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Addressing Challenges in Inhaled Antifungal Drug
Development

Moderated by Dr. Richard Moss, Dr. Kieren Marr

Friday, September 25, 2020

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Remote Proceeding

Silver Spring, Maryland 20910

Reported by: Carl Hellandsjo

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4 Dr. David Andes, University of Wisconsin-Madison	4 Dr. Robert Lim, FDA
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6 Dr. Rohit Bazaz, University of Manchester, UK	6 Dr. Sumati Nambiar, FDA
7 Dr. Lance Berman, Pulmocide, Inc.	7 Dr. Mark Needles, FDA
8 Dr. Radu Botgros, European Medicines Agency	8 Dr. Khalid Puthawala, FDA
9 Dr. Dale Christensen, TFF Pharmaceuticals	9 Dr. Thomas Smith, FDA
10 Dr. Cornelius Clancy, University of Pittsburgh	10 Dr. Christopher St. Clair, FDA
11 Dr. Russell Clayton, Pulmatrix, Inc.	11
12 Dr. David Corry, Baylor College of Medicine	12
13 Dr. Shampa Das, University of Liverpool	13
14 Dr. David Denning, University of Manchester	14
15 Dr. Anthony Durmowicz, Cystic Fibrosis Foundation	15
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<p style="text-align: right;">Page 6</p> <p>1 PROCEEDINGS</p> <p>2 RECORDING: Audio-recording for this</p> <p>3 meeting has begun.</p> <p>4 DR. FARLEY: Good morning, everyone.</p> <p>5 Shall we begin? Great. Good morning. This is John</p> <p>6 Farley, the director of the Office of Infectious</p> <p>7 Diseases at the Center for Drugs at FDA, and I want to</p> <p>8 welcome everyone to this virtual live workshop</p> <p>9 entitled Addressing Challenges in Inhaled Antifungal</p> <p>10 Drug Development.</p> <p>11 This is our third virtual workshop this</p> <p>12 year, actually in the last few months, focused on</p> <p>13 coming together as a community to facilitate</p> <p>14 antifungal drug development.</p> <p>15 We planned this workshop in response to</p> <p>16 the recent interest in development of inhaled</p> <p>17 antifungal products to address the needs of patients</p> <p>18 with allergic bronchopulmonary aspergillosis, which</p> <p>19 you'll hear during the day referred to as ABPA, and</p> <p>20 invasive pulmonary aspergillosis, which you may hear</p> <p>21 referred to as IPA.</p>	<p style="text-align: right;">Page 8</p> <p>1 For the audience, the speaker slides,</p> <p>2 transcripts and recordings will be available on the</p> <p>3 public webpage for this meeting in the coming days.</p> <p>4 For the highest quality audio for</p> <p>5 participants, speakers and panelists will be moved to</p> <p>6 presenter status and be able to connect their phone</p> <p>7 for both speaking and listening functions as the time</p> <p>8 for their session approaches. You will know that has</p> <p>9 happened because the phone icon will appear in the</p> <p>10 upper left-hand corner of your screen. You can then</p> <p>11 click on that phone icon and request the meeting</p> <p>12 software to call you.</p> <p>13 Otherwise, speakers and panelists will</p> <p>14 need to use their computer speaker for listening</p> <p>15 function only.</p> <p>16 Please use the comment box if any</p> <p>17 technical assistance is needed.</p> <p>18 At this point, I'm going to turn the</p> <p>19 program over to Doctors David Andes and Shampa Das.</p> <p>20 Dr. Andes is a faculty member and Chief of the</p> <p>21 Division of Infectious Disease within the Department</p>
<p style="text-align: right;">Page 7</p> <p>1 With no FDA-approved antifungal</p> <p>2 products, it is clear that a broad scientific</p> <p>3 discussion will be helpful as development programs are</p> <p>4 designed.</p> <p>5 Today brings together an</p> <p>6 interdisciplinary team from the FDA, which include</p> <p>7 specialists in infectious disease, pulmonary medicine,</p> <p>8 device development, pharmacology, toxicology, clinical</p> <p>9 pharmacology, clinical microbiology, biostatistics and</p> <p>10 outcome assessments joining together with academic and</p> <p>11 industry thought and patients.</p> <p>12 We want to thank all of our speakers</p> <p>13 and panelists for their efforts preparing for the</p> <p>14 workshop today. In particular, we thank those</p> <p>15 international thought leaders who are with us today,</p> <p>16 as well as our colleague from European Medicines</p> <p>17 Agency.</p> <p>18 Just a bit of housekeeping as we get</p> <p>19 started, we ask that folks speak clearly, stick to</p> <p>20 their allotted time so that we can stay on time today</p> <p>21 and ensure that we have adequate time for discussion.</p>	<p style="text-align: right;">Page 9</p> <p>1 of Medicine at the University of Wisconsin-Madison.</p> <p>2 And Dr. Das is a senior lecturer in the Antimicrobial</p> <p>3 Pharmacodynamics and Therapeutics Group at the</p> <p>4 University of Liverpool.</p> <p>5 So thank you very much and Dr. Andes</p> <p>6 and Dr. Das, please take it away and begin session</p> <p>7 one. Thank you.</p> <p>8 DR. ANDES: Thank you. Our first</p> <p>9 speaker, Dr. Richard Moss, who is Professor Emeritus</p> <p>10 Pediatrics at Stanford University, Center for</p> <p>11 Excellence in Pulmonary Biology. His recent work is</p> <p>12 focused on allergic fungal lung disease. His talk is</p> <p>13 titled What Place for Inhaled Antifungals in Pulmonary</p> <p>14 Medicine. Dr. Moss?</p> <p>15 DR. MOSS: Hello. Can you hear me</p> <p>16 okay?</p> <p>17 DR. ANDES: Yes.</p> <p>18 DR. MOSS: I hope so. Okay. Great.</p> <p>19 So I've been asked to give an introductory overview of</p> <p>20 today's topic. And the way I thought I would approach</p> <p>21 this is to start by using aspergillosis as the prime</p>

<p style="text-align: right;">Page 10</p> <p>1 example of fungal disease. And in fact, that is the 2 focus of the drug development we're talking about. 3 And starting by pointing out that we 4 all inhale spores from aspergillosis as well as other 5 molds. And normally, we do not have any illness from 6 that. We know that the host determines the risk of 7 illness by in large for this particular set of 8 problems. And on the bottom of this first slide, you 9 see a number of different phenotypes or syndromes that 10 have been recognized. 11 And I'll be talking firstly -- briefly 12 about the immunocompromised hosts who can develop 13 invasive pulmonary aspergillosis sometimes with 14 disseminated disease. And then later, the 15 immunocompetent patient who -- especially those that 16 are atopic that would develop allergic disease. 17 So to start with the immunocompromised 18 patient, we know that there are certain high-risk 19 situations that have been identified and these tend to 20 fall into a couple of different buckets. One main one 21 is people that are neutropenic either as a result of</p>	<p style="text-align: right;">Page 12</p> <p>1 aspergillus. I don't know why that went back. Okay. 2 And in immunosuppressed mice, and you can see that it 3 was compared to systemic, in this case intraperitoneal 4 amphotericin B deoxycholate, or a vehicle that was 5 given as treatment starting one day after the 6 challenge. And what's clear is that the inhalational 7 voriconazole was actually more effective than the 8 systemic amphotericin either when assessed during the 9 treatment period on the left or afterwards on the 10 right. So this gives kind of an example of the kind 11 of animal models that can be helpful in assessing 12 that. 13 And then in terms of looking at 14 particular novel products that are being developed, I 15 put a couple of different studies here. On the upper 16 left, you see a study that was also done in San 17 Antonio, in this case with immunosuppressed guinea 18 pigs who received a novel amphotericin B inhalational 19 powder that was developed initially by Nectar and 20 picked up by Novartis. Which four doses were given 21 one day before an aspergillus aerosol challenge and</p>
<p style="text-align: right;">Page 11</p> <p>1 induction chemotherapy for hematologic malignancy, or 2 those who are receiving stem cell transplantation. 3 And we know that the risk there, as you see in this 4 slide, is elevated. 5 The other group amongst patients who 6 have received organ transplants, we know that the lung 7 is the main risk factor, although disease can occur in 8 these other solid organs. And you'll note that 9 mortality across the board still remains distressingly 10 high. 11 So how might one think about 12 approaching this from an inhalational viewpoint? Of 13 course you have to start with the preclinical 14 situation in animal models to test out the 15 possibilities. And this is an illustrative study that 16 was done at the University of Texas, San Antonio, in 17 Tom Patterson's lab in which inhaled voriconazole, 18 using the intravenous solution which is what 19 clinicians may be using -- and we'll talk more about 20 that with regards to amphotericin in particular. This 21 is given two days before an aerosol challenge with</p>	<p style="text-align: right;">Page 13</p> <p>1 compared with oral voriconazole, two doses, starting 2 one day after the challenge. And at least one of the 3 doses of the amphotericin B powder is shown to be 4 relatively effective in proving survival to roughly 50 5 percent in this particular model. And that's 6 comparable to the optimal dose of voriconazole given 7 systemically as shown in the second panel there on the 8 left. 9 Moving to the right-hand side, we see a 10 study that was done by Pulmatrix and presented at the 11 Academy of Allergy meeting in 2018, in 12 immunosuppressed guinea pigs. And this was a 13 situation where they're a Pulmatrix novel product, 14 which is an inhalational form of itraconazole PUR1900 15 was given by nasal -- was given starting one day after 16 a challenge with a nasal inhalation of aspergillus for 17 a period of 10 days. And what you see there is that 18 in comparison to systemic itraconazole, it appeared to 19 be more effective in prolonging survival. 20 And interestingly, there's a 21 dissociation that's seen in the top there between the</p>

