1 studies are complete, and then later maybe multi-dose 2 comparisons as well. And you're going to see a little 3 bit more of this in a couple of slides coming up as 4 well.</p> <p>5 For pharmacokinetics and study design, the 6 conservative approach was this step-wise age de- 7 escalation. You would do adolescents and then you 8 would do junior high type kids and then elementary 9 kids, and then finally get down to younger kids. And 10 now I would say within the pediatric TB community, age 11 de-escalation is pretty much accepted as unnecessary 12 for the vast majority of drugs unless there is some 13 specific safety concern, especially for a particular 14 age child. And what I really want to emphasize is that 15 kids less than a year of age and particularly less than 16 three months of age have completely different PK and 17 pharmacodynamics than really any other population, yet 18 we don't even have data for isoniazid and rifampin in 19 that particular age group. And so, we really need to 20 develop that much easier, and these are just some of 21 the suggested age ranges in a consensus panel of 22 pediatric TB experts for how it might be useful to</p>	<p style="text-align: right;">Page 276</p> <p>1 For dosage formulations, they need to be age- 2 specific, they need to be palatable with acceptable 3 taste and acceptable all around, and that needs to be 4 developed while the drugs are going through the 5 approval process.</p> <p>6 Trial capacity, we need much more robust 7 network. There is very, very, very little funding to - 8 - relatively speaking -- for trial networks, like Andy 9 talked about, the trial networks that are based mostly 10 for adults.</p> <p>11 Incentive for child studies and formulations. 12 Again, there are people in this room that know much 13 more about this than I do, but extended market 14 exclusivity, priority review vouchers and so forth 15 really haven't worked for pediatrics. There is the 16 concept of advance market commitment that may be 17 something interesting to explore. Remember the numbers 18 that I showed you, internationally the potential 19 markets for childhood TB are huge, especially treating 20 tuberculosis infection.</p> <p>21 I think it's important to include pediatric 22 experts on data safety monitoring boards and other</p>
<p style="text-align: right;">Page 275</p> <p>1 break down kids in terms of study, but not in a de- 2 escalation but in sort of an all-in approach, in most 3 cases.</p> <p>4 Appropriate sample size for PK, there are some 5 challenges here. What is the appropriate sample size 6 for PK within each age group? How many kids do you 7 really need and where do you need to get them from? 8 You need them from different trial sites with different 9 genetics. And how much variation is there, really, 10 that you need to account for in doing these basic 11 studies? Probably single-dose sampling in all age 12 groups and then move to multi-dose sampling as well. 13 Rationalizing sample points, exactly when should blood 14 be drawn and trying to reduce the burden, especially in 15 the smallest children. Drug concentrations of CSF, 16 which in the CSF has been really neglected but is 17 really a very important point for pediatrics. So, 18 those 210,000 kids that are dying, a lot of them have 19 TB meningitis. Use of dosing simulations, which many 20 people in this room know way more than I do. And then, 21 of course, how to do trial design for children who also 22 have HIV infection.</p>	<p style="text-align: right;">Page 277</p> <p>1 things, and requiring pediatric studies for sources of 2 pediatric funding.</p> <p>3 I give this example, and I may rankle some 4 people in the room by doing this, but I'll do it 5 anyway. Many decades ago it was decided that 6 particularly in low resource, high burden countries, 7 the thing we were promoting to diagnose TB was sputum 8 smear, microscopy. And the good news, you know, you 9 find a lot of cases and you find the most contagious 10 cases. But by making that decision, it ensured the 11 exclusion of children from international tuberculosis 12 control. I'm going to let that one sink in, too, 13 because sputum is useless in children, next to useless. 14 So, there was no hope of diagnosing TB in children 15 using that as the particular standard. And that's why 16 it's so important to consider pediatric-related things 17 and have pediatric experts at the table when decisions 18 are being made about policy, about science, about study 19 design. How can we design studies to learn the most 20 that we can then apply to children as well?</p> <p>21 This is actually from the TB Alliance in 22 showing the traditional at the top, how we go through</p>

<p style="text-align: right;">Page 278</p> <p>1 the whole adult development process and then we go into 2 the pediatric development process, hopefully, and now 3 trying to combine these things and accelerate them. An 4 accelerated pediatric drug developmental pathway could 5 allow life-saving treatments to reach children sooner 6 than they do today.</p> <p>7 And this is just an extension of this, again, 8 from the article by Murray, and I won't go through the 9 entire thing. But it says many of the elements that 10 I've said about when during individual drug development 11 Phase 1, 2a, 2b and 3, we should be introducing various 12 aspects of pediatric drug development, and it's a nice 13 summary slide of all these principles.</p> <p>14 So, the overview of the approach. Create 15 regulatory and economic incentives for industry and 16 academia to develop and study pediatric formulations of 17 old and new drugs; create capacity-building for 18 pediatric trials; start development of child-friendly 19 pediatric formulations earlier; start pediatric PK 20 studies concomitantly with Phase 2b studies in adults; 21 establish function within childhood TB community. You 22 know, the HIV people have just passed us by incredibly,</p>	<p style="text-align: right;">Page 280</p> <p>1 "Children have the same right to benefit from research 2 as do adults." Thank you very much.</p> <p>3 DR. NAMBIAR: Thank you very much, Dr. Starke. 4 So, I think we will take a maybe 10-, 12-minute break, 5 and if we can be back by 3:40, that would be great so 6 we can get started exactly at 3:45.</p> <p>7 [Break]</p> <p>8 DR. SPIGELMAN: [Next is Dr. Christian 9 Lienhardt], who is the team leader for TB Elimination 10 within the global TB program. And Christian is going 11 to summarize, to a certain extent, on the lessons 12 learned from completed TB trials, and also those 13 implications. Christian, thank you.</p> <p>14 DR. LIENHARDT: Thank you very much. You're 15 right, Mel, summarize to a certain extent. So, good 16 afternoon, everybody. Thank you very much to FDA for 17 inviting me to come to this important workshop. I 18 really appreciate even more in the sense that when I 19 started the work at WHO to look at how to introduce -- 20 how to make sure that new drugs are being evaluated by 21 the World Health Organization and being proposed for 22 use in countries, which is really related to the World</p>
<p style="text-align: right;">Page 279</p> <p>1 and they have the pediatric anti-retroviral drug 2 optimization group that's been incredibly successful in 3 getting ART pediatric formulations available and 4 distributed throughout the world. So, we need to 5 develop some consensus priorities on these key drugs 6 and formulations for children in TB, identify the 7 research gaps and specific ways of going about trying 8 to approach them.</p> <p>9 I'm going to end with a quote, as many people 10 often do. This is from Bill Burman's paper a while 11 ago. First looking at this, "An overzealous attempt to 12 protect some children from the possible harms of 13 research perversely causes harm by either denying 14 access to treatment or through exposing children to the 15 risks of inappropriate dosages of new medications." 16 This is my life. This is what I do every day. 17 And in general, the people that want to not include 18 children in studies are never the pediatricians, 19 because we know that that means that we're then going 20 to have to use unstudied, unproven drugs and 21 formulations in children once those drugs become 22 available. And I certainly believe in the final quote.</p>	<p style="text-align: right;">Page 281</p> <p>1 Health Organization.</p> <p>2 I started circulating to the most important, 3 stringent regulatory authorities starting with FDA, and 4 I must admit that the way I've been received here was 5 really extremely welcoming and very warm. And we 6 started an extremely good collaboration, which has led 7 to the fact that when bedaquiline has been approved by 8 the FDA, then at WHO we're ready to immediately embark 9 on the evaluation of the product and the recommendation 10 we could do for the countries for the use of the drug. 11 So, that's, I think, is worth mentioning.</p> <p>12 So, in this talk where I've been asked to 13 speak about the lessons learned from completed trials 14 and implications for future trials, I will address the 15 various approaches to trial designs for tuberculosis; 16 mention a little bit about endpoints, some 17 considerations; summarizing all what has been said 18 today; touch upon the new trial designs; and then 19 mention briefly about the work we've been doing at the 20 World Health Organization on target regimen profiles 21 for TB treatment. And relate the lessons learned and 22 suggestions for future studies to how we at WHO</p>

