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UNITED STATES

FOOD AND DRUG ADMINISTRATION

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PUBLIC WORKSHOP

DEVELOPMENT CONSIDERATIONS OF ANTIFUNGAL DRUGS TO  
ADDRESS UNMET MEDICAL NEED

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DATE: Thursday, August 4, 2020

TIME: 9:13 a.m.

LOCATION: Remote Proceeding - MD

Virtual Silver Spring, MD 20903

REPORTED BY: Janel Folsom, Notary Public

Job No. CS3856635

<p style="text-align: right;">Page 2</p> <p>1                   A P P E A R A N C E S</p> <p>2</p> <p>3 DR. JOHN FARLEY</p> <p>4 DR. SUMATI NAMBIAR</p> <p>5 DR. RADU BOTGROS</p> <p>6 DR. ERIN ZEITUNI</p> <p>7 DR. THOMAS WALSH</p> <p>8 DR. JASON MOORE</p> <p>9 DR. WILLIAM HOPE</p> <p>10 DR. LAURA KOVANDA</p> <p>11 DR. YULIYA YASINSKAYA</p> <p>12 DR. KIEREN MARR</p> <p>13 DR. JOHN REX</p> <p>14 MATTHEW SCHUELER</p> <p>15 DR. PETER PAPPAS</p> <p>16 DR. CHERYL DIXON</p> <p>17 DR. AARON DANE</p> <p>18 DR. ASPASIA KATRAGKOU</p> <p>19 DR. LUIS OSTROSKY-ZEICHNER</p> <p>20 DR. TOM CHILLER</p> <p>21 DR. HELEN BOUCHER</p> <p>22 DR. BAOYING LIU</p>	<p style="text-align: right;">Page 4</p> <p>1                   P R O C E E D I N G S</p> <p>2                   DR. JOHN FARLEY: This is John Farley</p> <p>3 checking audio.</p> <p>4                   COURT REPORTER: Sounds good. We can</p> <p>5 hear you.</p> <p>6                   DR. JOHN FARLEY: Good. Shall I go</p> <p>7 ahead and start?</p> <p>8                   COURT REPORTER: Yes, you can start</p> <p>9 now.</p> <p>10                  DR. JOHN FARLEY: Okay. I'm very sorry</p> <p>11 for the delay, everyone. This is our first virtual</p> <p>12 workshop here in the Office of Infectious Disease.</p> <p>13 We've put in lots of preparation and weren't quite</p> <p>14 counting on doing this in the middle of a tropical</p> <p>15 storm, but we're hoping that the workshop goes</p> <p>16 smoothly today. In the event that you do lose</p> <p>17 Internet, please just log back in and join us.</p> <p>18                  I see that Tom Walsh is already losing</p> <p>19 connections but rejoining us right now. I want to</p> <p>20 welcome everybody this morning and thank particularly</p> <p>21 the speakers for the time that they've invested in</p> <p>22 preparing for this event.</p>
<p style="text-align: right;">Page 3</p> <p>1 DR. MICHAEL HODGES</p> <p>2 DR. DAVID ANGULO</p> <p>3 DR. TAYLOR SANDISON</p> <p>4 DR. GEORGE THOMPSON</p> <p>5 DR. DAVID DENNING</p> <p>6 DR. JOHN PERFECT</p> <p>7 DR. THOMAS PATTERSON</p> <p>8 DR. KAREN HIGGINS</p> <p>9 DR. JOHN BENNETT</p> <p>10 DR. SHAWN LOCKHART</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>	<p style="text-align: right;">Page 5</p> <p>1                   We're here today to focus on the</p> <p>2 development of new therapies to address unmet medical</p> <p>3 need for the treatment of infections due to invasive</p> <p>4 molds and Candida auris. Discussions today will</p> <p>5 include the current state and clinical trial design</p> <p>6 considerations for developing new therapies for these</p> <p>7 infections.</p> <p>8                   Fungal diseases with unmet need occur</p> <p>9 in people who live in or travel to certain areas. An</p> <p>10 example of that is Valley Fever, which will be our</p> <p>11 focus tomorrow. And they also commonly affect people</p> <p>12 with weakened immune systems, and an example of that</p> <p>13 is Candida auris, which we'll be focusing on later</p> <p>14 today.</p> <p>15                  Similar to antibacterial drugs,</p> <p>16 antifungal resistance can severely limit treatment</p> <p>17 options. The science of preclinical development is</p> <p>18 hard and it's very important to establish feasible</p> <p>19 clinical trial designs that will lead to interpretable</p> <p>20 data.</p> <p>21                  Like antibacterial drugs, there are</p> <p>22 significant financial challenges. The key to making</p>

<p style="text-align: right;">Page 6</p> <p>1 progress is coming together as a community.  2 Government staffs, academic researchers, healthcare  3 providers, patients and drug developers to frankly  4 discuss the challenges and ideas for making progress  5 together, and that's our main goal and our focus  6 today.  7       Just a bit of housekeeping. We ask  8 that folks speak clearly and stick to the time so that  9 we can stay on time today and have time for some good  10 discussion. For the audience, the speaker slides,  11 transcripts and recordings will be available on the  12 public webpage in the coming days.  13       So, at this point, I'm going to turn  14 the program over to Sumati Nambiar and Erin Zeituni.  15 Sumati is from our group at FDA and heads the Division  16 of Anti-Infectives, and Erin is from NIH and very  17 involved with support for antifungal drug development.  18 So, we'll ask them to start Session 1 at this point.  19 Thanks very much.  20       DR. SUMATI NAMBIAR: Yeah, thank you,  21 John. I hope everybody can hear me okay. Good  22 morning and I would like to add my welcome and thank</p>	<p style="text-align: right;">Page 8</p> <p>1 disease, resistance to existing therapies or  2 intolerance to currently available treatments.  3       This is certainly very encouraging, but  4 at the same time we do recognize that there are  5 scientific and practical challenges that need to be  6 addressed. We hope that in today's workshop we will  7 be able to identify some solutions to the issues at  8 hand, and also identify some key areas that we'll need  9 for the discussion.  10       As John has mentioned, you know, we  11 also recognize that there are several economic  12 challenges that face the field of anti-infectious drug  13 development at large, which includes both anti-  14 bacterial and antifungals. Unfortunately, it's not a  15 topic that we can address or cover in today's  16 workshop.  17       It's really important to keep in mind  18 that general principles for antifungal drug  19 development are similar in many aspects to those for  20 antibacterial drug development. And over the last  21 decade and maybe decade and a half, we've made  22 significant progress with antibacterial drug</p>
<p style="text-align: right;">Page 7</p> <p>1 you all for joining us for today's workshop. We look  2 forward to a productive meeting and hope that today's  3 discussions will set the stage for future  4 conversations as we continue to work together as a  5 community to advance the field of antifungal drug  6 development.  7       As John said, Dr. Zeituni from NIAID  8 and I will co-moderate the first session on the  9 background of clinical and preclinical concentrations.  10 I'll start with the first talk -- I'll cover regulated  11 considerations from an FDA perspective. And then I'll  12 also present on behalf of colleagues from PMDA, our  13 Japanese regulators, who unfortunately couldn't join  14 us for the workshop. So, with that, if I can have my  15 slides up? Thank you.  16       Over the last few years we've seen some  17 increased interest in antifungal drug development. In  18 addition to the standard indications as in Candidiasis  19 and invasive aspergillosis, there's also interest in  20 developing antifungal drugs for the less common molds,  21 and also for an unmet need population, which is  22 variously defined either by the presence of refractory</p>	<p style="text-align: right;">Page 9</p> <p>1 development and have clearly defined in scientifically  2 sound approaches that are feasible for many clinical  3 conditions that clinicians see.  4       This was not an easy task. It was  5 achieved by engagement with stakeholders. Some of you  6 on the call participated in those discussions. We  7 also engaged in public-private partnerships and  8 exercised some regulated flexibility, all supported by  9 good scientific evidence.  10       There are many important lessons that  11 we've learned from completed programs. Unfortunately,  12 many of them also from field programs, which is not  13 what we like to see but I think very important to keep  14 in mind that they teach us many important lessons. We  15 recognize the importance of those selections, the body  16 site of infection, and the role animal models of  17 infection play, particularly in streamlined  18 development programs that are designed to attract  19 unmet medical need.  20       Presently, there's more work to be  21 done. There is ongoing work in defining or using  22 novel endpoints. There's also discussion around</p>

<p style="text-align: right;">Page 10</p> <p>1 designing trials for difficult to study indications  2 and also how to develop drugs for special populations,  3 including children. All of these certainly have  4 relevance to antifungal drug development as well.  5         And just to make sure that we're all on  6 the same page, at the very high level, you know, we  7 have two regulatory pathways. The traditional  8 approval pathway is generally based on an endpoint  9 that measures how a patient feels, functions or  10 survives. An accelerated approval is based on a  11 surrogate endpoint that is reasonably likely to  12 predict clinical benefit or on a clinical endpoint  13 that can be measured earlier than irreversible  14 morbidity or mortality. It's important to keep in  15 mind that even for products approved under the  16 activated approval pathway, the statutory standards  17 for effectiveness as in traditional approval should  18 still be met.  19         So, the statutory standard for  20 effectiveness is substantially evident consisting of  21 adequate and well-controlled investigations. For  22 antifungal drugs, at least one adequate and well-</p>	<p style="text-align: right;">Page 12</p> <p>1 that during the course of our discussion today, when  2 we discuss alternate endpoints, I think we should keep  3 in mind that endpoints that are selected for clinical  4 trial should be well-defined and reliable.  5         The clinical endpoint should be one  6 that measures an effect on how a patient feels,  7 functions or survives. If it's a surrogate marker --  8 surrogate endpoint, it's usually a marker such as a  9 laboratory measurement or a radiographic change that's  10 likely to predict clinical benefit but is not in  11 itself a measure of clinical benefit.  12         So, today we'll also have a lot of  13 discussion about the role of diagnostics and how they  14 can help us with enrolling patients in clinical  15 trials. And we have allowed things for  16 candidemia/candidiasis trials, use of non-culture-  17 based tests for enrollment for aspergillosis drugs.  18 We've allowed the use of galactomannan test for  19 patient identification and defining patient  20 populations.  21         In general, diagnostic tests do not  22 have to be FDA cleared or FDA approved if they're</p>
<p style="text-align: right;">Page 11</p> <p>1 controlled trial should be conducted per indication.  2 The supportive evidence from this single trial can  3 come from nonclinical studies, in vitro studies, or  4 from another indication.  5         I also wanted to note that for products  6 with orphan designation -- I hope everybody can still  7 hear me. So, for products with orphan designation,  8 which many antifungal drugs do get designated as  9 orphan drug product, the statutory standard still  10 needs to be met. So, effectiveness needs to be  11 demonstrated in adequate and well-controlled (sound  12 drops).  13         Recent trials for aspergillosis,  14 candidemia/invasive candidiasis that have been  15 submitted to support an indication have used a non-  16 inferiority trial design. And for these conditions  17 there's a large treatment effect, and a justification  18 of the NI margin is possible.  19         Commonly used endpoints in antifungal  20 trials have included all-cause mortality or clinical  21 success at a fixed time point, which has varied from  22 six to twelve weeks. And I just wanted to point out</p>	<p style="text-align: right;">Page 13</p> <p>1 being used for enrichment purposes, and qualification  2 of an endpoint is also not a prerequisite for use in  3 clinical trials.  4         The size of the safety database I think  5 certainly will depend a lot upon the clinical  6 conditions being studied and the attributes of the  7 drug. I think it's important to keep in mind that  8 based on signals from nonclinical studies, the trial  9 will have to have appropriate safeguards such as  10 monitoring and enrollment of the appropriate trial  11 population.  12         We do recognize that particularly for  13 unmet need programs and safety database would be  14 small. We highly recommend that at the proposed dose  15 and duration, we get safety data on at least 300  16 patients. There might be a requirement for additional  17 data if a safety signal has been identified. Also,  18 there might be a need to collect additional safety  19 data post-marketing, either through post-marketing  20 requirements or enhanced pharmacovigilance.  21         So, here are some paths moving forward,  22 and a lot of this we hope will come up during our</p>

<p style="text-align: right;">Page 14</p> <p>1 discussion today. We may not have solutions to all of  2 these but it'll hopefully be some food for thought as  3 we continue to work together.</p> <p>4           How can we design data packages that  5 are feasible and provide interpretable data,  6 particularly for the more difficult to study fungal  7 infections? And how best do we leverage data from  8 nonclinical studies to support these small data  9 packages? What is the role of external controls,  10 particularly for certain types of fungal infections?</p> <p>11           We're hoping there'll be some  12 discussion around how we develop oral stepdown  13 therapies, particularly when the product is not  14 available as an intravenous and an oral combination.  15 And also talk about developing products for the  16 pediatric population, including neonatal infections.</p> <p>17           There are two other topics that I've  18 sort of grayed out, not because they're not important  19 but not within the scope of today's workshop:  20 Developing inhaled antifungal therapies and developing  21 therapies for prophylaxis of invasive fungal  22 infections. These are topics that we hope to bring to</p>	<p style="text-align: right;">Page 16</p> <p>1 meet certain criterion.</p> <p>2           I'm not going to read through all of  3 them. I've given you the reference. We have a  4 guidance, and then there's also certain criteria that  5 are included under the Food &amp; Drug Administration  6 Reauthorization Act of 2017. And if a PRV is issued  7 that can be used to obtain priority review designation  8 for a subsequent application, that by itself will not  9 have qualified for priority review.</p> <p>10           So, in addition to the existing list,  11 Section 524 of the FDA allows us to add by order "any  12 other infectious disease for which there is no  13 significant market in developed nations and that  14 disproportionately affects poor and marginalized  15 populations." We have an open docket to which  16 interested parties can submit additional diseases with  17 supporting materials and we review them on an ongoing  18 basis. As many of you are aware, cryptococcal  19 meningitis was added to the list of eligible disease I  20 think a couple years ago, and more recently, we made  21 the decision to not designate coccidioidomycosis.  22           The LPAD pathway, the Limited</p>
<p style="text-align: right;">Page 15</p> <p>1 a future public meeting.</p> <p>2           I just want to switch gears and talk  3 about some incentives and also about the LPAD approval  4 pathway. I think many of you are familiar with the  5 Qualified Infectious Disease Product designation  6 that's given to antibacterial and antifungal human  7 drugs that are intended to treat serious or life-  8 threatening infections.</p> <p>9           In addition to five years of --  10 additional five years of marketing exclusivity and a  11 priority review for the first application, these  12 products are also eligible for fast-track designation.  13 And so far we've granted QIDP designation to over 200  14 antibacterial/antifungal products and 26 of these  15 designated products have been approved.</p> <p>16           I understand there's some interest in  17 the community of the tropical disease priority review  18 voucher and its applications for antifungal drug  19 development. So, applications that have been  20 developed for the prevention of treatment of a disease  21 which is on the tropical disease list may be eligible  22 for a tropical disease priority review voucher if they</p>	<p style="text-align: right;">Page 17</p> <p>1 Population Pathway for Antibacterial and Antifungal  2 Drugs, became available under the 21st century cures,  3 and it's based on the benefit-risk assessment that  4 more flexibility takes into account the severity or  5 prevalence of the infection. And I understand that  6 this will come up for discussion and is included in a  7 couple of the other presentations that we will hear  8 today.</p> <p>9           So, there are three requirements for a  10 drug to qualify under the LPAD pathway. First is that  11 it should be intended to treat a serious or life-  12 threatening infection in a limited population of  13 patients with unmet needs. And, very importantly, it  14 does not change our standards for approval.</p> <p>15           So, the standards for approval under  16 505 or under 351 still need to be met. That does mean  17 to have substantial evidence of effectiveness. And  18 the written request has to be submitted from the  19 sponsor that the product be approved as an LPAD drug.  20 There are certain conditions for approval with regard  21 to labeling and promotional materials.  22           Now, so far we've approved two products</p>

<p style="text-align: right;">Page 18</p> <p>1 under the LPAD pathway: Arikayce, or amikacin, for  2 the treatment of non-tuberculosis mycobacterial  3 infections, and Pretomanid, as part of a combination  4 regimen for the treatment of certain populations --  5 patients with tuberculosis.</p> <p>6           The approved population for each of  7 these products is limited. It's very defined and  8 specific. Treatment effect was demonstrated in at  9 least one adequate and well-controlled trial for each  10 product.</p> <p>11           We considered the benefit-risk profile  12 of each of these products to be acceptable in the  13 indicated limited population of patients who have few  14 or no treatment options, and limitations of the data  15 are reflected in product labeling.</p> <p>16           And this is just the highlights section  17 of the prescribing information for these two products.  18 And as required under law, the sentences that are  19 highlighted were included in labeling to convey the  20 limitations of the data.</p> <p>21           So, before I conclude, I will just  22 touch upon pediatrics. Under the Pediatric Research</p>	<p style="text-align: right;">Page 20</p> <p>1           As I stated early on, we at the agency  2 recognize the unmet need and also the practical  3 challenges in developing these products. It is very  4 important that all of us work together to find  5 feasible and scientifically sound solutions to address  6 patient needs.</p> <p>7           And there are many important lessons  8 learned from antibacterial drug development that are  9 relevant to and can certainly guide further  10 discussions on antifungal drug development. So, with  11 that, I thank you for your attention and will now  12 present on behalf of our colleagues in PMDA. So,  13 maybe I can get those slides for that, please? Great.  14 Thanks.</p> <p>15           I'm just going to go through these  16 slides that the center has by PMDA and Shohko Sekine,  17 who's in the Office of New Drug at PMDA, has written  18 up these slides on the regulatory considerations for  19 antifungal drug development, perspective from Japan.  20           So, they note that there are no  21 guidelines currently for development of antifungal  22 drugs issued by regulatory authorities in Japan. The</p>
<p style="text-align: right;">Page 19</p> <p>1 Equity Act, pediatric studies are required unless  2 requirement is waived, deferred or not applicable.  3 And although antifungal products with orphan  4 designation are exempt from these requirements, we  5 encourage sponsors to consider developing products for  6 children. I think we all recognize that safe and  7 effective therapies are needed for this population.  8 And in most instances, it is possible to extrapolate  9 efficacy from adults to pediatrics. And we're also  10 willing to consider issuing a pediatric written  11 request if there is interest. Sorry, there's an issue  12 with formatting on the slide.</p> <p>13           I also wanted to point out that we  14 recently issued a guidance on anti-infective drug  15 development for pediatric population, and the  16 principle outlined in the guidance are applicable to  17 both antibacterial and antifungal drugs.</p> <p>18           So, in summary, I've provided a high-  19 level overview of the key considerations for  20 antifungal drug development and reviewed some  21 incentives and pathways that are relevant to  22 antifungal drug development.</p>	<p style="text-align: right;">Page 21</p> <p>1 development of antifungal agents is not very active  2 currently. In the last five years, they have approved  3 four products: Two of them were for the treatment of  4 nail ringworm, one was for the treatment of oral  5 candida infection, and the other product had both a  6 prophylaxis and a treatment indication.</p> <p>7           Provided as an example of the most  8 recently approved product in Japan, and that is  9 Naxafil or Posaconazole, both as a tablet and  10 intravenous formulation. The indications include  11 prophylaxis of deep mycosis in hematopoietic stem cell  12 transplant recipients or patients with hematologic  13 malignancy, and also for the treatment indication that  14 includes the following mycoses: Fusariosis,  15 mucormycosis, coccidiomycosis, chromoblastomycosis  16 and mycetoma.</p> <p>17           The data package included clinical  18 trial results from outside Japan and these data had  19 been submitted to EMA and FDA. In addition, there was  20 data available from a trial conducted in Japanese  21 patients. The sponsor's position was that the foreign  22 data could be utilized for evaluation of efficacy in</p>

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<p>1 Japanese patients because there were no differences in 2 the susceptibility of the clinical isolate between 3 Japan and foreign countries; the medical environment, 4 treatment algorithm and pharmacokinetic profile 5 between Japanese and non-Japanese was not different. 6         So, this is a summary of the Japanese 7 clinical study that was conducted to support the 8 approval to the active controlled open-label trial in 9 patients with systemic and deep mycosis. The primary 10 efficacy endpoint for invasive aspergillosis and 11 mucormycosis was a composite of clinical symptoms and 12 radiographic assessment and mycology assessed at day 13 42, and the chronic pulmonary aspergillosis of 14 clinical symptoms and radiographic assessments made at 15 day 84. 16         And they also noted that the study in 17 Japanese patients is a recommendation and as of now, 18 is not a requirement for programs moving forward. 19         So, with that, I would invite our next 20 presenter, Dr. Botgros, rather than infectious disease 21 specialist, working as a scientific officer for the 22 Office of Biological Health Threats and Vaccines</p>	<p>1 advisor requests that were made to the EMA by sponsors 2 that were seeking approval based on nonrandomized 3 studies with or without external or historical 4 controls, often in difficult to treat patients. 5         I would now like to present a few 6 important considerations that the EMA guideline is 7 making which I believe are relevant for the discussion 8 today. And one important aspect is related to the 9 selection of the dose regimen and the use of the PK/PD 10 in the process. And I think it's important to point 11 out that the guideline mentions the fact that the dose 12 selection should be based on nonclinical data, human 13 PK data and exploration of the PK/PD relationship. 14         It's important also to mention that the 15 EMA has a dedicated PK/PD guidance document that also 16 applies when developing an antifungal. So, I think 17 it's good to keep that in mind, and at the same time, 18 you know, to acknowledge that the experience with 19 PK/PD of antifungals is accumulating and has 20 accumulated during the last decade. 21         It's important to mention a few 22 recommendations that the guideline on antifungal is</p>
<p>Page 23</p> <p>1 Strategy at the European Medicines Agency. So, Radu, 2 thank you. 3         DR. RADU BOTGROS: Thank you very much, 4 Sumati. Can you hear me well? Can you hear me? 5         DR. SUMATI NAMBIAR: Yes, yes. 6         DR. RADU BOTGROS: Very good. Thank 7 you very much and thanks to the FDA for inviting me to 8 this public workshop. My presentation will try to 9 provide you with some important EU Regulatory 10 considerations for developing antifungal medicines. 11         As most of you know, the EMA has a 12 guidance document on the clinical evaluation of 13 antifungal agents for the treatment and prophylaxis of 14 invasive fungal disease. And this guidance has been 15 finalized ten years ago, back in 2010, and is still in 16 force. It reflects the recommendations and 17 categorizations of disease of the European 18 Organization for Research and Treatment of Cancer and 19 the Mycosis Study Group of the NIAID and is a revised 20 version of a 2003 document. 21         And I must say that these guidances 22 have been put together as a response to scientific</p>	<p>Page 25</p> <p>1 making for developers aiming at developing drugs for 2 treating invasive fungal infections produced by either 3 aspergillus or candida. 4         The recommendation is to conduct a 5 prospective randomized active controlled trial in 6 patients confirmed to have proven or probable invasive 7 fungal disease. The preference is to allow a single 8 comparator in the study or at least to restrict 9 choices of the comparator if choosing a single one is 10 not an option. 11         I should also mention the fact that the 12 CHMP, which is the EMA main scientific committee in 13 charge of approval of medicines, has accepted single 14 pivotal trials for these indications. 15         Determination of eligibility and 16 outcome should ideally be made by an independent 17 adjudication committee that is blinded to treatment 18 assignment. And I think it's important to mention the 19 fact that fungaemia should be persistent after removal 20 of catheters and that all primary -- possible primary 21 foci are investigated. And the patients that have 22 persistent fungaemia and/or established primary foci</p>

<p style="text-align: right;">Page 26</p> <p>1 can be counted in the primary analysis.</p> <p>2           The primary endpoint of the randomized</p> <p>3 controlled trials that is preferred in EU is the</p> <p>4 global clinical response at test-of-cure. The non-</p> <p>5 inferiority margin that has been accepted is 10</p> <p>6 percent and is actually derived from mortality in data</p> <p>7 sets of proven, provable and probable cases. It is</p> <p>8 actually what has been accepted so far, despite there</p> <p>9 is awareness of the fact that the relevance for the</p> <p>10 study populations may be questioned by some.</p> <p>11           It is important to note also that the</p> <p>12 predefined primary efficacy endpoint of all-cause</p> <p>13 mortality at day 42 or day 84 has also been accepted,</p> <p>14 provided that the global clinical response rates are</p> <p>15 supportive.</p> <p>16           When it comes to the treatment of rare</p> <p>17 invasive fungal disease, the guideline recommends that</p> <p>18 at least one randomized clinical trial in invasive</p> <p>19 fungal disease due to candida or aspergillus should be</p> <p>20 conducted before or in parallel with a rare fungal</p> <p>21 pathogen study. The dose used in the rare fungal</p> <p>22 pathogen studies should be justified using the</p>	<p style="text-align: right;">Page 28</p> <p>1 also the preference here.</p> <p>2           A few words on the treatment of</p> <p>3 refractory IFD. Here it is important, I think, to</p> <p>4 note that clinical studies in these patients should</p> <p>5 only be conducted after having shown satisfactory</p> <p>6 efficacy results in one or more specific types of IFD.</p> <p>7           The enrolled patients should have</p> <p>8 proven IFD that persisted or progressed despite</p> <p>9 previous antifungal therapy. The only exception being</p> <p>10 invasive aspergillosis, where also probable cases can</p> <p>11 be enrolled. The primary objective of such a study</p> <p>12 may need to be discussed depending on whether it is or</p> <p>13 it is not possible to use an active control.</p> <p>14           The prophylaxis part is, of course, not</p> <p>15 part of this workshop but I just wanted to mention</p> <p>16 very briefly that here the expectation is that</p> <p>17 prophylaxis studies are conducted only after showing</p> <p>18 satisfactory clinical efficacy in a treatment of IFD.</p> <p>19 And the fact that it is expected to conduct a</p> <p>20 randomized trial with an adequate comparator and to</p> <p>21 compare rates for proven or probably IFD during</p> <p>22 treatment and for a defined period after cessation of</p>
<p style="text-align: right;">Page 27</p> <p>1 efficacy results versus candida and/or aspergillus</p> <p>2 plus PK/PD analysis using patient PK data.</p> <p>3           I think it should be bore in mind that</p> <p>4 this recommendation is made in response to previous</p> <p>5 proposals of nonrandomized studies in patients with</p> <p>6 various rare fungal infections, some with historical</p> <p>7 controls, and which essentially were requesting</p> <p>8 approval based on data generated from such studies,</p> <p>9 plus-minus PK/PD to support adequacy of the dose.</p> <p>10           It's important to highlight that for</p> <p>11 now, the guideline does not foresee the possibility of</p> <p>12 approving an antifungal for treatment of rare invasive</p> <p>13 fungal infections based on a positive candida or</p> <p>14 aspergillus RCT plus PK/PD. So, there is a need to</p> <p>15 have a study in rare invasive fungal infections that</p> <p>16 one should be ideally randomized possibly using</p> <p>17 unbalanced randomization, and it should compare the</p> <p>18 candidate medicines with licensed medicines or best</p> <p>19 available treatment. And in case nothing is approved</p> <p>20 or considered adequate superiority of the test</p> <p>21 regimens versus best available treatment should be</p> <p>22 demonstrated. Separate studies by fungal types are</p>	<p style="text-align: right;">Page 29</p> <p>1 prophylaxis.</p> <p>2           The non-inferiority margin and power of</p> <p>3 such a study need to be discussed in advance and</p> <p>4 potential improved indication will likely reflect a</p> <p>5 generation of evidence for specific fungal types.</p> <p>6           Before I finish, since the workshop</p> <p>7 discusses development of antifungals for unmet medical</p> <p>8 needs, I wanted also to say a few words about how this</p> <p>9 concept is described in the EU regulations and about</p> <p>10 the use of the term in different regulatory settings.</p> <p>11 And I think it's important to mention that there are</p> <p>12 regulatory tools in place addressing products which</p> <p>13 cover recognized unmet medical needs in Europe.</p> <p>14           The first one is, of course, the</p> <p>15 conditional marketing authorization, which is a tool</p> <p>16 that can be employed for products where the benefit-</p> <p>17 risk balance is such that the immediate availability</p> <p>18 outweighs the limitations of less comprehensive data</p> <p>19 than normally required. And I won't -- I mean, you</p> <p>20 see on screen the definition of unmet medical need as</p> <p>21 presented in one of the regulations that we have. And</p> <p>22 so I think this is one of the tools that can be used</p>



<p style="text-align: right;">Page 30</p> <p>1 for such products.</p> <p>2           And apart from that, there is a</p> <p>3 possibility -- the other regulatory option that we</p> <p>4 have for medicines addressing an unmet medical need is</p> <p>5 the accelerated assessment. Here it's important to</p> <p>6 mention that these need to be requested by the</p> <p>7 sponsors and should be accompanied by a justification</p> <p>8 by the applicant where typically the applicant will</p> <p>9 argue to support that medicine addresses to a</p> <p>10 significant extent unmet medical need for maintaining</p> <p>11 and improving the health of the community.</p> <p>12           And this concept of unmet medical need</p> <p>13 is actually considered also in other regulatory areas,</p> <p>14 notably in the framework of granting orphan</p> <p>15 designation or in the context of the PRIME program,</p> <p>16 the priority medicines applications, or in agreeing</p> <p>17 with the pediatric investigational plans.</p> <p>18           So, just to summarize, I think it's</p> <p>19 good to keep in mind that we have an antifungal</p> <p>20 guidance in force in the EU; the fact that we had</p> <p>21 rather few applications for new approvals for</p> <p>22 antifungal agents, a bit more but also not too many</p>	<p style="text-align: right;">Page 32</p> <p>1 development at the NIH. Erin, I'll turn it over to</p> <p>2 you. Thanks.</p> <p>3           DR. ERIN ZEITUNI: Thank you, Sumati.</p> <p>4 Just checking that my sound is working?</p> <p>5           DR. JOHN FARLEY: Yes, loud and clear.</p> <p>6           DR. ERIN ZEITUNI: Thank you. I'd like</p> <p>7 to thank the organizers for giving me the opportunity</p> <p>8 to tell you all a bit about NIH's preclinical services</p> <p>9 for antifungal development. And throughout this talk</p> <p>10 I will be encouraging folks to reach out to my group.</p> <p>11 So, up front, I'd like to let you know that my email</p> <p>12 is my first name, dot, my last name @NIH.gov. And I</p> <p>13 have no disclosures.</p> <p>14           Because it's all oriented, the mission</p> <p>15 of the National Institute of Allergy and Infectious</p> <p>16 Diseases, or NIAID, is to lead research to understand,</p> <p>17 treat and prevent infectious, immunologic and allergic</p> <p>18 diseases.</p> <p>19           Within NIAID, the Division of</p> <p>20 Microbiology and Infectious Diseases, or DMID, has a</p> <p>21 broad mandate supporting research for over 300</p> <p>22 pathogens. Essentially, everything except for HIV,</p>
<p style="text-align: right;">Page 31</p> <p>1 for CHMP scientific advice, both for treatment and</p> <p>2 prevention of invasive fungal infections. The CHMP</p> <p>3 has been flexible on the primary endpoint for invasive</p> <p>4 aspergillosis, as I mentioned before, and I think it's</p> <p>5 worth consulting the guidance of antifungals when</p> <p>6 developing medicine targeting rare pathogens, in</p> <p>7 particular the recommendations on first establishing</p> <p>8 efficacy in candida and aspergillus and use those data</p> <p>9 to support the results obtained from small RCTs in</p> <p>10 target rare pathogens with support from PK/PD for the</p> <p>11 dose regimen. Of course, prophylaxis should be</p> <p>12 considered and investigated after treatment. And,</p> <p>13 last but not least, we have the regulatory tools</p> <p>14 available for products addressing an unmet medical</p> <p>15 need.</p> <p>16           With that, I thank you very much. Back</p> <p>17 to you, Sumati and Erin. Thank you.</p> <p>18           DR. SUMATI NAMBIAR: Thank you so much,</p> <p>19 Radu. Our next speaker is Dr. Zeituni from the</p> <p>20 Preclinical Services Program at the Bacteriology and</p> <p>21 Mycology Branch at NIAID. Erin's going to talk about</p> <p>22 the preclinical services for antifungal product</p>	<p style="text-align: right;">Page 33</p> <p>1 which has its own division.</p> <p>2           Our support for antifungal product</p> <p>3 development spans this full product development arrow</p> <p>4 shown on the slide, from early basic research through</p> <p>5 to clinical research. The support comes in a variety</p> <p>6 of mechanisms designed to inform and de-risk product</p> <p>7 development. Folks in the audience will be most</p> <p>8 familiar with NIAID's grant and contract mechanisms,</p> <p>9 which are the main drivers of NIAID's support for</p> <p>10 product development effort.</p> <p>11           However, we recognize that the path to</p> <p>12 produce approval is long and can be difficult. And,</p> <p>13 unfortunately, promising products can be lost across</p> <p>14 the so-called Valley of Death due to lapses in funding</p> <p>15 or access to resources. To help stem these losses,</p> <p>16 DMID has developed free services and resources for the</p> <p>17 research and development communities to access. Those</p> <p>18 include our resources for researchers, the Preclinical</p> <p>19 Services Program, which will be a main focus of my</p> <p>20 presentation today, and clinical support.</p> <p>21           In the interest of time, I will only</p> <p>22 briefly touch on NIAID's resources for researchers,</p>

<p style="text-align: right;">Page 34</p> <p>1 which provide free reagents and services to  2 investigators. These successful programs include the  3 Structural Genomic Centers, which characterize three-  4 dimension atomic structures of proteins playing  5 important biological roles in human pathogens,  6 including for eukaryotic pathogens, which will be of  7 particular interest to this audience, and also BEI  8 resources, which provide reagents to researchers such  9 as well-characterized fungal and bacterial isolates,  10 plasmas and more. More information about these and  11 other programs can be found on our website.  12 NIAID's Preclinical Services are a  13 suite of contracts designed to support anti-infective  14 product development. These free gap-filling services  15 are intended to lower the risk and help advance  16 promising discoveries along the product development  17 pathway.  18 Our mission is to keep product moving  19 forward rather than have them stalled due to  20 intermittent gaps in funding or access to resources.  21 Innovators from academia, nonprofit organizations,  22 industry and governments are eligible to apply for</p>	<p style="text-align: right;">Page 36</p> <p>1 in a certified lab or to explore their drug spectrum  2 of activity if they themselves don't have access to  3 multiple representative species of yeasts, molds,  4 dimorphs or rare fungi.  5 More advanced product developers  6 utilize our in vitro services to expand our MIC data  7 sets and explore activity against species outside  8 their critical path and target indication.  9 In vivo efficacy models are also  10 available for antifungal product developers. Since  11 2015, our contracts at the University of Texas Health  12 Science Center in San Antonio and at the University of  13 Cincinnati have provided in vivo efficacy studies to  14 over 25 institutions developing antifungal drugs.  15 This table lists the various models that we offer by  16 species and route of inoculation. Most of our models  17 include two arms: A fungal burden arm to assess the  18 impact of treatment on fungal burdens and tissues of  19 interest, and a survival arm to assess the impact of  20 treatment on mortality, both with drug on board and  21 during a washout period after therapy ends.  22 Most commonly product developers use</p>
<p style="text-align: right;">Page 35</p> <p>1 these free services. Both domestic and foreign  2 institutions may apply, and applicants do not need  3 to have NIH funding.  4 Because Preclinical Services are  5 intended to quickly fill discrete gaps in product  6 development programs and keep them moving forward,  7 there's a simplified request process allowing access  8 year round.  9 Focusing in on antifungals, I manage a  10 suite of in vitro and in vivo efficacy services that  11 provide supportive data to antifungal drug development  12 programs. To give a flavor of the scale of our  13 services, since 2015, our contractors at the  14 University of Texas Health Sciences Center in San  15 Antonio have performed antifungal MIT testing for over  16 120 compounds for more than 50 different institutions.  17 On the right side of this slide you  18 will see the fungal species against which we currently  19 offer MIC testing. Our MIC testing services inform  20 multiple stages of antifungal development. For  21 example, early product developers might utilize our in  22 vitro testing services to confirm antifungal activity</p>	<p style="text-align: right;">Page 37</p> <p>1 our in vivo efficacy services for three reasons: The  2 first is to access proof of concept studies to support  3 a grant application or resubmission; the second is to  4 test efficacy against additional strains of a target  5 species including alternate resistance profiles; and  6 the third is to test their drug against additional  7 priority pathogens that might not be the target of  8 their critical path of the program. We offer these  9 services to ensure that promising antifungals at a  10 variety of development stages, both early and late,  11 have a path forward to assess their microbiological  12 activity.  13 In the table on the right, the models  14 written in black are currently available under open  15 task orders, while the models written in red would  16 require a new task order to be solicited before coming  17 back online. We rely on the product development  18 community to drive which models we have available at  19 any given time, based on the requests that we receive  20 for testing.  21 Requests from product developers serve  22 a bona fide need for us to solicit new task orders and</p>

<p style="text-align: right;">Page 38</p> <p>1 I encourage you to reach out to us and tell us about  2 your antifungal programs and any gaps that you might  3 have.</p> <p>4       In addition to responding to requests  5 from product developers, at NIAID we also use  6 preclinical services contracts to pivot and support  7 product development needs for agents targeting  8 emerging infectious diseases. For example, when  9 <i>Candida auris</i> emerged as a pathogen of concern and  10 made its way onto a CDC clinical alert in 2016, we had  11 started planning for incorporating this pathogen into  12 our testing cascade. We first incorporated MIC  13 testing against clinical isolates of <i>Candida auris</i>  14 into our task orders and workflow and later updated  15 our panels to include the CDC, FDA, AR isolate bank  16 when that panel was published online.</p> <p>17       We then solicited a task order to  18 develop and validate a <i>Candida auris</i> infection model.  19 In this model, ICR mice are treated with five  20 fluorouracil to induce neutropenia and are inoculated  21 via the lateral tail vein with a clinical isolate of  22 <i>Candida auris</i> that is resistant to fluconazole and</p>	<p style="text-align: right;">Page 40</p> <p>1 documentation.</p> <p>2       There are many opportunities for you to  3 engage with us about your antifungal programs, and I  4 want to encourage you again to contact us and start a  5 discussion about support mechanisms that we offer,  6 from grants on through to preclinical services. We  7 would be very happy to hear from you.</p> <p>8       And before closing, I'd like to briefly  9 mention one more area of free services for product  10 developers which are our clinical trial units, such as  11 our Phase 1 units. These contracts provide Phase 1  12 trials at no cost to the requester. NIAID sponsors  13 the trial and holds the IND. Michovia's VT-1598 is a  14 novel antifungal compound with activity against  15 toxicity species and through our Phase 1 clinical  16 trial unit, VT-1598's single ascending dose study is  17 examining the safety of its administration to 48  18 healthy adults aged 18-45 years.</p> <p>19       And in conclusion, I hope that this  20 presentation was helpful to provide a clear picture of  21 the various mechanisms that NIAID is leveraging to  22 support antifungal product development. Again, I</p>
<p style="text-align: right;">Page 39</p> <p>1 sensitive to caspofungin. In the model, two study  2 arms, a fungal burden arm and a survival arm are used  3 to assess the impact of fluconazole and caspofungin  4 treatments on these outcomes in comparison to  5 untreated controls.</p> <p>6       The results of these model development  7 efforts were reproducible and the protocol was proven  8 transferrable by a subcontracting group led by Scott  9 Filler and Ashraf Ibrahim at UCLA Harbor. With a  10 validated model available, we have since solicited  11 multiple task orders and tested <i>Candida</i> antifungals  12 from eight institutions and counting, resulting in  13 three publications. This approach is just one example  14 of how we strive to develop and provide gap-filling  15 services to support antifungals across various stages  16 of development.</p> <p>17       In addition to efficacy assessments,  18 NIAID's suite of preclinical services also includes  19 chemistry and manufacturing, including GMP  20 manufacturing, toxicology and pharmacokinetics, rapid  21 ADMET and pharmacokinetics screening services, and  22 product development planning and assistance with IND</p>	<p style="text-align: right;">Page 41</p> <p>1 would encourage you to reach out to us. My email is  2 located at the top of the slide. And I'd also like to  3 acknowledge the team effort that it takes to manage  4 the portfolios and mechanisms that were described in  5 this presentation.</p> <p>6       Listed are members of the branch who  7 support antifungal therapeutic, diagnostic and vaccine  8 effort. Please reach out to me if you have any  9 questions, and I hope to hear from you soon. Thank  10 you. With that, I would like to give the rest of my  11 time back and get us a little bit closer to on time.  12 Thank you.</p> <p>13       DR. SUMATI NAMBIAR: Thank you so much,  14 Erin. So, our next speaker for this session is Dr.  15 Walsh, the Professor of Medicine, Pediatrics and  16 Microbiology at Cornell and an attending physician,  17 New York Presbyterian Hospital. So, Dr. Walsh will  18 talk to us about the animal models of fungal  19 infection. So, Dr. Walsh, I'll turn it over to you.</p> <p>20       DR. THOMAS WALSH: Yes, good morning.  21 Are you able to hear me?  22       DR. SUMATI NAMBIAR: Yes, we can.</p>