<p style="text-align: right;">Page 14</p> <p>1 microbiologic effect, which does not appear to have an 2 effect on fungal burden, versus the survival effect. 3 And this has been seen in a number of different 4 studies. So we have to remember that endpoints don't 5 necessarily reflect clinical outcome measures if -- if 6 one is focused solely on microbiology. 7 And finally, on the bottom, we see a 8 study from the Pulmocide group that was reported last 9 year in immunocompromised mice who were given daily 10 intranasal PC945, which is a novel azole inhalational 11 product, and compared to oral Posaconazole, or in this 12 case, a combination of the two. 13 And the -- this was done from one day 14 after the challenge for six days and showed that in 15 this particular model, combination therapy was 16 superior in preserving survival compared to either the 17 inhalational novel agent or the conventional systemic 18 agent. 19 In reviewing the literature, I think a 20 couple of broad conclusions are pertinent. First of 21 all, antifungal prophylaxis and lung transplantation</p>	<p style="text-align: right;">Page 16</p> <p>1 patients are add-on treatments to systemic treatments 2 for resistant or recalcitrant infections which are 3 mainly concerning emergent fungi that are multi- 4 resistant and often difficult to treat, even in 5 combination therapy. For example, 6 pseudocamarosporium, zygomycetes or fusarium. 7 And the -- area that I think is 8 important is the prophylaxis with inhaled amphotericin 9 in hematologic disease. These studies are usually 10 highly targeted to patients with anticipated extended 11 neutropenia. And these are high-risk patients often 12 selected where oral azole prophylaxis, which is the 13 recommended treatment, is problematic. 14 Those studies have shown a relative 15 risk reduction of roughly 50 percent versus no 16 prophylaxis in a few randomized controlled trials, but 17 no direct comparisons to oral azoles. 18 And again, a better toleration of the 19 niosomal formulation than the deoxycholate. 20 There is a fairly high discontinuation 21 rate due to adverse effects of about 10 percent in the</p>
<p style="text-align: right;">Page 15</p> <p>1 is something that has been reported on for many years 2 using off-label use of IV formulations, mainly 3 nebulized amphotericin B. There are a few case 4 reports in the literature with inhalational 5 voriconazole, also the IV solution. 6 And this is usually aimed at 7 aspergillosis and -- and many of these clinical 8 situations, combined with an oral anti-candid agent, 9 fluconazole. 10 These studies have shown that liposomal 11 amphotericin B is better tolerated versus the 12 traditional or older deoxycholic micelle formulation. 13 And overall, the studies differ 14 somewhat, but they show at least similar and in many 15 cases reduced incidents of invasive disease with an 16 unclear effect on anastomotic lung disease in lung 17 transplant recipients. 18 And unfortunately, I couldn't find any 19 direct comparative trials with oral azoles. 20 The second situation where I think 21 these antifungals may play a role in immunocompromised</p>	<p style="text-align: right;">Page 17</p> <p>1 clinical experience due to induction of cough or 2 bronchospasm, bad taste and nausea. 3 So current recommendations by the IDSA 4 do include patients with hematologic malignancy and 5 stem cell transplants. In areas of high azole 6 resistance -- which is especially true in several 7 areas of Northern Europe, but is a worldwide 8 phenomenon -- or patients with contraindications to 9 oral azole prophylaxis. 10 So turning from the immunocompromised 11 patient to the immunocompetent patient, we have the 12 issue of fungal asthma and its more severe phenotype, 13 ABPA. 14 The basis of this I believe is the 15 ability of the fungus to grow in the bronchial lumen 16 in mucous plugs in people who have underlying muco- 17 obstructive disease. So this includes not only 18 asthma, but importantly cystic fibrosis and 19 increasingly perhaps various forms of COPD. And the 20 key factor is that one can detect luminal fungal 21 growth that's shown here in the branching hyphae of</p>

<p style="text-align: right;">Page 18</p> <p>1 aspergillus fumigatus, and the presence of 2 endobronchial inflammation which you can see there in 3 the inset as represented with -- epithelial cells and 4 granule acidic infiltration. 5 I think that there is an extended 6 phenotype here which several syndromes can be 7 distinguished from each other, beginning with simple 8 asthma. 9 Moving to a more chronic asthma 10 associated with fungal sensitization on a chronic 11 basis. A more severe form in which the asthma is 12 phenotypically severe, accompanied by fungal 13 sensitization, so called SAS. And then ABPA of which 14 two different forms have been recognized, depending on 15 the presence or absence of central bronchiectasis. 16 And you can see there on the bottom 17 that this is a common problem in asthma with very high 18 numbers represented that actually dwarf those with the 19 various infective forms of aspergillosis in terms of 20 worldwide burden. 21 Now how can we -- how can we hone down</p>	<p style="text-align: right;">Page 20</p> <p>1 the key point here is that besides the biomarker IGE 2 being a good reflection of the fungal sensitivity, we 3 see lower lung function and less asthma control in the 4 group with fungal sensitivities. And the interesting 5 feature of this SAS, whether it's adult or pediatric, 6 is that it is usually multi-fungal in relationship to 7 particular agents, such as aspergillus which is the 8 most common, but also Alternaria, Cladosporium, 9 candida and some other prominent, known aeroallergens. 10 So this has led to the idea that one 11 might use anti-infective therapy for asthma, which is 12 not intuitively obvious, in those with fungal 13 sensitivity. And there have been two randomized 14 controlled studies of this in the UK. On the left you 15 see a study from Manchester from David Denning's group 16 which used itraconazole. You can see the 17 sensitivities of their group. And this was a -- 18 basically a half-year study with a significant primary 19 endpoint result of improved asthma quality of life as 20 -- as measured by the AQLQ score, as well as some 21 other changes which suggest that efficacy, such as</p>
<p style="text-align: right;">Page 19</p> <p>1 on fungal sensitivity as an associated problem? One 2 way to look at that is through epidemiologic studies, 3 like this one from a cohort in Sweden of 830 patients 4 who use three different definitions of severe asthma, 5 and looked at the prevalence of sensitivity to any 6 allergen, non-mold allergens and mold allergens. And 7 in terms of the association with severe asthma, we see 8 a clear, significant difference with mold sensitivity 9 being a prominent associated finding. And looking at 10 specific molds amongst the common mold allergens we 11 see that aspergillus fumigatus shows by far the 12 highest relationship with roughly 10 to 20 percent of 13 severe asthmatics showing fungal sensitivity to this 14 particular agent. 15 Now this is also true in pediatrics. 16 And this is a study from New York, and there's a very 17 similar one from London, both are cited there, which 18 look at kids. In this case, around age 10, and 19 describing the characteristics of those with or 20 without fungal sensitivity. And in addition, those 21 that might be sensitized to non-fungal allergens. And</p>	<p style="text-align: right;">Page 21</p> <p>1 change in some lung function measurements. However, 2 the follow-up study using voriconazole in Leicester, 3 the -- study on the right, failed to show any 4 difference in a 12-week randomized controlled trial. 5 So my conclusion is that at this point, 6 we don't know the role of azoles in SAS and we need a 7 better -- further clinical trials to see if this 8 approach could be used, and therefore then adapted for 9 use with antifungals since this is a chronic therapy. 10 And the whole -- one of the -- rationales is to avoid 11 toxicity and side effects as well as enhance local 12 concentrations. 13 Now turning to ABPA, we see that up to 14 five percent of those with severe asthma have been 15 found to have ABPA. In cystic fibrosis and other at- 16 risk groups, it's higher. It's about eight percent in 17 adults and registry figures. Again, representing a 18 large cohort of patients with an unmet need in terms 19 of effective therapy. 20 Current therapy, which goes back now to 21 the '60s, is oral glucocorticoid steroids which are</p>