<p style="text-align: right;">Page 282</p> <p>1 consider that as extremely important for the way we can 2 make recommendation for the use of drugs and regimens 3 for TB patients. 4 So, it's been a very intense day, so I'm going 5 to try and summarize the best I can. I tried to -- 6 inevitably there will be some (inaudible) things which 7 have been done, but I try to put all of that in 8 prospect. And starting to put in prospects is really 9 looking at the history and, as you can see here, taken 10 from a publication a couple of years ago, is that the 11 notion of development of treatment of tuberculosis has 12 always been in constant interaction both with the 13 amount of drugs, amount of regimens from the very 14 start, in 1946, which was the first randomized clinical 15 trial ever looking at streptomycin for the treatment of 16 tuberculosis and realizing it was leading to emergence 17 of resistance. And since then the history of TB 18 treatment has always been combining, trying new drugs 19 and finding the right regimens. And I think that's 20 important because this is exactly where we are placing 21 ourselves. 22 So, what are the approaches to trial design?</p>	<p style="text-align: right;">Page 284</p> <p>1 treatment to four months without substituting a new 2 drug. And as we heard earlier, it's all about what we 3 can set in terms of control regimen and expectations 4 from the new regimens. 5 You know about the publication of the three 6 trials and it has been shown already about the results, 7 that none of them were able to demonstrate 8 noninferiority of the regimens with substitution of 9 drug for moxifloxacin or gatifloxacin. 10 Interestingly, and that brings already to one 11 of the first questions. If you look here at the 12 results, in most of the arms we had a pretty good 13 collection of sputum culture at two months with very 14 high rates in all of the various arms, even though some 15 of them were doing quite badly in terms of relapse, as 16 you can see. And I put on the top here the Study A, 17 which interestingly showed that with exactly the same 18 regimen for infancy phase either for eight months or 19 six months' duration, there were similar conditions at 20 two months with different relapse rates at the end of 21 treatment. So, bringing already questions about the 22 use of the two-month culture conversion as a marker of</p>
<p style="text-align: right;">Page 283</p> <p>1 We have seen that today there are several of those, the 2 classical path in drug susceptible TB, the accelerated 3 approval in MDR-TB, the combination development path, 4 then the unified path in drug susceptible in MDR-TB and 5 on uncontrolled trials. That's again trying to 6 summarize what has been discussed. I'm going to look 7 at those quickly and try to draw the main lessons 8 learned. 9 In terms of classical path, the way we've been 10 learning in the TB, drug susceptibility has been the 11 three trials which have been carried out to substitute 12 EHRZ control regimen, ethambutol or isoniazid with 13 either moxifloxacin or gatifloxacin. And these were 14 the REMox, OFLOTUB and RIFAQUIN trials. 15 They were a noninferiority design and a margin 16 of noninferiority was determined by limit of what could 17 be expected to be achieved using reduced duration of 18 the control regimen. Delta was set at 6%, and I quote 19 here Stephen Gillespie in his paper on the result of 20 REMox that was expected to reflect consultation with 21 clinicians in high burden countries and reanalysis of 22 previous trials showing the effect of shortening</p>	<p style="text-align: right;">Page 285</p> <p>1 treatment outcome, treatment activity. 2 It's important to try and stop on these two 3 trials and try to reflect on what has been shown, and 4 we have embarked together with CPTR on the meta- 5 analysis of the three trials with a total sample size 6 of more than 3,000 patients. And that has been the 7 place of this so-called TB-ReFLECT, an analysis of 8 fluoroquinolone clinical trials to try and see what we 9 can learn from the trials and what's the failures of 10 treatment they can tell us and how the different arms 11 can be informing us about the way patients were 12 behaving in terms of bactericidal and sterilization 13 activity. 14 What can be found from this TB-ReFLECT and 15 these are the result which I showed the results shown 16 at the Union Conference in Liverpool last year and now 17 being presented -- is still being worked on. We showed 18 that the failures where in the standard of care and the 19 test arms were mostly associated with insufficient drug 20 levels and mainly rifampicin. So, that tells us 21 already about the importance of adherence to treatment. 22 The longer duration of treatment as expected</p>

<p style="text-align: right;">Page 286</p> <p>1 was beneficial and the culture-based predictors were 2 more efficient to predict outcome at four months than 3 two months. But interestingly, what we were looking at 4 was the baseline covariates, and we identified a group 5 of so-called hard-to-treat patients, which showed a 6 higher risk of unfavorable outcome with the following 7 covariates being HIV infected, older, underweight, with 8 a high initial smear in the sputum and the presence of 9 cavity in chest x-ray. 10 So, that tells us that there might be some 11 difference here within the various groups submitted to 12 the trials. Bias different in the groups and the 13 concept that maybe one duration or one type of trial 14 doesn't fit all. And the one duration for all will 15 need reexamination. So, it's interesting and that work 16 is still ongoing on that to try and see whether this 17 so-called hard-to-treat patients can be identified and 18 might need specific treatment, either treatment 19 duration or dosage. 20 So, that was the classical path to 21 substitution of one element of the regimen. The other 22 one is accelerated conditional approval on MDR-TB. We</p>	<p style="text-align: right;">Page 288</p> <p>1 combo, and that is what is being shown here. 2 So, combo in the Phase 2, 14-day EBA study, 3 and then being led to the 8-week serial sputum colony 4 count, and then if the combo is shown to be 5 statistically better than the control, HRZE being 6 brought into the Phase 3 trials. So, that's the 7 combination development, which has been further 8 refined, and you've seen this slide another time today. 9 That has been refined to the next stage, which is the 10 unified path in drug susceptible and drug resistant 11 regimen development, and that's the path taken by TB 12 Alliance, so that's today. 13 This unified path has been used for the B-PA- 14 Z-M combination -- bedaquiline, pretomanid, 15 pyrazinamide and moxifloxacin and CO5, who are patients 16 with newly diagnosed drug-susceptible or MDR-TB, 17 sensitive to moxifloxacin where randomized if they were 18 drug susceptible to comparison of bedaquiline, 19 pretomanid and pyrazinamide versus EHRZ. And those who 20 were MDR-TB were receiving the same combination plus 21 moxifloxacin. 22 The Phase 2 results, which we showed earlier,</p>
<p style="text-align: right;">Page 287</p> <p>1 spoke about that also today. That has been the path 2 followed for approval of bedaquiline, but the FDA and 3 similarly by delamanid by EMA a couple of years ago, 4 and no need to go back on those. But what is 5 interesting is that while the two studies provide 6 important information about the safety and efficacy of 7 the two new drugs, they do not provide any information 8 about the best way these drugs could be used within a 9 regimen. And therefore, a series of trials, and just 10 here is an example of all the various trials are 11 trying, among others, to try and see what is the best 12 combination these drugs can be used. So, this is again 13 part of the path being used but with the limitation 14 that we are speaking here about drugs and not about 15 regimens. 16 So, because of that, there has been a couple 17 of years ago, already the feeling that the development 18 pathway should be looking at combination, and that has 19 been an approach taken by the TB Alliance, and trying 20 to go from the stage of the Phase 2 trials to look 21 around the single drugs, being informed either by the 22 mouse model, trying to go to EBA studies with the</p>	<p style="text-align: right;">Page 289</p> <p>1 showed that there was evidence of substantial 2 additional benefit from the addition of moxifloxacin, 3 and that was an indirect comparison. And the next step 4 would be either a Phase 3 using a four-drug MDR regimen 5 among this group. 6 So, this is the unified path of being 7 followed, and all of those paths are bringing the main 8 issue about efficacy endpoints. And here I use slides 9 made by our colleague, Gerry Davies, from PreDICT-TB, 10 which shows very well what all the different aspects in 11 terms of what can be detected for considering the 12 bacillary load and over time, and what we are looking 13 at in terms of efficacy endpoints. And the fact that 14 we are always completely condemned by this limit of 15 detection and trying to see what we can obtain in the 16 various development of the bacteria in response to 17 treatment. And looking at either what happens during 18 the treatment in terms of culture conversion at two 19 months or time to culture conversion, and then presence 20 of failure during treatment. 21 And then after treatments, all those among who 22 might have been shown to have been (inaudible)</p>