<p style="text-align: right;">Page 42</p> <p>1 Thank you.</p> <p>2 DR. THOMAS WALSH: Very good. Very</p> <p>3 good. Well, first, I'd like to thank you so much for</p> <p>4 the opportunity and the invitation to speak on this</p> <p>5 very critical area of animal models of fungal</p> <p>6 infection. They indeed do service our critical</p> <p>7 systems in development of new antifungal agents.</p> <p>8 By way of disclosures, my staff and I</p> <p>9 have collaborated extensively with multiple industrial</p> <p>10 partners as critical elements of our advancing</p> <p>11 translational science from bench to bedside.</p> <p>12 By way of background, animal model</p> <p>13 systems are a critical component of the process in</p> <p>14 discovery and development of new antifungal agents for</p> <p>15 treatment and prevention of invasive fungal diseases.</p> <p>16 Models of invasive fungal diseases in murine, rat,</p> <p>17 guinea pigs and rabbits have been developed and</p> <p>18 studied for development of new and previous systemic</p> <p>19 antifungal agents.</p> <p>20 We will review today the conceptual,</p> <p>21 scientific and regulatory framework for utilizing</p> <p>22 these models, cite specific examples of their</p>	<p style="text-align: right;">Page 44</p> <p>1 And then to move into larger animal</p> <p>2 model systems, rats, guinea pigs and rabbits, and I</p> <p>3 will exemplify those as well. Clearly, one needs</p> <p>4 complementary systems in order to be able to de-risk</p> <p>5 and to identify potential new compounds -- one needs a</p> <p>6 complementarity of the different model systems. Many</p> <p>7 animal models, of course, are also studied in</p> <p>8 pathogenesis and host defenses, which we will not</p> <p>9 address today.</p> <p>10 What are the characteristics that are</p> <p>11 noteworthy for predictive in vivo models for invasive</p> <p>12 fungal diseases? They should reflect the host</p> <p>13 response relevant to the fungus. This is actually</p> <p>14 absolutely paramount, for the host response plays a</p> <p>15 critical role in outcome, both in the animal model</p> <p>16 systems as well as in our patients. They should have</p> <p>17 quantifiable outcome variables. At minimal, survival,</p> <p>18 human endpoints, residual fungal burden that we</p> <p>19 measure by culture and/or PCR, and a range of</p> <p>20 biomarkers including antigen and antibody but also</p> <p>21 other, for example, inflammatory biomarkers, and then,</p> <p>22 of course, the classical histology.</p>
<p style="text-align: right;">Page 43</p> <p>1 application and discuss their predictability for</p> <p>2 clinical trials. I just heard a beep. Are you still</p> <p>3 able to hear me?</p> <p>4 DR. JOHN FARLEY: Yeah.</p> <p>5 DR. THOMAS WALSH: All right, good.</p> <p>6 Thank you. Our objectives this morning, therefore,</p> <p>7 are to review the role of laboratory animal model</p> <p>8 systems and development of new antifungal agents to</p> <p>9 assess the predictability of these models for</p> <p>10 predicting outcome in clinical trials and to identify</p> <p>11 unmet needs and new directions particularly for</p> <p>12 biomarkers in preclinical and clinical studies.</p> <p>13 So, what is the role for animal models</p> <p>14 of invasive fungal diseases? First of all, clearly in</p> <p>15 development of new antifungal agents, one commonly</p> <p>16 sees particularly in industry or in drug discovery</p> <p>17 laboratories screening of murine models. They're</p> <p>18 relatively simple, straightforward with minimal</p> <p>19 outcome parameters. The next step then will be to</p> <p>20 explore farther the PK/PD parameters in murine</p> <p>21 systems, and I'll exemplify those in some of our</p> <p>22 discussion.</p>	<p style="text-align: right;">Page 45</p> <p>1 What are some of the more widely used</p> <p>2 or studied invasive fungal diseases? Certainly</p> <p>3 Candida dominates in the field of laboratory animal</p> <p>4 studies. Commonly we use a neutropenic thigh model</p> <p>5 but also there are models of disseminated Candidiasis</p> <p>6 to take us a step farther that can mirror acute,</p> <p>7 subacute, chronic and CVC, central venous catheter</p> <p>8 biofilm studies, hematogenous Candida</p> <p>9 meningoencephalitis, the diseases of cutaneous</p> <p>10 candidiasis, oropharyngeal and esophageal candidiasis,</p> <p>11 cutaneous and vulvovaginal candidiasis.</p> <p>12 For Aspergillosis, certainly there are</p> <p>13 the models of invasive pulmonary aspergillosis, which</p> <p>14 we see in murine, guinea pig and rabbit systems, and</p> <p>15 CNS disease, more challenging. But the laboratory,</p> <p>16 for example, of Dr. Stevens has done considerable work</p> <p>17 in CNS aspergillosis. In mucorales, we see pulmonary</p> <p>18 mucormycosis and models of disseminated disease.</p> <p>19 Although we will not address, in any</p> <p>20 greater detail, the endemic mycoses and Cryptococcus</p> <p>21 models, those models certainly are stalwarts of being</p> <p>22 able to have a firmer foundation before going into</p>

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<p>1 clinical trials. Emerging and very relevant to the</p> <p>2 new compounds under investigation now are hyaline and</p> <p>3 Dematiaceous molds and models including murine and</p> <p>4 rabbit model systems of fusariosis, scedosporiosis,</p> <p>5 some of the dematiaceous molds including in our</p> <p>6 system, for example, the rabbit model exserohilum</p> <p>7 rostratum CNS infection as an example of CNS</p> <p>8 phaeohyphomycosis.</p> <p>9 So, if we were to then explore farther</p> <p>10 now the application and use of these models, we can</p> <p>11 look to, for example, to the murine neutropenic thigh</p> <p>12 model for further understanding of the PK/PD</p> <p>13 properties. The model system has its origins</p> <p>14 originally in bacterial PK/PD studies and provides</p> <p>15 early guidance toward developing of dosing and PK/PD</p> <p>16 parameters. It identifies dosage parameters for</p> <p>17 further exploration, particularly in more advanced</p> <p>18 models representing different patterns of infection</p> <p>19 and different host groups.</p> <p>20 One of the key components of PK/PD</p> <p>21 modeling is that of fractionized dosing studies, which</p> <p>22 then allow one to be able to model the system and to</p>	<p>1 systemic agents and strategies.</p> <p>2 We then see with the advent of Candida</p> <p>3 auris, new models emerging of cutaneous Candidiasis.</p> <p>4 One in particular in the guinea pig, by Dr. Ghannoum</p> <p>5 and his colleagues, demonstrating the efficacy of</p> <p>6 reflects of ibrexafungerp. This is particularly</p> <p>7 important in launching into clinical trials for</p> <p>8 prevention or decolonization, as the skin serves as a</p> <p>9 distinctive source for harboring the organism, in a</p> <p>10 sense, and a source for transmission into the</p> <p>11 environment.</p> <p>12 If we look at different patterns of</p> <p>13 Candidiasis, there are acute, subacute and chronic</p> <p>14 that can be readily modeled both in the murine models</p> <p>15 but also in our rabbit model system. Typically the</p> <p>16 acute representing hemodynamically unstable patients,</p> <p>17 which is typically rapidly fatal, associated with high</p> <p>18 inoculant and a distinct series of clinical features.</p> <p>19 Subacute is much more commonly used in</p> <p>20 both murine and rabbit systems where one can have</p> <p>21 candidemia with deep tissue infection but are</p> <p>22 hemodynamically stable. And chronic reflects the host</p>
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<p>1 be able to identify, as depicted here, the appropriate</p> <p>2 parameter be it AUC:MIC ratio, peak plasma</p> <p>3 concentration or time above MIC.</p> <p>4 Mucocutaneous Candidiasis is a common</p> <p>5 ubiquitous series of infections, particularly</p> <p>6 oropharyngeal and esophageal Candidiasis. Earlier in</p> <p>7 HIV/AIDS, but now we continue to see this in a wide</p> <p>8 variety of immune deficiencies. Depicted to the left,</p> <p>9 there's a model for fluconazole-resistant esophageal</p> <p>10 candidiasis showing the time course of resistance</p> <p>11 versus susceptible and a striking difference in</p> <p>12 response as well as histology. And the predictive</p> <p>13 capability in echinocandin, in this case,</p> <p>14 Anidulafugin, showing a dose response relationship,</p> <p>15 which was highly predictive of the clinical outcome of</p> <p>16 that echinocandin as well as others in clinical trials</p> <p>17 of esophageal Candidiasis.</p> <p>18 There are numerous models of</p> <p>19 vulvovaginal Candidiasis and that has become an</p> <p>20 important area, particularly ever increasingly, and</p> <p>21 these unfortunate patients who suffer from refractory</p> <p>22 VVC and for whom there is a dearth of available</p>	<p>1 patterns of hepatosplenic candidiasis. These systems</p> <p>2 plus central venous catheter biofilm treatment studies</p> <p>3 have been the bulwark supporting the indications of</p> <p>4 amphotericin B lipid formulations, voriconazole, caspofungin,</p> <p>5 micafungin and anidulafungin for indications in this</p> <p>6 disease.</p> <p>7 One of the challenging features,</p> <p>8 however, remains in children, particularly children,</p> <p>9 hematogenous Candida meningoenophthalmitis. And then</p> <p>10 more commonly, although not exclusively, Candida</p> <p>11 endophthalmitis in adults.</p> <p>12 So, we do see endophthalmitis in our</p> <p>13 pediatric population as well. That prompted us to</p> <p>14 move to a distinctive model of experimental model of</p> <p>15 experimental hematogenous meningoenophthalmitis where we</p> <p>16 were able to show with a series of imaging, both in</p> <p>17 vitro and in vivo studies, the capacity for being able</p> <p>18 to identify disruption of blood brain barrier by</p> <p>19 gadolinium scanning.</p> <p>20 And then leading to the hypothesis, we</p> <p>21 were able to bring in echinocandins into a pediatric</p> <p>22 population that's highly vulnerable to HCME that we</p>

<p style="text-align: right;">Page 50</p> <p>1 would need to know that we could use in echinocandins  2 safely and effectively both in the brain and the eye.  3 And to that end, knowing whether one's compound will  4 be effective in adults as well in treating  5 endophthalmitis rather than later seeing breakthroughs  6 of this infection also becomes important.  7         So, to that end, in our laboratory in  8 collaboration with Dr. Hope, when he worked in our  9 laboratory with Drs. Petraitis and Petraitiene at the  10 forefront of this work as well, we demonstrated very  11 nicely dose-effect response relationship of more than  12 99 percent being able to achieve at 12 milligram per  13 kilogram in the rabbit model system and being able to  14 project the AUC.  15         Given that the kinetics for many of the  16 compounds that we use are very nicely reflected  17 between the rabbits and pediatric patients, we were  18 able to bring these findings into clinical trial,  19 those animal studies, laying the foundation  20 predictively that we were able to enter ultimately  21 through a series of dose escalation cohort studies in  22 the infant and pediatric population a randomized trial</p>	<p style="text-align: right;">Page 52</p> <p>1           So, with that, one has direct  2 endotracheal inoculation, colonization of the  3 tracheobronchial tree. And as immune suppression  4 progresses, colonization to nodular and segmental  5 pneumonia, and then initiation of therapy based upon  6 CT-scan findings. These findings, we believe, very  7 closely mimic and recapitulation the development of  8 invasive pulmonary aspergillosis in our neutropenic  9 and profoundly immunocompromised hosts going out 12-14  10 days therapy. And even to the extent of  11 radiologically demonstrating halo signs and  12 characteristic nodular infiltrates as I've seen in our  13 patient population.  14         So, what has been the impact of the  15 markers that we see? Since the initial development of  16 this model, we've been able to identify dosages, drug  17 disposition, safety, tolerability, efficacy for all of  18 the compounds seen here, laying the clinical  19 foundation for the clinical trials, and predictively  20 identifying outcome, both alone and subsequently, as  21 I'll show you, in combination therapy, in a very  22 robust, very predictive manner over the course of</p>
<p style="text-align: right;">Page 51</p> <p>1 of echinocandid versus deoxycholate amphotericin B  2 with no breakthrough endophthalmitis and with no  3 evidence of breakthrough of CNS candidiasis.  4         If we switch our attention from Candida  5 models to that now of pulmonary aspergillosis, I'll  6 begin initially with the rabbit model -- the  7 persistently neutropenic rabbit model of invasive  8 aspergillosis, which has been a highly predictive  9 system in identifying new antifungal agents for  10 treatment and prevention of this frequently lethal  11 infection.  12         The animal system has a central  13 silastic venous catheter for atraumatic venous access,  14 Ara-C for profound persistent neutropenia, further  15 modulation with cyclosporine methylprednisolone.  16 That alone can also be used to develop a model which  17 we've employed for chronic pulmonary aspergillosis, a  18 very distinctive and tenacious problem encountered  19 ever-increasingly. And then providing intensive  20 supportive care in the profound persistent neutropenia  21 host, similar to that with what we would encounter in  22 our oncology population.</p>	<p style="text-align: right;">Page 53</p> <p>1 time.  2         If we look at the initial studies of  3 AmBisome, liposomal amphotericin B applied milligram  4 per kilogram per day compared with high dosage of  5 deoxycholate, the AmBisome was found to be more  6 effective and safer, increasing survival, reducing the  7 number of viable organisms, decreasing tissue injury,  8 preventing nephrotoxicity and also showing decreased  9 galactomannan as a therapeutic marker.  10         If we then look to the AmBiLoad  11 clinical trial, those results accurately predicted the  12 outcome that is compared to 10 milligram per kilogram  13 per day, 3 milligram per kilogram was comparable in  14 achieving a favorable survival rate of 72 percent, and  15 an overall response rate of 50 percent. If we take  16 those data from our original comparative studies,  17 we're then in collaboration with Dr. Hope -- we were  18 able to identify a PK/PD model that found near maximum  19 antifungal activity using, for example, galactomannan  20 as well as the other markers at 3-5 milligram per  21 kilogram per day; and found further that with all  22 formulations that we were also able to induce a dose-</p>

<p style="text-align: right;">Page 54</p> <p>1 dependent reduction of lung injury and circulating 2 fungal biomarkers. 3           And the final model demonstrated that a 4 clinical dosage of liposomal amphotericin B of 3 5 milligram per kilogram was predicted to cause complete 6 suppression of galactomannan in the majority of 7 patients, which also correlated well with clinical and 8 experimental outcome -- once again, the robustness of 9 the system and the predictive capacity of this 10 particular model. 11           Also reflected in this was that of 12 further studies of Posaconazole at 2, 6 and 20 13 milligram per kilogram -- this is out of intra -- and 14 deoxycholate amphotericin B, where using the 15 parameters of survival, pulmonary influx for lung 16 weights and pulmonary lesion score, we were able to 17 demonstrate that at the two higher doses, Posaconazole 18 was superior to that of Itraconazole, also correlating 19 well with biomarkers of galactomannan, galactomannan 20 antigenemia, as well as correlating with CT-scanning 21 volumetric outcome. 22           Despite both Itra and Posa having</p>	<p style="text-align: right;">Page 56</p> <p>1 ITRA as being superior and lifesaving in prevention of 2 life-threatening invasive aspergillosis and other 3 mycosis. 4           To that point, with emerging resistance 5 in other pathogens, we further explored in combination 6 antifungal therapy where we were able to demonstrate 7 in this similar model system improvement across all of 8 the biomarkers using, again, CT-scanning as well as 9 galactomannan with the combination therapy, in this 10 case voriconazole plus anidulafungin with striking 11 correlation. 12           With the in vitro studies, in this 13 case, bliss analysis where the curve itself, the 14 three-dimensional curve going positive indicates 15 significant response. 16           And so, with that, moving forward into 17 the randomized trial voriconazole plus anidulafungin 18 versus vori alone, although the original analysis 19 primary endpoint was not fulfilled at 0.087, one post 20 talk analysis of six-week mortality did demonstrate in 21 the early patients and those with galactomannan 22 positivity a significant improvement in survival.</p>
<p style="text-align: right;">Page 55</p> <p>1 similar -- virtually superimposable plasma 2 concentrations at the 2, 6 and 20, the data has 3 clearly indicated the superiority of posaconazole in 4 this setting, suggesting that MIC may play a critical 5 role where the MIC was significantly lower for 6 posaconazole than that of Itra. 7           These findings were predictive of the 8 externally controlled trial where we were able to find 9 that there were significantly greater responses in the 10 Salvage study for posaconazole compared to externally 11 controlled recipients. 42 percent of posaconazole 12 recipients versus 26 percent for our control 13 recipients. 14           We further found that if one evaluated 15 survival with Kaplan-Meier analysis, that there was 16 also similar response. Further to the PK/PD of this, 17 we also found parallel to the rabbit model system, 18 1,250 micrograms per ml predicted favorable outcome 19 compared to the lower concentrations. 20           And, finally, our prophylactic studies 21 also, in the system, predicted and laid the foundation 22 for the definitive study of posaconazole versus FLU or</p>	<p style="text-align: right;">Page 57</p> <p>1           If we change our focus away from the 2 rabbit model system, we go now to a PK/PD approach 3 where here we see dose fractionation being performed 4 in the laboratory of Dr. Andes, Dr. Zhao, et al, where 5 efficacy was assessed by quantitative PCR. But not 6 many regressions using the Hill equation demonstrating 7 a 24-hour AUC/MIC ratio that predicted the best PK/PD. 8           And with a stasis and one-hour q 9 endpoint of 48 and approximately 89 mg/kg as dosages 10 achieving status in one long chill. And then with Dr. 11 Patterson's and Vederhold's model, for example in ASP 12 9726, a survival rate that demonstrates a dose 13 response relationship and parameters that also reveal 14 a correlation with clinical response. 15           Finally, we see in pulmonary 16 mucormycosis, a very nice correlation with clearance 17 in increased uptake in the -- by lipid formulations by 18 the laboratory of Dr. Pontionus and in the laboratory 19 of Dr. Ashraf Ibrahim, liposomal amphotericin B 20 showing a favorable dose response relationship all the 21 way to 7.5 milligram per kilogram in their murine 22 model of disseminated mucormycosis.</p>

<p style="text-align: right;">Page 58</p> <p>1 Notably, this model was also critical  2 in assessing the efficacy of isavuconazole, which was  3 relatively comparable to that of liposomal  4 amphotericin B being given at 15 milligram per  5 kilogram per day.  6 If we move from the traditional models  7 of mice, rats, guinea pigs and rabbits and look toward  8 zebrafish, this is increasingly being used, albeit not  9 for therapeutics but for pathogenesis and host defense  10 and may be a useful and less costly screening tool of  11 antifungal drug discovery.  12 And, finally in non-vertebrae animal  13 model systems, we see the role, for example of ganella  14 and we also see that of potentially dorsophila as  15 viable tools for, again, screening in early stages of  16 antifungal drug development.  17 As we look to the future, we're looking  18 toward implementation of biomarkers from preclinical  19 data into clinical endpoint response criteria;  20 development of new models of emerging pathogens; and  21 systematic integration of data from several models in  22 predicting outcome.</p>	<p style="text-align: right;">Page 60</p> <p>1 much, Dr. Walsh. That was a lot of information in a  2 very short period of time so I'm hoping that we can  3 discuss some of the ideas during the panel discussion.  4 Our next session is on clinical  5 pharmacology consideration for antifungal drug  6 development. We have two speakers, Dr. Jason Moore,  7 the first speaker, who's a clinical pharmacology  8 reviewer in the Division of Infectious Disease  9 Pharmacology at the FDA. And Dr. Hope is the second  10 speaker, and Dr. Hope is the Dame Sally Davies Chair  11 of AMR Research at the University of Liverpool in the  12 U.K. So, Jason, I'll hand it over to you. Thank you.  13 DR. JASON MOORE: Thank you very much,  14 Sumati. Can you all hear me okay?  15 DR. SUMATI NAMBIAR: Yes, thank you.  16 DR. JASON MOORE: Thank you very much.  17 As Sumati mentioned, I'll be discussing critical  18 pharmacology considerations for antifungal drug  19 development from a regulatory perspective.  20 As a disclaimer, note that the opinions  21 contained in this presentation are my own. The  22 objectives of this talk are to establish a framework</p>
<p style="text-align: right;">Page 59</p> <p>1 We conclude that the decision to move  2 from laboratory to clinical trials should be  3 predicated upon a portfolio of complementary and  4 mutually validating preclinical animal model systems  5 with meticulous preclinical investigation of candidate  6 antifungal agents in a robust series of predictive  7 model systems that will optimize study design, de-risk  8 clinical trials and ensure tangible benefit to our  9 patients.  10 I want to acknowledge the tremendous  11 effort and collaborations that we've had, particularly  12 noting Drs. Petraitis and Petraitiene, outstanding  13 clinical research collaboration and collaborations  14 that span three decades, including that of Dr.  15 Roilides and Dr. Groll, and Dr. Hope, and Dr. Perlin.  16 And our efforts could not be made without extensive  17 collaborations and support through the many agencies  18 and foundations that I've listed here as well as  19 through our industrial partners, who have spearheaded  20 so much of the work in developing these important  21 antifungal compounds. Thank you very much.  22 DR. SUMATI NAMBIAR: Thank you very</p>	<p style="text-align: right;">Page 61</p> <p>1 for further discussion as it applies to clinical  2 pharmacology. To do so, I will discuss at a high  3 level clinical pharmacology considerations that are  4 relevant for antifungals and perhaps have some  5 specific unique aspects relative to other therapeutic  6 areas. These will be along the lines of animal  7 models, formulation development, exposure response and  8 drug-drug interaction.  9 The first consideration pertains to  10 animal model utility. So, not to reiterate too much  11 about animal models after that last great talk, but  12 animal models, as we've seen, do have utility in  13 antifungal drug development to demonstrate proof of  14 concept and to identify those regimens. However,  15 challengers believe in the use of animal models to  16 establish clinical effectiveness. Part of this is due  17 to the appropriate selection of an animal model, one  18 that adequately reflects human critical disease.  19 As an example, we can turn to  20 micafungin. Micafungin was originally approved in  21 2005 in adults for candidiasis and later in pediatric  22 patients of four months of age and older. However,</p>



<p style="text-align: right;">Page 62</p> <p>1 there was difficulty establishing the effectiveness  2 for micafungin in pediatric patients younger than four  3 months. In part, this is due to the fact that  4 pediatric patients younger than four months of age  5 can't have meningoencephalitis.</p> <p>6       Thus, the assumption that the exposure  7 that would affected in the older pediatric patients  8 and adults would be -- would also be effective in  9 pediatric patients under four months, would not be  10 valid. And, thus, we needed more data in order to be  11 able to identify a dose regimen, first of all, in this  12 patient population.</p> <p>13       And that's where the rabbit model of  14 hematogenous Candida meningoencephalitis, the one that  15 Dr. Walsh mentioned in the previous talk, came in. It  16 was used to identify the dose regimen for further  17 clinical study.</p> <p>18       However, even with the clinical study,  19 robust clinical data in the pediatric patients younger  20 than four months of age were difficult to obtain.</p> <p>21       Thus, this model was used again to  22 support the labeling information, as you can see in</p>	<p style="text-align: right;">Page 64</p> <p>1 formulations available. As we've been discussing,  2 there are a wide range of fungal infection severity  3 from the more ambulatory patients to the patients  4 perhaps that cannot tolerate oral medication.</p> <p>5       Additionally, within the context of  6 critically ill patients, it's good to be able to  7 perform stepdown therapy starting with an intravenous  8 agent when they cannot tolerate the oral medication  9 and perhaps switching them to an oral formulation of  10 the same agent as their condition improves.</p> <p>11       With that in mind, there have been  12 concerns with the available antifungal formulations.  13 Echinocandins, for instance, are only available  14 intravenously. While the (inaudible) antifungals may  15 have both oral and intravenous formulations, there  16 occasionally have been concerns with the oral  17 formulations in light of variable exposure and  18 absorption. So it should be a consideration during  19 development for a candidate antifungal agent.</p> <p>20       The next consideration regards the  21 analysis of exposure-response. It is important to  22 evaluate exposure-response relationships to support</p>
<p style="text-align: right;">Page 63</p> <p>1 the graphic below. Essentially it indicated that  2 seeing that antifungal activity was shown in the model  3 and it included the corresponding human dose regimens  4 that were predicted to note comparable exposure to the  5 rabbit.</p> <p>6       Note that this information was included  7 in section 8.4 using special population pediatric use  8 and not section 1, indications and usage, or section  9 2, dosage and administration.</p> <p>10       This decision was made in part because  11 the rabbit ACME model was originally designed to  12 identify the dose with the anticipation of  13 confirmation from a clinical trial in patients.</p> <p>14       Additionally, upon review of the  15 individual animal data, we were able to identify a  16 range of dose measurements that were associated with  17 antifungal activity but we could not pinpoint a  18 specific dose regimen linked to clinical  19 effectiveness.</p> <p>20       The next consideration regards  21 formulation development. Generally speaking, it's  22 beneficial to have both intravenous and oral</p>	<p style="text-align: right;">Page 65</p> <p>1 efficacy and safety in clinical trials. They can help  2 to inform dose regimen selection, such as if one  3 identified in Phase 2 is used to further optimize the  4 dose before going into Phase 2 trials. They may also  5 indicate the need for therapeutic drug monitoring.</p> <p>6       As we see many antifungal agents do  7 include exposure-response data in the labeling,  8 there's an example shown there -- and therapeutic drug  9 monitoring itself is not mentioned in labeling often.</p> <p>10 However, it is used clinically especially for azole  11 antifungals. And I've lifted an example here from the  12 2016 IDC guidelines for aspergillosis that does  13 recommend therapeutic drug monitoring for select azole  14 antifungals.</p> <p>15       The fourth consideration regards drug-  16 drug interactions. As we've seen, several antifungals  17 have significant drug-drug interaction liability. The  18 azole antifungals in particular are substrates and  19 inhibitors which have to do with their mechanism of  20 antifungal action.</p> <p>21       Voriconazole and itraconazole in  22 particular have 30 plus listed drug-drug interaction</p>

<p style="text-align: right;">Page 66</p> <p>1 in labeling. This is a concern because many of the 2 patients who will be treated with this agents for 3 invasive fungal infections have severe comorbidities 4 that necessitate treatment by many concomitant 5 medications that may also have drug-drug interaction 6 liability.</p> <p>7 For instance, in the transplant 8 recipients, they are often treated with the agents 9 that are also CYP 3a4 substrates, so having liability 10 through that pathway, and also need to be maintained 11 within a certain concentration window to optimize 12 efficacy and safety.</p> <p>13 Additionally, patients with HIV may 14 also be on agents with DDI potential with these 15 agents, such as the protease inhibitors. Thus, it is 16 important to evaluate the drug-drug interaction 17 potential for a candidate antifungal, both in vitro 18 and in vivo, as applicable.</p> <p>19 For these last three considerations we 20 can use Posaconazole as an example. It was originally 21 approved as an oral suspension in 2006 and later as a 22 delayed-release tablet and an IV solution. The</p>	<p style="text-align: right;">Page 68</p> <p>1 With all that in mind, I've highlighted 2 four specific areas for antifungals that relate to 3 clinical pharmacology, but there are other important 4 clinical pharmacology studies that will need to be 5 done during a clinical development cycle, albeit 6 perhaps with not specific considerations for 7 antifungals. Still, these will often inform many of 8 the other studies or areas that we've been discussing.</p> <p>9 For instance, the in vitro CYP 10 metabolism and transporter studies will help to inform 11 what in vitro and in vivo drug-drug interactions 12 studies need to be done, the food effects, 13 bioequivalence/bioavailability studies will be very 14 important during formulation and development. The 15 mass balance study will help to inform the design of 16 the hepatic impairment and renal impairment studies, 17 which, again, will be important based on the severely 18 ill population that many of these agents will be used 19 in.</p> <p>20 With all that in mind, clinical 21 pharmacology drug development for antifungals on its 22 face is similar to other disease states for the most</p>
<p style="text-align: right;">Page 67</p> <p>1 original suspension had a few concerns related to 2 pharmacokinetics including variable absorption leading 3 to variable exposure. The later approval of the 4 tablet and the solution appeared to increase its 5 clinical utility and allow it to be used in more 6 situations.</p> <p>7 In terms of drug-drug interactions, 8 like many of the azoles, it can interact with CYP 3a4 9 substrates inducers and inhibitors. Additionally, the 10 (inaudible) formulation can interact with drugs 11 affecting gastrointestinal motility or pH.</p> <p>12 In terms of the exposure-response 13 relationship, it was assessed specifically for the 14 oral suspension. It was noted that there was an 15 increase in prophylactic efficacy with increases in 16 average concentration. This information was then 17 communicated in labeling. This revealed an 18 opportunity to optimize prophylaxis despite variable 19 absorption potentially using therapeutic drug 20 monitoring -- which, again, while not in the labeling 21 explicitly, is often used clinically and referenced in 22 the guidelines.</p>	<p style="text-align: right;">Page 69</p> <p>1 part. There are simply several areas that may require 2 special consideration relative to other therapeutic 3 areas in the arenas of animal models, formulations, 4 exposure response and drug-drug interaction 5 characterization.</p> <p>6 I would like to thank and acknowledge 7 contributions from my colleagues in the Division of 8 Infectious Disease Pharmacology and the Division of 9 Anti-Infectives. Thank you all very much, and I will 10 turn it back over to Sumati.</p> <p>11 DR. SUMATI NAMBIAR: Thank you so much, 12 Jason. William, can we start with your slides? Thank 13 you.</p> <p>14 DR. WILLIAM HOPE: Good morning, 15 everybody. Sumati, can you hear me?</p> <p>16 DR. SUMATI NAMBIAR: Yes, we can. 17 Thanks, William.</p> <p>18 DR. WILLIAM HOPE: So, thank you for 19 the invitation to speak from the chilly north of the 20 United Kingdom, in more ways than one.</p> <p>21 So, this talk addresses the key steps 22 and ideas to ensure patients receive the right regimen</p>

<p style="text-align: right;">Page 70</p> <p>1 of a novel agent the first time. So, it's going to  2 build on concepts that you've heard throughout the  3 morning. And there are two key areas for discussion  4 this morning.</p> <p>5           So, the first would be the  6 identification of an initial regimen, so that's a  7 selection of the candidate dose and schedule of a new  8 drug, and that's largely obtained from preclinical  9 models and PK/PD bridging techniques that we're going  10 to discuss in the next 10-15 minutes.</p> <p>11           And then, of course, a regimen is  12 chosen to ensure that it remains fit for purpose as  13 the compound transitions from healthy volunteers to  14 patients or other special populations, as it makes its  15 way from laboratories in Phase 1 units into real world  16 settings.</p> <p>17           So, in terms of the historical context,  18 the lethal diseases, as for invasive fungal infections  19 and other infections, it's not reasonable to design  20 clinical studies that delineate the entire dose-  21 exposure-response relationship. And so, nonclinical  22 PK/PD studies and other preclinical studies have to</p>	<p style="text-align: right;">Page 72</p> <p>1 plan for dosing schedule, and these models are being  2 reviewed extensively by Dr. Walsh and candida models  3 were used extensively by (inaudible) in the early  4 2000s.</p> <p>5           Aspergillus models were not available  6 until the early 2000s and then largely developed with  7 NIH funding. And the endpoint was the problem there,  8 with PCR galactomannan and survival used by different  9 investigators. And then Cryptococcus models in mice  10 really making meningoencephalitis also extensively  11 used by drug developers.</p> <p>12           So, generally, these models are robust  13 and I will just site John Perfect in saying that they  14 have never really let us down actually, and they may -  15 -- they enable a clear indication of the relevant  16 pharmacodynamics and therapeutic potential of a new  17 agent.</p> <p>18           So, this is something of a revelation  19 to me in my thinking recently that came after a recent  20 FDA workshop. And the models that we have can also  21 serve as adjunctive evidence of clinical efficacy.  22 But this is on a different part of the spectrum to PK</p>
<p style="text-align: right;">Page 71</p> <p>1 fulfill this purpose.</p> <p>2           Also, it's worth remembering that many  3 invasive fungal diseases are rare and difficult to  4 enroll into clinical studies, and clinical trials are  5 often simply infeasible. And that older antifungal  6 agents, those which we routinely used, were developed  7 -- what may now be considered relatively crudely. So,  8 plasma concentrations that exceed MIC 90 for the  9 proposed dosing interval. And voriconazole and  10 caspofungin were developed in this way -- and Mike  11 Hodges is on the call and would have plenty of  12 experience with this and I'd be interested in his  13 views about that.</p> <p>14           So, what are the key ideas and  15 challenges for identifying candida regimens for  16 patients? And that's for a new antifungal drug or a  17 new indication for a licensed compound. So, the first  18 is that we do have -- and this was alluded to by Dr.  19 Botgros -- we do have robust pharmacodynamics models  20 that are available to delineate initial PK and PD  21 relationships.</p> <p>22           These provide early information on the</p>	<p style="text-align: right;">Page 73</p> <p>1 and PD.</p> <p>2           So, there was this very interesting  3 debate that emerged at the last FDA meeting on the 5th  4 of March of this year on animal models to support  5 antibacterial development. And it's this idea of  6 separating relatively well-controlled and early models  7 designed to establish PK/PD relationships versus  8 models that might be more faithful mimics of human  9 disease.</p> <p>10           Now, John Rex summarized this very  11 nicely, and I've given the web link, on the 8th of  12 March of this year. And the rabbit models that you've  13 heard about from Dr. Walsh I think in many ways have  14 fulfilled this role. So, the model of invasive  15 pulmonary aspergillosis, the number of different  16 rabbit models, the candidate regimens; the CNS candida  17 model, and the Cryptococcus model in the rabbit  18 developed by John Perfect all really fulfilled this  19 role in that they generally have clinically relevant  20 background immunosuppression, they have comparable  21 pathogenesis to humans, they have clinically relevant  22 readouts, and that they're severe in that they usually</p>

<p style="text-align: right;">Page 74</p> <p>1 are universally lethal.</p> <p>2           And so the use of these models to mimic</p> <p>3 human disease -- I guess this example's come up on a</p> <p>4 number of talks -- but I think that this is a useful</p> <p>5 way of thinking about the contribution of preclinical</p> <p>6 models to dose identification.</p> <p>7           So, this is the first call from me to</p> <p>8 this community. That is, nonclinical data is being</p> <p>9 used as adjunctive evidence of clinical efficacy. So,</p> <p>10 Dr. Moore just told us about the labeling of</p> <p>11 micafungin or the animal model for the micafungin</p> <p>12 label. And then some thought needs to be given to the</p> <p>13 QA issues that are involved.</p> <p>14           So, secure data repositories may need</p> <p>15 to be considered by this community. They're</p> <p>16 extraordinarily extensive, I have to say. I will</p> <p>17 point out the GLP are not generally used -- is not</p> <p>18 generally used by academic laboratories. That would</p> <p>19 put all of us out of business. But as per the</p> <p>20 bacterial world, standardization of models may need to</p> <p>21 be further considered.</p> <p>22           So, point number 4, that there's a</p>	<p style="text-align: right;">Page 76</p> <p>1 from Dr. Moore. The bridge is pretty straightforward.</p> <p>2 So first-in-human PK providing insight as to whether</p> <p>3 exposures required for efficacy are achievable in</p> <p>4 humans. The data that's acquired can be modeled using</p> <p>5 population techniques, and simulation can be used to</p> <p>6 come up with the adequacy of proposed regimens.</p> <p>7           And the failure at this very early</p> <p>8 stage to achieve drug targets that may be desired or</p> <p>9 deemed to be clinically relevant can trigger the</p> <p>10 requirements for more PK studies. And Tom Walsh</p> <p>11 showed you this example of (inaudible). This is</p> <p>12 exactly what happened in the neonatal program where</p> <p>13 further clinical PK studies were required to</p> <p>14 demonstrate linearity and safety of higher dosages.</p> <p>15           This is an important point. Getting</p> <p>16 estimates of variability is key. It's not really the</p> <p>17 main or median that matters, it's rather the</p> <p>18 variability -- that's the key.</p> <p>19           So PK variability is generally higher</p> <p>20 in patients. The coefficient variation for clearance</p> <p>21 and therefore drug exposure AUC may double as you move</p> <p>22 from healthy volunteers to patients or generally</p>
<p style="text-align: right;">Page 75</p> <p>1 general problem that we have of defining study</p> <p>2 endpoints, and this needs more debate. And by this I</p> <p>3 mean what is the fungal equivalent of stasis? You</p> <p>4 heard Dr. Walsh use this term. Or a 1 or 2 log drop</p> <p>5 that's used extensively and is part of the</p> <p>6 antibacterial drug development lexicon.</p> <p>7           But this is really important because</p> <p>8 this is where clinical regimens are defined. And so</p> <p>9 this is where, generally, people will want to put an</p> <p>10 endpoint. But putting an endpoint where there's near</p> <p>11 maximal activity in the model that we have will</p> <p>12 generally take a drug beyond its safety margin.</p> <p>13           And then there's this other idea that's</p> <p>14 being developed -- and we all do this even if we don't</p> <p>15 do it explicitly or benchmarking -- so how license</p> <p>16 compounds perform in our models. At least matching</p> <p>17 this benchmark endpoint is a way that new compounds</p> <p>18 can be developed in the context of what's our existing</p> <p>19 knowledge.</p> <p>20           So, as we transition to the clinic, I</p> <p>21 want to make a few more points. The first steps, of</p> <p>22 course, are pretty standard, and you've heard of those</p>	<p style="text-align: right;">Page 77</p> <p>1 double. It's possible just with early relatively</p> <p>2 sanitized Phase 1 data to artificially inflate</p> <p>3 variance in simulators.</p> <p>4           So, you take the volunteer data, you</p> <p>5 inflate the variance, and this stresses the candidate</p> <p>6 regimen in terms of its performance. And by some sort</p> <p>7 of prediction as the heterogeneity of patients in</p> <p>8 terms of their PK and more variable PK, and the</p> <p>9 implications for achieving desired drug exposure</p> <p>10 targets.</p> <p>11           There's, of course, progressive</p> <p>12 learning and understanding that happens as programs</p> <p>13 advance, and so the effect of food, and renal</p> <p>14 impairment, and hepatic impairment, and other</p> <p>15 idiosyncrasies may be important and relevant. And</p> <p>16 also important to consider -- the PK sub-study in an</p> <p>17 early cohort of patients. Now, I see that this has</p> <p>18 already come up in a chat for later this afternoon --</p> <p>19 as it may be relevant to make sure that the desired</p> <p>20 exposure to maintaining patients, and it may be</p> <p>21 important to co-model those data with volunteer data.</p> <p>22           This is another important point.</p>

<p style="text-align: right;">Page 78</p> <p>1 Number 6, planning for PK and PD sub-studies in Phase  2 2 and 3. The importance for this community that  3 completes the bench-to-bedside loop -- so we can  4 understand how lab animal models, how particularly  5 they are unless they're based in some sort of reality.  6 But here are the issues, and many on this call will  7 hate me, but PK is generally a poor quality that is  8 obtained in real world and requires co-modeling with  9 richer data to provide tractable estimates of drug  10 exposure.</p> <p>11 It's important to also realize that  12 uninformative PK or just bad PK data results in  13 imprecise estimates of drug exposure or even bias.  14 And the other problem with these studies is that the  15 pharmacodynamics endpoints may be problematic. So,  16 galactomannan is being used in invadable  17 aspergillosis. The later decline of fungal burden has  18 been moved extensively in Phase 2 and 3 in  19 cryptococcal meningitis. It's a primary endpoint in  20 many Phase 2 studies. And all-cause mortality and  21 clinical response are relatively crude and noisy  22 endpoints because they're confounded by disease and</p>	<p style="text-align: right;">Page 80</p> <p>1 using very precise techniques is also possible that  2 need further work. But from a regulatory perspective  3 and an infrastructure perspective, who's going to pay  4 for it perspective, and demonstrating clinical  5 benefit, as defined by the FDA also remains  6 challenging.</p> <p>7 So, in conclusion, the models that we  8 have, the approaches and pathways for antifungal drugs  9 are progressively more mature. I have noticed some  10 differences between FDA and EMA in terms of the way in  11 which data from preclinical models especially is  12 weighted, and some consistency in debate about this  13 would be helpful, I think.</p> <p>14 And this is the last point and this is  15 the second infrastructure that requests were made to  16 this community. It's not the primary responsibility  17 of the FDA or the EMA. It significantly concerns me  18 that there does not appear to be a new generation of  19 investigators interested in antifungal therapeutics,  20 and that is a shame and also a significant threat to  21 all of us in the world. So, I will stop there,  22 Sumati, thank you.</p>
<p style="text-align: right;">Page 79</p> <p>1 toxicity. So it can be difficult to make linkages.  2 But here's the important point. That a  3 PK/PD sub-study really ensures patients are on top of  4 the dose-response relationship. So, you should see,  5 if everything has gone properly, all the patients up  6 here. So, if you do see the (sound drops) response  7 relationship, something has gone badly wrong  8 generally, so the dose is not right or the regimen is  9 not right. Either that or the drug is very variable  10 and patients have inadvertently slipped down with the  11 dose exposure response relationship. This would've  12 happened -- it's typical of well-designed clinical  13 development programs where you put everybody up,  14 having adequate drug exposure.</p> <p>15 And I'll make this point and it'll make  16 someone on the call shudder, I know. But all  17 information -- this is an important point -- all  18 information related to dose-exposure-response  19 relationship can be used for therapeutic drug  20 monitoring and in control. This is sort of embedded  21 in some of our thinking with therapeutic drug  22 monitoring for the triazoles, but routine control</p>	<p style="text-align: right;">Page 81</p> <p>1 DR. SUMATI NAMBIAR: Thank you so much,  2 William. So, that brings us to the end of Session 1.  3 Erin, if there are no comments from you, I think what  4 we can do is take a break. We are running a few  5 minutes late, so maybe we can reconvene at, I think,  6 11: 5:07 might be hard. So, let's all reconvene at  7 11 and, hopefully, we will try to make up some lost  8 time as the day progresses. Erin, would that be okay  9 with you? Maybe you have it muted. So, let's  10 reconvene at 11 and we'll start with Session 2. So,  11 thank you to all the presenters in this morning's  12 session and we'll talk to you soon. Thank you.</p> <p>13 (Break)</p> <p>14 DR. LAURA KOVANDA: Thank you,  15 everyone. I'd like to welcome everyone to Session 2,  16 the Current State of Mold Infections and Antifungal  17 Drug Development Consideration. I am Laura Kovanda  18 from Astellas Pharma Global Development, and I'm here  19 with my co-chair, Yuliya Yaskinskaya, who is the  20 Clinical Team Lead in the Division of Anti-Infectives  21 at the FDA. We're going to go through a series of  22 discussions. We'll start with Kieren Marr, who is the</p>