<p style="text-align: right;">Page 22</p> <p>1 still the mainstay of therapy, but these are -- these 2 are long-term treatments of months rather than a few 3 days. And can result, and in many cases do result, in 4 significant toxicity. And that's pushed the 5 development of alternatives, including monthly pulse 6 IV steroids which are being used in some patients to 7 spare the toxicity.</p> <p>8 Since the early '90s oral azoles active 9 against aspergillus starting with itraconazole have 10 also been used and validated in several placebo- 11 controlled trials. But again, the long-term treatment 12 increases the possibility of toxicity, and in 13 addition, depending on the azole we're speaking of, 14 there are issues with absorption, metabolism, 15 drug/drug interactions, which together really mandate 16 therapeutic drug level monitoring, which is both 17 expensive and troublesome.</p> <p>18 And importantly, azole resistance is 19 clearly increasing on a worldwide basis, especially in 20 areas where antifungals are widely used in 21 agriculture. And that's driven over decades the off-</p>	<p style="text-align: right;">Page 24</p> <p>1 characteristics. So there are wide ranges of dosing 2 and dose regimes used. But nevertheless, this is 3 something that is out there.</p> <p>4 So an example of the study which looked 5 at this is this particular one for new patients, adult 6 patients with asthma and ABPA, that was conducted in 7 India which compared the amphotericin B deoxycholate 8 formulation in combination with budesonide to a 9 control arm. So it's an active control study using 10 budesonide as the control. And in comparison to the 11 steroid-only arm, the patients who received the 12 antifungal had a significantly decreased number of 13 exacerbations after one year, and a trend towards 14 reduced -- towards an extended time to first 15 exacerbation.</p> <p>16 Hopefully we'll get better data from a 17 multicenter study in France with liposomal 18 amphotericin B, which is ongoing with enrollment 19 completed. So hopefully that will add to our 20 knowledge about that.</p> <p>21 This has also been applied to cystic</p>
<p style="text-align: right;">Page 23</p> <p>1 label use of nebulized amphotericin B. And in the 2 last 10 to 15 years, the advent of biologic agents, 3 mostly with omalizumab, the monoclonal anti-IGE, which 4 has been validated at both in open label and placebo- 5 controlled situations. But is expensive and requires 6 observation in an office or a clinic. And most 7 recently, other T2 high response biologicals have been 8 adapted for early use in ABPA, and reports of those 9 are in the literature.</p> <p>10 The amphotericin B aerosol therapy 11 unfortunately has issues related to the four different 12 IV preparations which are used. All of these are used 13 off-label, so they've not been specifically studied 14 and approved in a -- in the usual fashion for a 15 regulatory vetting.</p> <p>16 We do think that the lipid formulations 17 are better here as they seem to be in invasive 18 immunocompromised disease patients. One of the 19 problems in all these studies and systems is the wide 20 variety of delivery devices. So there's no vetted 21 drug delivery combo that has clearly defined</p>	<p style="text-align: right;">Page 25</p> <p>1 fibrosis which you see there on table two on this 2 slide. A number of studies have been done. Note the 3 very small number of patients. These are basically 4 case series or individual studies. A few others exist 5 in the literature. Now obviously, there is a 6 publication bias that may be involved here, but the 7 case reports do suggest positive clinical outcomes in 8 these patients with biomarker responses such as 9 reduction in IGE on the therapy.</p> <p>10 So turning to actual development of new 11 drugs, we now have at least the first published study 12 in healthy volunteers with the Pulmatrix dry powder 13 formulation of itraconazole which is shown here. And 14 as expected, what we see is a markedly higher sputum 15 level as compared to oral itraconazole. And a 16 markedly lower plasma level as compared to oral 17 itraconazole. So the plasma exposure is up to 400 18 times lower with sputum concentrations up to 70 times 19 higher, versus the oral formulation. And as shown in 20 the bottom left figure there, you can see that in some 21 cases, 24 to 48 hours, the MIC90 is still exceeded for</p>

<p style="text-align: right;">Page 26</p> <p>1 aspergillus using this intervention.</p> <p>2 Similarly, Pulmocide has also, with</p> <p>3 their PC945 formulation, starting to generate some</p> <p>4 data clinically. This is just an example which I was</p> <p>5 kindly provided by Pulmocide to show a patient with</p> <p>6 ABPA where there was, on top of systemic therapy,</p> <p>7 resolution to the pulmonary infiltrates and a positive</p> <p>8 change in the biomarkers particular IGE with the</p> <p>9 addition of the PC945 to the treatment program.</p> <p>10 And in terms of the immunocompromised</p> <p>11 patient, there also may be a clinical application as</p> <p>12 this case report which was presented last year in the</p> <p>13 UK, again using PC945 in a patient with anastomotic</p> <p>14 disease where the inhalational azole agent was added</p> <p>15 to a conventional combination systemic therapy</p> <p>16 resulting in clinical improvement.</p> <p>17 And finally, I just want to point out</p> <p>18 what I think is a neat system, the in vitro alveolus</p> <p>19 model which is a cellular bilayer model in which the</p> <p>20 upper chamber is coated with epithelial cells tied to</p> <p>21 pneumocytes, then there's a semipermeable membrane,</p>	<p style="text-align: right;">Page 28</p> <p>1 malignancies with neutropenia, adjunctive treatment of</p> <p>2 resistant or recalcitrant multidrug resistant fungal</p> <p>3 lung infections, and in the allergic patient,</p> <p>4 treatment of allergic pulmonary aspergillosis, and</p> <p>5 possibly treatment of severe asthma with fungal</p> <p>6 sensitization. And I'll conclude there. Thanks for</p> <p>7 your attention.</p> <p>8 DR. DAS: Hi. I would like to -- thank</p> <p>9 you very much, Professor Richard Moss for that</p> <p>10 excellent presentation. I believe all questions will</p> <p>11 be addressed in the panel session at the end.</p> <p>12 I would like to now introduce Dr. Owen</p> <p>13 McMaster. Dr. McMaster is a pharmacology and</p> <p>14 toxicology reviewer in the Division of Pharmacology</p> <p>15 and Toxicology for infectious diseases in the Office</p> <p>16 of New Drugs at the FDA. And he has review experience</p> <p>17 planning antifungals and antivirals.</p> <p>18 I'd like to hand over to Dr. McMaster</p> <p>19 now.</p> <p>20 DR. MCMASTER: Hi. My name is Owen</p> <p>21 McMaster. Good morning. This is Owen McMaster. I'm</p>
<p style="text-align: right;">Page 27</p> <p>1 and below it, a coating of the systemic side with</p> <p>2 pulmonary endothelial cells, recapitulating the</p> <p>3 air/liquid interface. And what we see on the top is</p> <p>4 that one can then add the conidia and the drug if you</p> <p>5 want. And then on the bottom, measurement of fungal</p> <p>6 penetration through the bilayer and -- and growth into</p> <p>7 hyphae as measured by the readout with galactomannan.</p> <p>8 So in this particular study which was</p> <p>9 published last year, this model was used to show that</p> <p>10 combination therapy was much more effective than</p> <p>11 either the monotherapy with the inhalational route of</p> <p>12 the PC945 that is on the top layer, or the systemic</p> <p>13 route with the addition of Posaconazole on the</p> <p>14 endothelial side on the bottom layer.</p> <p>15 So in summary, I would conclude that</p> <p>16 because of favorable pharmacokinetics,</p> <p>17 pharmacodynamics and toxicology specific respiratory</p> <p>18 developed drugs and device combinations may find</p> <p>19 validated roles in a number of different situations.</p> <p>20 I think prophylaxis of aspergillosis in lung</p> <p>21 transplant recipients and patients with hematologic</p>	<p style="text-align: right;">Page 29</p> <p>1 a pharm/tox reviewer in the Division of Pharm/Tox for</p> <p>2 infectious diseases.</p> <p>3 As the content of this presentation</p> <p>4 represent my own opinion and not the official position</p> <p>5 of this CDER or FDA. And I have no conflicts to</p> <p>6 declare.</p> <p>7 Now this morning, my brief presentation</p> <p>8 is intended to provide an overview of the pharmacology</p> <p>9 and toxicology data that are typically submitted</p> <p>10 during the I&D process.</p> <p>11 As I go through the presentation, I'll</p> <p>12 address any special procedures or modifications</p> <p>13 relevant to the development of an inhaled antifungal.</p> <p>14 And I'll finish by touching on what we might do in the</p> <p>15 future to improve predictability of these evaluations.</p> <p>16 So as mentioned in the previous talk, a</p> <p>17 quick search of the public literature reveals interest</p> <p>18 in inhalation formulations of previously approved</p> <p>19 antifungal drugs, like voriconazole, Posaconazole and</p> <p>20 itraconazole, but also drugs like PC945 which is being</p> <p>21 specifically developed as an inhaled treatment for</p>