<p style="text-align: right;">Page 290</p> <p>1 developing on recurrence either at early stage or at 2 the late stage with relapse. 3 And these efficacy endpoints are all the ones 4 which are being collected, and if we look at the Phase 5 2 studies and here this is a systematical review done 6 by Burnett (ph) and Gerry recently published in CID. 7 And looking at 133 trials with Phase 2a and B outcomes, 8 it has been shown that EBA days 0 to 2 and eight weeks’ 9 culture conversion were the most commonly reported 10 endpoints. And again, as mentioned by Andrew earlier, 11 there was striking heterogeneity in the way that the 12 endpoints were being reported along these various 13 studies. 14 Going back to the fact that we are looking at 15 the two months’ culture conversion, the effective 16 replacing ethambutol with moxi or gatifloxacin with 17 first-line therapy was being addressed through various 18 trials, and here I show the slides from the early 19 OLOTUB trial, the Phase 2. Because what interestingly 20 was done here is that the rate of decline of viable 21 colony counts was assessed in repeated cultures weekly 22 over the entire phase of treatment. So, what was being</p>	<p style="text-align: right;">Page 292</p> <p>1 advantage in addition to the time to culture conversion 2 at a very specific time point, like two months, of also 3 considering the dynamic effect of time to event 4 endpoints. 5 So, I mentioned about PanACEA, so PanACEA was 6 an attempt to integrate to use in tuberculosis, the 7 multi-arm Phase 2-3 trials, which were originally 8 developed in oncology with planned interim analysis. 9 The final analysis is done on the definite endpoint, 10 and the usual Phase 3 bacteriological endpoint of 11 failure or relapse can be used. An intermediate 12 endpoint used to compare each experimental arm with a 13 common control at interim analysis, and the arms are 14 dropped if there was insufficient evidence of benefit 15 using the prespecified critical values. So, the MAMS 16 approach was being used in TB because gave further 17 ability to screen multiple regimens and drop those 18 which are less promising, failing to achieve the 19 specified targets. 20 So, the feasibility of MAMS has been shown in 21 TB with the PanACEA trial. The arms without evidence 22 of sufficient efficacy were dropped early, thereby</p>
<p style="text-align: right;">Page 291</p> <p>1 modeled here was about the rate of decline, where the 2 traditional way is shown here in the study by Conde was 3 to just repeat over time the culture conversion and 4 looking at the evaluation between the test and the 5 control arms in terms of proportions of patients 6 converting or not. 7 So, we discussed at length about the 8 viability, the validity of the months to culture 9 conversion as the trial level surrogate markers, so 10 it's no need to go on further on that. But what it 11 tells us is the debate is still some hope and where we 12 should consider using longitudinal endpoints as well, 13 because they're for the advantage of being independent 14 of the sampling at time points. There is an 15 unrestricted scale of measurement that are open to 16 greater statistical power and well adapted to 17 cumulative meta-analysis. 18 This has been used in the PanACEA trial, where 19 the time to culture conversion were being assessed 20 through the various regimens and being shown here for 21 the regimen with 35 mg rifampicin as being much higher 22 significantly compared to other arms. So, there is an</p>	<p style="text-align: right;">Page 293</p> <p>1 reducing the sample size. There was a slight risk of 2 dropping an elective regimen; however, the trials were 3 shown to be logistically challenging, the culture 4 results for reasons described by Payam earlier. The 5 culture result was low and not being good predictors, 6 so that makes the case for better and real time 7 biomarkers that could be used earlier in treatment. 8 And the question is, would limited data on relapse 9 assist our decision-making process? 10 So, all that shows that we need real time 11 assessment of efficacy in TB regimen development, and 12 the major issue, as mentioned also earlier today, is 13 the lack of direct readout of response looking at the 14 amount of TB organism being killed. That severely 15 limits the measure of treatment effect, and the lack of 16 predictive quantitative relationship between the Phase 17 2 readouts, organisms killed, and the Phase 3 readout, 18 the cure. It is unclear how to translate culture 19 conversion outcomes. That has been mentioned as one of 20 the main problem in terms of translating Phase 2 to 21 Phase 3 results. So, we need new biomarkers for 22 conducting measurement of bacterial load in sputum and</p>

<p style="text-align: right;">Page 294</p> <p>1 the example has been given amply with the LAM assay 2 today. 3 Another way to accelerate development is the 4 Phase 2c step design in the sense that the culture 5 conversion is limited value and the regimen is likely 6 to be affecting Phase 3. So, a more informal Phase 2 7 study can be done which includes information on long- 8 term outcomes, and that is what is proposed with a 9 Phase 2c step trial proposed by Patrick Phillips and 10 collaborators. 11 Additionally, to study the interim duration in 12 Phase 2 and to generate richer data prior to more 13 informed Phase 3 go and no-go decision-making. And the 14 sample size will be similar to Phase 2b study. The 15 novel regimens would be given for the intended duration 16 of treatment -- three months or four months, and the 17 patients being followed for 12 months' post 18 randomization. And then the endpoint being measured 19 would be a composite failure relapse endpoint. 20 The last aspect of the unified path is the 21 uncontrolled confirmatory trial. So, we had some 22 development recently with the Ebola epidemics and this</p>	<p style="text-align: right;">Page 296</p> <p>1 somehow in quotes is can we apply that from XDR then to 2 the pre-XDR then to MDR-TB? And that is an important 3 question to address up to where can we go? Do we 4 consider that this is a situation of a complete new 5 regimen and pan-TB type of regimen that we can somehow 6 de-escalate on the various groups? Or is that a point 7 where we should start to use an historical control and 8 start to have properly randomized control trial? 9 So, speaking about that, we at WHO developed 10 target profiles for TB treatment and the idea was to 11 start with the goal in mind. That means that we wanted 12 to try and frame the fact that with these targets and 13 specifications that the developers should meet for the 14 performance of new TB treatment, and it should align 15 with the needs of the end users. So, with this in mind 16 and thinking about the target audience, the 17 pharmaceutical industry, research institutions, product 18 development partners, donors, NGOs, CSO, we thought we 19 would try and address this potential target profiles 20 for treatment regimens. So, here going away from the 21 simple aspect of the drugs but to the regimen itself. 22 And we placed ourselves in the view that there</p>
<p style="text-align: right;">Page 295</p> <p>1 paper from Lancet mentioned that the trials of new 2 treatment for Ebola were being justified on the fact 3 that when conventional care means such a high 4 probability of death, 70%, it is problematic to insist 5 on randomizing patients to it when the interventional 6 arm holds out at least the possibility of benefit. 7 Ethical arguments are not the same for all levels of 8 risk. And it was further mentioned that equipoise is a 9 useful principle but it can break down when 10 conventional care offers little benefit and mortality 11 is extremely high. 12 This is somehow the logic being followed here 13 with the Nix-TB trial about the fact that there was a 14 complete justification in the absence of inefficient 15 treatment to undertake the study with a completely new 16 regimen. 17 The particular consideration to address for 18 this uncontrolled confirmatory trials. The first is 19 about the arguments being used that are applying for 20 XDR, which is being used, but do they apply similarly, 21 and that's what Mel mentioned about going forward or 22 backward, and here I used the word de-escalation</p>	<p style="text-align: right;">Page 297</p> <p>1 would be a scale-up of expert more widely than what was 2 shown this morning, and that's the outcome of testing 3 patients who are suspecting to have tuberculosis will 4 be through Xpert being labeled as either being Xpert- 5 positive or not, so rifampicin-susceptible or 6 rifampicin-resistant. And we place ourselves in this 7 paradigm and developed target regimen profiles for 8 rifampicin-susceptible or rifampicin-resistant. And 9 then we took one further step of the pan-TB regimen 10 that could be given to patients in the situation where 11 there is no diagnostics available. 12 So, all the three target regimen profiles are 13 being described in this book and they are described in 14 such a way that we show for each of them the clinical 15 indications of the treatment, whether rifampicin- 16 resistant or forms of TB and pan-TB regimen. We list 17 the critical endpoints to be obtained and the way they 18 should be measured. For instance, nonrelapsing cure at 19 two, four, six or nine months after starting treatment. 20 We describe the target populations, like children, 21 adults, persons living with HIV. And we give 22 identifications about the treatment characteristics,</p>