<p style="text-align: right;">Page 82</p> <p>1 Professor of Medicine, Vice Chair of Medicine for  2 Innovation in Healthcare Implementation, and the  3 Director of Transplant and Oncology Infectious  4 Diseases at Johns Hopkins.  5 Her talk today will be on the current  6 state on invasive fungal infections, available  7 therapies and unmet needs. Dr. Marr?  8 DR. KIEREN MARR: Hi, good morning, can  9 you hear me?  10 DR. LAURA KOVANDA: Yes. Yes, we can.  11 DR. KIEREN MARR: Great. I'll say at  12 the onset, thank you for the invitation to speak. I  13 also want to apologize for hopefully what will not be  14 a problem in that I'm sitting in a very -- pretty  15 severe storm and have lost electricity and Internet  16 connection several times this morning. So, let's see  17 if we can get through this and I will try and go  18 without slides on my phone if I need to.  19 I've been asked to speak of the current  20 state of invasive fungal infections, and specifically  21 unmet needs from a more clinical perspective. My  22 disclosures are listed publicly on the Internet, I</p>	<p style="text-align: right;">Page 84</p> <p>1 and we have a unique unmet need, which is to support  2 early treatment indications when we're not certain on  3 the diagnosis. And I'm going to spend some time  4 outlining this because it is a real clinical problem  5 and I think an unmet need that hasn't had enough  6 attention.  7 We have many PK/PD limitations that  8 have been discussed to some degree. These include  9 limitations in formulations, infeasible dosing  10 frequency, unpredictable absorption and metabolism and  11 poor target exposure. And certainly we have  12 widespread and unacceptable safety features associated  13 with toxicities, as well as in the clinical context,  14 very important drug interactions. And, finally, we  15 have context-specific needs or the situation where  16 special populations really define the unmet need.  17 The first focus on spectrum of activity  18 and the problem of antifungal drug resistance, I think  19 it's very important to outline the importance of very  20 resistant molds or refractory infections. This figure  21 on the right is a table that I pulled from a recent  22 review. And I like it because it basically</p>
<p style="text-align: right;">Page 83</p> <p>1 believe. And this slide shows the antifungal agents  2 that we have available for treatment of Candida and  3 mold infections and the timeline in which they were  4 approved for use. There's a number of lessons  5 learned, which is a relative paucity of agents of  6 few classes, and enhanced activity after 2000 but not  7 very much after 2010. As this illustrates some of the  8 drugs that we currently have available but not in  9 study.  10 When we consider unmet needs, I wanted  11 to frame this talk from a clinical perspective because  12 this is the context in which it's not just the drug  13 and above issue. We have the host involved, and this  14 is a very real issue for treatment of infections as  15 well as prevention, although I'll focus most of the  16 talk on treatment.  17 Certainly the organism antimicrobial  18 resistance is a problem in conferring an inadequate  19 antifungal spectrum for a number of agents. We have  20 very resistant molds that are fortunately less common  21 but the outcomes are very poor. We also have failure  22 of these drugs because of acquired drug resistance,</p>	<p style="text-align: right;">Page 85</p> <p>1 demonstrates in broad strokes categorical issues both  2 with the drugs according to the infection, and these  3 are non-aspergillus or less frequent molds that cause  4 disease.  5 And the important lesson here is that  6 there are species such as Fusarium species,  7 Scedosporium, Lomentospora species that have many more  8 problems with drug resistance across classes and  9 specific drugs. Importantly also, what you see in  10 this table is that there's no one agent that can  11 reliably cover all of the organisms that may be  12 causing infection. And this is especially important  13 in the clinical context when we don't know what is the  14 cause of disease. And it's becoming more and more  15 important that we can treat these infections early in  16 the immunosuppressed host.  17 Mucorales -- I'm sorry for the typo  18 here -- can be considered really, in my opinion, a  19 refractory infection. We certainly have a problem  20 with the lack of activity with voriconazole when  21 voriconazole can be a primary choice for lesions in  22 the lungs that look like aspergillosis. But these</p>

<p style="text-align: right;">Page 86</p> <p>1 organisms also suffer in outcomes because they are  2 relatively refractory even when the best polyene-based  3 therapies are applied. And the unmet needs in these  4 situations can actually potentially be illustrated by  5 the need, for instance, for not only new agents but  6 combination therapies, potentially.</p> <p>7         There are innately resistant  8 <i>Aspergillus</i> species. And that includes classically  9 polyene resistance and <i>aspergillus terreus</i>. But I  10 want to highlight, for instance, the infections caused  11 by the <i>Aspergillus ustus</i> group of organisms in which  12 we have variable or high MICs to multiple different  13 drugs and poor outcomes, such as a larger study that  14 was recently published demonstrated greater than 50  15 percent mortality at six months. These are very, very  16 difficult infections to deal with.</p> <p>17         We also have unusual sibling species or  18 what has been called cryptic species. An example is  19 <i>Aspergillus lentulus</i>. These are organisms that are  20 being increasingly studied because they're being  21 increasingly found in multiple parts of the world.  22 They have high MICs to azoles that appear to be 51a</p>	<p style="text-align: right;">Page 88</p> <p>1 recently in the United States. I think that you can  2 safely conclude that this is a problem that has  3 emerged and is now of potentially global concern. And  4 that we probably don't understand the overall  5 importance of azole resistance currently because not  6 many clinical centers are actually measuring azole  7 resistance as a matter of routine, and this can be  8 certainly associated with failure of disease in  9 biomarker defined settings in which the organism is  10 not recovered.</p> <p>11         This also illustrates again what I'm  12 talking about when we put the problem in context.  13 That failure is contact-specific. In fact, the  14 discovery and the unmet need of azole resistance,  15 either as an acquired trait or as an innate phenotype  16 emerges after therapy is applied. And so we currently  17 have large populations of people in which the overall  18 goal is to either prevent or to treat early. And,  19 historically, we've referred to the early treatment  20 category as empirical therapy, previously defined by  21 fever. We've gotten much better at that and currently  22 our early treatment strategies can better be</p>
<p style="text-align: right;">Page 87</p> <p>1 mediated but also have high MICs to polyenes and  2 echinocandins with very poor clinical responses. In  3 fact, these were first identified as breakthrough  4 isolates in azole prophylaxis studies. And so these  5 MICs appear to be truly clinically important.</p> <p>6         And, again, I'm going back to the issue  7 that these are difficult to diagnose and study with  8 low frequency of disease and very poor outcomes. And  9 inevitably, when we have people with documented  10 infections caused by organisms such as <i>Aspergillus</i>  11 <i>ustus</i>, they're really pretty far advanced.</p> <p>12         Of course, we also have problems,  13 increasing emerging problems with azole-resistant  14 <i>Aspergillus fumigatus</i>. This is associated with  15 acquired resistance associated with multiple mutations  16 in the <i>cyp51A</i> gene. They occur at episodic frequency  17 in different environments, predominantly associated  18 with azole use in the agricultural setting, first  19 reported in the Netherlands. But when you review the  20 literature now, they're actually identified in many  21 different nations all over Europe, South American,  22 Japan, India, Taiwan, Africa, Australia and more</p>	<p style="text-align: right;">Page 89</p> <p>1 categorized as syndromic or radiographic evidence of  2 disease or even biomarker-guided therapy. And we do  3 have unmet needs in identifying the best clinical  4 trial pathway for approval of these patients that have  5 disease that has not been microbially defined.</p> <p>6         This is an example of what I'm talking  7 about. These are people that have early pulmonary  8 lesions, either with our without biomarker positivity.  9 Some of our biomarkers that can be used have very good  10 sensitivity but clearly poor specificity. But in this  11 context, we are forced to choose a first line therapy  12 for -- with activity against molds.</p> <p>13         Optimally, we would have a drug that  14 has activity without causing undue harm as an early  15 therapy, and that would have a very broad spectrum of  16 activity. I think this early treatment category is  17 really truly a current unmet need.</p> <p>18         I'll turn to unmet needs in PK/PD  19 limitations. I think we all agree that we have  20 abundant holes in all mold-active agents. Polyenes  21 and echinocandins lack enteral formulations, which  22 cause problems with regards to our overall strategy,</p>

<p style="text-align: right;">Page 90</p> <p>1 especially stepdown and administering drugs in people  2 who have long-term needs. And that is especially  3 important in the context of mold infections.  4       Azoles suffer from unpredictable  5 absorption and metabolism. And we have poor target  6 exposure. Some of the biggest problems that are  7 becoming apparent are getting drug into the airway,  8 especially into the epithelial lining fluid or the  9 lung lining fluid in the upper and lower parts of the  10 airways. This is critical for airway disease and  11 treatment in certain special populations, such as lung  12 transplant patients and people with chronic lung  13 disease for various different reasons.  14       And this is the setting in which people  15 are turning to more inhalational exposure to address  16 the balance between airway delivery and avoidance of  17 systemic toxicities. We won't spend a lot of time on  18 inhalational drug delivery during this day, but it's  19 certainly something to consider with regards to the  20 unmet needs of systemically delivered drugs as well.  21       And this is the reminder to discuss the  22 problems that we currently have with safety. There</p>	<p style="text-align: right;">Page 92</p> <p>1 an expanding list of agents that complicate our  2 ability to giveazole drugs, both for prevention and  3 for therapy, early therapy and definitive therapy.  4       And I'll just say at the onset that  5 this problem is not just solved by not giving the  6 anti-mold drug; the problem is defined by going on and  7 off of these drugs in settings where these anti-cancer  8 agents can be variably metabolized or even stopped and  9 started during regimens that require long-term therapy  10 in a maintenance setting in order to establish  11 effective anti-leukemia or anti-lymph activity. And  12 I've listed some of these here.  13       Historically, and the one that we've  14 appreciated the most would be for treatment of people  15 with ALL that are receiving Vincristine-based  16 remission induction chemotherapies. But there are  17 many more drugs that have emerged and are increasingly  18 used in the last several years. This includes the  19 treatment of acute myelogenous leukemia with use of  20 FLT-3 inhibitors, such as midostaurin, BCL-2  21 inhibitors, specifically venetoclax for IDH1 or 2  22 inhibitors listed here. This also includes people</p>
<p style="text-align: right;">Page 91</p> <p>1 has been actually a learned helplessness that we've  2 been taught in the youth and the development of  3 antifungal drugs as we've accepted toxicities in  4 almost every organ system, especially liver toxicities  5 with azoles and renal toxicities with polyenes.  6       I'll just note that it's very, very  7 apparent that cumulative exposure to toxicities in  8 multiple organ systems lead directly to poor outcomes  9 in complex and vulnerable people, especially in the  10 oncology setting, in the ICU setting, and in  11 transplant recipients.  12       And there is a growing problem with  13 regards to drug interactions that define an increasing  14 group of people that have unmet needs. Historically,  15 we've considered problems with givingazole drugs in  16 the anti-rejection -- or in the setting in which anti-  17 rejection drugs are being administered after a stem  18 cell transplant or a solid organ transplant, but this  19 problem has grown with the introduction, especially  20 with antibodies and biologics that can be metabolized  21 by the cytochrome p450 system in whichazole drugs are  22 relatively or absolutely contraindicated. And there's</p>	<p style="text-align: right;">Page 93</p> <p>1 with chronic lymphocytic leukemia or those that are  2 receiving targeted B cell therapies such as ibrutinib,  3 venetoclax and idelalisib. These are settings in  4 which we have many more difficulties in administering  5 drugs that interfere with cytochrome 450 metabolism.  6 And there are many other disorders in which these  7 drugs are being explored or are increasingly used.  8 That is, for CLL, Waldenstroms macroglobulinemia,  9 other lymphomas, severe chronic graft vs. host  10 disease, or relapsed/refractory lymphoma.  11       So, in my opinion, there is an  12 increasing number of special populations that are  13 defined by the optimal therapies in which they should  14 be receiving for treatment of their oncologic  15 underlying disease.  16       And there are other context-specific  17 needs or special populations that we need to consider  18 as unmet needs. Currently, I think, perhaps one of  19 the most well-established is the lung transplant  20 recipient. This is a setting in which both candida  21 and mold infections are relatively common, especially  22 the candida infections early because they develop</p>



<p style="text-align: right;">Page 94</p> <p>1 anastomotic and pleural space infections and  2 relatively later, with mold infections.  3       Recent studies have shown that the  4 prevalence is not small -- 19 out of 100 surgeries was  5 estimated from a review that was recently published  6 from Duke. We have a problem with airway clearance,  7 and it's because of this that there's a risk for  8 invasive disease as well as tracheobronchial  9 manifestations. And so that increases the weight of  10 importance of delivering the drug straight into the  11 airway itself.  12       And I'll just add that this isn't just  13 a problem with infections, because the activity, the  14 established infection, and potentially even  15 colonization can exacerbate and increase the risk for  16 longer term graft rejection. Because of this problem  17 that was recognized many years ago, the community has  18 turned to inhalational delivery for the most part  19 during the early period of time when the patient is  20 within the medical center. But the regimens used are  21 variable. They include conventional deoxycholate,  22 Amphotericin B, as well as lipid formulations ABLC,</p>	<p style="text-align: right;">Page 96</p> <p>1       Now, I was asked to also focus on the  2 post-viral aspergillosis condition that has been  3 increasingly outlined with the unfortunate emergence  4 of SARS-CoV-2. And in order to do that, I'm going  5 back as a reminder that influenza-associated  6 aspergillosis has been studied especially in Europe,  7 in Canada, as well as in Asia but not necessarily in  8 the United States. And for the past five years, some  9 very good cohort studies have estimated the incidence  10 of aspergillosis subsequent to severe influenza  11 infection to be ranging from 7-31 percent.  12       The CDC has sponsored a study, a survey  13 study that documents that it's poorly recognized in  14 the U.S. and largely leading to diagnostic bias. But  15 this certainly is an entity that requires more  16 attention to bring down the mortality associated with  17 severe influenza infections.  18       And, unfortunately, we also now have  19 witnessed the, what I think is a documented emergence  20 of a secondary complication of COVID involving  21 aspergillus in the airway as a cause of airway disease  22 and invasive disease that has been coined COVID-</p>
<p style="text-align: right;">Page 95</p> <p>1 liposomal Amphotericin. There are centers that deploy  2 early echinocandin therapy, especially during this  3 early peritransplant period to also avoid the candida  4 systemic problems, for instance, in the plural space.  5 And there are centers that provide routinely prolonged  6 azole-based preventative therapy. The problems here  7 are exacerbations and toxicities, and the rate of  8 early discontinuation is unacceptably high.  9       Other special populations that are  10 growing in importance include people with chronic  11 airway disease, necrotizing aspergillosis, and the  12 constellation of manifestations therein. But also the  13 growing indication of antifungal therapy in people  14 with cystic fibrosis. Increasingly the CF setting is  15 appreciating that antifungal administration for what  16 was historically considered benign colonization may  17 have a therapeutic effect at decrease CF  18 exacerbations, much like the classic scenario of  19 treating gram negative organisms such as pseudomonas  20 with inhaled tobramycin. So, I think this may be, for  21 instance, an emerging unmet need that has attracted  22 attention by the Cystic Fibrosis Foundation.</p>	<p style="text-align: right;">Page 97</p> <p>1 associated pulmonary aspergillosis or CAPA. This  2 emerged from many smaller case reports and case  3 series, first in Europe. I'll point you to, I think,  4 what is the definitive evidence of this as an  5 important clinical entity from a reasonably large  6 prospective study in Italy that is in a prepub form in  7 clinical infectious disease currently.  8       They used biomarkers and cultures on  9 BAL or other tracheal aspirate fluids to document  10 essentially 28 patients that are on mechanical  11 ventilation after COVID-documented disease have this  12 entity. They also applied multivariable modeling to  13 identify the significance and it is a predictor of  14 death, and there's some indication that therapy can  15 lead to potentially better outcomes.  16       And so this is something that is an  17 emerging unfortunate unmet need, I think, both in the  18 preventative context as well as for documented  19 treatment.  20       I like this slide that was given to me  21 by Cidara in that it illustrates that there are a  22 number of different manifestations that are</p>

<p style="text-align: right;">Page 98</p> <p>1 potentially of clinical importance here that include  2 not only invasive disease where there's hyphal growth  3 and invasive pneumonia, but this can involve the  4 airways, exacerbating inflammatory conditions and  5 causing an overt tracheobronchitis in which the  6 organism may be very difficult to eradicate, and in  7 which some of the complications can include, for  8 instance, post-obstructive bacterial pneumonia.  9 This slide is very quick. I think that  10 we should consider beyond the molds, although it's not  11 a topic for today -- cryptococcus histo and  12 coccidiomycosis are certainly important unmet needs.  13 So, I'll summarize here. We do have  14 good drugs but they have a limited spectrum of  15 toxicities and drug interactions. We have broad needs  16 for rare molds that have innate resistance, acquired  17 resistance, and we need to have a drug that we can  18 reliably use for earlier treatment. We have special  19 populations that include lung transplant, people with  20 chronic lung disease and post-viral syndromes. Thank  21 you very much.  22 DR. LAURA KOVANDA: Thank you, Dr.</p>	<p style="text-align: right;">Page 100</p> <p>1 disease status as well as orphan drug status was  2 granted by the FDA for both evasive aspergillosis and  3 mucormycosis, and later invasive candidiasis, which  4 was not included in the initial submission.  5 Over the 13 years leading to the market  6 authorization in 2015 in adults, the program included  7 44 clinical trials, which enrolled more than 2,100  8 subjects, nearly 1,700 of whom received Cresemba.  9 Importantly, just over 100 -- or, sorry -- 1,100  10 subjects were in the Phase 1 studies alone. 403  11 subjects were in the two Phase 3 trials for invasive  12 aspergillosis and mucormycosis but were in the NDA  13 package in 2014.  14 To put this into perspective with  15 regards to the resources needed to invest in this  16 program, the Phase 1 program alone cost nearly \$30  17 million. The Phase 3 invasive aspergillosis and  18 mucormycosis studies combined cost over \$100 million.  19 These finances do not include the development cost for  20 Basilea prior to licensure or the cost of the  21 licensure itself and the preclinical development,  22 including new toxicology, in vitro, in vivo, and</p>
<p style="text-align: right;">Page 99</p> <p>1 Marr. We'll go right into the next session, or next  2 talk, which is from myself, Laura Kovanda. I'd like  3 to thank the organizers from the FDA for asking me to  4 come today and talk about my experiences with  5 antifungal development.  6 To begin, I'll start with the orphan  7 designation that's available when a disease affects  8 less than 200,000 persons per year in the U.S. This is  9 important to today's discussion, as most systemic  10 fungal infections qualify for this designation.  11 The benefits include not only 7-year  12 market exclusivity but other benefits such as tax  13 credits and waivers for user fees. But this comes  14 with some challenges for orphan drug development,  15 namely, a small number of eligible patients and lack  16 of acceptable comparators, to name a few.  17 Which brings me to Cresemba. The  18 clinical development program was initiated by our  19 partner Basilea in 2002, and the Phase 3 program  20 commenced in 2007. In 2010, Astellas (sound drops)  21 license, development rights and assumed sponsorship of  22 the Phase 3 study ongoing. Qualified infectious</p>	<p style="text-align: right;">Page 101</p> <p>1 manufacturing. As a reminder, Rescempa,  2 isavuconazonium sulfate is a water-soluble prodrug.  3 The active moiety, isavuconazole, is a broad-spectrum  4 triazole antifungal. My finger's going...  5 Important points which have already  6 been discussed, these infections occur in severely  7 immunocompromised patients which have high  8 comorbidities. The rare infections, aspergillosis  9 occurring in, approximately, 12,000 cases per year and  10 500 cases per year of mucormycosis. They're difficult  11 to diagnose and treat.  12 The development path for invasive  13 aspergillosis was clear as the standard of care for  14 comparison was established with Voriconazole.  15 However, for mucormycosis the approach had to be  16 different. Treatment paradigms include a multimodal  17 approach including treatment of the underlying  18 disease, immediate antifungal therapy and surgical  19 debridement. Not treating mucormycosis is associated  20 with nearly 100 percent mortality, and delay in  21 therapy is almost as bad as no treatment.  22 So, can an active controlled study be</p>

<p style="text-align: right;">Page 102</p> <p>1 conducted in this extremely rare condition? What  2 comparator is available for study? No randomized  3 controlled trials have been conducted for  4 mucormycosis. The only available approved therapy in  5 the U.S. at the time was amphotericin B deoxycholate.  6 And it is only in IV formulation, has high toxicity,  7 and lipid formulations are typically the standard of  8 care, but not approved for mucormycosis.  9 We conducted two Phase 3 studies to  10 support the initial registration. The SECURE study in  11 Invasive Aspergillosis and the VITAL study which  12 included multiple rare invasive fungal infections but  13 focused on the inclusion of mucormycosis.  14 To put the study results for  15 mucormycosis into context, we performed a matched  16 case-control analysis using an invasive fungal disease  17 database called FungiScope out of the University of  18 Cologne. The matching criteria included severe  19 disease, hematologic malignancy and therapeutic  20 debridement. Matching was conducted independently and  21 blinded to outcomes. Up to three controls per  22 Cresemba case were included. All caused mortality was</p>	<p style="text-align: right;">Page 104</p> <p>1 that the monthly enrollment never exceeded 20 patients  2 per month. And with 30 countries open to enrollment  3 through the trial, only 25 countries enrolled at least  4 one patient. 80 percent of enrollment occurred in  5 eight countries. With 158 sites open to enrollment,  6 70 percent enrolled at least one patient. That's  7 great but we had 43 percent of these enroll two  8 patients or less. Spreading sites across multiple  9 countries globally is a huge cost driver for clinical  10 trials and a major resource burden to manage such a  11 large clinical trial footprint.  12 We tried many mitigation tactics, such  13 as closed nonperforming sites. We also decreased our  14 sample size by just 100 after reviewing, in a blinded  15 manner, the actual evaluability rate, which was  16 revealed to be 10 percent higher than the original  17 study design function. In the end, the final  18 evaluability rate and power were just over 90 percent.  19 This was a tremendous effort, however,  20 in the end, the trial did not meet its primary  21 endpoint. Which is another key point when designing  22 non-inferiority trials. Study design and endpoints</p>
<p style="text-align: right;">Page 103</p> <p>1 analyzed as the endpoint.  2 In the VITAL Astellas trial, 46  3 mucormycosis cases were included in which 21 had  4 primary therapy. The results showed better efficacy  5 relative to untreated historical controls and similar  6 efficacy relative to Amphotericin B from the  7 literature as well as the matched controls.  8 This approach is supported by 24 CFR  9 314.126, which states that "Because historical control  10 populations usually cannot be as well assessed with  11 respect to pertinent variables as can concurrent  12 control populations, historical control designs are  13 usually reserved for special circumstances. Examples  14 include diseases with high and predictable mortality."  15 Now, let's take a quick look at the  16 invasive candidiasis trial for Cresemba. This study  17 compared IV Cresemba to IV Caspofungin with the option  18 to switch to oral therapy after Day 11 in both arms.  19 The study included 450 subjects. The active trial, as  20 we called it, had significant enrollment challenges.  21 It took over 5 and a half years to complete  22 enrollment. If we dissect this a little bit, we see</p>	<p style="text-align: right;">Page 105</p> <p>1 are driven by the comparator chosen. To justify the  2 non-inferiority margin, you need a frame of reference.  3 Both the comparator regimen and the placebo for  4 historical untreated population.  5 For the active trial, the original  6 study design was caspofungin followed by voriconazole  7 with the primary endpoint assessment at two weeks  8 after the end of therapy. This regimen had never been  9 tested in clinical trials.  10 So, in order to anchor on the  11 historical registration trial for caspofungin, we  12 modified the study design and used the available  13 historical data. Unfortunately, the endpoint of end  14 of therapy -- IV therapy favors the echinocandin.  15 My last point brings me to the post-  16 approval stage. Once a drug gets approved, everybody  17 asks, what's next? Are you ready to study the next  18 super rare fungal infection? After a large  19 development program and three Phase 3 clinical trials  20 with one that did not meet its primary endpoint, there  21 are careful considerations of the next set of studies.  22 First and foremost are the post-approval commitments</p>

<p style="text-align: right;">Page 106</p> <p>1 that are required by the FDA. I show here the three  2 defined for Cresemba in the U.S. The cost for these  3 run in excess of \$10 million.  4       Our other priority is pediatrics.  5 Orphan drug status waives the requirement for  6 pediatric development, however, we at Astellas with  7 our partner recognized the significant unmet need in  8 invasive aspergillosis and mucormycosis in pediatrics.  9 Our pediatric program is ongoing but it can run in  10 excess of \$20 million, which our current program is.  11       Finally, the typical life cycle of a  12 post-approval rate is shown here. The first five  13 years approval life cycle is establishing product and  14 conducting post-approval commitment, including  15 pediatric studies. For Cresemba this also included  16 finishing the invasive candidiasis program at a cost  17 of more than \$80 million.  18       It's typically not until the fourth or  19 fifth year where the separation from the margin occurs  20 in order to look for areas of reinvestment and depends  21 on the market condition. The activities you look for  22 are areas of high unmet need as well as areas of data</p>	<p style="text-align: right;">Page 108</p> <p>1 such as commercial manufacturing and product  2 education, etc., are not a sustainable business  3 scenario today and weigh heavily on decisions to  4 reinvest post-approval.  5       Emphasizing the need to continue to  6 introduce new push and pull incentives to continue  7 investment in new antifungals to address the  8 significant unmet needs of patients. Thank you.  9       We'll go now to our next speaker, John  10 Rex, who is the current CDMO of F2G, Ltd., which is an  11 antifungal biotech, with more than 30 years of  12 development focused on antimicrobial agents. Dr. Rex?  13       DR. JOHN REX: Thank you, Laura. And  14 am I clear?  15       DR. LAURA KOVANDA: Yeah.  16       DR. JOHN REX: Wonderful. Thanks. And  17 thanks to the FDA for organizing. This has been a  18 great workshop so far. I'm really enjoying the  19 content.  20       So, I wanted to talk at length about  21 push and pull incentives for antimicrobials, but I'm  22 going to focus on something much more specific to</p>
<p style="text-align: right;">Page 107</p> <p>1 gaps. But you need to consider the financials. The  2 new activity has to either increase the life cycle  3 prior to the loss of exclusivity, increase the margin  4 enough, or at least cover the cost of the investment.  5       For invasive and fungal infection  6 studies where the typical costs are, approximately,  7 \$125,000 per patient, and where the durations are 3-5  8 years on average, this is challenging. And similar to  9 the antibacterial world where the net present value  10 calculations are nearly always negative.  11       So, to conclude, the Cresemba  12 development program is not likely to be replicated as  13 is. Each Phase 3 study costs in excess of \$125,000  14 per patient; it requires a global footprint and the  15 study durations are long. Alternative options to  16 randomized clinical trials are available for orphan  17 diseases, but generally accompany larger efficacy and  18 safety trials with another invasive fungal disease.  19       The high cost of antifungal drug  20 development from discovery to the initial marketing  21 authorization, post-approval commitments, pediatric  22 development topped with the cost of product upkeep</p>	<p style="text-align: right;">Page 109</p> <p>1 getting an antifungal developed. And before I can get  2 to the point I want to make today, I need to give you  3 a little background on the drug that we currently have  4 in Phase 2. It's called Olorofim. It's a novel  5 mechanism candidate antifungal drug that inhibits  6 pyrimidine biosynthesis.  7       It has broad microbiologic activity but  8 it's limited to the ascomycete mold fungi, which means  9 it covers Aspergillus, Lomentospora, Scedosporium  10 geserium, and all of the dimorphic molds -- histo,  11 lesto, coxi. But it does not cover candida, it does  12 not cover crypto, and does not cover mucola.  13       Dosed by mouth in a 30-milligram  14 tablet, it has breakthrough therapy designation based  15 on its preliminary clinical evidence showing  16 substantial effects. And it's now in an open label  17 Phase 2 study of patients with invasive fungal molds  18 and limited treatment options.  19       The key idea here that I want to point  20 out is that endpoints, as was already noted, are a  21 tricky thing, and I want to point to a specific  22 problem with endpoints, which is that we have to date</p>

<p style="text-align: right;">Page 110</p> <p>1 mostly used endpoints at 42 and 84 days, and all-cause  2 mortality has been a strong tool that we've liked  3 because it's so clear. And it does seem to work  4 pretty well for acute pulmonary aspergillosis. But  5 it's also a blunt tool and get entangled with  6 underlying disease and it -- because patients are  7 dying of leukemias and other things along the way.  8 And it also doesn't work at all for infections that  9 progress more inexorably and slowly.  10       The alternative that we heard about was  11 the EORTC-MSG defined overall global response  12 endpoint, which has three elements: Clinical,  13 radiological and mycological. And logically, success  14 requires improvement on all three sub-elements, and  15 failure, likewise, is going the wrong way.  16       But there is an intermediate space that  17 you see 20-40 percent of the time in which something's  18 better, something's worse. And this leads to a  19 categorization of stable. And a particular way this  20 occurs is just somebody will be clinical better but  21 the radiology has not yet improved. And when you get  22 scored as stable, stable is lumped with failure. So,</p>	<p style="text-align: right;">Page 112</p> <p>1 If you look at the dosing graph to the right, you'll  2 see there's a block of patients, loosely a third, that  3 declare that they're done at day 84. But there's a  4 pretty good sized group that go on for very extended  5 period. And that X-axis does run out to 500 days.  6       And this group that goes on long stable  7 at day 84 has been a common finding and a prelude to  8 ultimate success at the end of therapy. So, let me  9 show you a case that highlights this.  10       This is one of the cases that was part  11 of our breakthrough therapy designation request. And  12 it's that of a 49-year old healthy woman who had  13 breast augmentation surgery. She develops a  14 Lomentospora prolificans infection of the breast  15 implant. Lomentospora is resistant, as we heard  16 earlier to all of the antifungals and her infection  17 spreads through the adjacent cartilage, sternum, 4th,  18 5th and 6th ribs. She tries everything, serially and  19 in combination along with debridement and along with  20 hyperbaric oxygen. The infection remained  21 uncontrolled. And if you look at the picture on the  22 lower left, nine days before she came into our study -</p>
<p style="text-align: right;">Page 111</p> <p>1 stable is a failure on the overall clinical response  2 and that has a really big impact.  3       And for pulmonary IFDs it does work but  4 extrapulmonary IFDs can be very slow and even  5 pulmonary IFDs can be very slow. And I was going to  6 say that stable is very definitely the prelude to  7 success. It enables -- staying alive is the way you  8 get this done.  9       So, let's -- coming back to the trial  10 that we're running, we learned this in running our  11 current open label Phase 2 study. To get into the  12 study you have to have a proven invasive fungal  13 infection. Most of our patients are highly  14 immunosuppressed and they all come to us with limited  15 treatment options. That's why they come into the  16 studies because they're in trouble -- they've tried  17 pretty much everything else and it's not working for  18 them. Some of them come to us with months of prior  19 therapy.  20       We advise a main phase duration of 84  21 days, which is adequate for many patients, but  22 extended dosing is provided for complex infections.</p>	<p style="text-align: right;">Page 113</p> <p>1 - when they were bringing her, they had fungal  2 colonies growing in the base of the wound.  3       Olorofim monotherapy began in November  4 2018 and 84 days later, she looked better, her wound  5 was improving and she was a failure because her  6 radiology had not yet improved. Clinically she was  7 responding but she was an EORTC global response of  8 failure at day 90.  9       She goes on to take 322 days of  10 Olorofim. Day 140, nice granulation tissue at the  11 base of the wound. Day 243, closed up. She's now  12 been off-drug for ten months, and as far as we can  13 tell, it's a cure of her infection. Next slide. I  14 have the button.  15       So, here are my conclusions. Day 42  16 all-cause mortality, a useful tool but it has  17 limitations. EORTC-MSG defines an overall response  18 endpoint but, you know, it works okay at day 42 and 84  19 for many pulmonary disease but it does not work well  20 for extrapulmonary infections and sometimes lung  21 infections and anything that takes a long time for the  22 radiology to improve.</p>

<p style="text-align: right;">Page 114</p> <p>1 And my argument is that it is important  2 that stable be defined as success. Language matters.  3 You could argue that it comes out in the wash just to  4 define stable as failure. But this is not consistent  5 with clinical practice, and the word failure when  6 you're reading quickly, it failed. So, 20-40 percent  7 of the patients in recent studies that had a structure  8 kind of like our program have failed at day 84. No,  9 they haven't failed. They were stable and they were  10 on their way to getting better.  11 So, the scoring of failure sends the  12 wrong message to clinicians and payers, and some of  13 these people had very significant improvements in  14 their quality of life. If you go back to -- I'm not  15 going to go back to the slide, but if you look at the  16 footnote of the slide, we shared another case -- the  17 case I showed you was shared in Egment, or it was  18 shared in the Egment abstract, but there's another  19 case in the Egment abstract book. Same fungus. A  20 lady with leukemia who got many, many months of good  21 quality of life, control for osteomyelitis with  22 Olorofim.</p>	<p style="text-align: right;">Page 116</p> <p>1 different perspective, that from the patient. My son,  2 unfortunately, being a statistic of the unmet needs  3 that exist with the treatment of fungal disease. I'm  4 going to share with you a reflection that I prepared  5 and participated in part at the FDA hearings on  6 Cresemba back in February -- excuse me, January of  7 2015.  8 "The silence of the evening is broken  9 only by the sound of my footsteps on the sidewalk.  10 The sky is fading into night, illuminated in our  11 neighborhood by the house and porchlights which turn  12 on. Houselights now ablaze as dinner approaches. I  13 see the homes I know to be filled with families, moms  14 or dads busy in the kitchen, brothers and sisters  15 laughing in the living room, bickering over the TV  16 channel or lost on their phone.  17 "I imagine my own children in the  18 family room -- Henry, Anna and Joe, waiting to eat  19 together as a family. I see myself arriving home.  20 The workday is a bit shorter as summer winds down. I  21 imagine my arrival punctuated only by the over-  22 affectionate greeting that I get from our dog, a warm</p>
<p style="text-align: right;">Page 115</p> <p>1 So, and that quality of life measure, I  2 think, is an important bit that we need to think  3 about. So, the label of stable just is not right  4 anymore, and we developed these endpoints some years  5 ago before we understood some of the consequences of  6 managing more difficult and invasive fungal  7 infections, and it's something I'd like us to  8 reconsider. Thank you very much.  9 DR. LAURA KOVANDA: Thank you, Dr. Rex.  10 Our next speaker is Matthew Schueler. He has a  11 patient perspective. Mr. Schueler is Founder of the  12 Henry Schueler Foundation, which raises money to  13 support its mission to fund critical research into  14 rare subtypes of pediatric leukemia and fungal  15 infections like mucormycosis. Mr. Mueller --  16 Schueler?  17 MATTHEW SCHUELER: Thank you. Can you  18 hear me okay?  19 DR. LAURA KOVANDA: Yeah.  20 MATTHEW SCHUELER: Wonderful. Thank  21 you for having me. And I have been listening to some  22 of the presentations. I'm going to give you a very</p>	<p style="text-align: right;">Page 117</p> <p>1 greeting from my wife Susan, and a greeting shouted to  2 my children in the living room. An unenthusiastic but  3 normal response in return acknowledging my presence.  4 "We sit down to eat as a family in the  5 relaxed and sometimes careless fashion that families  6 do, never imagining that we would not be together,  7 taken for granted the warmth and joy of each other's  8 company. Individuals all, yet bound together by  9 sibling and parental ties, conscious of our closeness  10 despite the occasional rudeness that occurs at a  11 dinner table.  12 "And then it returns. That sickly  13 reminder that all is not the way I still imagined.  14 That one of us is absent. My oldest on removed from  15 life by nature. Cruel and unforgiving. His legacy  16 left for us to shape and keep alive. The lights still  17 burn for families intact removed from our reality.  18 For them, the dinner table still awaits. Into the  19 evening darkness I walk.  20 "Although we are now almost 13 years  21 removed from Hank's death, his loss is felt deeply  22 every day. No matter what I have done or will do in</p>

<p style="text-align: right;">Page 118</p> <p>1 my life, my greatest accomplishment and blessing is  2 and was to be a father to my three children, Henry,  3 Anna and Joe. Like any parent, you want to protect  4 your children from harm, teaching them the right  5 things to do, encouraging them to think before acting  6 recklessly. Cancer and its many complications,  7 including fungal infections, follow their own rules  8 despite a parent's best efforts.  9 "My oldest son Hank, as he was known,  10 received a diagnosis of acute lymphoblastic leukemia,  11 ALL, the most common of childhood leukemias, in early  12 November of 2006. He was 13-1/2 years old. However,  13 his ALL was a very rare subtype known as hypodiploid  14 ALL, which occurs very rarely, only 1-2 percent of all  15 ALL, and in 2006 had a very low survival rate, 20-30  16 percent with chemotherapy alone.  17 "Because of this prognosis, the  18 unanimous medical recommendation from several medical  19 academic institutions for Hank was that he undergo a  20 bone marrow transplantation immediately after his  21 initial heavy course of chemo at what is now known as  22 Lurie Children's Hospital in Chicago. Neither his</p>	<p style="text-align: right;">Page 120</p> <p>1 in a week to ten days. He underwent six surgical  2 sinus debridements in seven days and was given all the  3 antifungals available to him, including amphotericin  4 B, which wreaked havoc on his kidneys, and  5 posaconazole, the newest antifungal hope in this small  6 medicine chest of antifungal therapies. And it  7 wreaked havoc on his already weakened body by the  8 intense chemotherapy he had received to stave off the  9 raging return of his leukemia.  10 "Yet, he refused to quit, despite  11 overwhelming odds against survival. By a minor  12 miracle hastened by the absence of chemo for a few weeks  13 while he fought against this new infection, his new  14 immune system began to fight back and he began to show  15 signs of recovery from the fungal infection. By the  16 end of October, although still weak, he came back to  17 his family and neighborhood in Chicago and the giant  18 trees on his street bearing orange ribbons welcoming  19 him home.  20 "After receiving another bone marrow  21 transfusion the day after Thanksgiving, 2007 back at  22 Children's Hospital of Wisconsin, the fungal infection</p>
<p style="text-align: right;">Page 119</p> <p>1 younger sister Anna or his youngest brother Joe were  2 matches for him. He ultimately received marrow from  3 an anonymous 27-year old donor from Germany and began  4 the transplantation regimen on his 14th birthday, the  5 9th of March, 2007 at Children's Hospital of  6 Wisconsin.  7 "He did quite well. He even returned  8 to graduate with his 8th grade class at St. Mary of  9 the Woods Grade School on the northwest side of  10 Chicago, and in May to his spot as the captain for his  11 traveling baseball team. He was far from healed but  12 he was back in the game.  13 "Hank had a great summer and was doing  14 well medically. Unfortunately, over Labor Day, after  15 he had just begun high school, he relapsed. His odds  16 of long-term survival decreased to 10 percent. He  17 underwent additional chemotherapy which wiped out his  18 new immune system, and he eventually contracted a rare  19 and deadly invasive fungal infection known as  20 mucormycosis at the end of September.  21 "The doctors told us that the infection  22 present in his lungs and sinuses would likely kill him</p>	<p style="text-align: right;">Page 121</p> <p>1 returned and reemerged. He had undergone the  2 hyperbaric treatment, he had undergone the  3 amphotericin, he had undergone the posaconazole. The  4 infection now spread through his sinuses into his  5 orbital areas. It slowly took his eyesight. He was  6 placed on a ventilator to breathe to overcome the  7 respiratory effects of a disease which attacked his  8 lungs -- lungs which had never failed him on an  9 athletic field or a program or wherever a game was  10 being played.  11 "Hank suffered a massive cerebral  12 hemorrhage and died on the 14th of December, 2007.  13 More than 2,000 people came to his wake. More than  14 1,000 family, friends and neighbors attended his  15 funeral. We had to place dark sunglasses on him in  16 the casket to cover the black rings of disease around  17 his eyes. He loved his then 12-year old sister and 8-  18 year old brother, who loved him as their big brother  19 and protector and whom he loved with all his heart.  20 He left his parents with a broken heart that will  21 never heal.  22 "Hank was the last kid you would expect</p>