<p style="text-align: right;">Page 30</p> <p>1 pulmonary aspergillosis.</p> <p>2 The regulatory basis for the</p> <p>3 pharmacology and toxicology package comes from</p> <p>4 21CFR312.23, which indicates that I&D's just contain</p> <p>5 adequate information about the pharmacology and</p> <p>6 toxicology studies of the drug. The regulation also</p> <p>7 directs sponsors to the FDA for guidance on how these</p> <p>8 requirements might be met.</p> <p>9 This slide shows two guidance documents</p> <p>10 relevant to the development of inhaled antifungals.</p> <p>11 The first is ICH guidance on non-clinical safety</p> <p>12 studies for the conduct of human clinical trials and</p> <p>13 marketing authorization to pharmaceuticals M3. This</p> <p>14 describes the non-clinical safety studies recommended</p> <p>15 to support human clinical trials -- scope and</p> <p>16 duration, as well as marketing authorization for</p> <p>17 pharmaceuticals.</p> <p>18 The second is FDA's non-clinical safety</p> <p>19 evaluation of reformulated products and products</p> <p>20 intended for administration by an alternate route,</p> <p>21 guidance for industry and staff. I provide a link to</p>	<p style="text-align: right;">Page 32</p> <p>1 inhalation should undergo a short-term -- two to four</p> <p>2 week -- inhalation toxicity testing in two species.</p> <p>3 If the drug is to be chronically administered, this</p> <p>4 should be followed by a longer inhalation study, for</p> <p>5 up to six months, in the most appropriate species.</p> <p>6 Studies of new routes should not only</p> <p>7 contain a vehicle control, but also a -- control group</p> <p>8 as well, especially if novel excipients are used.</p> <p>9 Experimental inhalation exposures take</p> <p>10 many forms in the lab, including nose-only,</p> <p>11 oropharyngeal, oronasal, head-only and whole body</p> <p>12 exposures.</p> <p>13 This slide shows the rats being exposed</p> <p>14 to drugs by nose-only exposure.</p> <p>15 I also want to point out that dosimetry</p> <p>16 for inhalation toxicology studies is not as</p> <p>17 straightforward as, say, intravenous or oral device</p> <p>18 studies where a specific measured quantity of drug can</p> <p>19 be reliably delivered to the test animal.</p> <p>20 For inhalation toxicology studies,</p> <p>21 exposures are estimated by the formula shown above</p>
<p style="text-align: right;">Page 31</p> <p>1 these documents below.</p> <p>2 This slide describes the non-clinical</p> <p>3 studies referenced in ICHM3. I must point out that</p> <p>4 the primary pharmacology or pharmacodynamic studies</p> <p>5 which evaluate the mode of action or effects of a drug</p> <p>6 in relation to its desired therapeutic effects, are</p> <p>7 not reviewed by the pharm/tox team, but by my</p> <p>8 colleagues in the clinical microbiology and clinical</p> <p>9 pharmacology groups. You'll hear from them later in</p> <p>10 the day.</p> <p>11 Other studies recommended by ICHM3</p> <p>12 include secondary pharmacology, safety pharmacology,</p> <p>13 pharmacokinetics, acute and repetos toxicity studies,</p> <p>14 genetic reproductive carcinogenicity, immunotoxicity,</p> <p>15 phototoxicity and abuse liability studies --</p> <p>16 combination -- studies were necessary.</p> <p>17 FDA's non-clinical reformulation</p> <p>18 guidance addresses the additional testing that would</p> <p>19 be expected if a drug is being studied for inhalation</p> <p>20 administration as a new route of administration.</p> <p>21 Drugs being repurposed for use by</p>	<p style="text-align: right;">Page 33</p> <p>1 which is -- considers the delivered dose as being</p> <p>2 calculated by multiplying the aerosol drug</p> <p>3 concentration by the respiratory minute volume of the</p> <p>4 animal, multiplied by the duration of daily exposure,</p> <p>5 multiplied by the inhaled fraction of particles</p> <p>6 between one and five microns, and then divided by the</p> <p>7 body weight of the animal. Obviously, inaccuracies in</p> <p>8 any of these factors will impact the estimate of the</p> <p>9 amount of drug administered to the animal.</p> <p>10 The delivered dose is different from</p> <p>11 the dose, which is actually deposited to the innermost</p> <p>12 regions of the lung. This pulmonary deposited dose is</p> <p>13 determined by multiplying the delivered dose by a</p> <p>14 deposition factor, which varies by species. So for</p> <p>15 particles between one and five microns, the deposition</p> <p>16 factor is .1 for mice and rats, .25 for dogs and</p> <p>17 monkeys, and assumed to be 1 for humans.</p> <p>18 Pulmonary deposition varies across</p> <p>19 species and depends on the size of the drug containing</p> <p>20 particles. This slide compares a pulmonary deposition</p> <p>21 in nose-breathing rats and dogs and in nose-breathing</p>

<p style="text-align: right;">Page 34</p> <p>1 and mouth-breathing humans. Deposition in larger 2 species such as dogs and monkeys is more similar to -- 3 to that in humans than for rats.</p> <p>4 This slide shows the deposition curves 5 for an adult human as we extend the scale of particle 6 sizes down into the nano range. Of those -- data were 7 not corrected for inhalabilities also clear, the 8 deposition weight varies widely as we compare the 9 nasal/oropharyngeal region, to the trachea/bronchia 10 region and then to the pulmonary region.</p> <p>11 So back to the tox studies -- 12 pharmacology studies evaluating the cardiovascular, 13 CNF and respiratory effects are expected during the 14 development of an inhalation antifungal. This is a 15 reformulation. The safety pharmacology may already be 16 complete using the oral route of administration. If 17 not, safety evaluations may be incorporated into 18 general toxicity studies, which should be conducted 19 prior to human exposure.</p> <p>20 I've added a link to the ICH safety 21 pharmacology guidance below.</p>	<p style="text-align: right;">Page 36</p> <p>1 qualify novel excipients or impurities which may be 2 associated with this formulation.</p> <p>3 This shows a typical study design, and 4 I just want to point out the inclusion of the air 5 control groups which are important if we have novel 6 excipients, to distinguish between excipients effects 7 versus the drug effects. And also that the -- there's 8 a column for target and achieved doses because often 9 they are significantly different from each other.</p> <p>10 In vitro results from the genotoxicity 11 testing are expected prior to human trials. And in 12 vivo results are expected prior to phase two.</p> <p>13 Fertility and embryo -- development 14 studies should be conducted prior to phase three and 15 post -- pre and post-natal development studies should 16 be submitted by the time the NDA is submitted.</p> <p>17 The sponsor should conduct these 18 studies using a route of administration that results 19 in systemic exposure and exposure to the reproductive 20 organs. So for example, if adequate systemic exposure 21 is not achieved by the inhalation route, reproductive</p>
<p style="text-align: right;">Page 35</p> <p>1 Prior to human trials, in vitro, 2 metabolic and plasma protein -- data for animals and 3 humans are expected, along with in vitro pulmonary and 4 systemic exposure data in test species. Prior to 5 phase three, more extensive data will be expected.</p> <p>6 Repeat those inhalation toxicity 7 studies should be conducted in two species with 8 durations equaling or exceeding the proposed duration 9 of the clinical trial. Ideally, both species should 10 be dosed by inhalation mode of administration, 11 provided that this route of administration results in 12 systemic exposure in at least one species sufficient 13 to assess toxicity compared to the anticipated 14 clinical exposure.</p> <p>15 A full panel of -- pathology 16 evaluations is expected with new molecular entities 17 being developed for inhalation administration.</p> <p>18 Reversibility arms should be included 19 as needed to evaluate if observed toxicities resolve 20 or get worse at the end of dosing.</p> <p>21 These studies can also be used to</p>	<p style="text-align: right;">Page 37</p> <p>1 toxicology evaluation should be conducted using the 2 oral or intravenous route.</p> <p>3 Carcinogenicity studies will be needed 4 as the expected clinical use of the drug is at least 5 six months. The details may be can -- the studies may 6 be conducted by the inhalation route and should 7 include one long-term rodent carcinogenicity study, 8 plus a short or medium term in vivo rodent -- such as 9 a transgenic mice or a second long-term rodent 10 carcinogenicity study.</p> <p>11 Additional studies should be conducted 12 on a case by case basis. Combination studies may be 13 needed if the inhalation drug is co-packaged with 14 another drug, or if there's limited clinical 15 information regarding one or both the drugs in the 16 combination -- studies may be needed if the pediatric 17 population is the primary population for this drug, or 18 -- and/or if the existing animal data have identified 19 potential developmental concerns for target organs, 20 such as joints.</p> <p>21 Immunotoxicity studies should be</p>

<p style="text-align: right;">Page 38</p> <p>1 considered if there are immune-related signals in 2 standard toxicity studies. Studies with abuse 3 potential should be considered for drugs based on CNS 4 activity, similarity of chemical structure to known 5 drugs of abuse, receptor binding profile, behavioral 6 clinical signs from the non-clinical studies. 7 Impurities, metabolites and leachables 8 should be studied also as indicated. 9 So what are the gaps in existence we 10 need to extrapolate from non-clinical data to inform 11 clinical trials and drug development. The first 12 obvious difference is in device designs. Since 13 animals are tested using equipment that is very 14 different from the devices that end up being used in 15 the clinic. There are also obvious anatomical 16 differences in the respiratory tracts across the 17 various animal species used compared to humans. 18 There's also the fact that the doses 19 administered in inhalation toxicity studies are not 20 directly measured, but estimated based on assumptions 21 and calculations, which may or may not be accurate.</p>	<p style="text-align: right;">Page 40</p> <p>1 in subjects and patients. Now with toxicity studies 2 such as toxicology studies in animals with fungal 3 infections could enhance the predictability of 4 toxicology testing in these agents. Thank you. 5 DR. ANDES: Thanks, Dr. McMaster. Our 6 next presentation is from Dr. Tim Benson [ph] -- 7 Bensman, excuse me. Who is a clinical pharmacology 8 reviewer in the Division of Infectious Disease 9 Pharmacology in the Office of Clinical Pharmacology at 10 the FDA. His review portfolio includes inhaled drug 11 products for infectious diseases. And his 12 presentation is titled Orally Inhaled Antifungal Drug 13 Development, Clinical Pharmacology Perspective. 14 DR. BENSMAN: Thank you, Dr. Das. 15 Thank you, Dr. Andes. 16 All right. Good morning, everyone. 17 I'll take the next 15 minutes to talk about orally 18 inhaled antifungal drug -- from a clinical 19 pharmacology regulatory perspective. But I wanted to 20 quickly acknowledge the contribution that Dr. Saluja 21 [ph] has made to this presentation, specifically</p>
<p style="text-align: right;">Page 39</p> <p>1 And finally, there's use of -- in 2 healthy animals in toxicity studies, the interaction 3 between an inhaled drug and healthy tissue to be quite 4 different from the interaction with diseased lung 5 tissue, exposing infected lung tissue to an inhaled 6 antifungal may lead to greater or -- or less systemic 7 exposures compared to the healthy lung. 8 Toxicology studies which incorporate 9 the use of infected animals will be more complicated 10 to conduct, but may actually provide data that are 11 more relevant to inhaled antifungal use in patients. 12 So the non-clinical pharmacology and 13 toxicology studies recommend to characterize the 14 toxicity of inhaled antifungals that are described in 15 ICHM3. These data help define clinical doses, 16 inclusion, exclusion criteria and inform safety 17 monitoring. 18 Understanding the limitations of these 19 animal models relating to test article administration, 20 pharmacokinetics evaluation into species allows a more 21 realistic characterization of the risk to expand this</p>	<p style="text-align: right;">Page 41</p> <p>1 around inhaler device consideration. 2 In addition, this presentation will 3 reflect my own views drawn from review experience and 4 not represent policy of the FDA. 5 So the scope of this talk is to discuss 6 the factors for consideration that are germane to 7 developing an acceptable orally inhaled antifungal 8 drug product, with particular attention to three. The 9 device considerations, clinical pharmacokinetics, and 10 dose finding. 11 Well, the rationale -- rationale behind 12 orally inhaled drug products is the ability of 13 directly targeting the infected airway, achieving high 14 local drug concentration to the most systemic 15 concentration. And this is illustrated in the 16 schematic located at the bottom left corner of this 17 slide. The individual on the left is administered an 18 oral drug tablet and the individual on the right is 19 administered an aerosol drug. The red indicates high 20 drug concentration and pink indicates low drug 21 concentration.</p>