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<p>1 like expected duration, frequency route of 2 administration and the formulation. And for each of 3 those we give other priority or desirable attributes, 4 and the way we place that is to say that some of the 5 attributes should be considered absolutely 6 indispensable and with a go/no-go decision to what's 7 the development of a regimen, whereas, some other 8 attributes would be considered as desirable. That 9 means being in the place for a decision on the type of 10 -- how to say -- sorry, I don't find the words in 11 English now -- when you try and see what is the 12 respective advantage. So, that is what I can say, 13 sorry about that.</p> <p>14 So, what about lessons learned? So, if I try 15 to group the various aspects, which I went through very 16 rapidly in this conversation and taking into 17 consideration what has been discussed today, in terms 18 of the lessons learned from the various completed 19 trials, there are a series of implications for the 20 treatment to be used, to be tested, as well as for the 21 design.</p> <p>22 For the treatment implication, first of all</p>	<p>1 consider at the time and at the level of the trial. 2 Spot on to ensure appropriate representation 3 of this population to allow robust subgroup analysis. 4 And then it doesn't prevent us to go for a short for 5 future regimens, pan-TB regimen and the approach 6 between something which is much more individualized, 7 doesn't prevent for looking for pan-TB regimen that can 8 be used in certain conditions.</p> <p>9 In terms of design for future regimens, we 10 have seen that an increasing number of potential 11 regimens are being assessed and they need to be able to 12 be reviewed at the same time, so there is an increasing 13 wealth of various regimens to be tested and it will 14 more likely increase in the future.</p> <p>15 Alternative adaptive designs enable more rapid 16 differentiation between multiple candidate regimens, 17 but we are aware that there are still logistical 18 constraints that have to be addressed.</p> <p>19 And we are aware about the culture conversion 20 with limited value for predicting long-term outcome and 21 the high need of quantitative assays of bacterial 22 burden over time. They need new treatment response</p>
Page 299	Page 301
<p>1 and what quite strikingly, the most impactful 2 intervention is to ensuring adequate dosing and 3 adherence to treatment. This is the baseline situation 4 that we ought all of us to ensure.</p> <p>5 Looking at the reflect TB output, the 6 importance of rifamycins as the backbone of shortened 7 therapy was reemphasized and underscoring the role of 8 the high dose. And we heard from Payam and Andrew 9 about the various studies TBTC is doing on that.</p> <p>10 The patients with high bacterial burdens and 11 experiencing slow decline in bacterial burdens over the 12 initial four to eight weeks of treatment constitute a 13 subset most likely to relapse. And there is evidence 14 that different patient groups may require different 15 treatment duration. The so-called hard-to-treat 16 patients should be or may be considered as a specific 17 population for longer treatment duration and/or higher 18 dose.</p> <p>19 And these are implications for Phase 2-3 20 trials, because it raised a point of knowing whether we 21 need to consider initial patient stratification when we 22 decide to go on to treatment, and that is important to</p>	<p>1 biomarkers.</p> <p>2 The uncontrolled studies may have a place, 3 like shown with Nix-TB early in development, and then 4 the question is being posed about what I call the de- 5 escalation or expansion from the specific groups, like 6 the XDR-TB to a group, what Mel mentioned, about going 7 forward or back forward. And the choice of the 8 noninferiority margin needs careful consideration, as 9 does the need of bio-creep.</p> <p>10 In terms of PK/PD, we had a series of 11 important discussions today, but the PK/PD analyses are 12 critical. Using drug exposure to understand 13 intermediate endpoints in addition to dose selection is 14 key, and it is important to examine the relation 15 between dose and treatment duration for the efficacy 16 endpoints. So, PK/PD data should be incorporated to 17 build integrative PK/PD models that could reveal 18 further opportunities for regimen optimization, 19 including drug-drug interaction and safety, and improve 20 trial designs.</p> <p>21 Lastly, an important point is about data, 22 trial data collection. There is a need of consistency</p>

<p style="text-align: right;">Page 302</p> <p>1 in collecting clinical data across the trials, and this 2 is needed to expedite integrated learning and the 3 capacity to be comparing between trials and to merge 4 data for further meta-analysis for systematic review. 5 So, the definition of Phase 3 clinical trial 6 endpoints should be set at minimum with recurrence and 7 relapse. There is a need -- sorry, I missed that. 8 There is a need for global platform independent data 9 standards that enable data exchange and information 10 system, and that's the example given earlier about the 11 capacity to use, for instance, the C-DISC system. 12 So, we discussed at length about what should 13 be efficacy, but we shouldn't lose mind that safety 14 data are key as well. 15 So, in order to finalize this type of quick 16 summary of lessons learned, I want to place myself now 17 with the WHO hat and the fact that what we are doing is 18 to issue guidelines on new TB treatments. And we've 19 been using, as can be seen here, the -- we've been 20 evaluating the new drugs and new regimens, bedaquiline 21 and delamanid, and the new shortened regimen treatment 22 for MDR-TB. So, we are using all this type of analysis</p>	<p style="text-align: right;">Page 304</p> <p>1 then we are satisfied that we have the best available 2 evidence. For that we need to have a very strong 3 dialogue between developers, but also between 4 regulators and policymakers. And, of course, down the 5 line we need to make sure that once regimens are being 6 proposed there is full access to the novel products 7 that are arising from research. 8 So, with this in mind I would like to thank 9 the Task Force on New TB Drug Policy Development that 10 has been putting together the target regimen profile 11 mentioned, and all the colleagues mentioned here who 12 have been helping me in putting together this 13 presentation, and helping me looking at all the various 14 lessons learned from the various trials. So, with that 15 I thank you very much for your attention. 16 DR. SPIGELMAN: Any questions specifically for 17 Christian before we go into the general question 18 session? No, okay, great. So, we have, I guess, close 19 to a half hour or so for panel discussion or for any 20 questions from anybody in the room, and I guess we 21 probably could open it up, because clearly a lot of the 22 topics discussed this morning overlap, to a certain</p>
<p style="text-align: right;">Page 303</p> <p>1 and data in order to be able to do guidelines for the 2 countries. 3 And our guidelines are based on best available 4 evidence. We use the GRADE approach for evidence 5 assessments across a series of questions and outcomes. 6 And there are set criteria for moving from evidence to 7 recommendations. 8 Our main aspect is what is the best available 9 evidence that can be brought about that ultimately 10 would be benefiting patients? So, we need for clearly 11 and rationally justified approach about the choice of 12 drug combination, design, conduct, endpoints and 13 analyses. We need to have data that we can evaluate, 14 and for that, following the development of the target 15 regimen profile, we intend to develop information to 16 regimen developers that will describe the data that 17 would like to be seen so that we can review evidence 18 for policymaking. 19 What is important again is to look at -- to be 20 sure that from the time that development of new regimen 21 is being made the appropriate data are being collected, 22 and that when we receive all the data for application,</p>	<p style="text-align: right;">Page 305</p> <p>1 extent, with the topics this afternoon, too. So, let 2 me first see if there are any questions from either the 3 panel or from the floor, or topics that you want to 4 clarify. 5 DR. COX: So, Mel, let me just try and expand 6 a little bit on what you covered in our talk and invite 7 you to comment on it, too. So, and this overlaps, too, 8 with Cathy's talk. It sounds like really the goal of 9 what it is that you're trying to do with regimen 10 development is trying to move forward by leaps and 11 bounds rather than by smaller steps, if I'm 12 understanding things correctly. And you're trying to 13 do it in the most informed way by trying to use the 14 preclinical information as much as possible, whether it 15 be hollow fiber, animal models, you know, recognizing 16 that it doesn't give you the absolute answer, but it 17 allows you to make rational choices that you can then 18 move forward and test in clinical trials. With the 19 hope being that it's not just sort of changing one of 20 the components of a multidrug regimen, but it's 21 actually to try and use maybe three drugs that haven't 22 been combined before, in something totally new.</p>