<p style="text-align: right;">Page 122</p> <p>1 to get sick. Though bright in school and multi-sport 2 talent, he was not the best student nor the best 3 athlete in any one sport. Yet, he was an undisputed 4 leader on the field, on the baseball diamond and in 5 our neighborhood. Like so many childhood heroes that 6 we've all been witness to, he withstood the 7 devastating treatment of his outpatient chemo and the 8 barbaric regimen of a bone marrow transplantation 9 without complaint. He accepted what happened and 10 began preparing for the rest of his life.</p> <p>11 "Because of his death, many of our 12 close friends including several of his former coaches 13 approached us about forming a foundation in his honor 14 to remember him and perhaps provide some hope for 15 other similarly afflicted. Hank had told my wife 16 Susan after he experienced the relapse that he just 17 wanted to grow up and find out why this happened to 18 him so he could prevent it from happening to other 19 kids. Out of this pledge, we formed the Henry 20 Schueler 41 and 9 foundation.</p> <p>21 "We've sponsored targeted research at 22 St. Jude's Children Hospital on hypodiploid leukemia</p>	<p style="text-align: right;">Page 124</p> <p>1 true lack of progress in fighting fungal diseases. 2 "Hank never quit a game early and he 3 never quit fighting his disease. The family and 4 friends who comprise our foundation helped instill 5 that attitude in him when he was on the playing field 6 and we remain determined to carry that fight forward 7 in his absence.</p> <p>8 "We live and, yes, Hank lives to carry 9 the fight forward in his honor for future children and 10 adults who are also destined to face this nemesis, the 11 nemesis of cancer and fungal infections. Through our 12 work we assembled some of the foremost experts in the 13 world who voluntarily came to Hank's hometown to 14 brainstorm on the best medical approach to a fungal 15 infection that cruelly and silently attached him like 16 it does other patients, when they are most vulnerable, 17 and then it took his life.</p> <p>18 "December 14th is the day he died. 19 Nothing will ever change that. It is also the day 20 that inspired the seeds of a gift of life for others. 21 Yet, despite our best efforts and the work of so many 22 researchers and physicians who have supported our</p>
<p style="text-align: right;">Page 123</p> <p>1 through the work of Dr. Charles Mulligan and the 2 Mulligan Lab, which has drastically enhanced the 3 knowledge of the origins of hypodiploid and altered 4 the treatment regimens for those who are diagnosed 5 with it. The foundation has also proudly sponsored 6 the first United States based international conference 7 on mucromycosis chaired by Dr. Thomas Walsh, who spoke 8 earlier, who proudly serves as the Henry Schueler 9 Scholar on mucromycosis.</p> <p>10 "His first conference took place in 11 Chicago in January of 2010. Out of this inspired 12 conference came the research that formed the basis for 13 the most comprehensive medical supplement on 14 mucromycosis published as a supplement to the Journal 15 of Infectious Diseases in February of 2012. And just 16 last September -- excuse me, just last November, we 17 sponsored and hosted the second such international 18 conference here in Chicago, where we learned of the 19 advances that science and medicine have made in their 20 fight against fungal disease and learned alarmingly of 21 the greater prevalence of fungal disease throughout 22 the world, and perhaps even more alarmingly, about the</p>	<p style="text-align: right;">Page 125</p> <p>1 cause, we cannot do it alone. The work of this 2 committee and the many, many contributors today at 3 this meeting are a vital need to all those persons 4 facing known and emerging fungal pathogens without the 5 knowledge and medicines to fight back. More 6 education, more research and funding is needed. New 7 drugs are needed. Nothing was more devastating in 8 Hank's inspired fight against his leukemia than for 9 him to contract a deadly fungal infection. And 10 nothing was more helpless to have such few options to 11 fight that infection.</p> <p>12 "Hank did not die from the rare 13 leukemia he had; he died from a fungal infection that 14 cannot only attack immunocompromised patients but also 15 organ transplant patients, diabetic patients and 16 traumatically injured persons, including soldiers and 17 citizens injured in battle or by natural catastrophe. 18 Fungal diseases can attack a body and cause massive 19 disfigurement, infection and devastation. No person 20 should ever experience such an end of life. No parent 21 or family member should have to witness the ravages of 22 such a disease.</p>



<p style="text-align: right;">Page 126</p> <p>1 "Isoconazole, known as Cresemba,  2 approved by the FDA, made by Astellas -- approved by  3 the FDA was the first antifungal medicine that offers  4 an important option for treatment of some fungal  5 diseases such as aspergillus and mucor. Hank had only  6 one proven medicine, amphotericin B, which was  7 developed over 50 years ago to fight fungal infection.  8 That simply cannot be the best this country can  9 produce.  10 "After more than 50 years of only one  11 medicine for mucormycosis and now Cresemba, we still  12 need new antifungal agents to treat this and other  13 fungal infections and save the lives of future  14 children and adults. Henry wanted to find out why  15 this happened to him so he could prevent it from  16 happening to other kids. I hope and pray the work of  17 this committee will bring this medical and scientific  18 community closer to fulfilling Hank's living wish."  19 Thank you for allowing me to  20 participate.  21 DR. LAURA KOVANDA: Thank you, Mr.  22 Schueler, that was -- always heartbreaking to hear,</p>	<p style="text-align: right;">Page 128</p> <p>1 my disclosures are listed here. And then I want to  2 just talk in broad terms about the challenges to all  3 antifungal clinical trials. And I would say, you  4 know, a couple of obvious things, that with the  5 exception of invasive candidiasis throughout the world  6 and then cryptococcosis in lower income countries,  7 these are relatively rare infections and enrollment by  8 its nature tends to be very slow. And so numbers are  9 a big deal and we've talked about that already.  10 Delaying diagnosis is also an obstacle.  11 And as Kieren and others have spoken to, it really  12 calls for the need for, you know, rapid, sensitive and  13 specific nonculture-based diagnostics. This seems to  14 be a huge limiting factor. And in the setting of  15 cryptococcosis and certainly aspergillosis, we've  16 largely gotten around the need to culture -- have  17 culture positivity to include a patient into a study.  18 But it's certainly a major challenge for many of the  19 other fungal infections as well.  20 And determination of anti-fungal  21 resistance, which is a growing problem. It's been  22 spoken to already. But it's slow. And susceptibility</p>
<p style="text-align: right;">Page 127</p> <p>1 and thank you for bringing us this very important  2 patient perspective.  3 So, in the interest of time, we're  4 going to move quickly to the next presentation and  5 skip the break. Our next presenter is Dr. Peter  6 Pappas. He's going to present the design and conduct  7 of clinical trials for newer antifungal agents. Dr.  8 Pappas is Professor of Medicine, Infectious Diseases  9 Department and a scientist in the Cancer and AIDS  10 Centers at the University of Alabama at Birmingham.  11 Dr. Pappas?  12 DR. PETER PAPPAS: Thank you, Laura.  13 And thank you, the organizers, for asking me to spend  14 a few minutes talking about really what I see as some  15 of the challenges. Others have spoken to some of the  16 obstacles and the challenges, and subsequent speakers  17 will field this as well. So, I'm going to kind of  18 spend the next 10 or 12 minutes talking about some of  19 the things that I see as obstacles towards the conduct  20 of clinical trials. I'm making certain I can advance  21 this. Let's see... Okay, there we go.  22 My disclosures. There we are. Okay,</p>	<p style="text-align: right;">Page 129</p> <p>1 breakpoints -- what really determines resistance is  2 not clearly established for each organism.  3 And so when one puts all this together,  4 traditional, randomized, controlled, double-blind  5 clinical trials are problematic and they really are  6 only applicable, in my view, to candidiasis,  7 aspergillosis and cryptococcosis. And if one adds to  8 that -- let's say we want to study aspergillosis --  9 I'm sorry, Candida auris, as an example, well, then  10 we've really upped -- we've raised the bar even more  11 because we really don't have a quick way of  12 identifying and enrolling those patients. So, we have  13 to come up with different strategies.  14 Now, for invasive candidiasis,  15 antifungal resistance is now widely recognized as an  16 emerging problem. It's especially a challenge for  17 Candida glabrata among the more common organisms. And  18 taken as a whole, the antifungal resistance in Candida  19 constitutes, you know, maybe 5-25 percent. It varies  20 considerably, depending on the prevalence of glabrata  21 and auris, and if there are epidemic strains in a  22 particular institution. But if one were to choose to</p>

<p style="text-align: right;">Page 130</p> <p>1 study antifungal resistant Candida organisms, you're  2 really biting off quite a challenge.  3 Now, coupled with that, some of the  4 recent observations. If we look at the most recent  5 trials of invasive candidiasis, I think it best -- and  6 we don't have these numbers exactly but our estimates  7 are based on our own experience are about one in ten  8 patients qualify. Even though they have a positive  9 culture there are going to be other things that  10 disqualify these patients and the most common ones are  11 listed here.  12 Too much prior therapy, the patient is  13 too sick, contraindicated drugs, especially in the  14 cases of azole therapy, and then concomitant illness -  15 - preexisting liver or kidney disease or both.  16 Another obstacle is, you know -- well, one of the  17 endpoints has been global response, which includes  18 clinical, mycologic and being able to survive.  19 These clinical endpoints I think are a  20 particular sticking point and I'm going to suggest  21 that maybe we should reconsider this. The clinical  22 endpoints are soft. They include fever and/or</p>	<p style="text-align: right;">Page 132</p> <p>1 Laura's already talked about this.  2 This study was published, and I will simply just  3 underscore the fact that this is a disappointment  4 because it took five and a half years to complete this  5 trial, it went through a lot of fits and starts, and  6 the study failed for a lot of different reasons. And  7 Laura showed this slide in graphic form earlier. But  8 we didn't meet the non-inferiority margin. And so  9 Isavuconazole is not an approved agent for treatment  10 of invasive candidiasis.  11 Now, there are a lot of reasons for  12 failure of this trial, but one of them was that the  13 arm that is caspofungin followed by voriconazole had  14 never been studied. And there were many, many  15 challenges to investigators in putting a patient on  16 this trial.  17 In the recent trial, the rezafungin  18 trial, which is a Phase 2 study, looks at long-acting  19 echinocandin rezafungin given once weekly. And in  20 this Phase 2 trial with a randomized controlled trial,  21 double-blinded, etc., individuals could be treated  22 with either rezafungin once weekly or caspofungin</p>
<p style="text-align: right;">Page 131</p> <p>1 localized symptoms, and they are a requirement for  2 enrollment into a Phase 3 trial -- not so much a Phase  3 2 trial. But these are soft in the sense that fever  4 and localized symptoms, etc., can be caused from a  5 multitude of other disorders and not just an invasive  6 Candida infection. And so the reliance on these or  7 the requirement of these for enrollment into a trial  8 become, I think, again, just another obstacle, whereas  9 the mycologic and survival endpoints are pretty hard.  10 We don't yet know how to incorporate  11 for Candida these non-culture based assays. We can  12 use them for screening, we can potentially use them to  13 enroll patients, but then ultimately, at least for  14 Candida, we're left with basing our decision as to how  15 an individual responded based on the result of the  16 culture and its clearance.  17 And so while we have several tools  18 potentially to help us identify candidemia or invasive  19 candidiasis early, it's not clear how to use those  20 once the patient is enrolled and, again, without a  21 positive culture most trials are left with a patient  22 that's essentially unevaluable.</p>	<p style="text-align: right;">Page 133</p> <p>1 followed by fluconazole. A little bit more  2 traditional perhaps, and there's a lot of leeway in  3 the choice of when to transition to the azole when  4 that's appropriate. This trial went a little bit  5 smoother. It's recently been accepted for publication  6 in CID and all the details are going to be provided  7 there.  8 And I would argue that at least with  9 the rezafungin trial, that the main obstacle to  10 enrollment in that study really has to do with the  11 unique characteristic of rezafungin, and that's to do  12 with once weekly dosing and how comfortable clinicians  13 are or subjects, for that matter, being potentially  14 randomized to a drug that's only given once a week.  15 Even though there is sufficient pharmacokinetic data,  16 etc., to show that it makes plenty of sense, it is  17 enough of a departure that I think it presents a bit  18 of an obstacle. But certainly a sound agent. And as  19 this is studied, the Phase 3 trial comparing  20 rezafungin to caspo versus flu, which is ongoing, I  21 think is enrolling slowly in part because of this  22 perceived obstacle.</p>

<p style="text-align: right;">Page 134</p> <p>1 Now, what about focusing on resistant 2 candida species? Again in the absence of rapid 3 diagnostic that can identify these, you really, I 4 think, are left with having to develop strategies that 5 enrich a population for potentially MDR or drug- 6 resistant candida. And, you know, such as an 7 SICU/MICU or even stem cell transplants where everyone 8 was receiving fluconazole, prior exposure to 9 antifungals, breakthrough infections or recent 10 epidemiologic factors, which could include as a 11 consideration Candida auris.</p> <p>12 But those are the strategies we're left 13 with. We can't a priori enroll only patients with any 14 fungal-resistant strains at this point in time given 15 the limits of our technology. And so in designing a 16 study like this, one has to really define a population 17 that is enriched for a greater risk of having an 18 antifungal resistant strain. I think that's our 19 reality at this point. And so, for instance, a study 20 that would target Candida auris or Candida glabrata is 21 going to have to include some of these considerations 22 that are listed here.</p>	<p style="text-align: right;">Page 136</p> <p>1 to enroll. And with a target enrollment of 90, we 2 were able to enroll about 27 patients over the course 3 of 18 months. And the problem here was, again, either 4 patients or -- I'm sorry, subjects or investigators' 5 reluctance to step down to an oral therapy, 6 particularly after patients are beginning to feel 7 better.</p> <p>8 Now, the FURI study, which has been its 9 follow, follow study, or follow-on study, which is 10 sort of a salvage trial, seems to have done much 11 better in that it's able to target patients who have 12 drug-resistant Candida isolate or failing or 13 intolerant to conventional therapy. But in a 14 standards Phase 2 type of trial which had limited -- 15 which required limited exposure to echinocandin, for 16 instance, there just seemed to be a resistance to 17 transitioning to an oral agent, especially after 18 patients were beginning to feel better clinically. 19 And so it represents an ongoing challenge, even for a 20 compound which looks really quite good against -- in 21 an oral formulation against a host of Candida 22 isolates.</p>
<p style="text-align: right;">Page 135</p> <p>1 Let's see if we can get to the next 2 slide. Okay, we are, I think for the first time, 3 looking at an observational trial of candidemia and 4 echinocandin failure. This is a study that Ostrosky- 5 Zeichner is honchoing and it's an observation 6 retrospective trial. We're going to capture 120 7 patients that have been seen in the U.S. This study is 8 now really being rolled out at this moment. And I 9 think it'll give us a very good look at the isolates. 10 Sort of why individuals fail echinocandins in this 11 retrospective, but we do have the isolates and we do 12 have -- or will have the historical data on these 13 patients and treatment data. So, it should be a very 14 good and, hopefully, current look at some important 15 questions as to potential resistant strains.</p> <p>16 Ibrexafungerp. This is a compound that 17 has also expansive challenges. Most of you know this 18 agent. It's an oral glucan-synthase inhibitor. A 19 Phase 2 trial was completed. It was an MSG study, 20 MSG10. And this trial, despite the fact that the drug 21 has very good in vitro activity and seems to be well- 22 absorbed, well enough absorbed, for sure it struggled</p>	<p style="text-align: right;">Page 137</p> <p>1 This is a compound, Fosmangepix, which 2 -- APX study or APX compound, just completed a Phase 2 3 study, enrolled 22 patients. This really focused on 4 Candida glabrata, another azole-resistant Candida 5 species. But, again, even enrolling 22 patients, 6 approximately 10 sites, took about a year and a half 7 to complete this. Success looks very good but there 8 were obstacles to this, again, because the focus was 9 trying to enrich, encapture patients who had more or 10 potentially resistant agents including Candida 11 glabrata.</p> <p>12 Now, basically, if Candida -- 13 candidemia is a challenge, invasive aspergillosis is 14 also a major challenge. It has about a tenth of the 15 frequency of invasive candidiasis. Most cases 16 nowadays are diagnosed with serologic rather than 17 culture-based results or histologic results. There 18 are obvious challenges that I think have been touched 19 on earlier. And I won't go into this in great detail. 20 But again, I think the biggest challenge and one of 21 the things that has really saved invasive 22 aspergillosis is the development of sensitive,</p>

<p style="text-align: right;">Page 138</p> <p>1 reasonably specific non-culture based tests, including  2 galactomannan and PCR especially.  3           And so this, plus the definitions,  4 which have been accepted as reasonable ways to accept  5 a patient have really allowed this disease to be  6 studied. Otherwise, I think we would really be having  7 a major challenge in trying to enroll patients into  8 trials like this.  9           The traditional approaches. I'll just  10 give you some timelines. Voriconazole and  11 posaconazole monotherapy just got completed. It's in  12 its seventh year when it got completed. Kieren and  13 the group actually enrolled, almost in record time,  14 four years to complete a study which enrolled almost  15 400 patients. And this is a combination study. There  16 was a lot of enthusiasm for doing this. And then the  17 isavuconazole voriconazole study, also about four  18 years. But remember, what made these studies possible  19 was the fact that we were allowed to use surrogate  20 markers in order to enroll these patients.  21           Upcoming studies. I'll just mention  22 these. Amplyx, Scynexis potentially, F2G is well on</p>	<p style="text-align: right;">Page 140</p> <p>1 how using a surrogate endpoint has really  2 revolutionized the ability to do these studies, going  3 on endpoints that are not based purely on mortality or  4 clinical response.  5           I think the need for better diagnostics  6 is really, really clear here. And if we are going to  7 move forward with better design, more efficient, more  8 rapid and meaningful assays we just have to move to  9 markers that are not so culture based. And I think  10 that if we use the example of what we've seen with  11 cryptococcal meningitis and especially invasive  12 aspergillosis, I think we see a way towards the  13 future. What's lagging behind, of course, is the  14 technology. And the validation -- even if we have the  15 technology -- the validation of some of these markers,  16 the T2, the PCR, etc., that really would make for a  17 more rapid and efficient enrollment into these trials.  18           And I think, you know, it's obvious  19 that the future standard model for randomized control  20 trials targeting antifungal-resistant organisms really  21 doesn't work all that well, especially for the less  22 common infections. And I think that enriching these</p>
<p style="text-align: right;">Page 139</p> <p>1 its way toward developing a Phase 3 study comparing it  2 to a lipid formulation of invasive aspergillosis. And  3 they're likely to take the traditional approach,  4 requiring the large sample size as well.  5           Now, the exception to this, I think --  6 and I'm going to kind of end with this -- is the  7 combination studies or studies for cryptococcal  8 meningitis. And what really separates these studies  9 from others has been, I think in a word, a surrogate  10 endpoint, and that's the availability of this  11 mycologic endpoint, the CSF EFA, Early Fungicidal  12 Activity. This really has allowed us to use a tool to  13 -- that's correlated with clinical improvement,  14 survival as an outcome measure that allows one to  15 easily assess patients based on serial CSF cultures as  16 to whether patients are a success or not using really  17 a laboratory measure.  18           But in doing so, it has really changed  19 the way these studies can be done. And this allowed a  20 number of these trials to be done mostly in the  21 developing world. None of them have been conducted  22 primarily in the U.S. But this is a great example of</p>	<p style="text-align: right;">Page 141</p> <p>1 trials so that we target high-risk populations  2 together with rapid molecular diagnostics really  3 becomes essential if we're going to move into a new  4 phase.  5           Finally, I just want to say something  6 about the global population. We have -- certainly in  7 our antifungal trials, those would be -- we've gone  8 through the MSG, we've had really limited penetrance  9 into international sites. We have used them but with  10 a great deal of care. And I think that what we have  11 learned over time is that many of these international  12 sites are terrific. Many of them are highly  13 motivated, do phenomenal work, but I think those  14 opportunities are available but it does take  15 screening, familiarity with the sites, some education.  16 But there is enormous potential out in the global  17 community.  18           And with that, I will stop. And thank  19 you for your attention.  20           DR. LAURA KOVANDA: Thank you, Dr.  21 Pappas. We'll now go right through to the next  22 presentation, which is the statistical considerations.</p>

<p style="text-align: right;">Page 142</p> <p>1 We have two speakers for this. We'll start with Dr.                  2 Dixon. Cheryl Dixon is a statistical reviewer at the                  3 FDA Center for Drug Evaluation and Research in the                  4 Office of Translational Sciences. Dr. Dixon?                  5 DR. CHERYL DIXON: Hi, yes, good                  6 morning. Are you able to hear me? Hello?                  7 DR. JOHN FARLEY: Yes, we can hear you.                  8 DR. CHERYL DIXON: Okay, thank you.                  9 Well, I guess it's actually good afternoon now. And                  10 as was stated, I am a statistical reviewer from the                  11 Division of Biometrics IV that provides statistical                  12 support to the Division of Anti-Infectives. Today I                  13 want to discuss some general aspects of clinical trial                  14 designs in currently used endpoints for antifungal                  15 drug development along with some issues that have                  16 recently been considered.                  17 When it comes to the design of the                  18 clinical trial, our preference is still a randomized                  19 controlled trial, whenever possible. These trials can                  20 be designed with a non-inferiority or a superiority                  21 design. In order to interpret the results of a non-                  22 inferiority trial we need to have a data-driven</p>	<p style="text-align: right;">Page 144</p> <p>1 For invasive aspergillosis, the                  2 preferred non-inferiority margin is 10 percent when                  3 voriconazole is the control and six-week all-cause                  4 mortality is the primary endpoint. For candidemia and                  5 invasive candidiasis, the preferred non-inferiority                  6 margin is 10 percent when the control is a regimen of                  7 an echinocandin with a possible switch to an oral                  8 azole and 30-day all-cause mortality is the primary                  9 endpoint.                  10 Since there is a fairly wide effective                  11 treatment compared to no treatment for these                  12 indications, we have been willing to accept wider non-                  13 inferiority margins than those just mentioned to                  14 consider granting a limited use indication if a                  15 product has the potential to address an unmet medical                  16 need. However, to get a labeled indication without a                  17 limited use statement, a trial with a preferred non-                  18 inferiority margin will be needed.                  19 Although we have justified those                  20 margins, we need to keep in mind that they are trial-                  21 specific in that they depend on factors including the                  22 trial design, the control used and the patient</p>
<p style="text-align: right;">Page 143</p> <p>1 justification of the non-inferiority margin. The date                  2 needed will be a conservative estimate of the                  3 treatment effect of the active control on the same                  4 endpoint used for the clinical trial. In this way, we                  5 can be assured that the new drug is effective by                  6 showing the new drug is within this margin to the                  7 active control. External or historical controls may                  8 also be considered when a randomized control trial                  9 cannot be conducted.                  10 For the typical invasive aspergillosis                  11 and candidemia/invasive candidiasis trials, we have                  12 justified non-inferiority margins for an endpoint of                  13 all-cause mortality that allows us to conduct                  14 interpretable non-inferiority trials. Although an                  15 endpoint based on a global or overall response has                  16 been used in past trials, historical data is typically                  17 not available for new treatment to allow for a data-                  18 driven justification of a non-inferiority margin based                  19 on this endpoint without making many additional                  20 assumptions. Therefore, all-cause mortality is the                  21 preferred primary endpoint when a non-inferiority                  22 trial is proposed.</p>	<p style="text-align: right;">Page 145</p> <p>1 population being studied. There are some challenging                  2 situations where the currently justified margins may                  3 not be sufficient to interpret non-inferiority without                  4 further considerations.                  5 The first situation considers a new                  6 antifungal that is available only as an oral                  7 formulation. It will be studied for the treatment of                  8 candidemia and invasive candidiasis as an oral                  9 stepdown from an IV echinocandin. As I previously                  10 mentioned, the non-inferiority margin we have                  11 justified is based on a regimen containing an                  12 echinocandin followed by an oral azole. So, the                  13 interpretation of non-inferiority with such a control                  14 would be in the setting of the regimen containing the                  15 ecinocandin and the new oral antifungal, and not                  16 necessarily an assessment of the efficacy of the new                  17 oral antifungal itself.                  18 So, in order to assess the effect of                  19 the new oral antifungal and interpret non-inferiority,                  20 we will need to differentiate for the regimen the                  21 treatment effect of the IV antifungal therapy from                  22 that of the oral stepdown therapy. So, it will be</p>

<p style="text-align: right;">Page 146</p> <p>1 necessary to determine whether there is data that is 2 available that will allow us to make this assessment. 3       The second situation is a study where 4 the population to be studied is proposed to be one 5 with limited treatment options due to an azole not 6 being the treatment choice. This possibly includes 7 patients who might be refractory to a current 8 antifungal treatment. The non-inferiority margins we 9 have justified are based on the mutually treated 10 subjects. However, the treatment effect of refractory 11 subjects may not be the same as initially treated 12 subjects. It is possible that such subjects might 13 have a higher mortality rate, even with treatment, 14 which could lead to a smaller treatment effect when 15 it's compared to new treatment; or they might have a 16 lower six-week mortality, so that they've already 17 survived long enough to be refractory to treatment. 18 Thus, this will need to be considered in the 19 interpretation of non-inferiority in the margin used. 20       Of course, in any situation a 21 superiority trial can be proposed. Although most 22 likely a placebo control would be considered unethical</p>	<p style="text-align: right;">Page 148</p> <p>1 be found based on autopsy data, ensuring that 2 assessments are made at comparable time points in the 3 disease process, and the matching process of the 4 external controls to study subjects that may be 5 applied. Additionally, pathogen-specific external 6 controls are recommended when multiple molds are being 7 studied under a single protocol. 8       I've just briefly touched on some of 9 the issues regarding the use of external controls, but 10 Aaron Dane will further discuss external controls in 11 his presentation. 12       My next couple of slides you've already 13 seen this morning but I have a few additional points 14 to make. As mentioned, commonly used endpoints in 15 antifungal trials have been all-cause mortality or a 16 global overall response endpoint, both assessed at a 17 fixed time point from randomization. 18       Whatever endpoint is used, the endpoint 19 selected should be well-defined and reliable. 20 Clinical endpoints are most relevant as they directly 21 measure the therapeutic effect of a drug on how a 22 patient feels, functions or survives. Additional</p>
<p style="text-align: right;">Page 147</p> <p>1 in the list of indications that we are considering 2 today, and unless the new drug is a groundbreaker, 3 superiority to an active control may not be 4 achievable. However, a special case of a superiority 5 design would be an add-on trial where the new 6 antifungal is given in combination with another 7 antifungal and is compared to the other antifungal 8 alone. 9       In some situations it may be difficult 10 to design a randomized control trial, such as with the 11 rare molds in Candida auris where most of the 12 currently proposed trials are single-arm, uncontrolled 13 trials. Therefore, an external control is needed for 14 interpreting the results of the uncontrolled trials. 15 The interpretation of this uncontrolled trials can 16 also be strengthened by the conduct of an adequate 17 well-controlled trial in the more common molds or 18 yeasts. 19       Some issues that need to be considered 20 when proposing the use of an external control are the 21 availability of patient level data, the similarity to 22 the study population, noting that controls shouldn't</p>	<p style="text-align: right;">Page 149</p> <p>1 types of endpoints include surrogate endpoints, which 2 is a marker such as a laboratory measurement, 3 radiographic image, physical sign or other measure 4 that is likely to predict clinical benefit but is not 5 itself a measure of clinical benefit. These types of 6 endpoints will need more discussion with the agency 7 regarding their relevance and impact on the type of 8 approval. 9       Diagnostics play a large part in the 10 antifungal setting and are frequently used in clinical 11 trials for enrichment purposes. It is important that 12 the tests adequately detect the disease of interest, 13 and this is especially important in non-inferiority 14 trials where we need to ensure that the population 15 studied has the disease of interest. 16       For candidemia and invasive candidiasis 17 trials we have allowed the use of nonculture-based 18 tests for enrollment. However, an accompanying 19 positive culture taken during the screening period is 20 still needed to be included in the primary analysis 21 population. 22       For invasive aspergillosis trials we</p>

<p style="text-align: right;">Page 150</p> <p>1 I have used the galactomannan test for patient  2 identification as well as inclusion into the primary  3 analysis population. It is acknowledged that there is  4 growing interest in the field to also use these types  5 of diagnostics as endpoints. For example, a decline  6 in galactomannan levels for assessing response to  7 treatment.</p> <p>8 While qualification of an endpoint is  9 not a prerequisite for use in the clinical trials, it  10 will be necessary to understand the relevance of the  11 endpoint for predicting clinical benefit and  12 interpreting the effect of treatment before it would  13 be considered for use as a primary endpoint.</p> <p>14 I will conclude my presentation with a  15 couple final comments on the global or overall  16 response endpoint. As I previously mentioned, a  17 global overall response endpoint is not recommended as  18 a primary endpoint for non-inferiority trials due to  19 the inability to provide a data-driven justified non-  20 inferiority margin in most cases. However, it is  21 still recommended to be assessed as a secondary  22 endpoint in non-inferiority trials.</p>	<p style="text-align: right;">Page 152</p> <p>1 DR. JOHN FARLEY: Yeah.</p> <p>2 DR. AARON DANE: Oh, great. Thank you.</p> <p>3 So, hello, everyone. So, as was mentioned, I'm a  4 statistical consultant for the pharmaceutical and  5 biotechnology industry, and I'm going to talk through  6 some of the clinical trial design considerations for  7 antifungal development, particularly focused on areas  8 of rarer molds and more difficult to find patient  9 populations. So, the two areas I'm going to talk  10 about today, one is the use of external controls to  11 supplement clinical trial data and when is it this an  12 appropriate approach? And also the key points to  13 consider when that's undertaken. And also the idea of  14 looking at alternative statistical criteria in a study  15 of rare molds.</p> <p>16 So, first of all, I'll go through the  17 external controls in limited populations. So, the  18 first key issue here is when using external controls  19 with a small patient number, is how we do that. So,  20 it may only be possible to recruit 50-100 patients  21 with rare molds in a reasonable time period. So, the  22 choice is between a very small randomized trial or a</p>
<p style="text-align: right;">Page 151</p> <p>1 We currently consider treatment success  2 a complete or partial response in order to assess the  3 effect of the new antifungal. However, we understand  4 that for some, a stable response is considered a  5 positive outcome since it allows the patient to be  6 suitable for continued treatment of their underlying  7 disease.</p> <p>8 We have indicated our willingness to  9 look at additional analyses based on a dichotomy of  10 complete, partial, stable response versus progression  11 or death for assessing a global overall response  12 endpoint. And that the best way to describe the  13 results of treatment response in any future labeling  14 would be determined upon review of the final data.</p> <p>15 With that, I thank you for your  16 attention and I now turn the presentation back over.</p> <p>17 DR. LAURA KOVANDA: Thank you, Dr.  18 Dixon. We'll now go to Aaron Dane. Aaron Dane is a  19 Director of DaneStat, is a statistician with over 20  20 years of experience working in clinical development in  21 the pharmaceutical industry. Dr. Dane?</p> <p>22 DR. AARON DANE: Can you hear me okay?</p>	<p style="text-align: right;">Page 153</p> <p>1 single-arm trial.</p> <p>2 And when this is undertaken, a small  3 randomized trial gives randomization, so it may give -  4 - you know, remove any bias from treatment allocation.  5 But the problem is the heterogeneity may make it  6 difficult to compare treatments because the background  7 disease may be different in the two treatment groups,  8 which doesn't happen in a large randomized study.</p> <p>9 Alternatively, in a non-randomized  10 study, this would mean comparing with the externally  11 generated data, so there are still issues to consider  12 in terms of whether it's reasonable to make that  13 comparison, and that's what I'll come on to in later  14 slides.</p> <p>15 It's also key to say that when patients  16 have no treatment options, a single-arm study may be  17 the only option, so in that case, we do need to think  18 about how we would put any results into context.</p> <p>19 So, it's worth saying in all of this  20 that randomization is generally preferable. But if  21 there is no clear standard of care or there is a  22 robust external dataset, it might be that the external</p>

<p style="text-align: right;">Page 154</p> <p>1 data provide more reliable information than a very  2 small randomized study.  3           So, what are the key aspects of using  4 external controls -- is their robustness and their  5 comparability to the randomized data or the clinical  6 trial data. So, contemporary and matched controls are  7 most useful because you'd expect them to be more  8 similar in terms of disease setting and standard of  9 care to the clinical trial that was being conducted.  10 One question -- how contemporary does that control  11 have to be? And this would be something that would be  12 specific to the disease in question or the fungus in  13 question as to how quickly standard of care is changed  14 and how far back you could go.  15           Additionally, considerations would be  16 data validity -- so, can we verify the data that's  17 been used from that external control? And also a very  18 important aspect is the potential for bias or lack of  19 comparability to the randomized trial. So, there are  20 a number of features that would have to be considered  21 and document.  22           So, some of these have been mentioned</p>	<p style="text-align: right;">Page 156</p> <p>1 controls and trial patients identified at the same  2 point in the disease course? So, here it could be  3 that maybe the external cohort are identified in a  4 more acute phase of the disease, where if this  5 clinical trial identifies patients after that, then  6 that wouldn't be a meaningful comparison. So, again,  7 that would be necessary to consider that and be clear  8 about the groups who were comparable.  9           Other components are is the patient  10 prognosis similar? So, this could be are the risk  11 factors consistent between the external cohort and the  12 clinical trial? Or even are the risk factors  13 consistent across sites and countries within the  14 external cohort?  15           And also is there a consistent approach  16 to the management of patients in the external cohort?  17 So, again, this could be even within a country or  18 between countries. Is a standard dose and duration of  19 treatment used and is that appropriate? And is the  20 standard of care for each country or site used  21 sufficient to allow for comparison with the clinical  22 trial?</p>
<p style="text-align: right;">Page 155</p> <p>1 already, which are: Are the patient population and  2 treatment of patients similar? Were the data  3 collected under similar conditions? Are the regions  4 of the study similar? Are the endpoints defined in  5 the same way? And are there differences in the  6 reporting of cases or the identification of patients  7 of the external subgroup? And also another quick  8 question could be is matching possible or necessary  9 and could that help any comparisons be more robust?  10           One of the key elements I've mentioned  11 there is the patient population and patient care. So,  12 some of the things I've just touched on. So, are  13 patients identified in the same way? So, are all  14 available patients with the disease in question  15 included in the external cohort or is this a selected  16 subset? So, this could be important if that external  17 cohort only includes more severely ill patients, and  18 that was why they made their way into that external  19 group -- because that means they could look more  20 severe and that could bias any comparison with the  21 clinical trial data.  22           And, similarly, are the external</p>	<p style="text-align: right;">Page 157</p> <p>1           So, assuming that all of those features  2 have been considered and it is reasonable to use an  3 external control, there are two possible ways that  4 could be done.  5           Now, the first one could be to actually  6 use that external control data alongside a single-arm  7 trial. And the aim here -- so, this is an example  8 that was mentioned by Laura earlier, which is -- this  9 was isavuconazole and the FungiScope registry. And  10 the idea here is the top row is actually the survival  11 rates for the new agent.  12           So, what that shows is that the  13 survival rate is pretty good, it's 60 percent. And  14 then there's some uncertainty of the confidence  15 interval there. And then a registry such as  16 FungiScope could be used to provide some matched  17 control and show that for a patient who receives an  18 effective therapy, that they show a similar survival  19 rate.  20           If possible, in that registry, it may  21 also be possible to show a matched group who weren't  22 treated and show that there was a big difference and</p>



<p style="text-align: right;">Page 158</p> <p>1 the survival rate was much lower.  2 And, similarly the unmatched survival  3 rates from the literature and from a registry would  4 also provide additional information on treated and  5 untreated patients or patients with inappropriate  6 therapy, again, to show that there's a big benefit and  7 that treated patients tend to see a similar survival  8 rate in those groups.  9 So, the alternative approach, which may  10 require more patients, is using external data  11 alongside a randomized trial. So, an approach here  12 that's possible is a Bayesian-augmented control  13 design.  14 So, as an example, a traditional design  15 may require 700 patients, so that could be 350 per  16 arm. An augmented control design would recruit less  17 patients than that but in a 2:1 ratio with more  18 patients receiving the new agents. And then that data  19 would be supplemented with data from an external  20 clinical trial which use the same comparator. So,  21 that information would then be used together in the  22 analysis.</p>	<p style="text-align: right;">Page 160</p> <p>1 way that external data could be used when it's not  2 possible to recruit large numbers of patients into a  3 clinical trial. And the other approach is an  4 alternative statistical criteria for an area such as  5 rare molds.  6 So, this was an approach that I  7 developed in collaboration with Professor Nigel  8 Stallard at Warwick University in the U.K., and also  9 Paul Newell and John Rex have been very helpful in  10 finessing this as we've been working through it.  11 So, this was a talk I gave at the FDA-  12 Pew Workshop in November last year, and this is an  13 abbreviated version of the talk, which -- because the  14 issues still apply here with the rare molds, and a  15 possible approach that could be used.  16 So, the key aspects we talked with this  17 are that (sound drops) clinical trials has some key  18 areas. So, what we're most interested in is that we  19 want to be confident when we run a trial that we can  20 show an effective treatment works. But we also want  21 to be confident that we're not going to approve  22 ineffective treatments.</p>
<p style="text-align: right;">Page 159</p> <p>1 And provided the control group response  2 rate in the clinical trial is similar to that external  3 clinical trial, the external control rate, this would  4 allow similar Type 1 error and power with fewer  5 patients. So, Kurt Viele has outlined this possible  6 approach and the exact details are case-dependent, but  7 this does have the potential for more efficient trials  8 or being able to actually produce some outputs and  9 results in a more feasible way.  10 The main risk here is that the true  11 control arm is different from the external data. And  12 dependent upon the direction of that, it could lead to  13 reduced power in the analysis or it could lead to an  14 increase in Type 1 error or an increase in incorrectly  15 approving a new product. So, those two things are  16 important and would have to be considered, and that  17 would be part of a detailed consideration of that  18 external data in that previous clinical trial, whether  19 it was reasonable to use that alongside the clinical  20 trial data.  21 Okay, so that, hopefully, gives us an  22 idea of some of the points to consider and a potential</p>	<p style="text-align: right;">Page 161</p> <p>1 And the question is can we look at the  2 traditional statistical criteria differently for rare  3 molds? So, these patients are very hard to find for  4 clinical trials. And, really, the idea is that it's  5 better to provide a framework for evidence of effect  6 in these rare molds rather than having no data at all,  7 which may well happen if there is no clear path  8 forward in terms of how these trials are going to be  9 interpreted.  10 And what we've done with is looked to  11 draw on the ideas used in the orphan drug area. And  12 as I've just mentioned, the idea is that even with the  13 smaller studies we need a framework for decision  14 making so it's clear what study would be classed as  15 successful before that study's undertaken.  16 So, the aim here is to propose a  17 framework for decision making and sample size where  18 feasibility is very challenging. And just to clarify  19 that this is not an interim analysis where you look at  20 the data after a small number of patients have been  21 recruited and decide whether to continue. This is  22 about the total design and the total size of that</p>

<p style="text-align: right;">Page 162</p> <p>1 study.</p> <p>2 I also mentioned this talk focuses on</p> <p>3 traditional frequentist statistics, but this idea --</p> <p>4 we also consider this in a Bayesian framework, but the</p> <p>5 principles are the same which is why we're focused on</p> <p>6 the frequentist approach.</p> <p>7 So, firstly, when we were looking at</p> <p>8 this, one of the key areas we were considering was</p> <p>9 large versus small trials with rare pathogens. So,</p> <p>10 clearly a larger trial leads to higher power and more</p> <p>11 certainty, but the issue is -- in some of these</p> <p>12 settings, a very large trial is not feasible to do.</p> <p>13 So, if we're unable to run the study at all, then it</p> <p>14 deprives patients of this new therapy if no one can</p> <p>15 see a way forward.</p> <p>16 But, equally, a trial that's too small</p> <p>17 may be more feasible but it could lead to a large</p> <p>18 chance of making the wrong decision and, again, that's</p> <p>19 something that we want to avoid. And because of that,</p> <p>20 the common theme through all this is how to work with</p> <p>21 a smaller dataset and actually balance those two</p> <p>22 issues. So, how can we make sure we've got a good</p>	<p style="text-align: right;">Page 164</p> <p>1 power high.</p> <p>2 The key component here is when we run</p> <p>3 the trial, we don't know which of these situations is</p> <p>4 true, so we have to understand the Type 1 error and</p> <p>5 power for a range of scenarios and arrange of sample</p> <p>6 sizes.</p> <p>7 So, just to recap, so this idea of</p> <p>8 finding a sweet spot, which might be a reasonable</p> <p>9 sample size that's feasible but also manages the risks</p> <p>10 appropriate is we need to find a sample size where we</p> <p>11 have a good chance of success when a treatment's</p> <p>12 effective, a low chance of approval when it's</p> <p>13 ineffective, and a reasonable chance of success when</p> <p>14 it's similar. And another component we can consider,</p> <p>15 which I'll touch on later, is the expected number of</p> <p>16 patients benefitting after the trial is maximized.</p> <p>17 So, the following plot summarizes this</p> <p>18 information. And what this is showing -- so, this is</p> <p>19 an example which is showing the chances of</p> <p>20 demonstrating non-inferiority if you were using an 80</p> <p>21 percent confidence interval and a 20 percent non-</p> <p>22 inferiority margin. So, the 20 percent NI margin is</p>
<p style="text-align: right;">Page 163</p> <p>1 enough chance of bringing through effective treatments</p> <p>2 without increasing the chance of a wrong decision?</p> <p>3 So, what are we aiming for when we do</p> <p>4 this? So, really, in any trial, if a test is worth</p> <p>5 the control, ever patient randomized to test with in</p> <p>6 the study risks a worse outcome. Then they key</p> <p>7 component is if the test is approved, it's probably</p> <p>8 perpetuated. And this is why we want to minimize the</p> <p>9 chances of incorrect approval or the Type 1 error.</p> <p>10 On the other side, if the test is</p> <p>11 better than control, then ever patient randomized to</p> <p>12 control risks a worse outcome in a study. But if a</p> <p>13 test isn't approved, the problem is perpetuated in</p> <p>14 this case. So, this is why within this small dataset</p> <p>15 we want to keep the power high to make sure we pull</p> <p>16 through effective treatments.</p> <p>17 And, finally, if the test and control</p> <p>18 are similar, we would still want to make those</p> <p>19 additional therapies available because there may be a</p> <p>20 number of reasons why the existing therapies are not</p> <p>21 good enough and are not going to continue to be</p> <p>22 effective. So here, again, we'd want to keep the</p>	<p style="text-align: right;">Page 165</p> <p>1 used -- has commonly been used in areas of unmet need.</p> <p>2 And the 80 percent confidence interval is a departure</p> <p>3 from the usual 95 percent confidence used.</p> <p>4 The left hand plot shows that when the</p> <p>5 test agent is performing better than the control, the</p> <p>6 power would be high for a positive effect so that we'd</p> <p>7 have a good chance of bringing forward that treatment.</p> <p>8 The middle plot is showing what happens when the</p> <p>9 outcome is similar for test and control. And what it</p> <p>10 shows is the power is reasonable when you get to about</p> <p>11 50-60 patients per arm. I don't know if you can see</p> <p>12 on this plot, but what it's showing is that the power</p> <p>13 gets to about 80 percent at that point. So, you'd</p> <p>14 have a reasonable chance of success for a similar</p> <p>15 outcome.</p> <p>16 And the right hand plot shows that when</p> <p>17 it's less effective, so the test is worse than the</p> <p>18 control in this case, there would be a 10 percent</p> <p>19 chance of incorrectly concluding non-inferiority. So,</p> <p>20 this is still a reasonably low chance but the reason</p> <p>21 this is highlighted here is because that's a greater</p> <p>22 chance than you'd have traditionally with a 95 percent</p>