<p style="text-align: right;">Page 42</p> <p>1 So the theoretical advantages of the 2 orally inhaled drug compared to the preferential oral 3 drug is improving efficacy, reducing the amount 4 administered to the patient and minimizing adverse 5 effects that are associated with the preferential or - 6 - drug.</p> <p>7 Now, concerning local drug exposure, if 8 we look at the diagram on the right, you see this site 9 of infection and the site of drug activity are located 10 in the lung. And so clinical or pharmacodynamic 11 measurement, sometimes fungal lung -- are sampled from 12 the lung space to evaluate the therapeutic effects and 13 described dose response relationship.</p> <p>14 Concerning systemic drug exposure, the 15 portals of entry are via the lungs and 16 gastrointestinal organs. And they search and deliver 17 drug throughout the body, following oral drug 18 inhalation.</p> <p>19 The sampling the blood compartment via 20 PK studies provides us a way to except the levels of 21 systemic drug exposure and their relationship to</p>	<p style="text-align: right;">Page 44</p> <p>1 the lung, and especially in deep lung sites where 2 fungal infection has caused obstruction or capitation.</p> <p>3 The inhalation maneuver or technique is 4 -- is one such challenge to lung deposition and 5 distribution. A classic example for -- comes from 6 metered dose inhalers, or MDIs. But the same 7 consideration should be given to other inhaler 8 devices, such as the dry powder inhaler, which is 9 likely to be more used in this space.</p> <p>10 In this example on the left, asthmatic 11 patients inhaled what are labeled albuterol from a 12 conventional press and breathe metered dose inhaler, 13 before and after being trained to synchronize 14 exhalation with inhalation. And a -- X-ray of MDI was 15 evaluated in those who failed to coordinate.</p> <p>16 As you can see in this figure, the 17 deposited drug dose and distribution in the lungs was 18 substantially different in patients using their own 19 inhaler technique compared to a taught inhaler 20 technique, or a breath actuated device that was 21 triggered when the patient inhaled.</p>
<p style="text-align: right;">Page 43</p> <p>1 adverse effects.</p> <p>2 Unfortunately, as the blood 3 compartments downstream of the site of action as well 4 as downstream of many dynamic PK processes, blood 5 concentrations aren't considered surrogates for 6 pulmonary concentration. And they're unlikely to 7 describe the relationship between therapeutic lung 8 effects and systemic drug exposure.</p> <p>9 Now a distinguishing characteristic of 10 orally inhaled products is the strong influence that 11 drug, device and patient-related factors impact where 12 the drug is deposited in the lung or by the 13 deposition. It also impacts how fast or slow it could 14 grow and how fast or slow it's cleared from the 15 airway. Because of these intricate -- because of this 16 intricate interface of drug, device and patient- 17 related factors, you can get non-uniform lung exposure 18 and get -- disease. And this makes interpreting lung 19 concentrations made from sputum or epithelial lungs 20 more difficult as it's likely compartmentalized as 21 there's likely compartmentalization of drug throughout</p>	<p style="text-align: right;">Page 45</p> <p>1 In addition, physiological or 2 pathophysiological factors are another such challenge 3 to lung deposition and distribution. The lung -- on 4 the right of this slide depicts two different 5 individuals. The left lung is that of a healthy 6 individual while the right lung is of a chronic 7 obstructive lung disease with -- impaction and 8 structural airway abnormalities that result in reduced 9 lung function. Such abnormalities use an air 10 turbulence, causing the drug to deposit at obstructed 11 lung areas, as well as preferential airflow, and 12 therefore more drugs to healthier lung regions that 13 are able to expand.</p> <p>14 Such factors, therefore, are not only 15 impacting one drug distribution and drug deposition 16 pattern variability between individuals, but they also 17 -- also likely impact within an individual variability 18 as inhaler technique probably varies, for example -- 19 probably varies from day to day.</p> <p>20 The effect of the device among 21 deposition and efficacy is another important factor.</p>

<p style="text-align: right;">Page 46</p> <p>1 An example from a phase two clinical trial compared 2 two different inhaler devices delivering the same drug 3 to the lungs. A device ranking component was 4 conducted for the device one and compared to an 5 approved dose in device two. Efficacy was deemed to 6 be acceptable with the -- lowered dose with device one 7 compared to device two, based on an FEV1 measurement 8 or endpoint. But this underscores that both efficacy 9 and safety are dependent on the device used, so the -- 10 marketed inhalation drug product needs to be studied 11 in clinical efficacy and safety trials.</p> <p>12 As mentioned before, the clinical 13 pharmacokinetic considerations for orally inhaled 14 antifungal drug products are chiefly focused around 15 addressing systemic drug exposure issues. So one 16 needs to evaluate the safety/tolerability profile, 17 identify the maximum tolerated dose, gain information 18 on the drug's general body disposition and drug 19 kinetics through single and multiple -- dose PK 20 studies in healthy subjects as well as the targeted 21 patient population.</p>	<p style="text-align: right;">Page 48</p> <p>1 drug. However, for efficacy of the orally inhaled 2 antifungal drug, bridging these and systemic PK to the 3 approved systemically administered antifungal cannot 4 be made. And that's the reason -- that has been 5 discussed already.</p> <p>6 Initial dose regimen selection is often 7 times obtained from non-clinical or non-human animal 8 models with fungal lung disease through the estimation 9 of the clinical starting dose or dose regimen via the 10 delivered dose as outlined by Dr. McMaster.</p> <p>11 Lung PK -- targets for initial dose 12 regimen selection are not common. However, the 13 evaluation of the LF and -- drug concentrations do 14 provide information on drug exposure and penetration 15 in the lungs. And potentially, their association with 16 clinical efficacy. However, there is a knowledge 17 guess regarding the translation of the non-clinical 18 lung PK/PD targets to humans and their link to 19 clinical efficacy.</p> <p>20 Also, in patients with invasive fungal 21 lung infections, the interpretation of sputum and --</p>
<p style="text-align: right;">Page 47</p> <p>1 Now because of certain drug exposure of 2 the orally inhaled antifungal drug product is expected 3 to be low, in general, the lung has low drug 4 metabolizing activity compared to the liver, in vitro 5 approaches to evaluating drug/drug interaction 6 potential is a good place to begin to determine 7 whether there are potentially clinically significant 8 drug/drug interaction. And such approaches are 9 outlined in current FDA in vitro for drug interaction 10 guidance.</p> <p>11 Another noteworthy comment about this 12 route of administration is that given that the site of 13 action is upstream in the systemic -- exposure, a 14 dosage -- in renal or hepatic impairment are not 15 possible. And so it's deficient clinical experience 16 at exposures that are achievable in such populations 17 need to be considered in the drug development program.</p> <p>18 Also, for antifungals with approved 19 systemic formulation, the systemic orally inhaled 20 antifungal drug, PK, can be used to bridge the 21 systemic safety for that orally inhaled antifungal</p>	<p style="text-align: right;">Page 49</p> <p>1 antifungal drug concentrations are challenging. For 2 one, there is a high degree of variability between 3 individuals, especially for sputum where the relative 4 variability is commonly around 100 percent.</p> <p>5 Also, while it's generally rationalized 6 that efficacy is due to high local concentration, with 7 indirect approaches of -- different for the lung/drug 8 concentrations may not reflect free-soluble drug 9 concentrations at the lung target site infection.</p> <p>10 They also may result in different PK/PD values 11 depending on which matrix is what. So poor inferences 12 are -- are difficult.</p> <p>13 Recognizing these complexities and dose 14 response or dose findings should be an integral part 15 of the phase two drug development program. And to 16 form the phase three dose regimens, multiple ascending 17 dose phase two trials -- the anticipated phase three 18 inhaled clinical dose regimen as well as a range of 19 dose regimen that are above and below it to evaluate 20 efficacy and safety responses.</p> <p>21 Also, given the significant influence</p>