<p style="text-align: right;">Page 306</p> <p>1 And, if you don't mind, too, I remember a 2 comment that you made once that I felt was very 3 interesting and I think it underlies what it is that 4 the goal is here, which is if in fact you can -- you 5 know, we think of the terms drug-resistant TB, drug- 6 susceptible TB, and in essence if you can come in with 7 a wholly new regimen, those terms may in essence become 8 somewhat arcane, because new treatment options are 9 available and new mechanisms of action. So, did I get 10 that, right? I mean, and please do correct me, because 11 I think that is one of the newer aspects, I think, that 12 is being brought in the TB drug development through the 13 work of a number of folks, including yourself, and it 14 seems to be one of the ways to get to new regimens and 15 sort of make bigger steps forward more quickly. And 16 not without some degree of risk, but also to be able to 17 change things.</p> <p>18 DR. SPIGELMAN: Yeah. So, I think it's a 19 little bit of a cross between what you said in terms of 20 at least the first topic. I think most progress that's 21 ever been made in terms of product development is 22 incremental. You know, the real major, major leaps</p>	<p style="text-align: right;">Page 308</p> <p>1 DR. STARKE: Do you mind if I point out that 2 that formulation is not available in the United States? 3 DR. SPIGELMAN: Yeah, I was going to get to 4 that, Jeff. So, I wouldn't call that an unbelievably, 5 you know, sort of tremendous advance, but in the first 6 year this was taken up by well over, I believe, 50 -- 7 or the amount of sales, so-to-speak, or distribution 8 was over 50% of the documented population of pediatric 9 TB in children.</p> <p>10 So, I think it's really identifying the 11 combination of what's feasible and what's doable and 12 what's going to actually work. Now, clearly, if in 13 that process, you can totally revolutionize TB therapy, 14 sure, if we can get to the point that we do away with 15 all the old drugs and put in only new drugs that are 16 great. But I think the skeptics are accurate who have 17 said, look, the chances of getting three new drugs not 18 only from an efficacy perspective but from a toxicity 19 perspective, because obviously, that's probably as big 20 a challenge as the efficacy piece of it. Those are 21 pretty high bars to really cross. And we really should 22 certainly be prepared to undertake those but not be</p>
<p style="text-align: right;">Page 307</p> <p>1 are, relatively speaking, few and far between, 2 historically speaking. But, on the other hand, a 3 program or a development plan that's not going to be 4 adopted and adopted wholeheartedly by those for whom it 5 is intended to be used is probably not worth doing. 6 So, it really is walking that fine line between doing 7 the program that has enough net advantages so that the 8 adoption will be rapid and will be significantly 9 desirable by those for whom it's intended, but yet it 10 does not have to be so totally revolutionary.</p> <p>11 And one of the primary examples that I can 12 give is that over the last three years or so we were 13 involved in reformulating first-line pediatric drugs, 14 which really is not an unbelievable revolution. It's 15 simply taking -- it was taking three-year-old 16 guidelines from the WHO and getting known technology 17 and enticing manufacturers to actually do the proper 18 formulation, which is not mind-boggling science, to get 19 a pediatric formulation. That really is appropriate, 20 and what Jeff was talking about and, you know, not to 21 be crushing pills for kids, and not knowing what the 22 absorption is like, etc., etc.</p>	<p style="text-align: right;">Page 309</p> <p>1 naive in the sense that it's not going to be an easy 2 thing to do. So, that's the answer in terms of 3 threading that needle between significant meaningful 4 change, but it doesn't have to be totally 5 revolutionary.</p> <p>6 DR. COX: Interesting. It almost sounds like 7 advice, to some extent, for a financial portfolio, 8 which is you want to balance your risk, to some extent.</p> <p>9 DR. SPIGELMAN: Well, frankly, and we also 10 have to balance the ability to attract the funding to 11 do the work, which is not an inconsequential, you know, 12 I think barrier. Because if we could do everything 13 that we would like to do -- and this is just the TB 14 Alliance. I mean, it's the same for -- you know, 15 Charles said it, too. Within a company that's even 16 dedicated to TB, they are not going to get the 17 resources to do everything that probably the TB team 18 would like to do. I think that's probably a fair 19 assumption whether it's Sanofi or anybody else. So, it 20 clearly has to be balanced from that other side of the 21 perspective of where will the funding come from to do 22 the work? And I think that is really one of the major</p>

<p style="text-align: right;">Page 310</p> <p>1 -- this goes into a different point -- but I think one 2 of the major problems we have in TB is we simply don't 3 have the resources to take enough risk to do enough TB 4 -- to do enough, even, Phase 3 trials to give the 5 feedback to understand what are really the accurate 6 predictors of Phase 2 or of earlier development. And, 7 frankly, I mean, if I look at something like LAM, which 8 is great. It has great potential. 9 So, what are we -- what's the best we can do 10 right now? We're looking at it against the, quote, 11 gold standard of sputum conversion and of sputum 12 bacteriology, which we know, frankly, without opening 13 that debate right away, is not necessarily a great 14 predictor, but that's the gold -- that's the best we 15 have to measure LAM against. As opposed to having had 16 enough Phase 3 experience and even biobanks, etc., 17 etc., to use them as a predictor, not of an 18 intermediate endpoint, but of a final endpoint. So, 19 that's another area that really is, in my opinion, 20 unbelievably short-changed, because we don't have 21 enough of those trials. 22 REMOx, on the one hand, and OFLOTUB, RIFAQUIN,</p>	<p style="text-align: right;">Page 312</p> <p>1 Dr. Higgins talk about the importance of looking at 2 breakthrough regimens versus standard of care as well. 3 I think it's very important that we look at that. 4 Now, how you tease apart the contribution of 5 one of those drugs within seven becomes really quite a 6 challenge, right? So, I think the nonclinical data 7 does become even more important in that case, so I 8 think that is something that we have to always bear in 9 mind. It's not just the EBA study but the nonclinical 10 data, if you can come up with that, is critical. 11 So, I think for question 1 there, I think that 12 is -- it's going to be extremely difficult when we get 13 into more of these complex regimens and, frankly, I 14 think if you have a regimen that is clearly as good as 15 but much shorter or more convenient or safer, that that 16 should become a way to treat people with this disease. 17 The other comment I was going to make is 18 related to the other question 1 or question 4, 19 depending on how you look at it, which is the current 20 trial design challenges. So, what we found, right, was 21 we were already to do a very streamlined study, but the 22 amount of time it takes to align with health</p>
<p style="text-align: right;">Page 311</p> <p>1 etc., were "failed" trials. They weren't failed 2 trials; those trials have delivered an unbelievable 3 fund of knowledge that now informs so much of what we 4 do moving forward. 5 DR. COX: We often do find that the trials 6 that fail are the ones that oftentimes can teach us 7 very much, and we found that in a number of different 8 therapeutic areas. So, yes. 9 DR. HUGHES: Yeah, so I'd just like to build 10 on that comment about revolutionary change. Because I 11 think the one example that Charles mentioned briefly 12 but we are closely involved with, with Novartis, we're 13 responsible for clofazimine, which has been mentioned a 14 number of times here, is a very odd case. Because it's 15 really been reserved for leprosy, but obviously, it is 16 getting a lot more use in this area. But a group of 17 dedicated, genius, breakthrough clinicians in 18 Bangladesh really took a revolutionary approach to take 19 an entirely new regimen of seven drugs that they had in 20 the cupboard, all of which had some rationale of why 21 you would use them, and changed the MDR-TB paradigm 22 from 24 months to 9 to 12, roughly. So, glad to hear</p>	<p style="text-align: right;">Page 313</p> <p>1 authorities and then to get the approval of different 2 sites to get your contract set up, by the time all that 3 was done versus the standard of care, the field had 4 moved, right? And so, what we found was standard of 5 care was no longer achieving -- was no longer 24 months 6 achieving 50% success rates, particularly in the sites 7 you need to go to generate the data with good clinical 8 practice to change -- you know, to inform the field. 9 And there they were getting rates of 75%, 80%, 85%. 10 They were already starting to use shortened regimen. 11 Our own drug was the standard of care when we went in 12 to say, so it becomes very, very difficult. And, 13 again, it's a special case, but I think it's a special 14 case, but I think it's actually informative, because 15 many older drugs are used in TB field and the pace at 16 which the world moves is important to bear in mind. 17 DR. STARKE: So, I've often thought there is a 18 lot more analogy between TB and cancer than there is TB 19 and many other infectious diseases. You know, they 20 talk about logs of cells, we talk about logs of bugs; 21 they have induction and consolidation therapy, we have 22 initial and continuation. They're all about regimens,</p>