<p style="text-align: right;">Page 166</p> <p>1 confidence interval where that would be 2.5 percent.</p> <p>2 And this is where there would be a balance between the</p> <p>3 unmet need, what was required in terms of new agents,</p> <p>4 and whether this would be a reasonable risk.</p> <p>5         So, in addition to this -- so, why use</p> <p>6 the different statistical criteria? So, in addition</p> <p>7 to the power and the risk of incorrect approval I've</p> <p>8 mentioned, there's another consideration which is if</p> <p>9 the patients -- what they may receive after the study.</p> <p>10 So, in a trial where one treatment is less effective,</p> <p>11 many patients will receive this suboptimal therapy.</p> <p>12 So, as is true with any clinical trial, 50 percent</p> <p>13 would receive suboptimal therapy with a 1:1</p> <p>14 randomization. But in a limited population, this</p> <p>15 could be a large proportion of the patient population</p> <p>16 as a whole that are included in the trial. And as a</p> <p>17 result, that may be that there's a relatively large</p> <p>18 portion of the population that are receiving an</p> <p>19 ineffective medication, which is why you might want to</p> <p>20 make a decision earlier in that case.</p> <p>21         So, the size of the trial and how that</p> <p>22 relates to this expected number of patients beyond the</p>	<p style="text-align: right;">Page 168</p> <p>1 patients with rare molds can be informative, but we</p> <p>2 need clear criteria so that they can be agreed and</p> <p>3 it's clear what's required of the trial. And then it</p> <p>4 will be a case of how to maximize our chances of</p> <p>5 approving a more effective drug with, for example, 100</p> <p>6 patients. But also limiting the risk of approving a</p> <p>7 less effective new drug.</p> <p>8         So, the summary here is that</p> <p>9 considerations of power, chances of incorrect</p> <p>10 approval, and the estimated number of patients that</p> <p>11 may benefit during and after the trial will be</p> <p>12 important and could be used to agree to success</p> <p>13 criteria for trials of rare molds.</p> <p>14         So, just to finish, my final slide is</p> <p>15 just a summary -- studies of rare molds are incredibly</p> <p>16 challenging to recruit, and it's not possible to</p> <p>17 design studies in a traditional way with traditional</p> <p>18 statistical criteria. And two of the possible</p> <p>19 approaches could be to use external controls to help</p> <p>20 provide robust evidence, but the external rates need</p> <p>21 to be robust and comparable to a clinical trial. So,</p> <p>22 that's critical with any of this. And also a large</p>
<p style="text-align: right;">Page 167</p> <p>1 trial who might benefit is something that you can look</p> <p>2 at, and we can look at that graphically. All of that</p> <p>3 is beyond the scope of this talk, but really the key</p> <p>4 message here is that a much larger study does not</p> <p>5 always provide the best outcomes in a limited</p> <p>6 population because of this feature that actually there</p> <p>7 may be fewer patients left to receive therapy beyond</p> <p>8 the clinical trial. So, what that means is that it</p> <p>9 may be more of a balance to work out which is the best</p> <p>10 size of study to conduct.</p> <p>11         So, in terms of considering alternative</p> <p>12 statistical criteria -- so, really, this is a</p> <p>13 framework to display tradeoffs when only a small trial</p> <p>14 is possible. So, the questions are what's reasonable</p> <p>15 in terms of false positive and false negative rates?</p> <p>16 And as a community, deciding how to trade these risks</p> <p>17 when it's impossible to run a large trial. And the</p> <p>18 idea being to be able to run a trial which has got</p> <p>19 some statistical criteria and we can agree on what</p> <p>20 they are, rather than maybe the potential of having no</p> <p>21 trial at all.</p> <p>22         And really the idea that data on 100</p>	<p style="text-align: right;">Page 169</p> <p>1 treatment effect will be helpful if we're comparing</p> <p>2 with untreated controls and been given the difference</p> <p>3 in the data source. And also alternative statistical</p> <p>4 criteria can be useful for rare molds when there's a</p> <p>5 high unmet need and could make it feasible to actually</p> <p>6 conduct a randomized study. Thank you.</p> <p>7         DR. LAURA KOVANDA: Thank you, Dr.</p> <p>8 Dane. Let's go right to our last talk for this</p> <p>9 session. Dr. Aspasia Katragkou is currently a fellow</p> <p>10 in the Transplantation-Oncology Infectious Disease</p> <p>11 Program at Weill Cornell, and she'll provide an</p> <p>12 overview of pediatric antifungal development</p> <p>13 consideration. Aspasia? Are you... There you are.</p> <p>14 Okay.</p> <p>15         DR. ASPASIA KATRAGKOU: Hello?</p> <p>16         DR. LAURA KOVANDA: Yes, we can hear</p> <p>17 you.</p> <p>18         DR. ASPASIA KATRAGKOU: Hi. I'm</p> <p>19 Aspasia Katragkou. Good afternoon from New York. I</p> <p>20 would like first to thank the organizers for extending</p> <p>21 me the invitation to talk about pediatric antifungal</p> <p>22 drug development. I have no disclosures. Can you see</p>

<p style="text-align: right;">Page 170</p> <p>1 the slides that I'm changing? Because I'm using my 2 phone. 3 So, this is the outline of my talk. 4 I'm going to talk briefly about the epidemiology of 5 invasive fungal infections in children, about the use 6 of antifungal drugs in pediatrics. I'm going to talk 7 briefly about antifungal agent clinical trials in 8 kids, the pipeline of antifungal agents in kids, and 9 also I'm going to discuss about the challenges in 10 pediatric drug development and what can be done. 11 So, Candida species are the leading 12 cause of invasive fungal infections in children. In 13 children, typically there is a predominance of non- 14 albican species in pediatrics (inaudible)... There 15 are some emerging reports of Candida auris in 16 children. Mostly they come from South American Asia. 17 The risk factors seem to be common for all kinds of 18 species -- like prematurity, surgery and malignancy. 19 And the mortality range is depending on the study from 20 10-30 percent, which seems to be substantially lower 21 compared to adult mortality. The interesting thing is 22 that the incidence of candidemia neonates in infants</p>	<p style="text-align: right;">Page 172</p> <p>1 So, the use of antifungal agents in 2 pediatrics -- there are not many data regarding this 3 topic. Overall, there seems to be an increased 4 antifungal use over time as we have seen with 5 respective cohort studies and isolated studies from 6 Children's Hospital. 7 What is true is it seems to be 8 suboptimal use dosing of antifungal agents in 9 children. In a point prevalence study that has been 10 done in 2012 from the ARPEC study groups in 226 11 centers around the world, they found that the most 12 common indication for antifungal use was prophylaxis 13 followed by empirical treatment for febrile 14 neutropenia. The most frequently prescribed agents 15 were fluconazole and deoxycholate amphotericin B. And 16 the most interest finding is that almost half the 17 percent of the cases were receiving suboptimal 18 therapeutic doses. Something which indicates their 19 clinical trial designs were not very well regarding 20 the PK/PD data in neonates and in children. 21 What's been going on with the 22 antifungal agent trials in children, data from the</p>
<p style="text-align: right;">Page 171</p> <p>1 seems to be declining after 2009, while it remains 2 stable after 2012. 3 Regarding mold infection, aspergillosis 4 seems to be the most common with fumigatus and flavus 5 being the most prevalent species. The risk factors 6 here are hematological malignancies, solid organ 7 transplantation and primary immunodeficiencies. The 8 mortality is around 18 percent. And species of the 9 Mucorales family are more rarely mentioned in 10 children, and the risk factors here are hematological 11 malignancies, other malignancies, stem cell 12 transplantation (solid drops) -- 13 DR. LAURA KOVANDA: Aspasia, I think 14 we're having trouble hearing you. If you could move 15 closer to the mic, please. 16 DR. ASPASIA KATRAGKOU: Can you hear me 17 now? Hello? 18 DR. LAURA KOVANDA: That's better. 19 That's better. 20 DR. ASPASIA KATRAGKOU: So, the 21 mortality regarding the Mucorales family is higher, 22 like 33 percent.</p>	<p style="text-align: right;">Page 173</p> <p>1 United States show overall that the clinical trials in 2 children are ten times less compared to adults. In a 3 recent search in the clinicaltrials.gov website, I 4 found that the clinical trials in fungal infection in 5 adults are three times more compared to children. And 6 also from a relatively recent registry from October 7 2007 to 2017, from the 17,500 pediatric clinical 8 trials, less than 1 percent of them involved pediatric 9 clinical trials. And from these trials, 80 percent 10 involved antibacterials and only 19 percent 11 antifungals and just 1 percent both of them. And from 12 these trials, only 10 percent of antifungal trials 13 included neonates. 14 And as you can see to the right of this 15 slide, to the graph, these are the results from an 16 online survey done between August and September 2015 17 where pediatricians replied what are the barriers in 18 order to implement trials in children. The most 19 reason causes were difficulty in obtaining research 20 funds, and training research staff, or raising the 21 required number of patients. And from the ethical and 22 regulatory perspective, they were having difficulties</p>

<p style="text-align: right;">Page 174</p> <p>1 preparing all the required regulatory documents,  2 addressing IRB questions, and obtaining patient  3 concern.  4         So, to the next slide, which is taken  5 from an article from the New England Journal of  6 Medicine, children are not little adults. It sounds  7 like a cliché nowadays, but indeed, there are many  8 developmental changes that influence drug disposition  9 in infants, children and adolescents.  10         So, in all of these panels, for  11 example, in Panel A it shows how the activity of many  12 cytochromes in the liver changes over time. In panel  13 B it shows how the body disposition changes over time.  14 Panel C, how the structure and the function of the GI  15 tract changes. Lower, we can see how the tubular  16 secretion and the glomerular filtration rate changes.  17 And at the end we saw how the perfusion and hydration  18 diminishes from infancy to childhood.  19         So, children and adults have also  20 differences in the infections they acquire. For  21 example, the Candida CNS infection is more prevalent  22 in the small babies, less than three-months of age.</p>	<p style="text-align: right;">Page 176</p> <p>1 all the formulations of amphotericin, the relationship  2 between adult and pediatric doses seems to be linear.  3 This is not the case for azoles where Voriconazole  4 seems to be linear but nonlinear for the rest of the  5 azoles. And the next slide shows the echinocandins,  6 where there is linear also only for anidulafungin but  7 it's nonlinear for caspofungin or micafungin.  8         So, I'm moving to the next slide. So  9 there are specific considerations regarding the  10 antifungal agents in children. Historically,  11 pediatric drug dosing has been extrapolated from  12 adults by use of a linear modeling, namely dividing  13 the adult dose by an average adult weight like 70  14 kilograms automatically, or more rarely, dividing by  15 the body surface area divided by 1.73 square meters.  16         Nowadays, the antifungal treatment in  17 children has been advanced and studies until now have  18 shown us first that the antifungal pharmacokinetics  19 and doses differ --  20         DR. LAURA KOVANDA: Aspasia, I think we  21 lost you again. Can you speak closer to the mic?  22         DR. ASPASIA KATRAGKOU: Hello? Hello?</p>
<p style="text-align: right;">Page 175</p> <p>1 The mortality of candidemia is less in children versus  2 adults. Also, invasive aspergillosis has different  3 imaging findings in children compared to adults. And  4 the tinea capitis in children appear -- seems to be  5 specific for the children as compared to adults.  6         Also, there are differences in the  7 hosts that affect these infections. And in children,  8 the neonates seem to be more susceptible, children  9 with primary immunodeficiencies or they have different  10 rates of comorbidities than children.  11         So, this is a very busy slide which  12 wants to say that (sound drops) --  13         DR. LAURA KOVANDA: We're having  14 trouble hearing you again.  15         DR. ASPASIA KATRAGKOU: Can you hear me  16 now? Can you hear me?  17         DR. LAURA KOVANDA: Yes, that's better.  18         DR. ASPASIA KATRAGKOU: So, the  19 relationship between adult and pediatric doses can be  20 linear or nonlinear and this doesn't seem to be drug  21 class specific dependent.  22         So, for example, for amphotericin, for</p>	<p style="text-align: right;">Page 177</p> <p>1 Hello? Can you hear me? Can you hear me? Hello?  2 Hello?  3         WOMAN 1: We can hear you, Aspasia.  4         DR. ASPASIA KATRAGKOU: So, the  5 conclusions regarding antifungal agent use in children  6 until now is that antifungal pharmacokinetics and  7 dosing differs dramatically between children and  8 adults. Second --  9         DR. LAURA KOVANDA: Aspasia, I think  10 your connection is going in and out.  11         DR. ASPASIA KATRAGKOU: I think it's my  12 Internet connection. It's not probably good because  13 of the storm probably. So, second then in their  14 individual pharmacokinetics viability increases with  15 increasing developmental aids. And third, antifungal  16 drug exposure targets -- varies between young  17 children, children and adults. All these findings are  18 really important because of how --  19         DR. LAURA KOVANDA: Aspasia, I think  20 we're going to have to make an adjustment. I don't  21 know if others cannot hear as well.  22         DR. ASPASIA KATRAGKOU: Can I call you</p>

<p style="text-align: right;">Page 178</p> <p>1 back? Hello?</p> <p>2 DR. LAURA KOVANDA: Should we stop here</p> <p>3 and maybe --</p> <p>4 WOMAN 1: It looks like some people</p> <p>5 can't hear her.</p> <p>6 DR. LAURA KOVANDA: Yeah. I think</p> <p>7 either we have to make an adjustment or maybe we take</p> <p>8 a break now and maybe we can come back to it after</p> <p>9 lunch. Or how should we proceed? I'm not sure if</p> <p>10 it's going to get better right now.</p> <p>11 WOMAN 1: I think we probably will need</p> <p>12 to disconnect for lunch.</p> <p>13 DR. LAURA KOVANDA: Yeah. Why don't we</p> <p>14 go ahead and take a 30-minute lunch break? I'm sorry,</p> <p>15 Aspasia, I think we're having trouble with your</p> <p>16 connection, maybe because of the storm. So, go ahead</p> <p>17 and take a 30-minute break. It is one (sound drops)</p> <p>18 on the East (sound drops) so, let's come back in 30</p> <p>19 minutes.</p> <p>20 (Break)</p> <p>21 DR. LUIS OSTROSKY-ZEICHNER: This is</p> <p>22 Luis Ostrosky from Houston, and we're going to start</p>	<p style="text-align: right;">Page 180</p> <p>1 antimicrobial resistance. This is obviously important</p> <p>2 for this kind of thing that we're talking about today,</p> <p>3 drug development, as well as other issues that help</p> <p>4 prioritize these organisms in our scope when we're</p> <p>5 looking to develop both diagnostics, drugs, and</p> <p>6 measures to control, treat, and contain them.</p> <p>7 I always like to put this slide in</p> <p>8 there because, really, for all of us, this has been a</p> <p>9 paradigm shift, this new species for candida</p> <p>10 infections. We really have a yeast acting just like a</p> <p>11 bacteria. Resistance is the norm with this organism.</p> <p>12 It thrives on skin. It contaminates surfaces, patient</p> <p>13 rooms, and it spreads, now we know, readily in</p> <p>14 healthcare and even non-healthcare settings; although,</p> <p>15 most of the documented spread is in healthcare</p> <p>16 settings.</p> <p>17 Here's a current look at where we are</p> <p>18 with cases around the U.S. You can see that the major</p> <p>19 cases still remain in the three states of Illinois,</p> <p>20 New York, New Jersey. We are seeing more cases in</p> <p>21 both Florida and California, and you can see here that</p> <p>22 there have been new states that have reported one case</p>
<p style="text-align: right;">Page 179</p> <p>1 the afternoon session, Session 3: Current State of</p> <p>2 Candida auris and Antifungal Drug Development</p> <p>3 Considerations. The session is going to be chaired by</p> <p>4 Dr. Helen Boucher and myself, and it is my pleasure to</p> <p>5 introduce as first speaker, Dr. Tom Chiller.</p> <p>6 Dr. Chiller's the Division Chief for</p> <p>7 Mycotic Diseases Branch at the CDC and he is going to</p> <p>8 be talking to us and giving us an overview of Candida</p> <p>9 auris and emerging resistant candida. Tom.</p> <p>10 DR. TOM CHILLER: Thanks, Luis, and</p> <p>11 great to be with everybody. Look forward to giving a</p> <p>12 very short overview of Candida auris and sort of where</p> <p>13 we are. I know many of you, if not all of you, know</p> <p>14 about this organism and we've all been hearing about</p> <p>15 it for the last several years, so I'd like to focus</p> <p>16 more on some of the updated information, at least,</p> <p>17 that we have and then touch on briefly, unfortunately,</p> <p>18 other emerging resistant candida what we're starting</p> <p>19 to worry about.</p> <p>20 I don't have any disclosures. I think</p> <p>21 many of you saw recently, we put Candida auris on the</p> <p>22 urgent threats list from the CDC report on</p>	<p style="text-align: right;">Page 181</p> <p>1 in the recent past.</p> <p>2 This gives you a look at our numbers.</p> <p>3 You can see here we're up to over 1,200 clinical cases</p> <p>4 and about twice as many cases that we call screening</p> <p>5 cases, where we have gone and looked for, essentially,</p> <p>6 colonization in healthcare facilities or in long-term</p> <p>7 care facilities. We also have some COVID-related</p> <p>8 challenges with this particular organism. We know</p> <p>9 that decreased screening has been going on and so</p> <p>10 there are actually less observations as to how much is</p> <p>11 spreading with facilities.</p> <p>12 We have been doing screening,</p> <p>13 certainly, in hotspots and that, as you can imagine,</p> <p>14 has decreased dramatically. There's also been</p> <p>15 reporting delays and so I think those are just common</p> <p>16 for many of the things that are happening right now in</p> <p>17 the -- during this COVID pandemic, unfortunately.</p> <p>18 The other thing that we're concerned</p> <p>19 about is some of the changes in patient movement</p> <p>20 patterns and these changes have to do with sick</p> <p>21 patients going in from long-term care facilities and</p> <p>22 moving into ICUs and back out. Of course, the</p>

<p style="text-align: right;">Page 182</p> <p>1 vulnerable in this population are the exact patients  2 in these long-term care that we've been worried about,  3 MDROs, multidrug resistant organisms in general, but  4 Candida auris specifically.  5         So there's been some concern about  6 that, and then of course, widespread -- even more  7 widespread empiric anti, certainly bacterial use, less  8 so antifungal use, and you can see here from these two  9 graphs that all the colonization levels are down, but  10 we've seen some interesting sharp increases in C.  11 auris when there is culturing done in some of these  12 long-term care facilities, and that's what the graph  13 on the right.  14         So what about the epidemiology of this  15 organism that's been now around for a number of years?  16 You know, we have seen some outbreaks happening in  17 previously well-contained areas of the country like in  18 Southern California and the Mid-Atlantic. We also  19 have seen several cases reported to us without links  20 to any known cases or healthcare abroad, and so  21 understanding how those cases developed or arrived.  22         And then we're seeing -- and we always</p>	<p style="text-align: right;">Page 184</p> <p>1 in this long-term facility, despite the fact that  2 their bed -- not bedmates, but their roommates are  3 positive. And so there's some interesting dynamics  4 going on here where you can have a positive roommate  5 and yet you remain negative that entire time.  6         So we're still trying to understand  7 that transmission. This also, obviously, points out  8 that some people can be positive and stay positive for  9 hundreds of days or they can go positive, negative,  10 and back to being positive still not understanding  11 whether that's a reinfection or simply they just  12 remain colonized. We think it's more of the latter  13 that they remain colonized, and obviously colonization  14 testing is not a perfect sensitive way to document, as  15 we know they can -- that the Candida auris can be  16 found in multiple different body sites.  17         So talking briefly about resistance,  18 here's a look at somewhere around 1,600 isolates that  19 we've tested: 80 percent resistant to azoles, about a  20 third to the polyenes, and low numbers, which is good,  21 resistant to echinocandins. You can see about a third  22 are multidrug resistant, in other words, two or more</p>
<p style="text-align: right;">Page 183</p> <p>1 have, but it hasn't been the main source of  2 transmission in acute care hospitals, but we're  3 certainly seeing more of that now as well as just  4 regular skilled nursing facilities, not just the  5 skilled nursing facilities with ventilator care, which  6 has really been the crux of this outbreak occurring in  7 those ventilated patients.  8         Most common specimen sources of the  9 clinical cases that we've detected to date continue to  10 remain about half in blood, but we see a lot, up to a  11 third in urine, which of course are often not  12 identified, as we know, and then less so in wound and  13 in sputum. And then, of course, long-term  14 colonization has been one of the issues we've been  15 battling with and trying to understand, and you can  16 see here from -- this is from data, I think, out of  17 Chicago that was presented last year at SHEA, and just  18 gives you a snapshot of some of the different things  19 we're dealing with.  20         You can see some patients, by the blue  21 diamond, are negative upon screening culture, and they  22 remain negative throughout the duration of their stay</p>	<p style="text-align: right;">Page 185</p> <p>1 drugs, and we have found pan resistance in two  2 different states, but thankfully, this is still  3 exceedingly rare in this country.  4         There are, however, major difference by  5 clades. You know that Candida auris has principally  6 four but now five different clades that have been  7 identified, and this, you can look at some of this  8 resistance that can vary geographically, depending on  9 where the clade is and this is looking at azole  10 resistance. You can see South Asian clades have  11 almost all got azole resistance. The African clade,  12 again, has very high levels; whereas, the South  13 American clade, which is found principally in  14 Illinois, has very low levels of azole resistance.  15         In contrast, you can look at  16 amphotericin B resistance. Again, South Asian around  17 a third, the African much lower, and the South  18 American clade even lower amount, and then finally  19 looking at this sort of with a round-about way of all  20 three classes of drugs, you can see here that the  21 different regions and therefore different clades have  22 different levels of resistance, where echinocandin</p>

<p style="text-align: right;">Page 186</p> <p>1 resistance, again thankfully, remains relatively rare  2 in most of these isolates to date.  3         We have reported, as you all know, on  4 pan-resistant <i>C. auris</i> for completely unrelated cases  5 reported with resistance to all three classes: three  6 from New York, one from Maryland. None had  7 international travel or healthcare. All of these were  8 mechanically ventilated and had been in long-term care  9 and all cases initially had <i>Candida auris</i> cultures  10 sensitive to echinocandins but developed resistance  11 while being on echinocandin treatment, which of  12 course, is concerning.  13         Switching back, then, out of <i>Candida</i>  14 <i>auris</i> and into a couple new areas in <i>Candida</i>. First,  15 an old area, <i>Candida glabrata</i>, as we know, still  16 making up a large number of our candidemia patients in  17 this country we've got now 12 years of ongoing  18 surveillance in 10 sites with over 2,500 isolates and  19 you can see there that the resistance to fluconazole  20 remains relatively stable. The three-plus  21 echinocandin resistance has climbed over time.  22         You can see among those isolates</p>	<p style="text-align: right;">Page 188</p> <p>1 <i>Candida haemulonii</i>, not <i>Candida auris</i>.  2         But there is truly <i>Candida haemulonii</i>,  3 as well, out there, as well as <i>duobushaemulonii</i>, where  4 we've seen some fluconazole resistance and high  5 amphotericin B resistance and <i>Candida kefyr</i>, where  6 we've seen a few very high fluconazole MICs. And if  7 you look here at sort of the <i>Candida haemulonii</i>  8 species complex, you look at whole genome sequencing,  9 and I know this is very small, but suffice it to say,  10 these are separate species from <i>Candida auris</i>,  11 although close, and we've seen now transmission of  12 <i>haemulonii</i> and <i>duobushaemulonii</i> in Panama in hospitals  13 there and we're -- are wondering now as whether this  14 sort of transmission is going to be akin to the kind  15 of healthcare transmission we're seeing with <i>Candida</i>  16 <i>auris</i>.  17         And again, concerning, because again,  18 these are relatively resistant organisms. And  19 finally, <i>duobushaemulonii</i>. We have recently been in  20 touch with colleagues in Puerto Rico where you can  21 see, based on the whole genome sequencing here, we  22 have a very tight cluster of 12 isolates from 11</p>
<p style="text-align: right;">Page 187</p> <p>1 resistance to flu, around 10 percent are also  2 resistant to echinocandin, so suggesting that these  3 are sort of multidrug clusters, and you can see among  4 the echinocandin resistance, again, 25 percent  5 resistant to flu. So clearly, those that develop  6 resistance are more likely to be multidrug resistant.  7         Some of the familiar <i>Candida</i> species,  8 again, that we've seen, <i>Candida parapsilosis</i>, we're  9 seeing resistance approach around 10 percent in the  10 U.S. Certainly, this is higher in some other  11 countries, so it's one thing we've been wondering  12 about is how our <i>parapsilosis</i> will develop resistance  13 over time. <i>Guilliermondii</i> species complex, we've seen  14 some very high fluconazole MICs in our surveillance.  15         And then finally, some new species that  16 we're sort of watching and potentially concerned  17 about. These species are maybe for lack of a better  18 word, cousins or closely potentially related to  19 <i>Candida auris</i> in some way, and in fact, <i>Candida</i>  20 <i>haemulonii</i>, the first species where we do see  21 fluconazole resistance, was often mistaken with some  22 of the older ways to detect species in microlabs as</p>	<p style="text-align: right;">Page 189</p> <p>1 patients, 10 isolates actually from one facility.  2         These were collected over about a year-  3 and-a-half from both blood and abscess specimens, and  4 again, this is a very resistant, at least azole  5 resistant organism and we're wondering again is this a  6 newer emerging species that is also going to be  7 transmitted in those healthcare settings, and that's  8 concerning to us.  9         Finally, a few resources for you to see  10 about resistance and <i>Candida auris</i> on our web page,  11 and I will end there and just thank all the  12 collaborators that we work with on a daily basis,  13 especially our state and local health departments and  14 clinical, academic, and international partners as well  15 as NIH and the rest of the folks at CDC. So thanks  16 for your time.  17         DR. HELEN BOUCHER: All right, I'm  18 going to jump in. This is Helen Boucher from Tufts.  19 Good afternoon, everybody. I think my mike was  20 unmuted, Dr. Ostrosky. It's my pleasure to introduce  21 Dr. Baoying Liu from the NIAID, who's going to speak  22 to us about funding opportunities on clinical research</p>



<p style="text-align: right;">Page 190</p> <p>1 at the NIH. Thanks very much.</p> <p>2 DR. BAOYING LIU: Can anybody hear me?</p> <p>3 Hear me okay? Okay.</p> <p>4 DR. HELEN BOUCHER: Hear you well.</p> <p>5 DR. BAOYING LIU: Thank you very much</p> <p>6 for the opportunity to present. For today's talk,</p> <p>7 first I will provide some highlights from the NIAID</p> <p>8 Candida auris workshop. Which took place back in</p> <p>9 January. And then I will focus on our funding</p> <p>10 opportunity on clinical research.</p> <p>11 Understanding the biology, antifungal</p> <p>12 resistance, and the clinical implications of Candida</p> <p>13 auris workshop was held at NIAID conference Center on</p> <p>14 Fishers Lane of Rockville from January 28th through</p> <p>15 29th, 2020. NIAID sponsored this workshop. My</p> <p>16 colleague, Dona Love, who is a busy mycology program</p> <p>17 officer, along with NIH intramural investigators,</p> <p>18 Julia Segre, Mihalis Lionakis, and the CDC</p> <p>19 comptroller, Brendan Jackson and myself were on the</p> <p>20 organizing committee to put together the workshop</p> <p>21 agenda.</p> <p>22 And through the link on this slide, you</p>	<p style="text-align: right;">Page 192</p> <p>1 in the pipeline. Clinicians also shared their</p> <p>2 academic experience in managing Candida auris</p> <p>3 infection in the United States, United Kingdom, and</p> <p>4 South Africa. We united a total of 24 speakers</p> <p>5 including international speakers.</p> <p>6 Our next slide, I'm trying to capture</p> <p>7 the major takeaways from the breakout sessions. This</p> <p>8 is very high-level summarization. I could only pick</p> <p>9 several topics to share. One of the topics that</p> <p>10 consistently came up is the access to clinical</p> <p>11 isolates, especially isolates with sequence data.</p> <p>12 During the workshop, attendees also discussed about</p> <p>13 how much patient metadata we can get without</p> <p>14 compromising patients' privacy.</p> <p>15 After the workshop, based on the</p> <p>16 feedback from participants at the workshop, five new</p> <p>17 isolates were added to the AR isolate bank and are now</p> <p>18 available to the research community, so the link I</p> <p>19 provided here is the CDC/FDA AR Isolate Bank. Right</p> <p>20 now, multiple isolates from each clade are available</p> <p>21 in the collection.</p> <p>22 A second topic to share is about</p>
<p style="text-align: right;">Page 191</p> <p>1 can assess the workbook agenda and most speakers'</p> <p>2 presentation of the workshop.</p> <p>3 Objectives of this workshop is to bring</p> <p>4 together a diverse group of stakeholders including</p> <p>5 representatives from academia, industry, and the</p> <p>6 government agencies to determine what is known about</p> <p>7 this organism, what are the most serious knowledge</p> <p>8 gaps, and discuss how to best leverage resources to</p> <p>9 combat this unique fungal pathogen.</p> <p>10 The picture on the right is our Fishers</p> <p>11 Lane NIAID building. We are extremely lucky to have</p> <p>12 this meeting in person just before the pandemic. Our</p> <p>13 registration was maxed out with over 100 attending in</p> <p>14 person and over 100 remote attendees.</p> <p>15 This workshop has covered very</p> <p>16 ambitious agenda. It includes five scientific</p> <p>17 sessions, which are the first five bullet points here</p> <p>18 and the three breakout sessions in this one-and-a-half</p> <p>19 day.</p> <p>20 We covered topics from basic biology,</p> <p>21 resistant mechanism, immunology, epidemiology,</p> <p>22 decolonization, diagnosis, efficacy and therapeutics</p>	<p style="text-align: right;">Page 193</p> <p>1 decolonization, for example, questions like how to</p> <p>2 start a decolonization in the real-world setting.</p> <p>3 What are the facts to focus on? What is the goal of</p> <p>4 decolonization in the context of persistent</p> <p>5 colonization?</p> <p>6 The third topic I wanted to share is</p> <p>7 about special considerations for resource limited</p> <p>8 settings. For example, we need to first understand</p> <p>9 transmission dynamics in this setting, so those</p> <p>10 patient populations are different and often without</p> <p>11 surveillance systems in place.</p> <p>12 And lastly, we discussed about clinical</p> <p>13 studies. Currently, there's no treatment (inaudible)</p> <p>14 and there are very limited data to detail disease</p> <p>15 progression, treatment, and the treatment outcome.</p> <p>16 For example, a clinician shared a disconnect between</p> <p>17 blood culture clearance and the patient outcome.</p> <p>18 In other words, so some patients after</p> <p>19 antifungals were given, blood culture were clear but</p> <p>20 patient still died. So the question is, what's the</p> <p>21 treatment that could impact outcome? Is it due to the</p> <p>22 comorbidity? Maybe not.</p>

<p style="text-align: right;">Page 194</p> <p>1 So again, it comes to the same topics  2 that we discussed today, how to design a clinical  3 trial. This one-and-a-half-day workshop allowed the  4 community to work together to define the current  5 status of Candida auris with research and identify  6 that to allow development to move forward.  7 With the speaker's permission, slides  8 have been made available on the website I provided  9 here, I will repeat, you can access the workbook  10 agenda and the speak -- most speakers' presentation  11 through this workshop. So that's that.  12 For the second part of my talk, I will  13 focus on our funding opportunities. NIAID supports  14 basic (inaudible) and clinical research targeting  15 Candida auris. Approximately 50 percent of NIAID's  16 mycology portfolio have this candida species. Many of  17 them are incorporating Candida auris studies into  18 their research. Because this FDA workshop has a  19 clinical team to, today I'm going to focus on our  20 support on clinical research.  21 First, these investigator-initiated  22 clinical trials, which include standard R01, R21, and</p>	<p style="text-align: right;">Page 196</p> <p>1 Lastly, NIAID also have contract  2 mechanism to help conduct Phase I clinical trial. I  3 may already have mentioned that in morning. This  4 contract mechanism is a clinical service, just like  5 the preclinical services you heard this morning.  6 NIAID is holding the IND and then they sponsor the  7 clinical trial. Of course, it will be the  8 collaborators or partners so use that interest applied  9 entirely.  10 So this slide, I'm trying to provide  11 two examples for the current grant opportunities. For  12 U01, like I mentioned early, it support high risk  13 clinical trials. In addition, if your request equal  14 to or more than \$500,000 direct cost per year for any  15 year of proposed trial, then a prior consultation with  16 NIAID staff is needed.  17 The purpose of prior consultation is to  18 take into account program priority, visibility,  19 safety, and the cost. It's not scientific review and  20 will not replace peer review process. If you request  21 less than \$500,000 direct cost per year, you don't  22 need to go through this prior consultation process.</p>
<p style="text-align: right;">Page 195</p> <p>1 the U01 surveillance mechanisms. All these three  2 mechanism are clinical trial required. R21 and R01  3 grant mechanism do not need to include NIAID staff and  4 are designed for non-high-risk clinical trial.  5 For the high-risk clinical trial, NIAID  6 utilize the U01 mechanism. When I talk about high  7 risk, high risk refers to an unlicensed product or for  8 licensed product for an unapproved indication. NIAID  9 also supports clinical trial planning; it's called  10 R34. This mechanism is to support timely development  11 of all materials required for future clinical trial,  12 for example, to establish a team and to develop  13 clinical protocol.  14 I want to point out here, funding of  15 R34 doesn't guarantee all implied funding of  16 subsequent U01. Budgets are limited to \$150,000  17 direct costs for up to one year.  18 So NIAID also supports small business  19 to conduct clinical trials. We call this mechanism  20 U44. U44 is a very attractive mechanism for small  21 business to conduct clinical trials, so I will briefly  22 introduce U44 at the next slide.</p>	<p style="text-align: right;">Page 197</p> <p>1 Your application will go right to the review.  2 For U44, like I mentioned, is a small  3 business, Phase 2 clinical trial implementation grant,  4 just like SBIR small business Phase 2 grant, you can  5 request up to \$1 million total cost per year for up to  6 three years with waiver topics. You need to  7 adequately justify why such a budget is required. You  8 can apply a Fast Track Phase 2 if you have a prior  9 Phase 1 or Phase 2B if you don't have a prior Phase 2.  10 Here, I want to emphasize for the  11 implementation grant that new one and U44, in your  12 grant application package, you need to include all  13 elements that are necessary to conduct a clinical  14 trial. For example, you need to already have a  15 clinical protocol. You also need to have clinical  16 monitoring plan, data management plan, and they must  17 be used.  18 Finally, for updates on funding  19 opportunities, please consider to subscribe to NIAID  20 Funding News, so I have provided links here. I also  21 suggest you to look for NIAID council-cleared  22 concepts. It shows upcoming potential opportunities.</p>

<p style="text-align: right;">Page 198</p> <p>1 These initiatives are something we want to support and 2 we care deeply. 3       Again, these are the resources that are 4 available for the community. Please consider to 5 apply. We would like to see more clinical research 6 applications coming in. Please do not hesitate to 7 email me. I would like to help you to navigate this 8 process. With that, I conclude my presentation. 9 Thank you very much. 10       DR. LUIS OSTROSKY-ZEICHNER: Thank you 11 very much, Dr. Liu. We're going to move on with the 12 agenda. The next block is a block where we're going 13 to discuss lessons learned from antifungals for high 14 unmet medical needs, so it's going to be a rapid fire 15 with three speakers. We're going to start off Dr. 16 Michael Hodges, who's currently the Chief Medical 17 Officer at Amlyx. Mike. 18       DR. MICHAEL HODGES: Thanks. Good 19 afternoon everybody. Many thanks for inviting me to 20 speak at what is a timely workshop. I've previously 21 been involved with the development of fluconazole, 22 voriconazole, and anidulafungin, and now fosmanogepix.</p>	<p style="text-align: right;">Page 200</p> <p>1           Invasive fungal infections are 2 associated with high mortality, despite the treatment 3 and when looking at randomized control trials for 4 invasive candidiasis, day 30 mortality is between 10 5 and 18 percent. Invasive aspergillosis, the six-week 6 mortality is 20 percent. When you look at the real- 7 world picture, it is actually much higher. Invasive 8 aspergillosis recent review showed 38 to 85 percent 9 mortality and for Candida auris, 30 to 72 percent 10 mortality. 11       The cause of this residual mortality is 12 due, in part of course, to the underlying severity 13 disease, but also the poor diagnostics that we have 14 leading to a delay in treatment, and also the limited 15 choice of antifungals. As we've heard previously, 16 there are only three drug classes available: the 17 polyenes, the azoles, and candins. 18       Consequently, we need new antifungal 19 drugs pretty urgently. 20       If you go to the next slide, we heard 21 from Tom in recognition of the increase in drug 22 resistance, and the negative impact on public health,</p>
<p style="text-align: right;">Page 199</p> <p>1           My presentation will focus on two 2 important points highlighted in the FDA's earlier 3 presentation, namely the unmet medical need and 4 practical challenges developing antifungal drugs. 5 Now, the talk is applicable to both the unmet needs in 6 Candida auris, for example -- and also the rare molds. 7 My disclosure information is below, and as Luis said, 8 I'm a full-time equivalent and a Chief Medical Officer 9 at Amlyx Pharmaceuticals. 10       We have fosmanogepix in the clinic and 11 it has a broad-spectrum activity against yeast, molds, 12 and dimorphic fungi. Fosmanogepix has the drug 13 characteristics that have potential to address many of 14 the unmet needs I'm about to tell you, for example, 15 wide tissue distribution to the brain and deep into 16 the gut. Its two formulations, IV and oral, high 17 bioavailability, and no signs of the renal hepatic 18 toxicity that are the Achilles heel of some of the 19 standard of care therapies. 20       On the righthand side of this slide are 21 the Phase 2 trials that we are currently enrolling and 22 setting up.</p>	<p style="text-align: right;">Page 201</p> <p>1 the CDC has included three serious fungal infections 2 on the CDC Threat List: azole-resistant Aspergillus 3 fumigatus, drug-resistant candida species, and more 4 recently, Candida auris which is typically drug 5 resistant. 6       The fluco resistant candida is also 7 recognized on the WHO Priority List. Coming right up 8 to date with the SARS-2 pandemic, we see that patients 9 with viral pneumonia are at high risk for secondary 10 infections, including invasive aspergillosis, and 11 that's now coined coronavirus-associated pulmonary 12 aspergillosis. This has an extremely high mortality, 13 just like with the post-influenza pulmonary 14 aspergillosis. 15       Now more than ever, we need new 16 antifungal drugs. We need antifungal drugs that have 17 better drug characteristics to address both the unmet 18 -- sorry, to address the antimicrobial resistance, but 19 I want to really point out that equally important to 20 antimicrobial resistance, are what terms the drug 21 deficiencies, for example, the toxicities, the drug 22 interaction, the lack of available formulation, and</p>