<p style="text-align: right;">Page 50</p> <p>1 of patient-related factors to orally inhaled 2 antifungal drugs, it is also important to enroll 3 patients that will reflect -- that will reflect the 4 phase three target patient population. 5 So to summarize, there are many 6 influential factors. Drug formulation, device, fungal 7 lung disease severity and patient use, for example, 8 that affect lung distribution and therefore lung 9 pharmacokinetics of orally inhaled antifungal drugs. 10 Plus the to be marketed orally inhaled drug product 11 needs to be used in the phase two/three development 12 program. Also, non-clinical animal models with fungal 13 disease may be potentially informative, but at this 14 time, phase two trials are needed to support the phase 15 three dose regimen. 16 Certainly, there are a number of 17 uncertainties that challenge us in this phase and I 18 look forward to discussions throughout the day on how 19 we can best consider them and consider -- so ... 20 So to close, I wanted to acknowledge 21 Doctors Colangelo, Soluja and Reynolds after their</p>	<p style="text-align: right;">Page 52</p> <p>1 device reviews specifically. 2 Devices are regulated in three risk- 3 based classifications. Lower risk devices with well 4 understood safety and effectiveness profiles are 5 classified as class one devices where there is an 6 assurance or safety and effectiveness through general 7 controls. 8 General controls apply to all medical 9 devices and include fundamental requirements regarding 10 ensuring devices are not adulterated or misbranded, 11 and that manufacturers follow our quality systems 12 regulations for good manufacturing. Most of these 13 devices are exempt from premarket notification 14 requirements. 15 Moderate risk devices are considered 16 class two for which safety and effectiveness can be 17 assured through both the general controls and special 18 controls. 19 Special controls are usually device- 20 specific and can include things like performance or 21 labeling requirements. These devices usually require</p>
<p style="text-align: right;">Page 51</p> <p>1 very fruitful discussions and comments. They were 2 instrumental in putting this presentation together. 3 Thank you. 4 DR. DAS: Thank you very much. I'd 5 like to thank Dr. Tim Bensman. And then I'm going to 6 introduce Dr. Brandon Blakely. Dr. Blakely is a 7 biomedical engineer and acting team lead for the 8 respiratory devices team at CDRH-FDA. Brandon's 9 experience includes pulmonary diagnostic devices or 10 nebulizers. He was taught -- about regulatory 11 perspectives for device development for inhalation 12 combination products. 13 DR. BLAKELY: Thank you. As the name 14 of the talk suggests, I'm going to be going over the 15 regulatory perspectives for devices in general and 16 inhalation devices in particular, both CDER-led and 17 CDRH-led. 18 So I'm going to give a brief summary of 19 the classification system that medical device 20 regulations are based on, then I will summarize the 21 regulatory landscape for orally inhaled drug product</p>	<p style="text-align: right;">Page 53</p> <p>1 a premarket clearance through the 510K process which 2 requires demonstrating substantial equivalence to a 3 predicate. 4 Finally, high-risk and generally novel 5 devices, including implanted devices or those intended 6 to sustain life, are class three devices which usually 7 require a premarket approval or PMA. These devices 8 require valid scientific evidence, generally in the 9 form of well-controlled clinical studies, to 10 demonstrate a reasonable assurance of safety and 11 effectiveness. 12 As can be seen by the little cartoon 13 here, CDRH-led devices for the delivery of drug for 14 inhalation are generally regulated as class two 15 devices. 16 So you can all reference the definition 17 here, but you know, the basic idea is if a medical 18 product requires two or more different types of 19 regulated entities, for example a drug and a device, 20 to achieve its intended use, that is considered a 21 combination product. Review of combination products</p>

<p style="text-align: right;">Page 54</p> <p>1 requires a coordination of multiple centers with one 2 center acting as the lead and consulting the other 3 center or centers as needed.</p> <p>4 If a manufacturer wants feedback on 5 which center would be the lead for their product, they 6 can submit a request for designation, or RFD, to the 7 Office of Combination Products or OCP. OCP will make 8 their recommendation by determining the primary mode 9 of action of the product. For example, if the 10 product's primary mode of action is chemical action 11 and metabolism, it would be led by CDRH.</p> <p>12 There are two mechanisms to obtain OCP 13 feedback. A formal RFD and a more flexible pre-RFD 14 process. In the slide I am referencing the two 15 relevant guidance documents that provide overviews of 16 these types of interactions.</p> <p>17 All right. Back to inhalation devices 18 typical for orally inhaled drug products. There are 19 roughly two broad classes: nebulizers and inhalers. 20 Nebulizers are devices that, as the name suggests, 21 nebulize liquid drug formulations into a mist for</p>	<p style="text-align: right;">Page 56</p> <p>1 CDRH and are cleared for market through the 510K 2 process.</p> <p>3 For reference, here is the 510K 4 database from the FDA website. You can search all 5 510K cleared devices which are organized by product 6 code. The product code for nebulizers and nebulizers 7 accessories for example is CAF. If you enter those 8 three letters in the pro code field and search, you 9 can find a comprehensive history of all 510K-cleared 10 nebulizers. Most records should also include a 510K 11 summary which is a publicly available overview of the 12 device and the information, including performance 13 data, that was provided in support of the submission.</p> <p>14 For drugs intended for specific device 15 combinations, there are two possible ways to obtain 16 marketing approval or clearance. The most common path 17 is including the device portion as part of the drug 18 submission. In some cases, sponsors will clear a 19 device for delivery through the 510K pathway if 20 there's a predicate or another pathway is necessary. 21 However, CDRH will only clear or approve devices</p>
<p style="text-align: right;">Page 55</p> <p>1 inhalation. Since nebulizers generally work with any 2 appropriate liquid formulation of a drug, these are 3 most often sold as general use nebulizers, which are 4 regulated as devices by CDRH. This means that they 5 are clear to be marketed to nebulizer any drug that is 6 approved for nebulized solution route of 7 administration in the orange book, and they are not 8 co-packaged or cross labeled with a specific 9 nebulizer. In some isolated cases, nebulizers have 10 been designed and co-packaged specifically for one 11 drug in which case those would be approved under the 12 NDA for that drug.</p> <p>13 Finally, there are inhalers which 14 include metered dose inhalers or dry powder inhalers. 15 These are typically co-packaged with the associated 16 drug and are approved under the drug NDA submission. 17 These combination products would be CDER-led, usually 18 with consult from CDRH.</p> <p>19 Here are some examples of drugs that 20 are approved to be used with general purpose 21 nebulizers. These are devices regulated solely by</p>	<p style="text-align: right;">Page 57</p> <p>1 intended to be delivered -- intended to deliver drugs, 2 so long as the intended use of the device is 3 consistent with the approved drug label.</p> <p>4 As mentioned previously, the most 5 common pathway for CDRH-led orally inhaled drug 6 products is the 510K pathway. I'm going to quickly 7 provide an overview of the 510K process which is based 8 on demonstrating that the subject device is 9 substantially -- to a predicate device. Many of the 10 same review considerations also apply to NDAs or other 11 drug submissions with device components. So the 12 content presented here should also be informative of 13 CDRH expectations when we consult for CDR-led 14 combination products.</p> <p>15 And an NDA for example, instead of 16 evaluating the performance as compared to a predicate 17 using our recognized consensus standards and 18 guidances, we would be evaluating the safety and 19 effectiveness of the device component of the NDA 20 solely using our recognized consensus standards and 21 guidances.</p>

<p style="text-align: right;">Page 58</p> <p>1 In this slide, I am referencing the 2 primary CDRH guidance on the 510K process. To obtain 3 510K clearance, a 510K submission must demonstrate 4 that a newer modified device is substantially 5 equivalent in its intended use in safety and 6 effectiveness to a predicate device.</p> <p>7 A predicate device is most often a 8 legally marketed device that was cleared onto market 9 by the 510K process. In order to be determined 10 substantially equivalent to a predicate device, the 11 subject device needs to demonstrate one of two things. 12 Either it has the same intended use and the same 13 technological characteristics, or it has the same 14 intended use and different technological 15 characteristic which do not raise use of questions of 16 safety and effectiveness. And often through 17 performance testing, can be demonstrated to be at 18 least as safe and effective as the legally marketed 19 predicate device.</p> <p>20 The intended use is objectively 21 determined from the content of the submission,</p>	<p style="text-align: right;">Page 60</p> <p>1 deposition. Larger particles largely impact the mouth 2 or throat and do not reach the alveoli. Determining 3 the aerodynamic distribution of the omitted particles 4 from an orally inhaled drug product provides a 5 quantitative assessment of the performance of the 6 device and its capability to deliver a respirable 7 dose.</p> <p>8 The standard performance test to 9 determine aerodynamic particle size distribution is 10 cascade impaction. Cascade impactors separate 11 particles and droplets by aerodynamic diameter, 12 depending on inertial forces which are captured at 13 various stages with different cutoff diameters.</p> <p>14 CDRH evaluates cascade impactor testing 15 to assess the performance of orally inhaled drug 16 products. Generally, cascade impaction testing with 17 at least six stages is required, including -- some 18 reference to the relevant USP chapters that describe 19 this testing.</p> <p>20 When evaluating aerodynamic particle 21 size distribution testing, it's important to measure</p>
<p style="text-align: right;">Page 59</p> <p>1 including the labeling. The intended use encompasses 2 the indications for use, which would be the specific 3 patient population or disease the device is intended 4 to treat or diagnose, intended users and the 5 environment of use.</p> <p>6 Here is a list of the common subject 7 matter areas typically reviewed for device marketing 8 submissions. From the device description intended 9 use, CDRH evaluates topics related to the device's 10 performance to ensure that it can fulfill the intended 11 use, as well as issues related to basic safety from 12 risks of physical hazards. Many of these basic safety 13 topics are covered by various international consensus 14 standards and FDA guidance documents, which I'll touch 15 on briefly in the upcoming slides.</p> <p>16 In terms of orally inhaled drug 17 products delivery devices -- drug delivery devices, 18 the primary performance metric we were interested in 19 is the ability to deliver respirable aerosolized drug 20 particles. Roughly speaking, a particle smaller than 21 5 microns in aerodynamic diameter are needed for long</p>	<p style="text-align: right;">Page 61</p> <p>1 various sources of variability. So we assess both the 2 inter and intra device variability. So it is expected 3 that you would do tests with multiple actuations of a 4 particular device and with multiple devices.</p> <p>5 In addition, if the device is intended 6 to be used with various patient interfaces, for 7 example, with spacers or with a mask or a mouthpiece, 8 it's expected you would do the testing with all 9 available interfaces to ensure consistent drug 10 delivery.</p> <p>11 Among the most important elements of 12 basic safety in some of the most challenging is 13 biocompatibility. Biocompatibility of a device means 14 that the device's contact with tissue does not produce 15 an adverse effect during its intended use. 16 Biocompatibility evaluation is determined through a 17 risk management process which accounts both for the 18 type and duration of tissue contact.</p> <p>19 For biocompatibility assessments, CDRH 20 primarily relies on the ISO10993 series of standards. 21 FDA has also issued guidance on the application of</p>