<p style="text-align: right;">Page 314</p> <p>1 also. For instance, in pediatric cancer they've done 2 incredible things by making sure that all patients are 3 involved in trials. So, my question is, what can we 4 learn from oncology in terms of studying drugs -- 5 studying regimens as opposed to drugs? Because that's 6 largely what they do. It's a question.</p> <p>7 DR. COX: I think the folks that are trying to 8 do it in the TB field are teaching us, I mean, to be 9 honest with you. I mean, is there more we can learn 10 from oncology? It's possible. You know, I'm impressed 11 with what folks have been able to do in the TB area 12 with the, frankly, quite limited resources available in 13 this area relative to what's available in oncology. 14 But maybe there are additional lessons that could be 15 learned from oncology and how they approach things. 16 So, I don't know if others have additional thoughts on 17 that.</p> <p>18 DR. SPIGELMAN: Yeah, Jeff, I think one of the 19 problems that we have in TB is that we have the history 20 that really limits us. Most of the combination work 21 that, at least I see going on in oncology, is based on 22 pretty much all new compounds and it starts from</p>	<p style="text-align: right;">Page 316</p> <p>1 you determine the contribution of a specific drug to a 2 regimen, and that's what I was wondering if they had 3 some principles that would help. But the way you're 4 describing it almost is where cancer was maybe several 5 decades ago. Although, I've got to say, in pediatric 6 cancer they're still using a lot of the traditional 7 drugs, and so it's not quite just all about new, 8 totally new drugs and totally new regimens.</p> <p>9 UNIDENTIFIED SPEAKER: (Inaudible - microphone 10 inaccessible.)</p> <p>11 DR. COX: Do you want to respond to that?</p> <p>12 DR. PHILLIPS: Can I make some comments on --</p> <p>13 DR. COX: Yeah.</p> <p>14 DR. PHILLIPS: -- the analogies with cancer? 15 I think, first of all, I'll come back to that point. 16 First of all, I think we have a lot to learn from 17 happenings in oncology. I'm a statistician. Most 18 statistical methodology is done in oncology and we sort 19 of pick out sort of the dregs from there. So, the 20 MAMS, which has been talked about, that came from 21 oncology, and I think many adaptive designs that have 22 been proposed that we've discussed have been done in</p>
<p style="text-align: right;">Page 315</p> <p>1 scratch. You don't start out in oncology with the 2 standard being a seven-drug regimen that you're looking 3 to tease apart. It kind of grew up, the combination 4 programs that you're seeing now in the modern era, 5 almost like HIV grew up with one drug and then the 6 second was added and the third was added. And it was 7 in a much more rational or semi-rational, orderly 8 process. We're kind of stuck in that we've got poor 9 grade of evidence that defines standard four-drug, 10 five-drug regimens that we somehow now have to tease 11 apart and improve upon, which is a huge, bigger burden 12 than is there in oncology.</p> <p>13 If we could learn a lesson and wave a magic 14 wand, though, then what I would say is make TB regimens 15 be payable to the tune of \$100,000 or \$300,000 per 16 patient and then we'll see a lot more rapid progress in 17 terms of the work being done. But without being 18 facetious, that lack of commercial attractiveness in TB 19 makes, frankly, a lot of what goes on in oncology just 20 nonrelevant to what we're stuck with in TB.</p> <p>21 DR. STARKE: I think I was trying to ask sort 22 of a more basic question. We were talking about how do</p>	<p style="text-align: right;">Page 317</p> <p>1 oncology. So, we have lots to learn there, and I think 2 the more we read that sort of literature the better.</p> <p>3 In terms of the comment that was made about 4 getting data from routine practice, I think one 5 difference in TB trials from cancer trials is the 6 endpoints. So, Mel talked about doing large, simple 7 trials, which I guess are easier to do in settings 8 where the endpoint is something like mortality, which 9 it's a hard endpoint, which is relatively easy to 10 collect that data.</p> <p>11 The challenges in TB are patients need to be 12 followed up after the end of treatment. Most of the 13 programmatic endpoints that you've heard presented 14 today are about end-of-treatment cure. There is very 15 little programmatic data about post-treatment, whereas, 16 in trials we need that follow-up, because it's about 17 relapse. So, you need patients to remain in follow-up, 18 which is why it's more challenging just to get routine 19 data to answer some of the questions we've talked about 20 here. And so, I think that's one of the issues. And I 21 think that's also why large, simple trials are more 22 challenging in TB. Or I think it's worth thinking</p>

<p style="text-align: right;">Page 318</p> <p>1 about how they could be done, but follow-up is so 2 critical in trials that a simple trial would still need 3 to involve very careful follow-up schedules. Even if 4 not many sputum samples are taken for culture, follow- 5 up would be critical.</p> <p>6 DR. COX: And maybe I'll just add, too. Folks 7 may recall, too, Rick Pazdur and I, from the head of 8 our oncology office, and I did a panel at CBTR on this 9 very topic. And I can tell you one of the things that 10 came up -- and this doesn't mean you can't learn from 11 the area of oncology -- was really the number of 12 differences that exist between oncology and TB, and why 13 the two fields are different and why it may be 14 challenging to essentially directly translate things 15 over. That doesn't mean you can't learn, but there are 16 differences. It does make it challenging.</p> <p>17 DR. MITNICK: Can you hear me now? So, a 18 couple of comments. This has been a really interesting 19 discussion. My name is Carole Mitnick. I work at 20 Harvard Medical School and work with the 21 nongovernmental organization, Partners in Health. On 22 the clofazimine issue, I just wanted to point out that</p>	<p style="text-align: right;">Page 320</p> <p>1 So, I think we do need to continue to be aspirational, 2 and we do need to not be settling as we have for so 3 many decades. And that's part of the reason that we 4 still have more than 10 million new cases of TB every 5 year and more than half a million of new cases of MDR 6 every year.</p> <p>7 So, one of my questions is in the paradigm of 8 the pan-TB regimen, I mean, it sounds to me a lot like 9 where we came from, where the four-drug regimen was 10 supposed to be for everybody. The World Health 11 Organization and other entities discouraged any sort of 12 differentiation in treatment, and now we have at least 13 a half-million cases of MDR every year. So, what is 14 the role in evaluating a pan-TB regimen for modeling or 15 other activities that would try to predict how long 16 such a regimen would be useful, and what the 17 implications would be of having a single regimen that's 18 for what we today call drug-susceptible TB and MDR-TB. 19 It is based on the same nucleus of drugs that is now 20 used for a salvage regimen in the same development 21 portfolio. So, I'm curious about how that fits into 22 evaluation of the pan-susceptible TB regimen.</p>
<p style="text-align: right;">Page 319</p> <p>1 that new regimen is a standard of care for a subset of 2 MDR patients, that is, MDR-TB patients who have not 3 been previously treated with second-line drugs and 4 whose isolates are not resistant to the drugs in that 5 regimen. So, there are still opportunities to learn 6 about the role of clofazimine in MDR-TB treatment, and 7 also there are still obviously open questions about the 8 optimal dose of clofazimine. So, looking in other 9 populations is another possibility. It's not all lots 10 with the adoption of the shortened regimen in that 11 subset of MDR patients. That's one point.</p> <p>12 A second point is just in thinking about the 13 model of scarcity. I mean, I have now been doing TB 14 work for, like, 20 years. I can't believe I can say 15 that. And it's true, I mean, we have always worked 16 within a model of scarcity. But we also have 17 innovated, and I think we shoot ourselves in the foot 18 by continuation to say, oh, we have to be cautious, we 19 have to limit our failures, because there aren't enough 20 resources. So, Mel, you describe three trials that 21 have been considered by some as failures, by others not 22 as failures, and there is still more money for trials.</p>	<p style="text-align: right;">Page 321</p> <p>1 DR. SPIGELMAN: So, I think there are two 2 separate kind of questions on the table. One I think 3 is really the more generic question, it doesn't matter 4 whether a regimen is approved for DS, MDR-TB, pan-TB 5 etc. There has to be, I think, greater planning for 6 how to protect that regimen for as long as possible 7 within reason. And I'm not sure we've devoted as much 8 attention to that type of sort of oversight of how the 9 drugs are being used. And obviously, that's now a big 10 deal in the whole AMR field, you know, so-called 11 stewardship of antibiotics and all that.</p> <p>12 And so, I think that that question is 13 independent of whether a new drug or a new regimen is 14 more limited or very broadly applicable is there has to 15 be sort of more planning for stewardship, so-to-speak, 16 of new therapeutics so that none of them will last 17 forever, but they'll last longer than they otherwise 18 last for.</p> <p>19 The other point, at least for me is, what's 20 the real attractiveness of a pan-regimen? The 21 attractiveness to a great extent is that, I think, even 22 if we come up with a really, really great regimen for</p>