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<p>1 the lack of suitable exposure in some tissue 2 compartments. 3       Also as FDA have pointed out, we won't 4 solve the problem of the unmet without better 5 diagnostic tests and we really need to take a one- 6 health approach to tackle this public health crisis. 7       We've heard from the FDA earlier that 8 the antifungal and antibiotic development share 9 similar aspects of drug development and we would agree 10 with this, but we also think that there are unique 11 challenges and I would like to point these out. 12 Antifungal clinical trials have always been difficult 13 to recruit, and they probably are getting harder to 14 recruit patients. We are, in essence, an orphan drug 15 population and this will require a global search for 16 the eligible patients. 17       Clinical trials in invasive fungal 18 infections are extremely complex, take a long time to 19 conduct, and can cost upwards of \$100,000 to \$200,000 20 per patient, and I think this was confirmed in an 21 earlier talk by Laura Kovanda. 22       The Phase 3 randomized controlled</p>	<p>1 recruit any patients and it required much more 2 resources to manage and monitor these sites than other 3 trials that were being conducted at the same time. 4 This study took four-and-a-half years to enroll, and I 5 think the example presented by Laura Kovanda would be 6 as with fluconazole trial which required twice as many 7 patients, took eight years to conduct. 8       Again, the trial I'm most familiar with 9 is the Herbrecht study, the VORI vs. AmB, and this, 10 again, was a high resource intensive trial taking 11 three years to conduct. 12       So in summary, we think that invasive 13 fungal infection drug development would benefit from a 14 new paradigm for demonstrating the statutory 15 requirements of substantial evidence, similar to other 16 orphan rare -- drugs to treat life threatening 17 diseases. 18       Clinical trials, as I've said, have 19 historically been difficult to conduct and I think 20 it's going to become harder and this trend will 21 continue. Drugs to treat life threatening rare orphan 22 diseases have been approved based on small datasets</p>
<p>Page 203</p> <p>1 trials in invasive candidiasis have historically 2 required numbers of around 300 to 600 patients; 3 however, recruitment per site is extremely low. These 4 trials have taken many years to conduct and require 5 many sites to be open in the chance that a site will 6 recruit a patient. In reality, many of these sites 7 will not recruit any patients and they will likely 8 screen hundreds of patients but will not enroll. This 9 is both expensive and inefficient. 10       More recently, these trials have been 11 conducted in patients with limited or no treatment 12 options, for good reason; however, it will just 13 increase the scarcity of these patient who might be 14 eligible for the trials, and these practical 15 challenges, along with the scientific and economic 16 challenges, discourages sponsors and investors to 17 develop antifungal drugs. 18       On the next two slides, I provide some 19 examples of the randomized control trials that have 20 been conducted. The trial that I'm most familiar with 21 is the VORI vs AmB/FLUCO trial, and we had 101 sites, 22 my colleagues and I at Pfizer, and 50 percent did not</p>	<p>Page 205</p> <p>1 that support the substantial evidence of effectiveness 2 required for approval of all drugs. 3       Recently, and FDA are to be 4 congratulated for this, they have issued the LPAD 5 pathway guidance document for drugs intended to treat 6 serious or life-threatening infections in a limited 7 population, and this would permit the risk-benefit 8 assessment to be flexible to consider the severity, 9 the rarity, and the prevalence. However, LPAD pathway 10 does not alter the overall FDA approval standards. 11       Two drugs, as listed, have been 12 approved through the LPAD pathway; however, it is 13 unclear how far this flexibility might extend in the 14 approval of new antifungal drugs that address high 15 unmet medical need of invasive fungal infections. 16       And I'll pause there and pass over to 17 my colleague, David. 18       DR. LUIS OSTROSKY-ZEICHNER: Thank you 19 very much, Dr. Hodges, and it is a pleasure to 20 introduce Dr. David Angulo, who's the chief medical 21 officer at Scynexis. 22       DR. DAVID ANGULO: Candida auris.</p>

<p style="text-align: right;">Page 206</p> <p>1 Thank you, Dr. Ostrosky. I'm going to focusing my                  2 talk in the development considerations for Candida                  3 auris specifically, and as a disclosure, I'm a full-                  4 time employee of Scynexis.</p> <p>5           As an outline of what we are doing and                  6 as an example for what we are -- we care very deeply                  7 about these -- participating in this particular                  8 workshop that I think I can praise the agency for                  9 organizing and thank you for inviting us. We are                  10 developing the ibrexafungerp, which is a novel glucan                  11 synthase inhibitor that has a different structure from                  12 the echinocandins, which are the only glucan synthase                  13 inhibitors approved today. This different structure                  14 allows for oral bioavailability which is, we know, a                  15 limitation of the echinocandins at this point, that                  16 they're only available intravenously.</p> <p>17           It also results in a different                  18 interaction with glucan synthase that has shown to                  19 lower the impact of common FKS mutations that can show                  20 resistance to echinocandins. The in vitro and the in                  21 vivo activity of the compound includes all kind of                  22 relevant species of candida, including Candida auris,</p>	<p style="text-align: right;">Page 208</p> <p>1 regulatory background that may apply to the                  2 development of new drugs for candida. The typical                  3 development program for invasive candidiasis included                  4 a single, randomized controlled trial, Phase 3, and to                  5 demonstrate noninferiority against the standard of                  6 care.</p> <p>7           This model has been successful for the                  8 development of several antifungal agents to date, but                  9 we've just heard from previous speakers that these are                  10 very challenging studies to conduct, long and                  11 expensive. The LPAD pathway may provide a framework                  12 for alternative approaches. Based on the scope of the                  13 LPAD, I think that we could all agree that Candida                  14 auris infections could be subject to an LPAD                  15 consideration.</p> <p>16           They are certainly severe, at least                  17 most of them, with low prevalence, very few treatment                  18 alternatives. They are life threatening and                  19 additional treatments are definitely an unmet medical                  20 need. The LPAD allows for a more streamlined clinical                  21 development program while keeping in mind that                  22 substantial evidence of effectiveness must be</p>
<p style="text-align: right;">Page 207</p> <p>1 aspergillus, pneumocystis, and coccidioides. And in                  2 particularly interesting attributes of ibrexafungerp                  3 is the extensive volume of distribution which allows                  4 to achieve high concentrations in most patients.</p> <p>5           The clinical development with the oral                  6 formulation has in progress in several fungal                  7 diseases. We have completed two Phase 3 studies in                  8 vulvovaginal candidiasis, one study in invasive                  9 candidiasis, and we have ongoing studies in patients                  10 with the recurrent vulvovaginal candidiasis, invasive                  11 aspergillosis, refractory invasive fungal diseases,                  12 and infections to Candida auris.</p> <p>13           Now focusing on, really, the challenges                  14 of really one of the aspects that are very relevant                  15 for Candida auris development, developing new drugs                  16 for the treatment of Candida auris infections is                  17 challenging. And I hope to be able to highlight some                  18 of these challenges that would allow the conversation                  19 to move forward towards addressing those challenges,                  20 joining as a scientific, regulatory, and industry                  21 community.</p> <p>22           Let's start by highlighting some of the</p>	<p style="text-align: right;">Page 209</p> <p>1 provided, but allows the acceptance of a greater                  2 uncertainty, based on a risk-benefit assessment.</p> <p>3           I think this provides us an opportunity                  4 for the whole community to work together, identifying                  5 physical ways to provide substantial evidence of                  6 effectiveness for this infection, considering the                  7 current unmet needs and limited treatment options.</p> <p>8           The typical development program for                  9 invasive candidiasis includes a Phase 2 study,                  10 typically, followed by a Phase 3 study randomized                  11 control, power to demonstrate noninferiority to                  12 standard of care.</p> <p>13           And I'm just going to take here as an                  14 example the most recent development program                  15 implemented for invasive candidiasis which is still                  16 ongoing. They estimated a sample size needed for the                  17 Phase 3 about 220 patients, which is lower to what is                  18 typically needed in a Phase 3 program and with the                  19 need to demonstrate noninferiority of the standard of                  20 care and they estimated it will take about two years                  21 to enroll these number of subject in 64 hospitals                  22 worldwide.</p>

<p style="text-align: right;">Page 210</p> <p>1 Any one of us involved in conducting  2 large multicenter clinical trials would recognize this  3 is a very substantial task. So if it takes about two  4 years to enroll 220 subject in 64 centers, for a  5 condition that has a U.S. incidence of about 25 cases  6 a year in the United States and the overall  7 development program here will take about four to five  8 years with a cost easily north of \$60 million.  9 This particular development path is  10 difficult to be fully applied for very rare organisms  11 like Candida auris.  12 Development. Some of the enrollment  13 challenges for development, specifically challenges  14 for Candida auris is that enrolling patients with  15 Candida auris in clinical trials is difficult. There  16 are a limited number of patients. We're talking about  17 here an incidence of about 500 cases a year in the  18 U.S., and many are heavily treated before they even  19 are identified for potential participation in a  20 clinical trial.  21 They have a high mortality. They are  22 difficult to enroll. You need to identify multiple</p>	<p style="text-align: right;">Page 212</p> <p>1 drug against these multidrug resistant pathogens, and  2 this is the opportunity to discuss what is the weight  3 of the contribution that each of these elements can  4 provide to the overall conclusion, considering that a  5 large clinical dataset may not be feasible, at least  6 not in a reasonable timeframe. Here, new antifungal  7 agents that -- sorry. The new antifungal agents will  8 typically have available a robust set of clinical data  9 showing interactivity and efficacy in animal models,  10 and also typically we will have PK/PD analysis showing  11 or justifying the selected doses.  12 So there is here the opportunity to  13 discuss how much weight these particular clinical  14 assessments can contribute to the evidence of  15 effectiveness, and this is something that altogether  16 community, scientific community, regulators, and  17 industry should be involved with. We should also have  18 sufficient -- obviously, sufficient safety data for  19 intended doses and duration.  20 However, the most challenging part is  21 the demonstration of efficacy in the clinical setting  22 and following only traditional approaches, may limit</p>
<p style="text-align: right;">Page 211</p> <p>1 centers in multiple countries in order to really try  2 to get a sufficient number of cases. In this  3 particular case, makes those trials very expensive and  4 long, and then you need to chase the hotspots because  5 those hospitals that were initially identified as  6 potentially good sources for these type of patients  7 into your clinical trials few months on the road, they  8 may not be as good alternative as they look at the  9 beginning.  10 They -- you need to be really chasing  11 countries. You need to be chasing hospitals that  12 really may have that incidence. Clinical evidence  13 from a statistically powered randomized controlled  14 trial in patients with Candida auris will be,  15 obviously, unlikely feasible. So alternative  16 approaches are needed to generate the substantial  17 evidence of effectiveness, and a well-balanced  18 definition of substantial, in light of the unmet  19 medical need, will facilitate and accelerate the  20 availability of new therapies.  21 There are multiple elements that  22 contribute to the evaluation of the effectiveness of a</p>	<p style="text-align: right;">Page 213</p> <p>1 the ability of new therapeutics in the future, so we  2 should be open to discuss how to implement alternative  3 and more feasible approaches that will still provide  4 substantial evidence of effectiveness we need with the  5 acceptance of a greater uncertainty based on the risk-  6 benefit assessment.  7 Here's some of the options. There's  8 really four opening for discussion. Probably the most  9 common option is a randomized controlled trial in all  10 invasive candidiasis, all the species, that is  11 enriched with candidiasis patients. I think that  12 nobody would argue that this is invisible alternative  13 or this is an alternative that has been following the  14 path; however, it does take about four to five years  15 to get new products through these paths and certainly  16 it's multiple millions of dollars.  17 There should be other alternatives.  18 For instance, a randomized controlled trial in other  19 candida or other fungal diseases plus or supplemented  20 with a small study in Candida auris patients. This  21 could be there are no randomized comparables to system  22 that controls external controls or it could be, as it</p>

<p style="text-align: right;">Page 214</p> <p>1 has been suggested in the past, a randomized                  2 controlled trial but it will not be necessarily                  3 powered, so discussion of what is the pros and cons of                  4 these alternatives, I think, is warranted.                  5           There are other alternatives, multiple                  6 studies, a smaller in different fungal diseases that                  7 are particular relevant to the condition that we're                  8 talking here. It could be esophageal candidiasis.                  9 Could be other type of candida infection that really                  10 together all put the weight of evidence that this                  11 particular product does give activity or the product                  12 that is being in question has activity against candida                  13 infections.                  14           So the development opportunities. We                  15 need to identify efficient development paths for new                  16 therapeutics for these challenging infection that are                  17 well defined, streamlined, feasible within a                  18 reasonable timeframe, and obviously endorsed by                  19 regulatory authorities, scientific community, and                  20 executable within the industry framework.                  21           They should be supported by funding and                  22 funding in this case needs to come from different</p>	<p style="text-align: right;">Page 216</p> <p>1 nonclinical models to really be able to better predict                  2 or at least better estimate what is the treatment                  3 effect of a particular drug. I think that we should                  4 take advantage of those models as well to really help                  5 us moving these development programs forward.                  6           So with this, that is -- I end my                  7 presentation here, really trying to highlight some of                  8 the areas that we consider. We can all work together                  9 to really have better definitions of substantial                  10 evidence of effectiveness, particularly for these                  11 particular condition that will allow us to find a                  12 clear and physical development path for new                  13 therapeutics. Thank you.                  14           DR. LUIS OSTROSKY-ZEICHNER: Thank you,                  15 Dr. Angulo. And to finish this rapid-fire session,                  16 it's my pleasure to introduce Dr. Taylor Sandison                  17 who's the Chief Medical Officer at Cidara.                  18           DR. TAYLOR SANDISON: Thank you, Luis                  19 and appreciate the opportunity to talk, so thanks to                  20 the organizers. I'd just start off by saying that                  21 David and Michael and I talked and kind of organized                  22 our talks so we didn't overlap, so there are some</p>
<p style="text-align: right;">Page 215</p> <p>1 sources. We know that most of us in the industry, we                  2 rely upon not necessarily from grants. We rely upon                  3 really investors from investment community and they                  4 need to really see an opportunity for return of                  5 investment for these type of conditions; otherwise,                  6 the funding would not come.                  7           We also are very appreciative of                  8 funding from other -- several institutions, et cetera;                  9 however, it needs to be a roundup approach that really                  10 enable these particular programs to keep moving                  11 forward.                  12           Alternative development approaches                  13 seems justified bases on the unmet need, the limited                  14 number of cases, the high mortality, the high rate of                  15 multidrug resistance that we're seeing with these                  16 particular pathogen, the transmission potential and                  17 the potential public health impact. We need to                  18 understand how to really address the fact of permanent                  19 colonization that we saw in some of Dr. Chiller's                  20 slides and how this impact public health and how we                  21 can impact that as well.                  22           And we all have advanced the</p>	<p style="text-align: right;">Page 217</p> <p>1 things -- what they have said already, I fully agree                  2 with and I think my job here is just to real -- paint                  3 a little bit of the lessons learned from our                  4 individual trials and then maybe summarize some of the                  5 key points of our consolidated talks.                  6           So just to kind of paint the picture                  7 where I'm coming from, this is rezafungin. It's a                  8 novel echinocandin that's once weekly dosing with                  9 prolonged PK and the studies that we've conducted,                  10 we've done a number of Phase 1s, but I think the ones                  11 we'll be most interested in will be, we have a                  12 completed Phase 2 study which had -- numbered 207                  13 patients which yielded 183 MITT patients.                  14           And then we have an ongoing Phase 3                  15 trial similar to that Phase 2 in the treatment of                  16 candidemia and invasive candidiasis, and an ongoing                  17 Phase 3 trial in prophylaxis of invasive fungal                  18 disease in the allogeneic blood and marrow transplant                  19 population. And then the proposed indications would                  20 be for the treatment of candidemia and invasive                  21 candidiasis as well as prophylaxis.                  22           So our goals are aligned in that we're</p>

<p style="text-align: right;">Page 218</p> <p>1 trying to enable approval of safe and effective  2 antifungal drugs to improve the options, to improve  3 patient outcomes, but we have a number of challenges  4 and one is the changing environment. I think we've  5 seen over the past few years how Candida auris has  6 changed a little bit how we're looking at fungi and  7 alerted us to the needs for new antifungal options.  8       And of course, even the epidemic with  9 COVID most recently kind of highlights the unexpected  10 nature of these future challenges, and then just the  11 need to expand our antifungal armamentarium so that  12 either new mechanisms of actions or improvements in  13 toxicity or drug-drug interactions, all these things  14 are available for doctors to enable them to improve  15 outcomes for these patients.  16       We've already heard from Dr. Kovanda  17 and Pappas and Hodges and Angulo about the enrollment  18 challenges, so I'm not going to dwell on that except  19 to say that we did experience that in our Phase 2  20 STRIVE study as well with the enrollment below what we  21 expected it to be from past pivotal studies and I  22 think just to give you a frame for that Phase 2, it</p>	<p style="text-align: right;">Page 220</p> <p>1 due to 96 hours from randomization for the candida  2 cultures and greater than 48 hours of prior antifungal  3 therapy. As it's already well documented and  4 physicians on the call realize, really, you got to  5 control the source and early, directed, appropriate  6 antifungal therapy is the way you decrease mortality.  7       So most sites don't wait to find out  8 and so, you know, with these slow-growing cultures,  9 often greater than two days, antifungal therapy  10 already on board. Another high impact reason for  11 exclusion was the lack of abnormal vital signs, so  12 fever, hypothermia, hypotension, tachycardia,  13 tachypnea, things that are attributable to invasive  14 candidiasis. This was determined to be imperative by  15 the FDA as it's felt to reflect how a patient feels,  16 functions, and survives.  17       However, I think many of the doctors  18 also understand that means immunosuppressed  19 populations, who are the ones who are at risk of  20 invasive candidiasis, often don't develop the same  21 types of signs of infection that other patients would  22 ordinarily or they would ordinarily, if they weren't</p>
<p style="text-align: right;">Page 219</p> <p>1 took us for the 183 mITT subjects, we had about 60  2 sites and it took us almost three years.  3       So that kind of gives you an idea of  4 how difficult it can be, and those challenges are  5 multiplied even before COVID came along. There's  6 always issues with decreasing amounts of candida from  7 sites, and then COVID, of course, has increased the  8 complexity and challenges: fewer sites available for  9 clinical research, increased risk of missed visits due  10 to COVID, threatening the study visits for these  11 immunosuppressed patients that are really at risk of  12 getting COVID. We can see why they wouldn't want to  13 come back to the clinic or hospital.  14       So I'm just going to touch on that  15 briefly, but the true magnitude and duration of this  16 impact is still really to be determined, whether it  17 needs to be addressed in terms of our experience for  18 antifungal drug development.  19       The other thing I wanted to discuss  20 briefly was exclusion criteria. So the largest  21 reasons in our STRIVE study in the Phase 2 study for  22 failures were prescreen failures, I should say, were</p>	<p style="text-align: right;">Page 221</p> <p>1 in the situation with either some sort of  2 immunosuppressive disease or drug.  3       So where does this lead us? I think we  4 talked about some of the development options in both  5 Michael's slide and David's slides and -- but I think  6 there are still a number of unanswered questions. I  7 think Dr. Kovanda brought up a good one, which is,  8 have we reached the point where large scale Phase 3  9 studies for antifungal agents are no longer feasible?  10       We have a lot of things to consider.  11 We brought up the fact that the negative MPD  12 associated with these new antifungal agents, in part  13 because of these large randomized global trials leads  14 to decreased interest from big pharma and from  15 investors and things like this.  16       There's also the added issue of you get  17 studies that go on for three, four, five or more  18 years, you start risking confounding and kind of  19 undermining your trial with the risk of that  20 confounding due to improvements in diagnostics and  21 treatments and standard of care between the beginning  22 of a trial and the end of trial, so that supportive</p>



<p style="text-align: right;">Page 222</p> <p>1 therapy may lead to differences in outcomes.</p> <p>2           More patients may be surviving later in</p> <p>3 the trial as compared to the beginning, and if you</p> <p>4 have any kind of imbalance in the randomization from</p> <p>5 one to the next, that could potentially confound your</p> <p>6 study as well. So there are a number of things to</p> <p>7 consider about this, in addition to whether it's</p> <p>8 feasible from a business standpoint, but also from a</p> <p>9 scientific standpoint, does it really make sense.</p> <p>10           And then under substantial evidence,</p> <p>11 David talked about this a little bit, but given the</p> <p>12 recent advances in PK/PD target attainment, can we put</p> <p>13 more emphasis on that in lieu of a Phase 3 clinical</p> <p>14 trial powered for inferential statistics, depending on</p> <p>15 the unmet needs and sort of other categories and</p> <p>16 things that are part of the assessment of what's</p> <p>17 required?</p> <p>18           I think in the past, Dr. Nambiar has</p> <p>19 brought up a number of places where PK/PD looked good</p> <p>20 and then the clinical trial, they didn't look so good.</p> <p>21 So I think you can't just get rid of the clinical</p> <p>22 trials completely, but maybe some balance between</p>	<p style="text-align: right;">Page 224</p> <p>1 experience with these candida drugs? It may take, for</p> <p>2 instance, if you take out some of these, like the 48</p> <p>3 hours or the 96-hour limits for empiric therapy for</p> <p>4 drug culture -- I'm sorry, candida culture, could you</p> <p>5 include more patients, then you get more experience</p> <p>6 and see how the drug works and, of course, there is</p> <p>7 some concern, obviously, that they get too much of a</p> <p>8 drug or the candida's been there for too long and</p> <p>9 maybe it's more of a subacute infection, but there are</p> <p>10 some things that can be done in terms of</p> <p>11 stratification and analyses that could also help</p> <p>12 assess that in a analysis way, rather than just taking</p> <p>13 them out from the beginning.</p> <p>14           And then the other option I discussed</p> <p>15 before is also this idea of including abnormal signs</p> <p>16 of infection, where -- in a patient where if you have</p> <p>17 candida growing from a blood culture or another</p> <p>18 normally sterile site, there's not really a way to say</p> <p>19 that they're not truly infected and the fact that they</p> <p>20 don't mount a systemic response with abnormal signs</p> <p>21 could be because of the steroids they're on or because</p> <p>22 of their underlying leukemia or something along these</p>
<p style="text-align: right;">Page 223</p> <p>1 those needs to be assessed and certainly there's been</p> <p>2 a lot of progress made over the past 10 years in that</p> <p>3 kind of targeted payment assessment.</p> <p>4           And then given the described</p> <p>5 challenges, how can we define -- I mean, this seems a</p> <p>6 bit like a moving target. We don't really know what</p> <p>7 to aim for in terms of what's substantial evidence of</p> <p>8 effectiveness. And is that even considered for, like,</p> <p>9 the full kind of candidemia, invasive candidiasis stud</p> <p>10 or whether it's a single species development program,</p> <p>11 like for Candida auris alone or even for a salvage</p> <p>12 therapy study where considerations have to be made for</p> <p>13 -- not just for patients that fail but why did they</p> <p>14 fail.</p> <p>15           Did they fail for -- because of poor</p> <p>16 source control or is it really resistance and things</p> <p>17 like this, so trying to get definitions and some kind</p> <p>18 of pathway assigned would be extremely helpful in</p> <p>19 helping to allay some of the concerns and challenges.</p> <p>20           And then finally, should we consider</p> <p>21 some leniency in some of the key exclusion criteria,</p> <p>22 if only to prevent or in -- sorry, increase patient</p>	<p style="text-align: right;">Page 225</p> <p>1 lines that really limits our ability to test these</p> <p>2 drugs in the patients that really need them.</p> <p>3           So those are just kind a brief summary</p> <p>4 and a few ideas of what we've seen at Cidara and what</p> <p>5 we've discussed amongst ourselves from the industry</p> <p>6 perspective, and so I appreciate the attention and the</p> <p>7 invitation, and I'll pass it back to the moderators.</p> <p>8 Thank you.</p> <p>9           DR. HELEN BOUCHER: Thank you so much.</p> <p>10 Those were great talks and lots of food for thought</p> <p>11 for our discussion. For the last speaker of this</p> <p>12 session, I'm privileged to introduce Dr. Luis</p> <p>13 Ostrosky-Zeichner from the University of Texas where</p> <p>14 he is the Vice Chair of Medicine for Healthcare</p> <p>15 Quality, the Director of the Laboratory for Mycology</p> <p>16 Research, and professor in the Division of Infectious</p> <p>17 Diseases. Welcome, Luis.</p> <p>18           DR. LUIS OSTROSKY-ZEICHNER: Thank you</p> <p>19 very much, and for the next few minutes, we're going</p> <p>20 to be discussing some clinical trial design</p> <p>21 considerations for Candida auris specifically. These</p> <p>22 are my disclosures: I've been participating with most</p>

<p style="text-align: right;">Page 226</p> <p>1 of the sponsors in this seminar and I've been involved  2 in antifungal development for the past 20 years.  3       So we are a long way from amphotericin  4 B research. The package insert for amphotericin B has  5 six pages compared to the multiple, multiple pages  6 we're seeing in package inserts right now, and it's  7 very interesting to consider that this is the  8 antifungal that has the widest and broadest indication  9 for most of the mycosis we're treating currently and  10 most of the data are based on in vitro susceptibility  11 testing or anecdotal cases.  12       Since then, we've been steadily  13 developing antifungals; 1950s was primarily the  14 polyenes. We have griseofulvin and 5-FC in the 1960s  15 and '70s. The '80s was the era of the first-  16 generation azoles. We moved on to second-generation  17 azoles and then we go in the lipid formulations, the  18 second-generation triazoles, and the echinocandins in  19 the 2000s. And we're in 2020 and we haven't really  20 released a new antifungal since then.  21       So how do we use antifungals in candida  22 at this point? This is the new sort of continuum of</p>	<p style="text-align: right;">Page 228</p> <p>1 invasive disease, and immunocompromised patients.  2 We've treated patients for two weeks, usually, from  3 the first nadir culture and we always work on an  4 intent to treat population that receive at least one  5 dose of the antifungal and most of that comes our  6 clinical microbiological success at the end of  7 therapy.  8       The problem is that the system no  9 longer works in 2020 and definitely doesn't work for  10 Candida auris for the reasons I'm going to show you  11 coming up ahead. So this is the anatomy of a candida  12 trial and everything starts with screening where you  13 have a patient that needs to have signs and symptoms,  14 may or may not have radiological findings.  15       This is less relevant for candida than  16 (inaudible) infections, and you want to have some  17 evidence of infection. Then there's a couple of days  18 that you get to enroll the patient. At that point,  19 you need to confirm that your microbiology was  20 positive back then is still positive, and then we go  21 into therapy where we monitor signs and symptoms,  22 again, radiology to a certain extent for candida, more</p>
<p style="text-align: right;">Page 227</p> <p>1 treatment that we've created and for the most part, we  2 are working on the right hand of the slide, which is  3 full-blown disease and sequelae, but where we should  4 be working, because the evidence has shown time after  5 time that by the time we're working with positive  6 culture or histology or invasion, we're probably a  7 little bit too late.  8       We should be working on prophylaxis,  9 preemptive therapy that is based on markers and  10 empirical therapy which is based on high-risk profiles  11 in a setting where we know that our microbiology is  12 less than perfect.  13       We actually have a pretty good sort of  14 pipeline of candida clinical trials, starting with the  15 now classic Rex in 1994, fluconazole. We pretty much  16 use the same mold for any clinical trial trying to  17 bring a candida drug to market, which is -- so you can  18 see here in the slide which is a summary of the AMBIS  19 paper, Meta-Analysis of these Clinical Trials. In  20 general terms, we deal with candidemia, plus/minus  21 signs and symptoms.  22       We have limited representation of</p>	<p style="text-align: right;">Page 229</p> <p>1 for molds. We continue to get microbiology at the end  2 of therapy, signs and symptoms, radiology if  3 available.  4       We look at microbiology outcomes and we  5 look at crude mortality, for the most part. And then  6 there's usually a follow-up visit where, again, we  7 look at signs and symptoms, microbiology, radiology,  8 mortality, and this is where we assess for relapses  9 that has always been a concern for any candida  10 therapy.  11       Common pitfalls in the scheme. Well,  12 the first one has always been the disease definitions.  13 And although we just released the revised update to  14 the consensus definitions late last year, we still  15 have a problem with candida definitions because for  16 the most part they focus on a positive culture or  17 possible histology and we sort of still relegated the  18 role of beta-glucan or another biomarker which is T2  19 Candida as evidence for not proven but for probable  20 disease.  21       Another big problem with the  22 definitions is that we actually could not reach</p>

<p style="text-align: right;">Page 230</p> <p>1 consensus for ICU settings regarding risk factors and  2 definitions, so we elected to take out the whole ICU  3 theater so that we could get ahead and publish the  4 definitions and there's a group still working on ICU  5 definitions. So a big problem, specifically, when you  6 deal with candida and Candida auris.</p> <p>7       The second pitfall we have is that we  8 are dealing with a framework for assessing outcome  9 adjudication that was published 12 years ago. We  10 probably -- we started to work on it two years before,  11 so we're working with definitions that are 14 years  12 old and as I'm going to show you in the next slide, we  13 have learned a lot over those 14 years that have not -  14 - all of the elements that we chose for the framework  15 are applicable or work anymore for fungal infections.  16 So again, this is, mea culpa, we need to as a group  17 really sit down and re-look at these outcome  18 definitions and update them, bring them to 2020.</p> <p>19       Among the pitfalls within the  20 definitions, we have that we require signs and  21 symptoms. And as all of you know that work in  22 mycology clinical trials, signs and symptoms are not</p>	<p style="text-align: right;">Page 232</p> <p>1 may not correlate with overall clinical improvement  2 with radiology or with microbiology, so when we're  3 really heavily based on signs and symptoms, we're  4 already working behind the eight ball.</p> <p>5       Talking about the eight ball,  6 microbiology. So sort of the natural history of  7 growing, identifying, and getting susceptibilities of  8 candida and the contemporary microbiology lab usually  9 takes at minimum three days and at maximum or under  10 ideal conditions five to seven days. So if we're  11 relying on a process that is going to be taking  12 anywhere from three to 96 hours, we're immediately  13 behind the eight ball when we're trying to enroll  14 patients into clinical trials within a very limited  15 time window. So again, working with contemporary  16 microbiology, we're automatically narrowing the  17 enrollment window to very critical times.</p> <p>18       So once we have a culture that is  19 growing candida that has been identified as Candida  20 auris, we probably have eight hours to enroll the  21 patient in the clinical trial, given the current  22 constraints of timing that we have been working with.</p>
<p style="text-align: right;">Page 231</p> <p>1 always present, even in the setting of proven disease.  2 So we used to think that candida could be a  3 contaminant. We used to think that molds could just  4 be present in bronchiolar lavages, but not anymore.</p> <p>5       At this point in time, we do understand  6 that some of these organisms may be there and may not  7 be giving signs and symptoms acutely. And we still  8 are requiring signs and symptoms as criteria to end  9 treatment to clinical trials, mainly because that's  10 one of the things we follow.</p> <p>11       However, signs and symptoms, when  12 present, can be multifactorial given the complexity of  13 the patients we're working with in fungal infection  14 and the fever that the patient is having could be  15 related to the patient's underlying disease, other  16 interventions that we're doing to them like several  17 chemotherapeutic agents, and these patients don't  18 exist in a bubble. They can have other infections so  19 this could be the trichomonas infection and not  20 candida that's continuing to give the patient fever.</p> <p>21       And finally, we've learned to  22 understand that again the signs and symptoms may or</p>	<p style="text-align: right;">Page 233</p> <p>1 Another problem is that blood cultures have very poor  2 sensitivity where they do not have specificity and  3 molecular ID is not mainstream yet throughout the  4 world.</p> <p>5       It is relatively well represented here  6 in the United States, but in many of the countries  7 where we need to be working to enroll Candida auris  8 patients or patients with resistant candida species,  9 molecular microbiology is not mainstream by any means,  10 so again, a very big limitation here.</p> <p>11       Another issue with assessing  12 microbiology is that it's not always feasible to  13 resample invasive sites. So for blood cultures, it's  14 pretty straightforward. We can do as many blood  15 cultures as we want, but for that hepatic abscess,  16 it's a big production to go back in and get a  17 resampling to declare the patient has been a  18 microbiological success.</p> <p>19       Biomarkers and serologies. I think we  20 can all agree that beta-glucan, T2, and other  21 biomarkers have been clearly established as an  22 enrollment criteria for clinical trials. They give us</p>

<p style="text-align: right;">Page 234</p> <p>1 sort of evidence that the patient has a fungal  2 infection. Where we have struggled is to really nail  3 them down as surrogate markers for success of therapy.  4       So despite some publications out there  5 specifically about beta-glucan and to a more limited  6 extent to T2, we do not have the level as yet, but we  7 need to accept them as surrogate markers for outcomes.  8 So this is another big problem with microbiology.  9       Radiology. Radiology has a very, very  10 high sensitivity, but probably the lowest specificity  11 of any diagnostic modality we have. So the problem we  12 have, again, primarily with mold infections but to a  13 certain extent with candida is that radiological  14 findings don't necessarily correlate with clinical  15 improvement.  16       So I'm showing you here a brain  17 abscess. I'm showing you hepatosplenic candidiasis  18 and this -- the brain abscess, of course, is something  19 that you expect to resolve on imaging when the patient  20 is being treated and has a success, but hepatosplenic  21 candidiasis is a much more complicated disease to be  22 evaluating by radiology as changes may last for months</p>	<p style="text-align: right;">Page 236</p> <p>1 the reason that people are dying.  2       We don't really know most of the time  3 if people are dying because of candida or with candida  4 at any given time. So I was always taught that you  5 shouldn't bring up problems without bringing solutions  6 and these are my proposed solutions to these problems  7 that I've just mentioned.  8       I think we need disease definitions  9 that are very nimble in a dynamic process. We cannot  10 be taking 10 years to update the ER -- the CMS  11 definitions anymore. We need to really be addressing  12 them in a living website with live information, much  13 like we're trying to do with some of the other  14 guidelines that we're working on and sort of bringing  15 this to 2020 where not everything has to be published  16 in a print journal.  17       We need a new panel by experts for  18 really talking about what are the new response outcome  19 definition looking like. So I think we need to  20 deemphasize signs and symptoms. We need to really put  21 some thought on using biomarkers as surrogate  22 endpoints. I think, again, there's some evidence that</p>
<p style="text-align: right;">Page 235</p> <p>1 and months and months, when a patient is probably  2 completely cured.  3       And then, we have to consider a  4 patient's safety and think about the ethics of  5 repeated exposures to radiation if we want to use this  6 end point.  7       Finally, another end point that has  8 been very, very controversial is mortality. This is  9 the classic paper by Dick Wenzel that explored that  10 attributable mortality of candidemia that really gives  11 sort of the piece of information we needed to know  12 that candida was not just a colonizing agent and that  13 it had an impact on mortality and on eventual state,  14 but again since this paper, which is a couple decades  15 old we really haven't made much of an effort in  16 studying attributable mortality for candida and  17 therefore we're stuck with crude mortality, which as  18 all of you know, the population that is likely to  19 experience candida is a population that is likely to  20 die from many, many, many other things, so we're  21 stuck, again, with a very imperfect measure where  22 candida is probably contributing only a percentage of</p>	<p style="text-align: right;">Page 237</p> <p>1 we can use them to a certain extent. We need to  2 definitely deemphasize radiology in outcomes.  3       I can't tell you how frustrating it is,  4 not for candida, but in some of the VRCs that I've  5 participated in to be seeing patients with  6 mucormycosis or other failed mycosins that are alive  7 and well at two, three years out but they still have  8 some imaging changes and we're calling them stable or  9 failures because of imaging, so we really need to  10 address radiology in a completely different way.  11       Again, I think we need to deemphasize  12 crude mortality and work towards attributable  13 mortality, and one thing that I think we need to do  14 away with is composite endpoint. We haven't had much  15 chance to talk about this here, but we had a few  16 clinical trials that were amazing, sort of  17 breakthrough trials, but by using composite endpoints,  18 we always had kind of a scratch your head reaction  19 after the clinical trial results came out.  20       So we need clear, single end points and  21 try to avoid composite endpoints going forward. I  22 think immediately, what I think we need to do is</p>

<p style="text-align: right;">Page 238</p> <p>1 expand enrollment and prior antifungal windows,  2 recognizing the way microbiology works currently and  3 the forces out there that are sort of pushing  4 empirical therapy as fast as possible because it is  5 associated with increased mortality and I feel this is  6 what LPAD was created for.</p> <p>7           This is exactly the setting where we  8 need to be working on an LPAD framework where I think  9 we need small open label trials in high incidence  10 areas both in the United States and EX-U.S. primarily,  11 where we can collect a key series of 20 to 30 very,  12 very well studied cases and compare them to  13 contemporary controls, so I know the Fungiscope  14 database was kind of the big example of semi-  15 contemporary controls, but I think we can be  16 collecting data in a contemporary fashion along with  17 the studies so that we have sort of the data we need  18 to have a control that is relevant to the disease  19 state that we're studying.</p> <p>20           Again, I think this needs to be paired  21 up with very strong preclinical and safety data and  22 this is a path forward, in my opinion, for Candida</p>	<p style="text-align: right;">Page 240</p> <p>1 years where we have whole genome sequencing in  2 clinical laboratories, at least in the United States  3 and other developing -- developed countries, and we  4 are going to be working with point of care biomarkers,  5 so again, all this lateral flow work is really going  6 to bring enrollment and outcome monitoring to the  7 bedside as opposed to working with reference  8 laboratories, which is what we have to work with right  9 now.</p> <p>10           Again, I think we need to be doing away  11 with traditional trials and moving into strategy  12 trials looking at prophylaxis versus preemptive,  13 preemptive versus empirical, empirical versus full,  14 and all the iterations that you see there and that is  15 really going to move the needle as opposed to just  16 another sort of licensing clinical trial for an  17 antifungal.</p> <p>18           And finally, I think we are already in  19 the era of personalized medicine and this is exactly  20 where we need to be working on, which are uncommon  21 pathogens, resistant pathogens, taking advantage of  22 the tools that are coming up right now, really looking</p>
<p style="text-align: right;">Page 239</p> <p>1 auris. Again, I just want to emphasize that the space  2 we should be working on now is really the left hand  3 side of the slide, where we need to start thinking not  4 only of the traditional clinical trials that look for  5 a patient with a positive culture and see what happens  6 afterwards, but we need to keep pushing the envelope  7 into prophylaxis, preemptive, and empirical therapy,  8 even for Candida auris where this is going to be a  9 little more difficult.</p> <p>10           Again, at this point, this kind of  11 information has permeated throughout the United States  12 and worldwide, where we understand that waiting for  13 positive culture is going to double or triple your  14 mortality off the bat and most hospitals in the United  15 States are really working on an empirical framework  16 where we're starting antifungals empirically the day  17 we're culturing the patient, and this is where we need  18 to be going.</p> <p>19           So next generation clinical trials,  20 this is my forward looking statement here, have to be  21 really grounded upon molecular microbiology and I  22 truly believe that it's just a matter of five to 10</p>	<p style="text-align: right;">Page 241</p> <p>1 at pharmacogenomics and again, a little bit of forward  2 thinking, genetic risk will really be the key to  3 enrolling some of these patients into the more high-  4 risk and strategy trials.</p> <p>5           This is my last slide. I want to  6 really invite you to read this paper that came out of  7 the MSG annual meeting. This is our blueprint for  8 research that was drafted a couple years ago,  9 published this year. We are going to be postponing  10 the next MSG meeting due to our friend COVID until  11 next year, but this is a really good thing to take  12 home and read and look at where the priorities for  13 medical mycology are in the next couple years.</p> <p>14           Again, I want to thank you for your  15 attention and I'm going to turn it back to Helen.</p> <p>16           DR. HELEN BOUCHER: Thanks very much,  17 Luis. I think we are now scheduled for a break -- for  18 a 10-minute break. So guess we should plan to be back  19 at around 3:15 for our panel discussion. Thanks very  20 much.</p> <p>21           (Break)</p> <p>22           DR. HELEN BOUCHER: Hi, it's Helen</p>

<p style="text-align: right;">Page 242</p> <p>1 Boucher. We're ready to start the panel discussion.  2 Along with Luis Ostrosky-Zeichner, I'm here to guide  3 us through some discussion of these six questions over  4 the next about hour-and-a-half and the way we're going  5 to manage this is we'll go through each question and  6 we'll direct it to one person to start and then invite  7 everyone to join in and just ask you to use the "raise  8 your hand" feature on the software and we'll just go  9 through as many as we can in the order that we  10 received the questions.  11         So the first question is asking us to  12 discuss important factors to consider regarding trial  13 populations like host factors, length and type of  14 immunosuppression and predisposing conditions  15 including COVID, and to address the question about  16 heterogeneity in the trial population, whether that's  17 a good thing or whether it raises concerns and how  18 that should be handled.  19         And so we thought we might ask Dr.  20 Thompson if he wants to kick this one off. G.R.,  21 would you like to chime in?  22         DR. GEORGE THOMPSON: Sorry?</p>	<p style="text-align: right;">Page 244</p> <p>1 look at the non-neutropenic patients, there's a very  2 big difference in outcome.  3         But because the numbers enrolled were  4 small, it didn't quite reach statistical significance  5 but it was about a 30 percent difference in outcome,  6 which wasn't something that came out of the discussion  7 in the paper, probably because of the numbers not  8 quite reaching statistical significance. My theory is  9 the prophylaxis being sort of almost universal in  10 neutropenia, we -- if we want to do invasive  11 aspergillosis studies, we have to move away from that  12 population, to a great extent, and that means thinking  13 about patients who have COPD, influenza, COVID-19,  14 other types of -- lung transplants, other non-  15 neutropenic type of patient groups and that, I think,  16 is going to require working across the definitions of  17 the MSG or RTC because some of them we haven't got  18 definitions for.  19         They didn't work very well and it's  20 going to require a different way of thinking about  21 outcome because the scans in many of these patients  22 are abnormal with their underlying disease, let alone</p>
<p style="text-align: right;">Page 243</p> <p>1         DR. HELEN BOUCHER: G.R., would you  2 like to chime in on the first question?  3         DR. GEORGE THOMPSON: My connection's  4 not very good. Can you --  5         DR. HELEN BOUCHER: Okay.  6         DR. GEORGE THOMPSON: -- repeat it?  7         DR. HELEN BOUCHER: How about Dr.  8 Pappas?  9         DR. PETER PAPPAS: G.R., we can see  10 you. Want to give it a shot?  11         DR. DAVID DENNING: This is David  12 Denning. I'm happy to make one comment on that, if  13 you wish.  14         DR. HELEN BOUCHER: Thanks, David. Go  15 ahead. Can hear you great.  16         DR. DAVID DENNING: Well, when you look  17 at the combination trial with invasive aspergillosis  18 with voriconazole and meningitofungin, if you look at  19 the outcomes in neutropenic patients, there was really  20 no difference at all between the patients at all in  21 outcome, and that includes this stem cell transplants,  22 although there weren't very many of those, but if you</p>	<p style="text-align: right;">Page 245</p> <p>1 their aspergillosis. So I think there's -- I think  2 the answer to your question, yes, there's a lot of  3 difference in the aspergillosis area.  4         DR. HELEN BOUCHER: Great, thanks for  5 that. Looks like Kieran Marr has a comment.  6         DR. KIEREN MARR: Hi, there. Hi, I  7 think I can be heard now, I hope.  8         DR. HELEN BOUCHER: Hi, Kieren. Go  9 ahead.  10         DR. KIEREN MARR: Fabulous comment by  11 David about the combination therapy study and the  12 heterogeneity in outcomes witnessed within that study.  13 I'll add that I think that the issue is not that  14 there's no heterogeneity with neutropenia. It's that  15 if you looked very closely at the underlying disease,  16 it's apparent that neutropenia itself is, as John Rex  17 calls too blunt an instrument.  18         It's a -- it encompasses people that  19 have outcomes that are very heterogeneous within and  20 if we looked -- when we looked, actually, at the  21 underlying diseases of the population, the populations  22 that did worse within that are people that had acute</p>