<p style="text-align: right;">Page 62</p> <p>1 ISO10993 to the biocompatibility assessments of 2 medical devices. In general, the expected number and 3 types of in vitro and in vivo tests are outlined in 4 this guidance. 5 In terms of the type of contact, orally 6 inhaled drug products could have multiple types of 7 contact as categorized by ISO10993. 8 For example, a face mask or mouthpiece 9 would have direct intact skin contact, however, any 10 device component, including anterior surfaces or ports 11 over through or which gasses or liquids could be 12 inspired by the patient, are considered externally 13 tissue communicating-type contact. 14 Furthermore, there are specific 15 biocompatibility hazards for gas pathway contacting 16 devices not addressed by the ISO10993 series. 17 Therefore, CDRH also recognizes the ISO18562 series 18 which specifies both additional tests to ISO10993 and 19 additional test approaches instead of some of the 20 tests described by the ISO10993 series. 21 As I summarized already, there are many</p>	<p style="text-align: right;">Page 64</p> <p>1 review expectations. 2 Besides biocompatibility hazards, there 3 are other hazards we evaluate for the basic safety of 4 medical devices. The general safety standard for 5 medical devices is published by the International 6 Electrotechnical Commission, or IEC, and is the 7 primary document of the IEC60601 series of basic 8 safety standards for medical devices. 9 The IEC60601-1 standard is the primary 10 or general standard that describes basic safety 11 requirements applicable to most electrically powered 12 medical devices. 13 Basic safety includes freedom from 14 unacceptable risks from a range of potential hazards, 15 including electrical and mechanical hazards, as 16 covered by the requirements of IEC60601-1. 17 In addition to the electrical safety 18 general standard, there are collateral standards to 19 the 60601-1 general standard. One of the most common 20 applicable to almost any electric device is IEC60601- 21 1-2, which describes the requirements for emissions</p>
<p style="text-align: right;">Page 63</p> <p>1 potentially complicated specifics to consider when 2 evaluating biocompatibility of medical devices. For 3 example, if you use an identical material to approved 4 or cleared device, which includes the raw materials 5 and manufacturing processes and other steps, you may 6 under certain circumstances be able to provide a 7 material certification statement as opposed to 8 biocompatibility testing. There are additional 9 biocompatibility endpoints for gas pathway contacting 10 devices, such as particulate matter of volatile 11 organic compound testing described in ISO18562. 12 Another important consideration is that 13 some of the in vivo endpoints in the ISO10993 series 14 can be substituted with a chemical characterization 15 and toxicological risk assessment, depending on the 16 intended use. 17 These tests are generally time 18 consuming and expensive, so we strongly recommend that 19 you interact with FDA early on in the product 20 development process to ensure that the 21 biocompatibility assessments are consistent with our</p>	<p style="text-align: right;">Page 65</p> <p>1 and immunity from electromagnetic radiation. So 2 essentially that the device does not -- is not -- the 3 performance of the device is not impacted by 4 electromagnetic radiation from other devices and that 5 it does not adversely impact other devices. 6 Finally, an increasingly important 7 aspect of medical device development and review, 8 including combination products and other drug delivery 9 devices is software. Safety and effectiveness is 10 often dependent on functioning software. There are 11 industry standard designed verification and validation 12 activities to ensure that device software conforms to 13 user needs and the intended use of the device. 14 We have a guidance that describes the 15 minimum software information needed in support of 16 premarketing submission, depending on the level of 17 concern. 18 Additionally, there are software 19 verification and validation requirements per IEC60601- 20 1 that I referenced earlier. And there is an FDA 21 recognized consensus standard on the processes and</p>

<p style="text-align: right;">Page 66</p> <p>1 activities related to the development and maintenance 2 of medical device software. 3 So similar to CDR, CDRH encourages 4 early communication interaction as you develop your 5 product. Analogous to CDR is type A, type B, type C 6 meetings. CDRH has a number of pre-submission or also 7 known as Q-submission meetings, including 8 informational meetings, pre-meetings or submission 9 issue meetings that you can reference the guidance 10 here. 11 For more details on the types of 12 meetings available and the timelines for interactions, 13 please refer to this 2019 Q-submission guidance 14 document. 15 In conclusion, I hope I've summarized 16 the importance of drug device synergy for safe and 17 effective combination products and CDRH-led orally 18 inhaled drug product reviews. We reviewed these 19 devices using our regulations, guidances and 20 recognized consensus standards under pen by risk-based 21 approach. We aim to work with manufacturers to ensure</p>	<p style="text-align: right;">Page 68</p> <p>1 What does that refer to? And we'll end with some 2 specific considerations as it relates to the 3 development of inhaled antifungal. General 4 disclaimer. 5 So let's -- let's start with a 6 definition. When we talk about human factors, or you 7 may hear the term ergonomics sometimes used 8 interchangeably, really what we're referring to is the 9 scientific discipline that's concerned with the under 10 -- of interactions among human beings and other 11 elements of a system. 12 So when we say system, of course that 13 can mean many things. For the purposes of our 14 discussion, we're talking about medical products. 15 That can include drug device combination products. 16 So there are many definitions that 17 reside out there when it comes to human factors. I'm 18 showing you another one that's actually derived from a 19 national standard. And in this, the definition of 20 human factors talks about the application of knowledge 21 about human capabilities and limitations to the design</p>
<p style="text-align: right;">Page 67</p> <p>1 that safe and effective devices are available to the 2 public. Thank you. 3 DR. ANDES: Thank you, Dr. Blakely. 4 Our next speaker is Irene Chan who currently serves as 5 Deputy Director in the division Medication Error 6 Prevention and Analysis at FDA and is currently 7 involved in oversight of safety recommendations, such 8 as labeling, packaging and product design. The title 9 of her -- is Human Factors Considerations for Inhaled 10 Antifungal Drug Development. Dr. Chan? 11 DR. CHAN: Hi. Does everyone hear me 12 okay? 13 DR. ANDES: Yes. 14 DR. CHAN: Okay. Perfect. Thank you 15 and welcome, everyone. I'm happy to be here. As 16 mentioned, I will be talking about human factors 17 considerations for inhaled antifungal drug 18 development. I realized for some of you, there may 19 not be as much familiarity with human factors, so I'll 20 walk you through. If it comes up today, talk about, 21 you know, what do we mean when we say human factors?</p>	<p style="text-align: right;">Page 69</p> <p>1 and development of tools, devices, systems, 2 environments and organization. 3 So really, to keep things simple when 4 we're talking about human factors, what -- is the 5 compatibility of a system that's been developed with 6 people's needs, abilities and limitations. And what's 7 important to keep in mind is where your product is 8 going to be used. That use environment. The scenario 9 under which that product will be used can influence an 10 individual's needs, their abilities or limitations. 11 So let's talk about a different 12 definition now. What is a medication error? Well, a 13 medication error is any preventable event that may 14 cause or lead to inappropriate medication use or 15 patient harm while the medication is in the control of 16 the healthcare professional, patient or consumer. 17 So the reason I mention this definition 18 as well is when we think about medication error 19 prevention and we think about human factors, it's very 20 much a natural fit because at the end of the day, what 21 we want to do is optimize human wellbeing. We want</p>