<p style="text-align: right;">Page 322</p> <p>1 something like MDR-TB, there still are a huge amount of 2 structural problems in the way TB is treated 3 realistically in the countries that are most affected. 4 And 500,000 on the one hand is a huge number; 500,000 5 scattered across a whole bunch of countries and 6 resource-poor environments, etc., etc., still presents 7 a really big challenge to get on top of it. As opposed 8 to if we could present a common regimen that would 9 encompass both what are presently called drug-sensitive 10 and MDR-TB patients, and lump those together into a 11 common treatment paradigm that countries could adopt 12 that would be much easier to give. And that would have 13 tremendous ramifications in terms of the cost structure 14 of the health delivery system; have tremendous 15 ramifications in terms of the cost structure of the 16 drugs by virtue of the volumes. And so, I see it as 17 just a practical way to get on top of the problem of TB 18 in a much, much quicker format than if we continue to - 19 - or if we attack DS totally separately from MDR-TB. 20 That's just a practical issue, in my mind, of how 21 quickly can we solve the problem of MDR-TB. So, I 22 think it's sort of a combination of all of those as to</p>	<p style="text-align: right;">Page 324</p> <p>1 large, simple trial and, depending upon what the 2 problem is, if it's the appropriate design for what it 3 is that you're trying to study. 4 There have been safety trials in certain areas 5 where people looking at cardiovascular outcomes as an 6 adverse effects, you know, those sorts of things are 7 done. And so, if the large, simple trial is in fact 8 the appropriate trial design for what it is that you're 9 trying to study, then it would be a perfectly fine way 10 to evaluate that issue. 11 DR. VERNON: Thank you. 12 DR. COX: Go ahead. 13 DR. NAHID: I just wanted to raise a point of 14 friction that I would love the panel to comment on, and 15 that's the role the regulatory bodies take versus the 16 role that guideline makers take. And having recently 17 led a couple of guidelines for TB drugs and TB 18 treatment, and being involved in others, some at WHO, 19 it's occurred to me that is there a way to jump that 20 bridge, to bring that gap to be a smaller gap? Because 21 the regulatory bodies want to know what the individual 22 components do. The guidelines committees and, frankly,</p>
<p style="text-align: right;">Page 323</p> <p>1 what some of the benefits are of a pan-TB regimen. 2 DR. VERNON: I wanted to ask a question about 3 a topic that you raised, Mel, which is large, 4 simplified trials. Payam Nahid and I and others have 5 been discussing for a while now the potential to use a 6 simple, a large, simple trial design to improve our 7 management of INH-resistant TB by doing the trial in 8 resource-rich settings, where simple doesn't mean 9 lacking many of the kinds of data and tools that we 10 would otherwise have in a trial. The potential for 11 such designs to help us with bringing new agents or 12 older agents that lack a current approval in the US, 13 for example, is interesting to us. I wondered if FDA 14 has any examples of having used a large, simple trial 15 design as the basis for approvals? 16 DR. COX: So, I'm sure there are. I mean, I 17 think of the essence of a large, simple trial is it's 18 usually big, and you're not going to collect a whole 19 lot, but you're going to get an outcome that's 20 important to you. And if it's something that occurs 21 relatively infrequently, then maybe you need a bigger 22 trial. So, there is no reason you couldn't use a</p>	<p style="text-align: right;">Page 325</p> <p>1 the people out there want to know how to use the drug. 2 Is that an argument for exclusively or intensively 3 pursuing regimen development approaches to approvals -- 4 regimen approvals and maybe large, simplified trials 5 would be another, I guess, approach. But what's the 6 panel's thoughts about that, because it's really 7 challenging to make that leap? 8 DR. COX: So, I will try and make a few 9 comments. It's a very good question, and we do see 10 times when, in essence, drug labels get sort of out of 11 date. You know, the dosing regimen that's in treatment 12 guidelines is different, sometimes the uses are 13 different. And so, if you think about what are some of 14 the factors that can contribute to that? Well, if it's 15 an area where the pharmaceutical company is involved 16 in, say, the initial development of the drug for 17 whatever indications, and then development is happening 18 by groups other than those that actually own the new 19 drug application, that actually own the drug here with 20 us, sometimes there can become a disconnect. I'm not 21 trying to say that that research isn't important; it 22 can be extremely important in some areas. But you can</p>