<p style="text-align: right;">Page 246</p> <p>1 leukemia that was relapsed. And this, to me, outlines  2 progressive learning that we continue to experience in  3 that there are ways to understand the outcomes within  4 categories. Neutropenia and non-neutropenia itself  5 are not adequate to actually -- to encompass,  6 actually, the predicted outcomes, especially if you're  7 looking at survival.  8         So I think it's really important to  9 discuss heterogeneity. I agree with David completely  10 and that we need to go deep within the underlying  11 disease and other predictors of outcomes within those.  12         DR. HELEN BOUCHER: Great, thanks very  13 much, Kieren, for that. Dr. Pappas.  14         DR. PETER PAPPAS: Hey, how are you  15 doing?  16         DR. HELEN BOUCHER: Great. Nice to  17 hear your voice.  18         DR. PETER PAPPAS: Good to hear you as  19 well. Something that comes to mind that I guess could  20 be obvious but it needs to be stated, and I think that  21 the -- one of the areas where heterogeneity really  22 does play a role in general, I believe, is in these</p>	<p style="text-align: right;">Page 248</p> <p>1         DR. MICHAEL HODGES: Thank you. Just a  2 couple of comments on the underlying diseases. I  3 think Pete, in one of your papers with the late  4 Claudio Viscoli, Jack 2009, where you looked to  5 caspofungin for the treatment of invasive  6 aspergillosis, you found that Karnofsky score and  7 whether the patient was in remission for leukemia had  8 a big impact on the outcome.  9         I might also throw in length of  10 neutropenia or neutropenia recovered or ICU  11 ventilation as well, high grade graft versus host,  12 mismatch unrelated transplant, and even a high serum  13 galactomannan greater than 1.5 may all be big  14 prognostic factors. That's one point.  15         I want to make another point about the  16 randomized controlled trials, the three randomized  17 controlled trials that have been conducted for  18 invasive aspergillosis. They tended to be in the  19 hem/onc population, for example AML, neutropenic GM  20 positive.  21         And what we're finding is the patients  22 who are on the ICU who don't have hematological</p>
<p style="text-align: right;">Page 247</p> <p>1 cryptostudies and I guess the day of throwing all  2 these patients together, HIV and non-HIV, really, I  3 think, is over.  4         And within the HIV population itself, I  5 mean, there really kind of four populations -- I mean,  6 within the cryptopopulation itself, there are really  7 four populations. There's the transplant; the HIV;  8 the non-HIV, non-transplant but still compromised  9 patients, patients with renal failure, hepatic  10 failure, steroids, et cetera; and then the normal  11 host.  12         And those are so different in terms of  13 their responses and so forth that a trial that would  14 throw them all together or just divide them into HIV  15 and non-HIV, really I'm not sure that would teach us a  16 lot. And I don't know how many ways you can stratify  17 patients of that nature, so it seems to me that that's  18 a group where same disease but very different  19 populations lead -- could lead to very, very different  20 outcomes.  21         DR. HELEN BOUCHER: Great. Thanks very  22 much. Mike Hodges.</p>	<p style="text-align: right;">Page 249</p> <p>1 oncology malignancies but have viral pneumonia either  2 the kappa or the influenza, they have a far greater  3 mortality than the patients who have the underlying  4 disease of hem/oncs and as people around the panel  5 will note better than me, there are people looking to  6 get better definitions for the coronavirus-associated  7 pulmonary aspergillosis and there are already existing  8 definitions called the AspICU definitions for  9 pulmonary aspergillosis secondary to influenza.  10         So two points there, and I'll pause and  11 hand it back to Helen.  12         DR. HELEN BOUCHER: Thanks very much,  13 Mike. Dr. Perfect.  14         DR. JOHN PERFECT: Hi, thank -- okay,  15 thank you very much. It's my pleasure today to listen  16 to this. It's going to cost me about five hours  17 tonight rounding on the transplant ID service, but  18 other than that, I wanted to make a statement on  19 heterogeneity. It is all -- they're all heterogeneous  20 type situations and what I wanted to do is make some  21 kind of statement which I think is probably off base,  22 but I think it's important.</p>

<p style="text-align: right;">Page 250</p> <p>1 In this day and age of computerized --</p> <p>2 for the amount of information we get today, we should</p> <p>3 be changing the game completely. We should have</p> <p>4 centers that actually know what these patients</p> <p>5 actually do and what happens to these patients. It's</p> <p>6 unconscionable that we do a candidemia study and we</p> <p>7 have 50 -- 30 to 50 patients that can't be put in the</p> <p>8 study and we get one on the study. That's not right.</p> <p>9 So what I would say is trying to pick</p> <p>10 the heterogeneity in this thing is, what's the</p> <p>11 solution. I think part of the solution would be is</p> <p>12 you take 10, 15 centers throughout the United States</p> <p>13 or Europe or wherever that's got these type of</p> <p>14 patients and you dive down. I know things change, but</p> <p>15 if you dive down in the type of patients that they</p> <p>16 have and understand what they are and what their</p> <p>17 outcomes are, we may not need -- and our controlled</p> <p>18 population is right there.</p> <p>19 It's right there with us and we can</p> <p>20 reduce the number of patients we put in the studies</p> <p>21 and we could control for the heterogeneity.</p> <p>22 DR. HELEN BOUCHER: Thanks very much,</p>	<p style="text-align: right;">Page 252</p> <p>1 know, goal number one has to be to make the compound</p> <p>2 get to the place where it actually stays available to</p> <p>3 us and that means initial approval with an adequate</p> <p>4 data package to get you started, and then we do the</p> <p>5 rest -- then we do the next 10 years' worth of work</p> <p>6 after that.</p> <p>7 And so heterogeneity early on, I think,</p> <p>8 you do want to pick up some of it and I think you want</p> <p>9 to bias it towards the -- bias towards greater degrees</p> <p>10 of immune compromise.</p> <p>11 DR. LUIS OSTROSKY-ZEICHNER: Thank you.</p> <p>12 thank you very much, Dr. Rex. We're going to move on</p> <p>13 to the second question which is, what are the settings</p> <p>14 in which external controls and other alternative trial</p> <p>15 designs need to be used to obtain adequate and</p> <p>16 interpretable data? Are there gaps in those sources</p> <p>17 for external controls and what do we need to do to</p> <p>18 address them?</p> <p>19 And to start off the discussion, we</p> <p>20 would like to invite Dr. Patterson to chime in. Tom,</p> <p>21 are you available?</p> <p>22 DR. THOMAS PATTERSON: Yes, I sure am.</p>
<p style="text-align: right;">Page 251</p> <p>1 John. John Rex, and then we'll turn it to Dr.</p> <p>2 Ostrosky to go to the next question.</p> <p>3 DR. JOHN REX: There we go. The little</p> <p>4 voice said the microphone is on now. Heterogeneity</p> <p>5 cuts two ways and only -- I think there are two things</p> <p>6 you want to know about a compound. You want to know,</p> <p>7 does it work, and then how best can you use it. And</p> <p>8 the question of does it work needs to be answered as</p> <p>9 cleanly as possible and I would actually argue that</p> <p>10 you want the heterogeneity because it reflects the</p> <p>11 real world, but you also want to bias it towards a</p> <p>12 greater degree of immune compromise, because that's</p> <p>13 where the signal efficacy is the sharpest. But then</p> <p>14 the question how best to use it is something that can</p> <p>15 take years to study. I know -- Pete, your comment</p> <p>16 about HIV versus non-HIV, I fully recognize, very</p> <p>17 different diseases.</p> <p>18 What I think is probably true, that</p> <p>19 HIV, cryptococcal meningitis, is a harsher testbed for</p> <p>20 a new engine. If it works there, probably work</p> <p>21 elsewhere, but may use it a different way, so I want</p> <p>22 to just emphasize the idea that getting a drug, you</p>	<p style="text-align: right;">Page 253</p> <p>1 Thanks, Luis and Helen. I think that that's a really</p> <p>2 important area that we do need to explore. Clearly, I</p> <p>3 think, we've heard the challenges of looking at sort</p> <p>4 of our standard randomized trials and how it's really</p> <p>5 become truly almost impossible to do, so that I think</p> <p>6 we do need to look at these external controls as ways</p> <p>7 to facilitate enrollment and get results quicker so</p> <p>8 that we'll have more interest in developing drugs in</p> <p>9 the field.</p> <p>10 I think that's been painfully clear</p> <p>11 from the discussion today, but I hope we can also move</p> <p>12 to alternative trial designs, specifically using</p> <p>13 alternative end points. I think we've seen the</p> <p>14 potential for -- in crypto, where that can happen and</p> <p>15 be very valid. I think it's been shown pretty well</p> <p>16 that those alternative measures of, like, declining</p> <p>17 counts and such have clearly not only been shown</p> <p>18 initially to be useful, but then validated by large</p> <p>19 trials which are possible, or were possible at least,</p> <p>20 in crypto and so I hope that'll happen.</p> <p>21 I hope that'll be able to happen with</p> <p>22 other sort of markers that we can use to develop</p>



<p style="text-align: right;">Page 254</p> <p>1 (sound drops).</p> <p>2 DR. LUIS OSTROSKY-ZEICHNER: Thank you.</p> <p>3 Thank you, Tom. I see Thomas' hand up.</p> <p>4 DR. THOMAS WALSH: Hello.</p> <p>5 DR. LUIS OSTROSKY-ZEICHNER: Yes.</p> <p>6 DR. THOMAS WALSH: Hi. This is Tom --</p> <p>7 Tom Walsh. I'd like to address, and it ties in with</p> <p>8 the first question as well as the second and that is,</p> <p>9 the question of heterogeneity but also controlling for</p> <p>10 that. Granted, we've been successful with candidemia</p> <p>11 trials and those (inaudible) but unfortunately going</p> <p>12 on an extended time, but the real challenge is well</p> <p>13 before us, are the less common mold and yeast</p> <p>14 pathogens. We've heard again and again the challenges</p> <p>15 that are in those. Problems are going to be</p> <p>16 exaggerated dramatically.</p> <p>17 If we see these as true public health</p> <p>18 risks, then clearly waiting for five, even years is</p> <p>19 just not acceptable. We have a number of registries</p> <p>20 that have been very well developed, expanding and</p> <p>21 strengthening those and using the external control</p> <p>22 strategies with even better statistical refinement</p>	<p style="text-align: right;">Page 256</p> <p>1 DR. LUIS OSTROSKY-ZEICHNER: -- very</p> <p>2 much, Tom. I see Kieren has her hand up. Kieren, do</p> <p>3 you want to make a statement?</p> <p>4 DR. KIEREN MARR: Hello, this is</p> <p>5 Kieren. Are you talking to me? I didn't have my hand</p> <p>6 up. That's old.</p> <p>7 DR. LUIS OSTROSKY-ZEICHNER: John</p> <p>8 Perfect, you have your hand up. Would you like to</p> <p>9 make a remark?</p> <p>10 DR. JOHN PERFECT: Well, that was an</p> <p>11 old hand, like Kieren, but I'll make a remark. Yeah,</p> <p>12 I agree completely with Tom. As I said before, my</p> <p>13 first talk was -- my first discussion was the question</p> <p>14 of external control and I think we're missing the</p> <p>15 complete boat. It's going to take time. It's going</p> <p>16 to take money. It's going to take effort. But we can</p> <p>17 extract an awful lot of information on what we already</p> <p>18 have today and put everything in the context when we</p> <p>19 study a new drug and I think to use it completely --</p> <p>20 completely change that way, so I agree completely with</p> <p>21 Tom's statement.</p> <p>22 I'm sorry, my hand was up for the other</p>
<p style="text-align: right;">Page 255</p> <p>1 greatly enhanced the capacity for enrolling patients</p> <p>2 robustly who have a need or the option for receiving a</p> <p>3 potentially life-saving antimicrobial agent, for</p> <p>4 example, for Lomentospora prolificans or for</p> <p>5 mucormycosis and strengthening, therefore, the</p> <p>6 external control and having the robust database can</p> <p>7 help immensely.</p> <p>8 But aligning along with the</p> <p>9 heterogeneity, which is really also something that</p> <p>10 would need to be controlled, is the -- if we are</p> <p>11 having randomized studies, is the need for robust</p> <p>12 stratification. We're told commonly, well, you can</p> <p>13 only have two strata.</p> <p>14 But we know painfully from the DEFEAT</p> <p>15 study in mucormycosis that if you do not stratify on</p> <p>16 the key areas of heterogeneity, it can be a disaster</p> <p>17 and can give you conclusions completely the opposite,</p> <p>18 and those conclusions are going to be -- and the need</p> <p>19 for having the proper external controls and having the</p> <p>20 proper stratification with a typical investment become</p> <p>21 all the more critical with the less common mold and</p> <p>22 yeast pathogens.</p>	<p style="text-align: right;">Page 257</p> <p>1 one, but same. I agree with this kind of study of</p> <p>2 external control. Very in depth of control, so we</p> <p>3 really know the patients we have. We have so many</p> <p>4 patients out there, but we're not using them</p> <p>5 adequately.</p> <p>6 DR. LUIS OSTROSKY-ZEICHNER: We have</p> <p>7 Aaron Dane who wants to make a remark.</p> <p>8 AARON DANE: Hi. Again, following up</p> <p>9 from Tom's comment, I think it's right that we've got</p> <p>10 some good external control data in some of the more</p> <p>11 common areas. When we go into the rarer areas, that's</p> <p>12 probably where we could derive most benefit and what</p> <p>13 it would be worth thinking about is whether we've got</p> <p>14 external control databases or whether we need to build</p> <p>15 them which are more complete.</p> <p>16 So the idea that it should be a</p> <p>17 complete case series, for example, rather than a</p> <p>18 selected subset who -- where there's maybe more</p> <p>19 interest in reporting a case. So I think that's the</p> <p>20 important component for some of these rarer molds and</p> <p>21 these rarer areas where we might need to think about</p> <p>22 whether we've got a complete external control set or</p>

<p style="text-align: right;">Page 258</p> <p>1 whether it's something we need to think about how we 2 get to that.</p> <p>3 DR. LUIS OSTROSKY-ZEICHNER: Thank you 4 very much, Aaron. We have Dr. John Rex.</p> <p>5 DR. JOHN REX: So am I -- can you hear 6 me?</p> <p>7 DR. LUIS OSTROSKY-ZEICHNER: Yes.</p> <p>8 DR. JOHN REX: It's hard to know when 9 you're on and off mute. So external controls can 10 definitely be used here and there's an advantage, not 11 for all of the fungal infections but for some of them 12 in that they are relatively chronic. Acute infections 13 do get better sometimes on their own and I'm reminded 14 here of that paper by Fleming and Ellenberg entitled, 15 "Why We Need Randomized Controlled Trials for Ebola." 16 The shorter the duration of the 17 infection to either spontaneous resolution or any 18 other outcome that can be influenced by supportive 19 care, the harder it is to know what it means when you 20 intervene in the course of an ongoing process.</p> <p>21 On the other hand, somebody's been 22 running along with cryptococcal meningitis for several</p>	<p style="text-align: right;">Page 260</p> <p>1 study anything else, assuming that you had a mold 2 active drug or a yeast active drug. I mean, there are 3 clear indications for rarer infections and I think it 4 would be really helpful for the MAA to consider 5 somebody who had, for example, a mucormycosis only 6 drug and how they would approach that because doing an 7 RCT in that context would be impossible, I think. 8 That's one comment.</p> <p>9 And then the second, related to that, 10 is that within a population of patients, so you might 11 decide to set out to do an RCT in aspergillosis, but 12 actually your drug has little merit in azole 13 resistance or in rare species such as -- or rarer 14 species such as terreus, which are amphotericin 15 resistant, and you want to be able to take a subset -- 16 preplan a subset analysis of those resistant strains 17 with your new drug, that I don't think you'll get 18 enough within an RCT to get that set, so therefore 19 historically controlled parallel group or group 20 collected alongside in other centers with a natural 21 history of what happens in those patients, to me, 22 would be essential to try to get that additional</p>
<p style="text-align: right;">Page 259</p> <p>1 months; they're not going to get better tomorrow. And 2 when you intervene with a new agent and they -- and 3 you bend the shape of the curve of their clinical 4 course, it -- I know the plural anecdote is not data, 5 but when you have diseases that are relatively chronic 6 and that do not remit, that's just what they do in the 7 cancer world.</p> <p>8 This is what we do in metabolic 9 diseases. We look at relatively small numbers of 10 individuals with progressive inexorable processes and 11 we say, look, they didn't get better today because of 12 magic, so I think that we really -- I think we're 13 underusing it, but we have to use them very 14 selectively. Over.</p> <p>15 DR. DAVID DENNING: Luis, can I make 16 another point? Or Helen.</p> <p>17 DR. HELEN BOUCHER: Sure, go ahead.</p> <p>18 DR. DAVID DENNING: The -- I think one 19 of the things that's tricky and I was slightly 20 perturbed about, that is indication from the MMA that 21 in order to take a drug through you have to have an 22 RCT in candida or aspergillus before you could really</p>	<p style="text-align: right;">Page 261</p> <p>1 indication for not only aspergillosis but azole 2 resistant or resistant aspergillus.</p> <p>3 So I see multiple ways in which this 4 might be helpful, the rare pathogens and resistant 5 pathogens within a population as the two key areas.</p> <p>6 DR. LUIS OSTROSKY-ZEICHNER: Thank you 7 very much. Let's see, Karen Higgins.</p> <p>8 DR. KAREN HIGGINS: Hi. Hi, I'm the 9 statistical team leader working with the Division of 10 Anti-Infectives at FDA and I agree with a lot of the 11 discussion so far. You know, I think there are cases 12 where externally controlled trials can be useful, but 13 I do think we need to keep in mind, they really are 14 weaker trials. They're not able to control for many 15 factors.</p> <p>16 The patients come from different sites 17 and they're just not the gold standard as randomized 18 controls, so as Cheryl said in her talk, having a 19 historically controlled trial be supported by a 20 randomized controlled trial is certainly helpful and 21 we'd love to see that whenever possible, so we do 22 understand there are certain circumstances where that</p>

<p style="text-align: right;">Page 262</p> <p>1 would be difficult to do. I just wanted to point that  2 out. Thank you.  3 DR. LUIS OSTROSKY-ZEICHNER: -- much.  4 Let's try Dr. Bennett again.  5 DR. JOHN BENNETT: I had a comment  6 about John Perfect's statement about using data from  7 one's own institution. Looking at my institution, the  8 problem I see is switching from one drug to another  9 and back again, so it's hard to know what each  10 individual drug is doing and in addition, because the  11 data is prerecorded and each patient is different,  12 it's fair to use the same criteria to look across  13 sets.  14 So I think having external data has  15 some value, but if you don't control for it and get  16 the right data and there's some control over drug  17 usage, it's very difficult to interpret the data. I  18 noticed in the mucormycosis approval for  19 isavuconazole, a fair number of the patients were  20 started on the other drug first, salvage therapy if  21 you will. When they were given isavuconazole then  22 switched to another drug, but because an ITT, intent</p>	<p style="text-align: right;">Page 264</p> <p>1 we're collecting contemporary data is the nature study  2 that Dr. Pappas mentioned, where we're actively  3 collecting people that failed antifungals in candida  4 in a way that would be almost ready for a clinical  5 trial, a way -- exactly the same way we collect data  6 for a clinical trial.  7 So I think launching these types of  8 initiatives where we're sort of intentionally  9 collecting contemporary controls in a compliant  10 fashion is going to get us a very long way, so that's  11 what I would like to contribute there.  12 We have Dr. Botgros.  13 DR. RADU BOTGROS: Thank you very much.  14 Can you hear me?  15 DR. LUIS OSTROSKY-ZEICHNER: Yes.  16 DR. RADU BOTGROS: Yeah, on the  17 external controls, you know, what I wanted to say is  18 of course our view is that they should never be the  19 first choice, but we accept that for instances like  20 rare fungi with high mortality, it might be  21 unavoidable to have this approach. And I was thinking  22 that maybe in view of the fact that matching the</p>
<p style="text-align: right;">Page 263</p> <p>1 to treat analysis was used, the final outcome was  2 recorded as if they were still on isavuconazole, but  3 they weren't.  4 And I think this just indicates they  5 probably have external data. It's not as clean as if  6 you were trying to control it from the beginning. So  7 that's the end of my comment. Thank you for asking.  8 DR. LUIS OSTROSKY-ZEICHNER: Thank you,  9 Dr. Bennett. Dr. Nambiar.  10 DR. SUMATI NAMBIAR: Hi. I've been  11 muted and unmuted repeatedly. So mine was more with  12 stratification. I think we've heard that there are  13 concerns with using external controls but there, in  14 fact, might be some situations where that might be the  15 only option. We've also heard that the need to  16 collect the data on external control, how do we go  17 about doing it and does anyone have suggestions on how  18 such data can be collected in a systematic manner so  19 that it can be available and applied in a more  20 consistent manner. Thanks.  21 DR. LUIS OSTROSKY-ZEICHNER: Thank you,  22 Dr. Nambiar. I think one of the examples of the way</p>	<p style="text-align: right;">Page 265</p> <p>1 external control is generally difficult and difficult  2 to interpret sometimes, whether it would not be good  3 to have efforts focused on aiming to construct through  4 BAFF datasets that could be accepted and used in the  5 regulatory process. Thanks.  6 DR. LUIS OSTROSKY-ZEICHNER: -- very  7 much. Back to Aaron Dane. Aaron, do you want to try  8 to answer Dr. Nambier's...  9 AARON DANE: Yes, so it took me time to  10 come off mute. So when -- yeah, in response to Dr.  11 Nambier's question, I guess similar to the previous  12 comment, it was -- I think one approach that could  13 help would be if there were certain sites which were  14 known to have a particular issue with a particular  15 pathogen, for example, then getting complete cases  16 with patient level data could be a way that we could  17 do that and hear that, so that may be available  18 already in some situations.  19 That could be a case where you know  20 you've got everybody with that pathogen in question  21 and you know you've got the level of data you need to  22 be able to try and match them up with the clinical</p>

<p style="text-align: right;">Page 266</p> <p>1 trial population appropriately and that could include  2 prior therapies and the time on those prior therapies  3 as important components of any comparison.  4 DR. LUIS OSTROSKY-ZEICHNER: Thank you,  5 Aaron. Dr. Walsh, do you want to make a comment? Or  6 Dr. Pappas?  7 DR. PETER PAPPAS: Yes. Can you hear  8 me?  9 DR. THOMAS WALSH: Are you able -- yes,  10 can you hear me? In addition to the very fine points  11 that have been already made, may I suggest please that  12 we appreciate that we are not working in a clinical  13 trial vacuum. There are two areas where there --  14 where we could grow tremendously. One is from  15 national -- from the National Cancer Institute  16 efforts. There is, for example, the Experimental  17 Therapeutics Committee for Rare Cancer. There's also  18 the Alliance for Clinical Trials in Oncology.  19 There are a number of organizations  20 that specifically focus on rare cancers without  21 massive, randomized trials and I would just wonder  22 whether it might be worthwhile addressing to the --</p>	<p style="text-align: right;">Page 268</p> <p>1 That good outcome, if it does correlate  2 well with the clinical -- with one's preclinical  3 research, provides the reassurance in that regard.  4 For example, with you look at isavuconazole, as Dr.  5 Bennett said, yes, there were significant limitations,  6 obviously, in that clinical trial design. But we're  7 talking about a deadly, life-threatening disease for  8 which we really have no other therapeutic options  9 other than a nephrotoxic agent, which sometimes works.  10 And that is the robustness of the  11 preclinical data, and one of the reviewers at that  12 time said, yes, I understand the limitations of the  13 clinical dataset but "I am persuaded by the  14 preclinical data." Our EMA colleagues do take a very  15 robust approach and quite often a working translation,  16 we're asking ourselves is this working.  17 Is this working in the dose and in the  18 host in well-developed preclinical models to  19 ostensibly be able to interpret limited clinical data,  20 so I think integrating that into our decision making  21 can help immensely.  22 DR. LUIS OSTROSKY-ZEICHNER: Thank you.</p>
<p style="text-align: right;">Page 267</p> <p>1 within the FDA regulatory setting, even potentially a  2 combined conference as well as perhaps pioneering in  3 deficiencies where clearly there are -- there's little  4 opportunity, especially for the metabolic diseases, to  5 be able to do robust randomized trials to use some of  6 the -- to adapt some of the regulatory and statistical  7 models that they employ.  8 This is not the first time that we're  9 looking at rare diseases and, in that regard, it might  10 inform us in terms of subtleties of clinical trial  11 design, and also rationale and president that we  12 haven't used. That's one.  13 Two is jumping ahead a little bit, but  14 there -- as proof of concept and working with rare  15 molds, rare yeasts, multidrug resistant organisms  16 including auris, if we are working in the context also  17 of preclinical data, strong preclinical models,  18 redundant, consistent PK/PD driven model systems that  19 are also co-spaced, it provides a reasonable  20 underpinning of proof of concept that the results that  21 are being seen in clinical trials are not just random  22 error.</p>	<p style="text-align: right;">Page 269</p> <p>1 Tom. Pete, you wanted to say something?  2 DR. PETE PAPPAS: Yeah. Yes. I've  3 heard what everybody's said and I want to kind of go  4 back to what John said, and I particularly -- I mean,  5 this particularly relates to candidemia. One of the  6 comments that I made during my presentation is really  7 the sheer numbers of patients who are screened but  8 don't get enrolled into candidemia studies.  9 In every one of our annual meetings or  10 biennial meetings, we have always put as a priority  11 and unfunded priority, the -- our capacity but kind of  12 inability to capture what happens to those patients  13 who are screened for but never enrolled into a  14 candidemia study.  15 And again, the ratio is, I think on the  16 low end, 1 to 10. On the high end, it may be 1 to 50.  17 So for every patient that's enrolled, there are  18 somewhere between 9 and 49 patients who are not  19 enrolled for candidemia, for a variety of reasons that  20 don't have to do with patient just refusing consent.  21 The understanding -- our understanding has been that  22 there is tremendous value in really understanding what</p>

<p style="text-align: right;">Page 270</p> <p>1 happens to those patients, particularly at sites that 2 are already participating in a clinical trial. 3           Understanding what Jack Bennett said, 4 too, because there's a lot of heterogeneity in these 5 patients in terms of coming on and off drugs and so 6 forth, but surely we can -- well, again, we won't know 7 until we gather data, but until we gather that data 8 and are incentivized to do it financially and then -- 9 and therefore given the capacity to do it, we're 10 really missing just a huge opportunity to find out 11 what happens in the real world and really understand 12 what the outcomes really are in these diseases, and 13 whether it's candidemia or other rare molds doesn't 14 really make any difference, but capturing those 15 patients, the data pertaining to underlying diseases, 16 treatment, and outcome can -- the limiting factor here 17 is not a lack of interest. 18           It's not heterogeneity. It's really 19 nobody gets funded to do that, no companies and no 20 institutions pay for that kind of information, which I 21 think is really a treasure trove and it's something 22 that we're -- we just have always overlooked and I</p>	<p style="text-align: right;">Page 272</p> <p>1 can't try to learn from what's happening with that 2 data, I think just as Pete was alluding to, for 3 example the 9 to 49 patients with candidemia that 4 never make a trial, someone needs to be looking at 5 that data (sound drops) et cetera. 6           So I think that's the role for our 7 group and working with others, is to try to look at 8 that. There are lots of problems with big data, as 9 you know, and with hospital data, trying to 10 characterize definitions, but I think we continue to 11 try to look at that data to at least be able to inform 12 you guys on what's out there on risk factors and on 13 what populations might be worth studying. 14           And I think one of the things we've 15 been surprised about in looking at mold surveillance, 16 and we're only doing this in one site in Atlanta, is 17 that the classic patients that we all describe as 18 getting mold, these transplant patients, these 19 patients with leukemia, et cetera, are the 20 overwhelming minority of patients that are coming out 21 in our surveillance study. 22           So it's more steroids, chronic lung</p>
<p style="text-align: right;">Page 271</p> <p>1 think everybody recognizes that we're not really 2 seeing maybe the true picture of candidemia outcomes, 3 et cetera based on our clinical trials alone. That's 4 all. 5           DR. LUIS OSTROSKY-ZEICHNER: Thank you 6 very much, Peter. Before I turn it over to Helen, I'd 7 like to see if Tom Chiller wants to chime in and 8 discuss, is there any databases that the CDC that have 9 sufficient granularity where they could be used as 10 controls? 11           DR. TOM CHILLER: Yeah, thanks. 12 Thanks, Luis, and I'm just here listening to the 13 discussion, I think, more than anything else and 14 learning from all you guys who are out there battling 15 these clinical issues. I think from the CDC's 16 standpoint, we would like to figure out, because this 17 is -- I think as Tom Walsh and others have described, 18 because this is a unique population, a unique bunch of 19 diseases that are quite different, some of which are 20 more rare than others, it just lends to us working 21 together as a community to when things are -- when 22 trials are conducted or tried to be conducted, we</p>	<p style="text-align: right;">Page 273</p> <p>1 disease, et cetera. It's -- so a lot of the studies 2 that we do looking at these infections are done 3 potentially in a very minor part of those who actually 4 are getting these infections in our hospitals. I know 5 you all know that, but it's interesting to see it play 6 out in pretty rigorous surveillance, albeit in one 7 site. 8           So, yeah, I don't have great insight 9 into harnessing big data because of all the 10 limitations, but what I do think we ought to be doing 11 is working together on this and trying to squeeze as 12 much out of any study, pre-study, et cetera that we do 13 so that we can inform the next one. 14           DR. LUIS OSTROSKY-ZEICHNER: Thank you 15 very much, Tom. Two quick more comments before I turn 16 it over to Helen for the next question. One is from 17 Mike Hodges. 18           DR. MICHAEL HODGES: Yeah, just a quick 19 one on the external controls or historical controls. 20 We want somewhat of an external control. Two drugs 21 have been approved. Two antifungal drugs have been 22 approved using external controls. One, caspofungin,</p>

<p style="text-align: right;">Page 274</p> <p>1 one isavuconazole. The latter used a database called  2 Fungiscope from University of Cologne, and that  3 database is still up and running and still increasing  4 patients' data into its database as we speak. So it  5 is contemporaneous.</p> <p>6 DR. LUIS OSTROSKY-ZEICHNER: Thank you.  7 Thank you very much, Mike. And final comment of this  8 question, David Angulo.</p> <p>9 DR. DAVID ANGULO: Thank you, Dr.  10 Ostrosky. So a provocative question here regarding  11 what could be the right source for this external  12 control and I do wonder, are there regulatory datasets  13 that have been used for approvals previous drugs, a  14 potential source of external controls.</p> <p>15 Because if those datasets are  16 extraordinarily comprehensive, many of them may be  17 relatively recent and probably regulatory agencies are  18 the ones that have in their hands the largest amount  19 of data about issues of invasive candidiasis and  20 outcomes, risk factors, et cetera, invasive  21 aspergillosis, so is there any possibility to have  22 access in some way, supporting not a specifically</p>	<p style="text-align: right;">Page 276</p> <p>1 was also assigned to outpatient today, so Aspasia, are  2 you on the line? No, hearing not. So I'm then taking  3 Aspasia's role in trying to address this really  4 important question. Certainly, the strategies that we  5 have taken previously and I think the overarching  6 effort given the population of newborns, premature  7 infants, toddlers, children, adolescents is to provide  8 a tangible benefit wherever, whenever possible.</p> <p>9 That has been the overarching approach  10 that we've taken in 14 different clinical trials,  11 pediatric clinical trials for antifungal therapy. You  12 have to ask, where might that be. Obviously, for  13 defined interactions, that's as possible, but before  14 we do so, we need as Aspasia described, a really solid  15 foundation for the pharmacology and classic safety  16 tolerability PK.</p> <p>17 And we talk about heterogeneity and  18 nowhere is it really so vitally important as to  19 recognize the different age groups, and so there is a  20 neonatal network that's chaired by Dr. Danny Benjamin,  21 which has certainly been tremendously successful and  22 that would really be the best place in which to</p>
<p style="text-align: right;">Page 275</p> <p>1 particular drug, to a particular study, but is there  2 any way that that information that has been collected  3 by multiple sponsors can be leveraged to facilitate  4 the development of other antifungal agents in the  5 future.</p> <p>6 DR. LUIS OSTROSKY-ZEICHNER: All right  7 --</p> <p>8 DR. DAVID ANGULO: Thank you.</p> <p>9 DR. LUIS OSTROSKY-ZEICHNER: -- David.  10 I'm going to turn it back to Helen for the next  11 question.</p> <p>12 DR. HELEN BOUCHER: Great. Thanks very  13 much, Luis. Great discussion, everybody. We're going  14 to turn our attention now to children and ask about  15 novel approaches and strategies to facilitate  16 development of antifungal therapies for children and I  17 thought we might ask Dr. Tom Walsh to kick off this  18 part of the discussion.</p> <p>19 DR. TOM WALSH: I want to first ask as  20 to whether Aspasia is available. Aspasia Katragkou is  21 completing her second chief residency now at Queens  22 Hospital in New York Presbyterian Hospital System, but</p>	<p style="text-align: right;">Page 277</p> <p>1 characterize new antifungal agents in the newborn  2 population.</p> <p>3 The timing of that, though, really  4 depends largely upon the findings in the older  5 population, in which case, then you're looking at  6 patients usually between two to 12 years of age and  7 that might include a stratification, then, in the  8 adolescent population. Historically, we've attempted  9 to provide the benefit in pediatric oncology,  10 particularly in a prophylactic or an empirical  11 setting, increasingly would use prophylaxis for ease  12 and practicality and its comparable efficacy, and so  13 in that regard, one can envision a target population  14 in AML, treatment for blastic leukemia, patients where  15 there are already adult data, where we can have  16 specific centers, we'd have our consortium. There are  17 other consortiums as well and with that, collaborating  18 with our industrial partners and a classic dose  19 escalation cohort design.</p> <p>20 Those studies can be done relatively  21 efficiently and yield tremendous -- tremendously  22 important data. As Aspasia indicated, there is</p>

<p style="text-align: right;">Page 278</p> <p>1 considerable interpatient variability, for a number of  2 reasons that she articulated. But with that, with  3 proper modeling, one can usually obtain, especially  4 based upon good preclinical data and the preexistent  5 patient population of adult data, in part a dosage  6 that would hit target attainment.</p> <p>7         The next question, though, now that we  8 know the dosage, in which populations do we aim to  9 show some efficacy? There are different regulatory  10 requirements and I will defer to our colleagues  11 insofar as what those may be, depending upon the  12 requirements of the compound, but nonetheless, we do  13 need that experience in target populations. And with  14 that, we really look toward the networks that have  15 been established both in Europe and U.S., in order  16 that we can identify patients and who might those  17 patients be: certainly, oncology but also primary  18 immune deficiencies, patients with cystic fibrosis,  19 many of the medical and surgical patients who are  20 hospitalized. These are the common conditions that we  21 encounter in typical case series.</p> <p>22         Ultimately, it requires an approach</p>	<p style="text-align: right;">Page 280</p> <p>1 regard to enrollment and if I go back to some of our  2 experiences. Once you're able to establish the PK and  3 you're able to do that, maybe if you're lucky to do  4 that, in the setting of a prophylactic population, but  5 the enrollment can go quite well as Dr. Walsh alluded  6 to, but as we go and we need to explore as we are with  7 CRESEMBA, in the population that really needs the drug  8 and at a dose that we hope to recommend in the future,  9 that is in a population that requires therapy.</p> <p>10         So now we're talking about a very --  11 even more rare than in the population that -- adult  12 population where we already did a randomized  13 controlled trial so I thought I'd just share maybe an  14 opportunity that we thought that we at Astellas could  15 pilot and we're working with the International  16 Pediatric Fungal Network just more recently to enroll  17 in our trial and in a way that hopefully can be a  18 little bit more innovative with smaller set of sites  19 but allow for an expedited startup process.</p> <p>20         It sort of requires us to be more  21 nimble on the sponsor side and work harder to find  22 patients, but it allows the patients' physicians to</p>
<p style="text-align: right;">Page 279</p> <p>1 that we work way, way and against anticipation as we  2 see new compounds beginning to be approved and not  3 wait for the regulatory approval, but instead already  4 contemplating which patients may benefit and which  5 would be the likely organisms that we should target  6 with a given compound.</p> <p>7         DR. HELEN BOUCHER: Great, thanks very  8 much. Laura Kovanda.</p> <p>9         DR. LAURA KOVANDA: Can you hear me?  10         DR. LUIS OSTROSKY-ZEICHNER: Yes.  11         DR. LAURA KOVANDA: Okay.  12         DR. HELEN BOUCHER: Yes.  13         DR. LAURA KOVANDA: So thank you. I  14 just wanted to make a couple of comments, having been  15 through the pediatric development for a couple of  16 different compounds now and through some challenges in  17 this effort. I thought I would just echo one -- what  18 Tom said with regard to the PK/PD and understanding  19 that exposure response relationship in other  20 populations, especially when very good evidence in  21 either animals or in adults to bridge.</p> <p>22         And the other is the challenges with</p>	<p style="text-align: right;">Page 281</p> <p>1 sort of come to us almost in a compassionate use sort  2 of setting where you allow the physician to come to  3 you versus already having the site set up.</p> <p>4         We just started the pilot and we  5 haven't had anybody knocking on our door, so to speak,  6 yet. But we're hoping that this could eliminate the  7 need for a large global trial where we see some of  8 these sites to get 30 patients across the globe, and  9 hopefully that could be an option in the future,  10 working closely with these networks.</p> <p>11         But I will say, at this point, it's  12 just a pilot and it requires a lot of -- basically 96  13 hours from diagnosis to start of the study drug, so  14 it's not a very long time to get the paperwork  15 involved completed. But I thought I'd share that.</p> <p>16         DR. HELEN BOUCHER: Great. Thanks very  17 much, Laura. Luis, back over to you.  18         DR. LUIS OSTROSKY-ZEICHNER: Thanks,  19 Helen. So question four is please discuss if  20 consideration should be given to pooling different  21 types of fungal infections or whether there are enough  22 differences between the species to warrant separate</p>

<p style="text-align: right;">Page 282</p> <p>1 studies. Also discuss if there are important  2 considerations with the body site as seen with  3 antibacterial drugs. And to kick off the discussion,  4 we would like to invite Dr. John Rex.  5 DR. JOHN REX: Is -- sorry for the  6 delay, but my microphone has now been turned on.  7 Thanks, Luis. You know, there are -- so the answer to  8 this is both yes and no. There are times when it is  9 appropriate to think separately if you've got really  10 disease patterns. You know, cryptococcus has got a  11 really different disease pattern from aspergillus.  12 But separating by shape and color also has its limits.  13 I mean, is aspergillosis really different from  14 scedosporiosis? And is that really different from  15 fusariosis? I mean, you know, sometimes, they spread  16 a little bit differently in the body, but at the end  17 of the day, they are filamentous fungi and if you've  18 got -- and it doesn't come down to just, as Paul  19 Ambrose would say, "It's the MIC, dummy."  20 And interesting, if you say -- if you  21 insist on, I want separate data for scedosporium,  22 scopulariopsis, rasamsonia, and name two other rare</p>	<p style="text-align: right;">Page 284</p> <p>1 somebody with a brain infection as well as somebody  2 with a pulmonary infection, I think, is helpful  3 because that's the kind of stuff that when we're  4 taking care of patients, we have to know.  5 The fact that it's -- that the disease  6 the patient presents with -- name a fungus and body  7 site that's not in the label. I can't look at the  8 patient and say, oh, I'm so sorry. We can't treat you  9 because you're not in the label. We actually have to  10 do what we can do. And I think we should be trying to  11 collect those cases and I think the more diverse the  12 dataset we represent in the label and in our  13 collective publications about the data, the better off  14 we are because the fungi are very diverse and each one  15 of them is so rare. Over.  16 DR. LUIS OSTROSKY-ZEICHNER: Thank you  17 very much. We have Dr. Shawn Lockhart from CDC  18 wanting to make a comment.  19 DR. SHAWN LOCKHART: Yeah. So in  20 actuality, we really already group them together in  21 general groups, because I mean, we say, oh, well,  22 we're studying candida. But candida is not actually a</p>
<p style="text-align: right;">Page 283</p> <p>1 ones, you'll never have anything for anything. I  2 mean, it really is not -- it's not even helpful to  3 say, gee, every fungus has to be studied by itself.  4 There are a few that we can study reasonably well and  5 maybe -- they may really reduce to three: candida,  6 crypto, and aspergillus. Those are the only three  7 that you can study in a large enough scale to fully  8 understand them, I'm just saying, the list may stop.  9 There may have been more chosen, but there aren't many  10 and so the vast majority where we have -- we  11 (inaudible) mucor, no I don't see how you can do a  12 randomized trial there. The (inaudible) common  13 aspergillus, you're not going to do that. And on body  14 sites, I come back to my heterogeneity comment from  15 earlier. I think body sites, they are different. Not  16 going to deny that, but you need to leverage what you  17 know about your compounds and there's actually value  18 in collecting heterogenous patients.  19 Fungi don't stay put. We know  20 aspergillus can involve pretty much any part of the  21 body. And in actually collecting some information in  22 which you've got somebody with osteomyelitis and</p>	<p style="text-align: right;">Page 285</p> <p>1 genus. Candida is huge. It's just a group of yeasts  2 that don't have sets. It's this ginormous  3 polyphyletic group that includes everything from  4 saccharomyces up to Candida auris and down to these  5 meyerozymas and these pichias and these hortaes and  6 all these really diverse yeasts, and yet we just call  7 them all candida because that's how they're lumped  8 together and we treat them as, okay, this cures  9 candida.  10 So in a way, we're really already doing  11 that, but the other argument is if you have a drug  12 that seems to work good against dematiaceous mold, how  13 long is it going to take you to find enough  14 dematiaceous molds, and quite a few of them react the  15 same way, at least, in vitro to drugs and I think  16 grouping them in those general ways is about the only  17 way you're going to do some things.  18 Do we separate rhizopus and mucoid? I  19 don't think we can do it and have a trial. It was  20 hard enough to get 12 cases, so how are you going to  21 get 24, if you have one rhizopus in there -- in your  22 study and one mucor? So I think they have to be at</p>



<p style="text-align: right;">Page 286</p> <p>1 least roughly grouped.</p> <p>2 DR. LUIS OSTROSKY-ZEICHNER: Thank you</p> <p>3 very much. Any other comments on this question? We</p> <p>4 have Dr. David Denning from across --</p> <p>5 DR. DAVID DENNING: Yeah --</p> <p>6 DR. LUIS OSTROSKY-ZEICHNER: --</p> <p>7 Atlantic.</p> <p>8 DR. DAVID DENNING: Yeah, I've got one</p> <p>9 comment. I think there are a couple of situations</p> <p>10 where you would naturally group. Mycetoma is an</p> <p>11 example. There are quite a lot of fungi that cause</p> <p>12 mycetoma. They're not easy to grow and even more</p> <p>13 difficult to identify and -- but the immunological and</p> <p>14 the histopathological characteristics are fairly</p> <p>15 distinctive, so you could definitely enroll those and</p> <p>16 then you could look at -- that's happening, of course</p> <p>17 with the ravuconazole study which is ongoing,</p> <p>18 primarily in Sudan.</p> <p>19 I think the same could be true for</p> <p>20 chromoblastomycosis, so it, like mycetoma, these are</p> <p>21 both neglected tropical diseases with the WHO, so I</p> <p>22 think that would be helpful. I -- if one was to do a</p>	<p style="text-align: right;">Page 288</p> <p>1 thing to do, but -- medically, but also from a</p> <p>2 strategic drug development perspective. But</p> <p>3 obviously, not everywhere.</p> <p>4 DR. LUIS OSTROSKY-ZEICHNER: Thank you</p> <p>5 for that comment, David. We have Mike Hodges again.</p> <p>6 DR. MICHAEL HODGES: Yeah, hi.</p> <p>7 Question for the panelists or perhaps George Thompson</p> <p>8 as well. What about grouping the endemic mycoses?</p> <p>9 And also another question, what about grouping</p> <p>10 talaromyces with cryptococcus? Thank you.</p> <p>11 DR. GEORGE THOMPSON: Yeah, hi, this is</p> <p>12 G.R. Can you all hear me now?</p> <p>13 DR. LUIS OSTROSKY-ZEICHNER: Yes.</p> <p>14 DR. GEORGE THOMPSON: I do think that</p> <p>15 the endemic mycoses really are one of these pathogens</p> <p>16 that really should be grouped together for the</p> <p>17 purposes of study. There's tremendous heterogeneity</p> <p>18 in these different groups. Some are immunocompetent.</p> <p>19 Some obviously are not, and then the host immunology</p> <p>20 is vastly different between these different patients</p> <p>21 who, for example, a Filipino patient may get just</p> <p>22 severe cocci meningitis whereas other ethnicities</p>
<p style="text-align: right;">Page 287</p> <p>1 study in mucormycosis, I think it's inevitable that</p> <p>2 they're grouped, but -- and the disease patterns, not</p> <p>3 only are the fungi different, but the patterns are</p> <p>4 different, of course, so you have primary</p> <p>5 rhinocerebral, but you also have other patterns of</p> <p>6 disease, particularly pulmonary, but also cutaneous.</p> <p>7 So you're going to mix and match study</p> <p>8 different patterns of disease, different underlying</p> <p>9 diseases such as diabetes or leukemia or whatever, as</p> <p>10 well as different pathogens. And I could imagine a</p> <p>11 study where it wouldn't be difficult -- it wouldn't be</p> <p>12 easy to do, of CNS fungal infections which would</p> <p>13 include maybe taking out crypto, but you could have a</p> <p>14 whole load of different dematiaceous fungi,</p> <p>15 aspergillus, (inaudible) mucor, (inaudible) and so on,</p> <p>16 and they can all be grouped together and look at the</p> <p>17 outcome, because that's a difficult diagnosis to get</p> <p>18 to fast, and speed of treatment is very important, and</p> <p>19 then you try and sort out the different pathogens</p> <p>20 later.</p> <p>21 So I can see that there are definitely</p> <p>22 some indications where I think this would be the right</p>	<p style="text-align: right;">Page 289</p> <p>1 handle it different immunologically.</p> <p>2 So it may be very difficult to tease</p> <p>3 those groups apart for purposes of a trial, and we've</p> <p>4 been fairly successful grouping these together with --</p> <p>5 MSG 15 study is ongoing, doing quite well. There's a</p> <p>6 number of others sort of in discussions for</p> <p>7 development, so I do think they really need to be put</p> <p>8 together for the purposes of these trials, given the</p> <p>9 difficulty in not doing that. And then the question</p> <p>10 about crypto and talaromyces, I think the conduct of</p> <p>11 those studies is actually fairly similar as far as the</p> <p>12 ability to look at CFUs and some of these things as</p> <p>13 surrogate markers of endpoints, but probably would</p> <p>14 defer to David or John Perfect for that as well.</p> <p>15 DR. DAVID DENNING: Can I make one more</p> <p>16 comment on that? I think one of the challenges is</p> <p>17 that particular grouping is that most of the patients</p> <p>18 are HIV, and we now know that we need to delay ART in</p> <p>19 crypto cases, but we don't delay it in talaromyces</p> <p>20 or histoplasmosis, so I think there might be a very</p> <p>21 technical reason for not grouping them there.</p> <p>22 DR. JOHN PERFECT: Yeah, I agree. I --</p>

<p style="text-align: right;">Page 290</p> <p>1 DR. LUIS OSTROSKY-ZEICHNER: Go ahead, 2 John. 3 DR. JOHN PERFECT: Sorry. Sorry, that 4 thing went off and on on me. Mike, I'm shocked you 5 said, I thought talaromyces. The pathophysiology, the 6 organism, the -- and crypto would be pretty 7 dramatically different. Sites on infection would be 8 different and I wouldn't put -- I'd split the 9 talaromyces with -- closely to end endemic mycosis 10 with HIV, but I don't think there's things go 11 together, personally. 12 DR. LUIS OSTROSKY-ZEICHNER: Thank you, 13 John. Pete Pappas. 14 DR. PETER PAPPAS: -- muted. 15 DR. LUIS OSTROSKY-ZEICHNER: We can 16 hear you now. 17 DR. PETER PAPPAS: Thank you. Thank 18 you. No, I just wanted to agree with G.R. and John. 19 I think endemic can be studied together. I think they 20 are rare enough but also similar enough that they can 21 be grouped and cocci is the one that kind of stands 22 out to me that's -- of course, they're all unique, but</p>	<p style="text-align: right;">Page 292</p> <p>1 DR. WILLIAM HOPE: Thank you, Helen. 2 I'm not -- this is difficult, isn't it, because we 3 don't really have the preclinical tools that we have 4 for candida and aspergillus and cryptococcus, so I 5 think at the end of the day, that's all the 6 preclinical models do offer is, it is supportive and I 7 think that our main tactics still have to be to 8 generate deep knowledge in preclinical and early phase 9 clinical studies in one of those three main diseases, 10 not only because they're most important numerically, 11 but because we have the most robust tools to start 12 there and then if there are other -- for those rarer 13 diseases and there are some models, but they're much 14 less... 15 DR. HELEN BOUCHER: William, we lost 16 you. Okay, we'll give William a minute to see if he 17 can reconnect. Erin Zeituni, did you want to add any 18 comments in this regard? 19 DR. ERIN ZEITUNI: Thank you, Helen. I 20 was waiting to be taken off mute. Very excited to 21 hear all of the comments from this panel. This has 22 been excellent. Thank you all so much.</p>
<p style="text-align: right;">Page 291</p> <p>1 cocci does kind of stand out as being sufficiently 2 different than -- maybe you can study it by itself, 3 but you can -- you certainly can include paracocci 4 sporo, even some of the newer endemic mycoses. 5 I'm not sure that -- I mean, the newer 6 forms of blastomycosis that have been described, I 7 think they're all similar enough at this point that 8 they -- in order to study them, they sort of have to 9 be grouped. That's all I wanted to say. 10 DR. LUIS OSTROSKY-ZEICHNER: Perfect. 11 Thank you very much. I'm going to turn it back to 12 Helen for the next question. 13 DR. HELEN BOUCHER: Great. Thanks very 14 much, Luis. So we've heard some allusions to PK/PD, 15 and now we're going to get to talk about PK/PD. So 16 the question is, what is the role of supported 17 preclinical animal models to provide proof of concept 18 that an antifungal agent is active against uncommon 19 fungal diseases, for example, scedosporium, fusarium, 20 et cetera. 21 And I thought we could ask William Hope 22 to kick this one off.</p>	<p style="text-align: right;">Page 293</p> <p>1 I think this is a conversation that's 2 very familiar to a conversation we're having in 3 bacterial models for hep and bap for resistant 4 bacteria where you have these rare patients to try to 5 access and the possibility of having preclinical 6 models so the supportive data to support those trials, 7 so it's a conversation that we're continuing to have 8 there and I'm curious to hear what the panel thinks 9 about it in this context. 10 DR. HELEN BOUCHER: Great, thanks very 11 much. William, were you able to reconnect? 12 DR. WILLIAM HOPE: Without problem, 13 yes. 14 DR. HELEN BOUCHER: Great, go ahead. 15 DR. WILLIAM HOPE: I'm not -- I didn't 16 hear the last contribution, but I don't know whether - 17 - how much you heard. Was I -- sorry, I apologize, 18 speaking to myself for five minutes, but well my main 19 comment was I think that the first models of rarer 20 molds have relatively little to offer because (sound 21 drops) than for candida, aspergillus, and 22 cryptococcus.</p>

<p style="text-align: right;">Page 294</p> <p>1 So the majority of the preclinical dose 2 exposure response relationships have been established 3 in those very well-validated and characterized model 4 systems. 5 DR. HELEN BOUCHER: Great, thanks very 6 much. Luis, I'll hand it back over to you. 7 DR. LUIS OSTROSKY-ZEICHNER: Thanks, 8 Helen. So question six is "Discuss how clinical trial 9 networks can facilitate antifungal drug development 10 and some of the barriers to establishing such 11 networks." First, I'd like the current president of 12 the mycosis study group to -- 13 DR. JOHN PERFECT: Okay, Luis thanks 14 for the opportunity to talk about the clinical trial 15 network. Actually, the mycosis study group has done 16 this for many, many years. I think it's still very 17 effective at doing that. I think that one of the 18 things I actually believe is that there needs to be a 19 more even robust clinical trial network. 20 Have to realize that what we have here 21 is evolution which no one really talks about which is 22 dealing with the infrastructure of all this, more and</p>	<p style="text-align: right;">Page 296</p> <p>1 external controls. If they had money and things, they 2 can suck all that data out. It just takes a little 3 bit of time, but they can see what they're system is 4 and then bring new patients in and have a system set 5 up to actually be pretty facile, be pretty quick on 6 it. 7 So without going farther with kind of 8 details with this type of stuff, I think that on a 9 practical basis, I think having trial networks that 10 are ready and robust and can do these kind of things 11 is actually the wave of the future, just as you had 12 cancer centers and stuff like that, you have fungal 13 centers that have all the abilities, if they're 14 supported with an infrastructure, that can move very, 15 very fast on these things. 16 Surely, the patients are there. That's 17 not the problem. The problem is actually funding the 18 infrastructure and coordinating it. 19 DR. LUIS OSTROSKY-ZEICHNER: Thank you 20 very much, John. We're going to go with Pete Pappas 21 and then after him, John Rex. Pete, go ahead. Go 22 ahead.</p>
<p style="text-align: right;">Page 295</p> <p>1 more regulations, more and more coordination, various 2 things. 3 It's very, very costly and very, very 4 expensive for many of these systems to actually get up 5 and by the time they get up, the study's over or you 6 don't get any patients and stuff like that, so the 7 networks that we do today have been kind of ma and pa 8 operations and stuff like that, and the truth of the 9 matter is, the amount of demands on them are so 10 incredible today that it can't be ma and pa. They 11 don't have the resources to be ma and pa. 12 So I think clinical networks are 13 extraordinarily important, but I think coming down to 14 one big word, which is money. Is somebody going to 15 take the time and effort to set up clinical trials, 16 whether it's in the United States or Europe, a series 17 of places, because there's big places, have tremendous 18 amount of fungal infections and we're not utilizing 19 them very well because the infrastructure is hard to 20 keep up. 21 But I think that antifungal development 22 needs to go into that group, just as I said with</p>	<p style="text-align: right;">Page 297</p> <p>1 DR. PETER PAPPAS: Thank you. Thank 2 you. I like what John says, and of course, obviously, 3 we believe in networks. I think the MSG was the first 4 real successful clinical trials network and what 5 you're really asking for is administrative support. 6 That is, if the system that existed and could exist 7 now includes one where companies can innovate, people 8 can think, people can create new compounds. 9 There's a huge incentive now or a 10 better incentive now to create these new compounds by 11 virtue of the Gain Act and other initiatives, making 12 it a little bit easier and more profitable to develop 13 these, but you still need -- and I agree with John. 14 It doesn't have to be one network. I mean, there 15 could be multiple international networks, but as it is 16 right now, certainly within the U.S., I mean, the MSG 17 serves a purpose now of consulting with a number of 18 different companies how to design this particular 19 trial, which are the best sites historically that 20 perform. 21 I mean, these are the sorts of things 22 that could be enhanced, could be tremendously</p>

<p style="text-align: right;">Page 298</p> <p>1 buttressed, and MSG could not only -- or a clinical  2 trial network, whatever you want to call it -- could  3 be empowered to go out and train sites more than we do  4 instead of simply relying on the same sites, because  5 quite honestly, one of our roles has to be the  6 training of the next generation of clinical mycology  7 experts.</p> <p>8           Our group is a group that's growing  9 older and there has not been an incredible influx into  10 our discipline, as say, there has been, you know,  11 hepatitis C or HIV. There need to be that kind of  12 investment. I mean, this -- these are collective --  13 collectively, this is a public health issue, a major  14 public health issue.</p> <p>15           And there's been not a lot of  16 investment on the part, you know, the government in  17 terms of supporting these networks. We have done it  18 mostly on our own and we have, to the extent that we  19 can, gone out and tried to lasso in some of the better  20 international sites, but certainly not all of them.  21 And even not all of the national -- of the U.S. sites.  22           But, I mean, these are the types of</p>	<p style="text-align: right;">Page 300</p> <p>1 developing drugs and from the moment you've got a  2 molecule that actually is looking like it probably is  3 a drug, you only need another \$100, \$150 million to  4 get it to initial approval, and then you only need  5 another few hundred million dollars to keep it on the  6 market, manufacture, do the pharmacovigilance, and do  7 all the pediatric requirements and so forth that keeps  8 it on the market.</p> <p>9           Those are big numbers and the theme for  10 this whole community to pay attention to is the notion  11 that the antibacterial enterprise has fallen flat on  12 its face because of the economic of antibiotics. Five  13 of the last 15 antibacterials that were approved in  14 the United States, the companies behind them are now  15 bankrupt.</p> <p>16           Antifungals might have a little bit  17 easier of a path because the unmet need is a little  18 crisper for a period of time, but you get one or two  19 interesting new compounds approved and all of a  20 sudden, there will be no new antifungals because there  21 is no reimbursement for them. And the theme that I  22 would like everybody to start to pay attention to is</p>
<p style="text-align: right;">Page 299</p> <p>1 things that a network can do that can facilitate the  2 conduct of these trials, even run simultaneous trials,  3 give the best advice that can be given to entities,  4 including competing entities. And getting back to  5 another point, we have just a huge, huge denominator  6 of patients who are screened, never enrolled, and then  7 we don't know what really happened to them.</p> <p>8           The individual investigator pretty much  9 has to do that on their own and there's no collective  10 or community effort to do that because the funding is  11 lacking. So lots of opportunities. Most of them are  12 being missed by -- through really, lack of funding and  13 I agree with John. I think the main issue right now  14 is administrative support, funding, and how to capture  15 those patients in detailed registries that otherwise  16 escape us.</p> <p>17           DR. LUIS OSTROSKY-ZEICHNER: Thank you  18 very much. Very thoughtful. Dr. Rex.</p> <p>19           DR. JOHN REX: There we go. My  20 microphone's on. So I want to broaden this just a  21 little bit and go back to some of the things that  22 Laura Kovanda said. She pointed out the cost of</p>	<p style="text-align: right;">Page 301</p> <p>1 that the lessons in the antibacterial world about the  2 need for appropriate polling centers, and that was  3 briefly mentioned by Laura Kovanda, and let me just  4 decode that.</p> <p>5           This is the idea that we pay for new  6 antimicrobials in the same way that we pay for fire  7 extinguishers, fire departments, and life insurance.  8 That is, we don't get up and say, gee, I think I'll  9 buy a fire extinguisher because my house is on fire.  10 We actually buy on in advance of my house catching on  11 fire and we're actually pleased to have it, even  12 though my house doesn't catch on fire.</p> <p>13           And antibiotics need to be paid for in  14 very much that same way. So when you come down to  15 this idea of funding clinical trial networks, we've  16 looked at that exhaustively. We funded antibacterial  17 networks through the New Drugs 4 Bad Bugs Project in  18 the United States, the ARLG and the -- I'm sorry, the  19 E -- ARLG in the United States.</p> <p>20           And for a while, you can keep them  21 going, but if they don't have things to work on, the  22 gas runs out of the car and the car comes to a stop.</p>

<p style="text-align: right;">Page 302</p> <p>1 And the way that you have stuff to work on is you've 2 got industry able to actually bring products forward 3 and get them appropriately reimbursed. So it's a very 4 deep pocket with -- we've touched a few times in the 5 cost of doing this work, the costs are serious and 6 it's important that we as a community speak clearly 7 and frequently to the need for appropriate 8 reimbursement for new antibacterials and antifungals. 9         And I commend to you a variety of 10 materials on this and I don't mean to be self-serving, 11 but if you follow the -- my AMR Solutions newsletter, 12 you'll learn about this over time. There's some great 13 stuff in the Lancet ID recently about this and we want 14 to pay -- look at the writings of Helen Boucher about 15 New Drugs 4 Bad Bugs, look at the writings of Neil 16 Clancy. 17         So please pay attention to this, 18 because otherwise none of this stuff will stay active. 19 It'll work for a little while, but then it'll run out 20 of steam, so, over. Thank -- sorry about the rant but 21 thank you for listening. 22         DR. LUIS OSTROSKY-ZEICHNER: Thank you</p>	<p style="text-align: right;">Page 304</p> <p>1 hard question. 2         It's not with -- such a chronic 3 disease, it's really hard to sort that out, but I 4 think with more agents coming along with activity 5 against a number of these disease -- in these diseases 6 we've talked about is really going to be important to 7 try to sort that out, and I do think that preclinical 8 models can help answer that question to get rid of 9 some of the heterogeneity, of course. 10         With cocci, it's harder because there 11 are not very many groups that work with cocci now 12 because it's really hard, too. It's hard in animals 13 and so I think those are -- make it more expensive and 14 more difficult to do, but I think it's still a really 15 important question. G.R. may want to comment. 16         DR. HELEN BOUCHER: Sure. G.R., do 17 you want to comment? 18         DR. SHAWN LOCKHART: So going back to 19 the first question, unfortunately the way the CLSI 20 works, there really aren't going to be any breakpoints 21 for most bug-drug combinations unless there's outcome 22 data, and I see that as a real problem and one that</p>
<p style="text-align: right;">Page 303</p> <p>1 very much. I'm going to turn it back to Helen. 2 There's some questions in reserve we have. 3         DR. HELEN BOUCHER: Great. Thanks very 4 much, Luis. So we thought that was difficult. Now 5 let's talk a little bit about susceptibility testing. 6 So the question is, how can we obtain data that can 7 adequately support susceptibility testing, 8 interpretive criteria for new antifungal drugs, in 9 general? And then second, what is the role of 10 interpretive breakpoint in developing drugs for cocci 11 and what is the impact of that pathogen being BSL-3? 12         So two questions in the breakpoint 13 category that we can put out. And let's see, if 14 nobody raises their hand, Dr. Patterson, do you want 15 to take a stab at that to kick us off? 16         DR. THOMAS PATTERSON: -- give that a - 17 - yeah, so I think that that's a really important 18 question, you know, from the fungus testing there in 19 the study that G.R. led with Nathan. They looked and 20 showed a number of strains of coccidioides that were - 21 - that have higher MICs to fluconazole. It's kind of 22 our clinical opinion that that's relevant, but it's a</p>	<p style="text-align: right;">Page 305</p> <p>1 UCAS seems to have moved past, at least to some 2 degree. 3         But right now, as far as the CLSI is 4 concerned, without outcome data, they are not going to 5 establish breakpoints and so we're always going to 6 have relatively few breakpoints and we're always going 7 to be dependent on clinicians' intuition, so to speak, 8 for deciding whether or not an MIC of 2 to drug X is 9 going to be efficacious in a particular patient. So 10 that is a handicap of the way that the system works in 11 the U.S. right now. 12         As far as cocci testing, in preclinical 13 trials, I think it's a great idea, but it's never 14 going to go beyond that. Being a BSL-3 agent, no 15 one's going to do cocci testing in their laboratories 16 in their hospitals or probably not even in most 17 reference laboratories outside the fungal testing 18 laboratory. 19         DR. HELEN BOUCHER: Great, thanks. And 20 just for the record, that was Shawn Lockhart, and now, 21 G.R., you're up. 22         DR. GEORGE THOMPSON: Oh, they unmuted</p>

<p style="text-align: right;">Page 306</p> <p>1 me. So I think that cocci is an example of how this  2 investigation has gone backwards. So, you know, we  3 had sort of salvage studies. We have one randomized  4 trial and then we looked to try to explain the results  5 of that ITRA versus FLU study by looking at, you know,  6 large scale susceptibility testing almost 20 years  7 later for all the reasons that Shawn just illustrated.  8 You know, in vitro testing is pretty difficult. You  9 do it in the (inaudible) form rather than the  10 spirulina spore form, so there is some criticism with  11 that as well.  12 But, you know, this week, we found --  13 we think the in vitro results sort of line up with  14 what we found clinically. MIC-50 for flu was 8  15 compared to very low MICs for the mold activate  16 azoles, so -- and we think that explains pretty nicely  17 why ITRA basically beat fluconazole on the animal  18 study.  19 So I do think that this is important.  20 I agree with Shawn, we're probably not going to have  21 outcomes data. I think that as a clinician, I think  22 that's fine. We're forced to do that on a regular</p>	<p style="text-align: right;">Page 308</p> <p>1 allergic and chronic disease.  2 I suspect it will also be true for  3 invasive disease, but it's harder to generate the  4 data, and if you use a much hard -- larger volume, you  5 get many more cultures and then you can do more  6 susceptibility testing. So there's also a need, I  7 think, for those organizations that approve laboratory  8 methods and care about such things to adopt a much  9 better, more sensitive systems for culture than are  10 there.  11 So it's a call for better culture and  12 it's a call for using non-culture and resistance  13 detection as part of our regulatory approach in the  14 future.  15 DR. LUIS OSTROSKY-ZEICHNER: Thank you  16 very much, David. We have two specific questions from  17 the audience. The first one is, "Can NIAID  18 Preclinical Services provide access to specific  19 antibodies?" I don't know if you want to answer that,  20 Erin?  21 DR. ERIN ZEITUNI: Sure, thank you.  22 And thank you to the individual who submitted that</p>
<p style="text-align: right;">Page 307</p> <p>1 basis in the care of patients with other fungal  2 infections, too. But I think that this does sort of  3 illustrate the importance of in vitro testing, animal  4 models, and then seeing if we sort of agree with that  5 by just clinical acumen. I'll stop there.  6 DR. HELEN BOUCHER: Great, thanks so  7 much. So Dr. Denning next and then back to Luis.  8 DR. DAVID DENNING: So just a quick  9 comment about the aspergillus world where with the  10 azoles, we now can detect resistance without growing  11 any organism at all using either the diagnostic PCR or  12 para-sequencing, in our lab, and I think there will be  13 others who can do that.  14 I would really like to see the  15 regulatory team address this issue of non-culture  16 based resistance detection as opposed to depending  17 upon culture, because I think this is a very important  18 new area of development and something that would  19 really accelerate the development of drugs for  20 resistant pathogens. We have just written a --  21 published a paper on high volume cultures for  22 aspergillus in respiratory samples for patients with</p>	<p style="text-align: right;">Page 309</p> <p>1 question. So it's a little bit difficult to  2 understand exactly what they're looking for, but as  3 far as access to antibodies, if those antibodies are  4 found in the BIV sources, it would be something that  5 you could have as available.  6 If you're looking for development of  7 antibody program, a biotherapeutic, we do support  8 those programs, but without additional information  9 about exactly which specific antibody they're looking  10 for, I would just encourage that individual to get in  11 touch with us and we could very happily discuss it  12 more.  13 DR. LUIS OSTROSKY-ZEICHNER: Thank you  14 very much. The final question we have is, "Please  15 elaborate on FDA EMA differences in the weighing of  16 preclinical data." And I'd like to invite William  17 Hope to start off the discussion there.  18 DR. WILLIAM HOPE: Thank you, Luis. So  19 I -- this is slightly sensitive, isn't it? So I'll  20 just try and keep it as general as I can. So I think  21 -- and I'm going to talk about everything that I've  22 witnessed. I think that in the U.S., there's been a</p>

<p style="text-align: right;">Page 310</p> <p>1 lot of interest in using survival in laboratory animal  2 models and that's both in antibacterial as well as in  3 antifungal drug development.</p> <p>4       And in Europe, there's an interest in  5 using complex in vitro systems like (inaudible). So I  6 think the way, just on reflection, that -- and as I've  7 tried to say in my talk, there are two separate but  8 completely complimentary systems, and that is, there's  9 useful information from a PK/PD perspective, trying to  10 understand how the drug is docking with its target.</p> <p>11       And then there's the more clinically  12 relevant, if I could use that term, model systems, the  13 rabbit model system, for example, where survival  14 actually may be very reasonable and clinically  15 relevant endpoint, so I think that what people are  16 sort of expressing, this range of model readouts, but  17 I -- we had similar model systems and we had so many  18 biomarkers.</p> <p>19       I do not believe that they delayed  20 quota in terms of one being any better than the other.  21 They should be views as a complimentary package. But  22 the problem, of course, these model systems are</p>	<p style="text-align: right;">Page 312</p> <p>1 the discussion, that the most immediate unmet medical  2 need is obviously for delayed-resistant factory molds,  3 both that developed acquired resistance and had innate  4 resistance to antifungal therapies.</p> <p>5       These invasive fungal diseases are rare  6 and have high morbidity and mortality (inaudible). We  7 have issues of adequate antibacterial (inaudible) of  8 activity and also potential difficulties in attaining  9 efficacious exposure in target organs, have problems  10 with drug-drug interaction, specifically for azoles,  11 given their metabolism -- metabolic pathways and also  12 organ toxicity that eventually result in poor outcomes  13 both in clinic and on clinical trials.</p> <p>14       Obviously, underlying diseases, immune  15 suppression, site of invasive fungal diseases, as well  16 as propensity to dissemination affect the management  17 and pose therapeutic challenges.</p> <p>18       So we also know that there are a lot of  19 difficulties now in enrolling even in, you know,  20 common, in these candidiasis, invasive aspergillosis  21 studies in very efficient manner.  22       (Inaudible) put strains on the</p>
<p style="text-align: right;">Page 311</p> <p>1 expensive and they are very time consuming and so if  2 you go down one path with one agency and then get told  3 to do a whole other experiments down another path,  4 that may cost six or 12 or more months and a lot of  5 money, so that -- I think there could be a degree,  6 given that the reliance on these model systems to get  7 them maybe better aligned as has happened in other  8 contexts.</p> <p>9       DR. LUIS OSTROSKY-ZEICHNER: Thank you  10 very much for that answer, William. With three  11 minutes to spare I'm going to turn it back to the FDA.  12 Dr. Yasinskaya's going to do a summary and closing  13 remarks. Thank you very much.</p> <p>14       DR. YULIYA YASINSKAYA: Thank you very  15 much. Good late afternoon to all of you. This was an  16 amazing discussion, presentations, and very robust  17 discussion today on what development consideration we  18 have for antifungal drug development at -- for the  19 drugs that aim to address unmet medical needs.</p> <p>20       The major takeaway from today's  21 presentation discussion, you know, given that we had a  22 very ambitious agenda and very loaded questions for</p>	<p style="text-align: right;">Page 313</p> <p>1 scientific community, investigators alike, and  2 investors as well. So the existing clinical trial  3 framework appears to be time consuming and costly, so  4 we're looking for more efficient ways to conduct  5 medical trials. And while such standards for approval  6 of antifungals for common and uncommon invasive fungal  7 diseases do not change, regulatory agencies in the  8 U.S. and across the pond are willing to exercise  9 flexibility in accepting smaller data packages and  10 additional supportive both clinical and nonclinical  11 data.</p> <p>12       We cherish our collaborative efforts,  13 public and private partnerships, and engagement with  14 stakeholders along with the robust scientific research  15 and evolving understanding of natural history of  16 invasive fungal diseases and their response to the  17 therapies, both in clinical and nonclinical models and  18 these will help inform and more streamline approaches  19 for antifungal development.</p> <p>20       We think that alternative clinical  21 trial design and use of biomarkers to select trial  22 participants as well as monitor their responses to</p>

<p style="text-align: right;">Page 314</p> <p>1 therapy are critical for future antifungal development  2 for invasive fungal diseases. We know that pediatric  3 population is a therapeutic orphan population and as  4 the diseases -- antifungal diseases, invasive fungal  5 disease are -- generally have orphan designation,  6 pediatric population tends to be left out.  7 We commend Astellas and other companies  8 that take it upon themselves with help of BPC as well  9 to take upon themselves and evaluate pediatric  10 patients with the invasive fungal diseases, both in  11 the randomized controlled setting as well as in  12 investigating nonclinical models and also conducting  13 very thorough PK/PD assessment to inform dosing in  14 pediatric patient, including neonates.  15 So we might consider animal models  16 going forward to inform dosing specifically in  17 neonatal patient population, but that would also need  18 reach PK and safety data. We also need to consider  19 when we're thinking about developing trials --  20 clinical trials for invasive fungal diseases, we need  21 to think about emergent multidrug resistance pathogen  22 with ability to spread extensively in healthcare</p>	<p style="text-align: right;">Page 316</p> <p>1 might mean in this particular scenario.  2 And the animal model data might be very  3 helpful also to be used in support of clinical trials  4 for difficult to study mycosis, such as multidrug  5 resistant fungal infections, invasive aspergillosis,  6 and mold. Also, there was the discussion about  7 potentially using nonclinical model for informing rate  8 points for fungal pathogens.  9 With regards to clinical trials, there  10 was a lot of discussion with regards to how to vet and  11 develop the clinical trials to streamline them to  12 (inaudible) more efficiency potentially enrolling  13 patients with infections in multiple body sites at the  14 extremes of age with different underlying  15 comorbidities, understanding that that will bring  16 significant heterogeneity in the outcomes.  17 Also there were thoughts of potentially  18 combining and pooling across different fungal species  19 as it relates to crude grouping, like for example  20 MUCORALES rhizopus, as well as endemic mycosis  21 together. And although they're potentially different  22 -- the (inaudible) to a particular drug study, these</p>
<p style="text-align: right;">Page 315</p> <p>1 setting and/or complicate viral infection in the many  2 healthy ventilated hosts such as flu or COVID-19.  3 What we have learned today, what --  4 clinical models and their routine and potential  5 notable uses is that of course we use (inaudible)  6 proof of concept studies and also in those (inaudible)  7 PK/PD modeling support clinical trial just like the  8 dose and exposure of the target in clinic. We now  9 start thinking about potentially using animal model  10 data to supplement clinical randomized controlled  11 trial. In that, we need to think about using  12 potentially multiple animal models to complement each  13 other.  14 We approach both quantitative outcomes  15 and qualitative outcome which is, you know, user  16 biomarkers, burden reduction, humane endpoints, and so  17 on. And the more animal data we have, specifically if  18 we have individual animal data that the regulatory  19 agencies can review and how it correlates with  20 available clinical trial outcome data, that will  21 obviously alleviate some uncertainties of what --  22 certainly not clinical, not a clinical trial endpoint</p>	<p style="text-align: right;">Page 317</p> <p>1 data would definitely enrich the clinical concepts  2 generated and might be helpful and formative for  3 clinicians.  4 What do we? We got to multidrug  5 resistance fungal infections, whether we need enrich  6 patient population, that is something for us to  7 consider going forward and designing clinical trials  8 for invasive fungal diseases.  9 So additional endpoint that -- the  10 point that had been brought up on multiple occasions  11 during today's presentations and discussion was the  12 use of point of care diagnostics to improve trial  13 efficiency in both enrollment and obtaining treatment  14 response and particular targeting high risk for fungal  15 infections. That might be concerns in delay of  16 treatment and also improve speed of enrollment and  17 shortened duration of clinical trials as well.  18 We had discussed that stable outcome  19 potentially to be considered to be included to figure  20 in the success for outcome assessment in clinical  21 trial due to length of time in changing that stable  22 outcome into success over time. Again, because we</p>

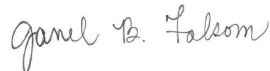


<p style="text-align: right;">Page 318</p> <p>1 want to make the trial more efficient. And a lot of  2 discussion in regard to trial networks.  3         We want them to be more robust,  4 understanding that they're very expensive and we need  5 administrative and governmental support, to support  6 the evolution, also, and the maintenance of the  7 infrastructure as well as putting money and feeding  8 the development of new clinical scientific  9 investigators.  10         Going forward, we still have a lot of  11 gaps, uncertainties, and remaining challenges in sort  12 of honing into very straightforward path for  13 antifungal drug development. We're not sure that the  14 animal model for rare unmet medical need in invasive  15 fungal disease is of high enough quality to really  16 support regulatory actions or labeling; however, we're  17 seeing already a lot of discussion and actually  18 evaluation of data submitted for animal models that  19 being included in the U.S. package inserts, and  20 particular in Section 12.4 Microbiology, to provide  21 some data for the clinician; although, you know, it  22 might not necessarily result in the indication and</p>	<p style="text-align: right;">Page 320</p> <p>1 obviously, the questions remain with regards to margin  2 justification. We know that the margin justification  3 ties to a particular comparator for which we have data  4 relative to placebo and therefore there might be some  5 uncertainties with regards to the margin and therefore  6 that does impact the trial design going forward.  7         Also, there were discussions about  8 expanding, potentially, enrollment criteria in order  9 to simplify antifungal trials, but we need to keep in  10 mind that extending the duration of the trial  11 antifungal therapies might drive the trial --  12 noninferiority trial physically towards a  13 noninferiority as well.  14         So we do expect regulatory flexibility  15 in accepting certain smaller packages with additional  16 support data were from -- made in nonrandomized  17 clinical trials but also from nonclinical data. We  18 need to define more what that flexibility actually is  19 and what kind of uncertainty we're willing to accept  20 for particular indications.  21         We understood that there's some  22 questions about feasibility of using (inaudible)</p>
<p style="text-align: right;">Page 319</p> <p>1 specific dosing recommendation, but it will provide  2 them with additional information that they can use in  3 deciding what type of therapy and at what particular  4 dosing range will be effective for their patients at  5 hand.  6         We do lack randomized controlled trials  7 in pediatric patients and neonates, understandably  8 that we're able to slide some PK/PD data from adult  9 and older patients and with some supplemental  10 information from animal models, we potentially might  11 be able to reach some certainty of the dosing regimen  12 that -- be appropriate for this patient population.  13         There was a lot of discussion on  14 external control data sources and availability. We  15 would like to have a current matched external controls  16 with -- where patients would be readily identified  17 with risk factors characterized and sufficiently  18 adjusted and matched for stages of invasive fungal  19 disease.  20         We also would like to see patients  21 level data to make -- to assure data validity for the  22 external controls. And for noninferiority studies,</p>	<p style="text-align: right;">Page 321</p> <p>1 mortality, the fact that this endpoint is particularly  2 noisy, whether we can start moving towards an outcome  3 that's described by actual simple mortality, and also  4 potentially using biomarkers, but we need to  5 understand that in order for a biomarker to be  6 considered to be a primary endpoint, we need to know,  7 particularly for accelerated approval, that it's  8 predict the clinically meaningful outcome.  9         As we talked about heterogeneity in  10 outcomes related to underlying disease and risk  11 factors, there was understanding that different  12 groups, neutropenic versus non-neutropenic, might  13 potentially have different outcomes and -- or HIV  14 positive versus non-HIV patients for cryptococcosis,  15 for example, and therefore that that needs to be  16 thought through when the trials are designed. We  17 heard pros and cons of having heterogenic population  18 in the study.  19         And there was a point brought up about  20 nonculture basis in testing for endemic and nonendemic  21 fungi, whether this needs to be considered going  22 forward. We need to see more data, how this non-</p>

<p style="text-align: right;">Page 322</p> <p>1 culture-based testing is better and more sensitive  2 relative to what we know about the cultures and that  3 obviously will have help with regulators as well as  4 the clinicians at the bedside.  5         We see multiple ways of taking this  6 discussion, this presentation forward into designing  7 more efficient clinical trials and the fact that we  8 will continue engagement with the stakeholders with  9 the industry, with the public-private partnerships,  10 and reviewing the data presented today and the data  11 presented during continued discussion with the agency  12 of what type of flexibility we can exercise and how  13 that will be supported by the scientific evidence.  14         Again, we're going to be looking  15 closely at the nonclinical model data to support  16 smaller data packages as Dr. Walsh had presented  17 today. We are really looking for redundant,  18 consistent animal models and that defining that PK/PD  19 driven. We're going to be looking more closely at the  20 novel endpoints and looking justification for those  21 endpoints and predicting clinically relevant outcomes.  22         Also was interesting, fascinating,</p>	<p style="text-align: right;">Page 324</p> <p>1 obtaining very robust PK data using physiologically  2 based PK and clinical trial simulation for study  3 design optimization in order to achieve appropriate  4 dose finding in this patient population.  5         We need to achieve consensus on design  6 definition, outcome adjudication, using signs and  7 symptoms versus clinical improvement as endpoints and  8 utilizing biomarkers as endpoint in clinical trials.  9         So lots of work has been done in the  10 past (inaudible) and a lot of work to be done going  11 forward, but I think we're in that sweet spot where we  12 can -- if we'll be probably able to change outcome for  13 the new antifungal in the works and thank you very  14 much.  15         DR. SUMATI NAMBIAR: Hi, Yuliya, can  16 you hear me?  17         DR. YULIYA YASINSKAYA: Yeah.  18         DR. SUMATI NAMBIAR: Hi, this is  19 Sumati. Thank you very much, Yuliya, for that  20 excellent summary and we're coming to close this  21 workshop and on behalf of everybody at the FDA I would  22 really like to thank all the speakers and panelists</p>
<p style="text-align: right;">Page 323</p> <p>1 innovative trial designs that have been presented by  2 Aaron Dane with data augmented controls and randomized  3 control setting as well as smaller clinical trials in  4 trying to find that sweet spot for a sample size and  5 potentially using 80 percent confidence intervals with  6 a 20 percent noninferiority margin for some of the  7 harder to study fungal infections.  8         And natural history clinical studies  9 with contemporary best available therapy or -- yeah,  10 best available therapy will help us to enrich our  11 external control data benchmarking. Particularly,  12 it's most important for rare invasive fungal disease  13 and molds and then endpoint was brought up with a  14 patient who has been screened but actually are not  15 able to be enrolled in the clinical trials, outcomes  16 of these patients also will potentially inform this  17 internal control data.  18         And then we discussed the pediatric  19 data. We understand that master protocol clinical  20 trial works are extremely helpful and the (inaudible)  21 sampling and extrapolation from all the kids, it's  22 helpful as well. Again, we need to do microdosing,</p>	<p style="text-align: right;">Page 325</p> <p>1 for joining us and for your contributions to the  2 discussion today.  3         Special thanks to Mr. Schueler for  4 joining us and sharing his story. We want to assure  5 you that we're all in this together and we hope to  6 work together to find safe and effective therapies for  7 patients. I think that clearly is our intent.  8         Also, many thanks to all the  9 participants for calling in. I know it's been a long  10 day, but certainly very fruitful and as I said at the  11 beginning of the day, hopefully one of a series of  12 discussions that we will have on this topic.  13         So I know many of you will be joining  14 us tomorrow when we'll talk about drug treatment for  15 cocci and I look forward to that discussion. Those of  16 you that would not be joining us, again, many thanks  17 for participating in today's workshop and really  18 appreciate everybody's input. Have a good evening and  19 back online tomorrow. Thank you.  20  21  22</p>

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