<p style="text-align: right;">Page 326</p> <p>1 sometimes over time get this disconnect as drugs age 2 and they become generics. There can also be a 3 disconnect, too, with further study. It's not good for 4 anybody when the drug label starts to get separated 5 from the treatment guidelines. So, to the extent that 6 those that are actually out there doing trials, can 7 continue to engage with the pharmaceutical companies, 8 and we can also engage with both of those parties, we 9 have to do it through the pharmaceutical company, it 10 can help to decrease that degree of separation. So, 11 that's sort of one aspect of it.</p> <p>12 The other is that sometimes there are 13 situations where the level of information that's 14 available out there is quite limited and maybe not 15 ideal. You know, low-quality evidence. Clinicians 16 oftentimes are faced with that and have to make 17 decisions. Those writing treatment guidelines may also 18 try and help out in that scenario. So, there may be 19 information that is really of low quality that may be 20 hard for a regulator to look at and say that it meets 21 sort of the standard that we would be looking for in 22 order to give an indication. But clinicians may have</p>	<p style="text-align: right;">Page 328</p> <p>1 very, frankly, stringent look at the data, to use that 2 word. And whether there should be a mechanism by which 3 these groups talk to each other and circle back so that 4 gap gets closed and usage of the drugs are done 5 appropriately, there is not -- we're not leading 6 providers out in the lurch, because we're telling them 7 to use a drug in a way that it doesn't have an 8 indication for, for example.</p> <p>9 DR. COX: Right. I mean, that would be the 10 ideal, to keep that degree of separation as infrequent 11 as possible. It is certainly something where I think 12 the community can work together. You know, the 13 aspiration here would be quality trials that would be 14 available to both those writing treatment guidelines 15 and to those that have new drug applications, so that 16 things can remain congruent. So, it is certainly an 17 aspiration that is laudable and one we should try for. 18 Whether it's attainable is another question, though, 19 because there still are going to be areas where, quite 20 frankly, treatment guideline folks and clinicians are 21 going to be trying to make decisions and trying to 22 provide recommendations when the level of evidence is</p>
<p style="text-align: right;">Page 327</p> <p>1 to make decisions, treatment guidelines folks may, too, 2 and that's sometimes another area where you can get a 3 gap.</p> <p>4 So, that argues for trying to do good trials, 5 trying to get to good studies before the -- you know, 6 to support the standard of care that's present. If the 7 standard of care becomes sort of non-evidence-based but 8 more just based upon poor quality information because 9 that's all that's available and it's a very difficult 10 situation and people have to make choices and be 11 advised, that's another reason that things can get 12 separated. I'm sure there is more than that, but it is 13 best if the guidelines, the standard of care and what's 14 in the drug label, to the extent that those things can 15 avoid being separated to a great deal, that's usually 16 best for everybody.</p> <p>17 DR. HUGHES: Just to follow up on that 18 excellent point there. Perhaps it is something to 19 explore as a community, that circling back between the 20 regulatory bodies and the guidelines makers. I mean, 21 these are people who are using great principles, the 22 WHO, the CDC. These are entities that are taking a</p>	<p style="text-align: right;">Page 329</p> <p>1 just limited. But there are valued treatment 2 guidelines, no question. They do help clinicians.</p> <p>3 MS. LESSEM: Thanks. I just wanted to go back 4 to an earlier point, Mel, that you had made about 5 stewardship, because I think we need to be really clear 6 with what we're talking about. The new drugs that we 7 have seen come out for TB are so overly stewarded that 8 nobody is getting them. And they're actually being 9 "reserved" in an attempt to protect the drug, that 10 we're not thinking about protecting patients. And, in 11 fact, we're not even protecting the drug, because only 12 severely resistant cases are getting them, which in 13 some ways is priming the market for more resistance 14 than if we just use them a little bit more liberally 15 earlier on in treatment. So, I don't think that we've 16 seen -- I think we haven't necessarily seen great 17 responsible practices towards using TB drugs 18 historically, but I think with the new drugs, 19 stewardship has gone so far in the other direction, we 20 have fewer than 5% of patients who need them, by 21 conservative estimates, actually accessing the drugs. 22 So, I just wanted to set the record straight on that.</p>

<p style="text-align: right;">Page 330</p> <p>1 I certainly think countries need to have proper systems 2 in place for diagnosing TB, for being able to see what 3 people are susceptible to, and give them appropriate 4 regimens. But I think stewardship as a blanket term 5 has been thrown around really to the detriment of 6 patients and to the longevity of these drugs. Thanks. 7 DR. NAMBIAR: I would like to add something to 8 Payam's earlier point about the connection between 9 regulators and policymakers, especially when it comes 10 to issues that Dr. Peloquin explained in his study, 11 that is population PK an variability of drug exposure 12 profiles. Because drugs get approved based on a 13 specific dose, but once they're used in the field, the 14 exposure profile is very, quite dramatically might 15 affect how the effectiveness -- how effective they are 16 in combination with other chemical entities. So, to 17 what point could one consider basing recommendations 18 for use or even the drug approvals on exposure profiles 19 rather than drug doses, and have specific targets that 20 are based on solid population PK rather than dose 21 ranges in kilograms. 22 DR. COX: Right. So, this is done, and the</p>	<p style="text-align: right;">Page 332</p> <p>1 that, but at the same time we're looking to get the 2 data. 3 So, another appeal is both to look more at 4 real world evidence that is generated through single 5 arm or observational studies, but just broad 6 programmatic research to be able to have that in the 7 equation. And also, the broader discussions today 8 about collecting data, better data from the 9 programmatic implementation. 10 I'm looking at the WHO, who is a very powerful 11 advisory and counselor to some of the countries both on 12 efficacy and safety data, so that we can then move the 13 field forward collectively. Because we're sort of 14 feeling the pain of that weakness in the data 15 collection currently. 16 DR. GEITER: Yeah, I was just -- you already 17 brought up the CPTR discussion you had with Dr. Pazdur 18 and comparison with oncology. And one of the things 19 that struck me was that he was talking about in 20 oncology they can go for an early endpoint for 21 reduction in tumor size. And if they shrink tumors, 22 they have a drug preliminarily. They then later need</p>
<p style="text-align: right;">Page 331</p> <p>1 way to do it is to design the trial that actually 2 evaluates the drug in such a way so that your dosing is 3 guided by exposure. So, it is doable, and it's just a 4 matter of what is done in the clinical trials that, in 5 essence, for the basis for approval? Are there 6 opportunities if the initial approval was based on a 7 dosing regimen that was a fixed dosing regimen not 8 guided by therapeutic drug monitoring, or not guided by 9 exposure. Certainly, if there is additional data, 10 additional studies that are done subsequently, that 11 could be used to inform the dosing future. So, it's 12 all doable, it's just a question of, in essence, 13 whether it's been done. 14 DR. HUGHES: David Hughes again. I wanted to 15 come back a little bit to Dr. Mitnick's point in that I 16 did not mean to imply that our journey is over or the 17 party is done. Actually, we are in active discussion 18 with two stringent health authorities, one of them 19 represented here today, as well as we have recently had 20 recognition and ability to import into three countries 21 of high need. And so, we're continuing to work 22 actually feverishly to meet the demand and to inform</p>	<p style="text-align: right;">Page 333</p> <p>1 to show increased survival. And so, they've got a very 2 hard endpoint there. We can talk about is it two 3 months or three months, or is it the rate of decline or 4 time to sputum culture conversion, but we do have a 5 microbiologic endpoint that seems to likely predict a 6 favorable outcome. But then at the end we're still 7 tied to a microbiologic endpoint. We really don't have 8 a hard endpoint in TB. It's cure, and what is a cure? 9 Well, cure is, at least in the guidelines, that it's a 10 certain period of relapse-free survival following 11 sputum culture conversion, but that is still based upon 12 a microbiologic endpoint. So, we're a little bit 13 challenged in that way. 14 It would be nice if we had something else. It 15 was very interesting to see, I think, measurement of 16 mRNA levels that you have a negative microbiologic 17 outcome but you still have messenger RNA hanging 18 around. So, there are obviously some TB bacilli doing 19 something, and if we could develop that into a harder 20 endpoint. And I would just, you know, speaking up for 21 sputum tests, it's what we got and it works pretty 22 well. I mean, in terms of -- you know, if we're going</p>


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1 to go with a microbiologic endpoint, it does pretty
 2 well. And that if we could get more rapid results that
 3 are equally sensitive and specific, like with the LAM
 4 assay or any of the other things that have been
 5 provided, I think that as long as we're tied to a
 6 microbiologic endpoint, I think that can contribute a
 7 great, great deal to the design of trials and the
 8 evaluation of regimens going forward in the future.
 9 DR. SPIGELMAN: And now let's turn it over to
 10 Ed to final --
 11 DR. COX: Yeah, so we're at the five o'clock
 12 hour, so I know folks are planning to head out and
 13 catch planes and all that, so I'll keep it very short.
 14 But I wanted to thank everybody for joining us here
 15 today. I found it very useful; I hope you did, too.
 16 And I remain impressed with the degree of
 17 accomplishment, the progress that has been made in this
 18 area, you know, recognizing that it is not the most
 19 resourced area of therapeutics development. But
 20 because of the thoughtfulness and commitment of the
 21 folks in this room, on the webcast, who have been
 22 involved in this area who are not here today, I think

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1 there has been tremendous progress, and I think that's
 2 wonderful. And we look forward to continuing to work
 3 with the TB community on TB drug development, and I'm
 4 sure colleagues and CDRH are interested in continuing
 5 to work in those involved in diagnostic development,
 6 too. So, we stand ready to continue to work with folks
 7 and to try and improve the situation out there for
 8 patients with TB. We regulate for the US. We
 9 recognize, also, the global implications of a disease
 10 like TB and our broader responsibility to the global
 11 community, too.
 12 So, with that, I want to thank you all for
 13 joining us today and wish you the best, and safe
 14 travels.
 15 (Whereupon, at 5:02 p.m., the workshop
 16 was concluded.)
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