<p style="text-align: right;">Page 70</p> <p>1 appropriate medication use. Ultimately, we want 2 people to be able to use the products as they were 3 intended.</p> <p>4 So in terms of who looks at medication 5 errors, that's where the Division of Medication Error 6 Prevention and Analysis comes in. So we're aligned by 7 therapeutic areas and we lead CDER's review as it 8 pertains to medication error prevention and analysis, 9 and the evaluation of human factors information within 10 CDER.</p> <p>11 So our mission is to increase the 12 safety of drug products -- use error that is related 13 to the naming, labeling, packaging or design of drug 14 products.</p> <p>15 So why do we care about human factors? 16 Well, what it comes down to is we want you to optimize 17 the user interface design of your medical product. 18 And so when I use the term user interface, what I'm 19 saying is a user interface is all those components of 20 a product with which a user would interact. So that 21 could include, for example, the labels and labeling,</p>	<p style="text-align: right;">Page 72</p> <p>1 the device as intended to inhale it.</p> <p>2 So one thing that's important to note 3 is of course your inhaled antifungal product is 4 probably going to be a combination product. And my 5 colleague, Dr. Blakely, touched on this definition in 6 his presentation. Within the context of what we're 7 talking about, we're talking really about drugs with 8 devices even though a combination product could also 9 be biologic with the device or a combination of all 10 three of those components. They can be physically or 11 chemically combined. They can be co-packaged in the 12 kit, or they can be separate, cross-labeled products.</p> <p>13 So this slide just presents some 14 examples of combination products and certainly aerosol 15 delivery devices or inhalational products are included 16 in that list.</p> <p>17 So what's our regulatory basis for 18 evaluating human factors -- where the device 19 constituent part is -- is concerned, we have certain 20 regulations that apply. Specifically, my colleague 21 had mentioned, quality system regulations. And so</p>
<p style="text-align: right;">Page 71</p> <p>1 the packaging itself, the delivery device constituent 2 part, as well as any associated controls and displays 3 that come with that.</p> <p>4 And why would we want to do that? Why 5 would we want to optimize that user interface? Well, 6 ultimately what we want to do is minimize errors. 7 This is, you know, one example of something that we've 8 seen that when you think about sort of proactive 9 product design and -- and thinking about what user 10 errors that could occur, what we've seen is -- is with 11 this particular inhalational -- inhalational device, 12 it's a product that requires a capsule to be pierced 13 such that the contents can be inhaled.</p> <p>14 However, when you think about normal 15 mental modes and what people typically associate when 16 they think about a capsule, what we've all been taught 17 pretty much since we were, you know, seven, eight, 18 nine years old is you swallow it. So it's probably no 19 surprise to this audience that when this product is on 20 the market, what happens is we start getting reports 21 of people swallowing the capsule instead of utilizing</p>	<p style="text-align: right;">Page 73</p> <p>1 when we think about 21CFR820.30, there's specific 2 language that speaks to the need to validate the 3 device user interface.</p> <p>4 The drug constituent side, 5 fundamentally the Food, Drug and Cosmetic Act, focuses 6 on the need to ensure prescription drug effectiveness 7 and safety. And what we do is we seek to reduce risk 8 from medication errors through improved product 9 design, which can include focus on the packaging, the 10 nomenclature of the labeling. And one of our PDUFA 11 development goals was to ensure that drug safety is -- 12 is established by prospectively designing a drug that 13 minimizes the risk for errors made by intended end 14 user.</p> <p>15 There is also information that's 16 contained in the quality system regulation preamble 17 that speaks to the appropriateness of human factor 18 studies, analyses and [virtual connectivity 19 interruption] because you have tools available to you 20 to consider how best to design your product throughout 21 your development process.</p>

<p style="text-align: right;">Page 74</p> <p>1 So what's important to emphasize is 2 that designing a medical product, it's not just like 3 following a recipe. There are a lot of design and 4 safety standards that exist and certainly they need to 5 be adhered to. But it isn't a box-checking exercise. 6 Ultimately, what we want you to be doing is following 7 a human factors engineering process. And the key 8 point is that it is a process. It's not just 9 completing a single study, though often times I think 10 sometimes there's a lot of emphasis on conducting 11 what's called a human factors validation study. But 12 really, if you want to develop and design something 13 that's safe and effective for your user, you want to 14 think about it throughout your product development. 15 So this human factors engineering 16 process is laid out here. I know this is a little bit 17 of a busy slide, but what it comes down to is starting 18 with understanding -- who are you designing this for? 19 What does that person look like, or persons? Because 20 often times, products have multiple users. What is 21 that environment that it's going to be used in? How</p>	<p style="text-align: right;">Page 76</p> <p>1 here. 2 But ultimately, what this slide is 3 intended to illustrate is that when you implement the 4 human factors engineering process, the idea is that 5 you want to take -- continually refine it and in that 6 way, you're able to optimize your design and lower 7 risk. 8 As we know, healthcare is increasingly 9 complex. We're certainly getting into an era where 10 there's a lot of intersection with digital health. 11 There's a lot of interest in terms of -- I guess you 12 could say special tool software, apps, other things 13 that exist that really are intended to enhance that 14 user experience and also help that end user use their 15 product. But with that can come complexity. So the 16 more complex products are, of course, the more 17 opportunities that may be introduced for errors to 18 occur. 19 So when errors occur, these 20 consequences of course can be devastating. We want to 21 eliminate the hazards, if possible, in the design of</p>
<p style="text-align: right;">Page 75</p> <p>1 do we expect to use it? Why is it being used? You 2 want to think about use-related hazards that can occur 3 while using this product. You want to think about 4 then how do you implement risk control so that you can 5 decrease risk overall in the design of your product. 6 And ultimately, to validate the use of that product 7 and be able to demonstrate to the agency that any 8 residual risk that -- that still exists after the 9 design process is risk that's acceptable. 10 So as I mentioned, it is a process 11 which means that this is something that you want to be 12 thinking about throughout your drug development. And 13 so that means as early as pre-I&D, you can already be 14 thinking about, you know, what goes into design, doing 15 your preliminary analyses, doing some focus work, 16 doing ethnographic studies, etcetera, as you develop 17 your product so that when you get to your marketing 18 application, you have a set of data and you have a 19 narrative story to help the agency understand what 20 went into your design process. How did you arrive at 21 this final -- oops. Apologies. Formatting issue</p>	<p style="text-align: right;">Page 77</p> <p>1 these products and that way we can prevent hazardous 2 situations that can ultimately lead to harm. 3 In some cases, even if we can't 4 completely eliminate a specific hazard, we try to 5 minimize the risk through implementation of risk 6 mitigation strategies that I eluded to earlier. 7 So, you know, in conclusion, when we're 8 thinking about designing specifically antifungal 9 inhalational products, I think there are some special 10 considerations that -- that need to be taken into 11 account. I think it's important to think about 12 comorbidities in this space, especially likely 13 comorbidities that can impact your understanding of 14 what your user needs. Their capabilities as well as 15 their limitations. 16 Also, depending on the product that's 17 being developed, the dosing that may be required. 18 There may be issues related to that that can actually 19 restrict which platforms that you choose for your 20 product or what type of a design that can be feasibly 21 made to actually deliver the intended dose.</p>

<p style="text-align: right;">Page 78</p> <p>1 Some delivery device platforms are also 2 optimized to deliver to essential lung regions, for 3 example. They may not reach other regions of the 4 lung. So these are things that you want to consider 5 early when you're thinking about lung deposition, when 6 you're thinking about, you know, distribution. 7 And there can also be some challenges. 8 So when you think about solubility considerations, 9 this can also impact ultimately the end user because 10 if there's additional tasks that are introduced that 11 that end user will need to complete in order to 12 ultimately administer that drug product, then that has 13 to be considered as well in the overall complexity of 14 the product design. Thank you very much for 15 listening. 16 DR. DAS: Thank you very much. We'll 17 be now going to a 10-minute break. I believe that 18 we'll be resuming at 10:40, and there should be a 19 timer displayed on your screen. 20 (Off the record.) 21 DR. DAS: I'd like to welcome everyone</p>	<p style="text-align: right;">Page 80</p> <p>1 considerations for COAs. 2 So first, some definitions here. COAs 3 measure or describe how a patient feels, functions or 4 survives. And COAs are different from biomarkers, of 5 course. We generally think of four major categories 6 of COAs. The first one here are the patient reported 7 outcome assessor, naturally the patient itself 8 reporting on their own experience. And then we have 9 clinician reported outcome assessments, which are of 10 course conducted and scored by a clinician who's 11 trained to do the assessment. Then we have observer 12 reported outcome assessments, and one example of this 13 would be an assessment completed by caregiver based on 14 observable finds from the patient. And then we have 15 performance outcome assessments which measure the 16 patient's performance on a standardized task -- though 17 not listed here, digital health technologies are 18 emerging in importance and they can be used to capture 19 clinical outcomes such as mobility and sleep. And 20 that's something we're still -- still exploring and 21 learning more about.</p>
<p style="text-align: right;">Page 79</p> <p>1 back. Thank you to all the speakers for an excellent 2 session this morning. The session's going to continue 3 now with Dr. Christopher St. Clair. Dr. St. Clair is 4 a reviewer in the Division of Clinical Outcome 5 Assessment in the Office of New Drugs at the FDA where 6 he provides expertise on development, validation and 7 interpretation of clinical outcome assessments. And 8 he'll be talking about considerations for clinical 9 outcome assessment development. 10 DR. ST. CLAIR: Thank you and good 11 morning. This is Chris St. Clair. So today, I'm 12 going to be outlining some considerations for 13 selection or -- assessments, which I'm going to 14 abbreviate as COA's from here on for use in clinical 15 trials. 16 The general disclaimer here that I've 17 used in this presentation here are mine. 18 So in the course of my talk today, I'm 19 going to go over some definitions for COAs and then 20 give some thoughts related to the development of them. 21 And then I'm going to close with FDA review</p>	<p style="text-align: right;">Page 81</p> <p>1 So a patient -- for a clinical trial 2 really requires a good understanding of the disease or 3 condition being studied, as well as the possible 4 clinical benefits of the intervention and what is 5 important to patients and caregivers. So knowledge in 6 these areas will help you select which COAs to use in 7 a clinical trial. So we're going to go into these 8 aspects in more detail here. 9 So when you think about the disease or 10 condition, think about its natural history. Think 11 about possible heterogeneity in its clinical 12 presentation. And similarly, consider any patient 13 subgroups that may be important to account for in your 14 measurement strategy, as well as standards of care 15 that may affect how you approach measurement. 16 The patient perspective is so important 17 in many ways. So talk to patients, talk to 18 caregivers, interview the focus groups. These are 19 good ways to get this information and find out how the 20 disease impacts patients -- how patients feel, how 21 they function, and also what kind of clinical benefit</p>

<p style="text-align: right;">Page 82</p> <p>1 would be meaningful from the patient perspective. 2 What does clinical benefit look like to them? 3 And that leads into my next point which 4 is for you to conceptualize what clinical -- for your 5 intervention. The first component here is to identify 6 the concepts of interest, which are the things that 7 are important to measure. And again, it's important 8 to talk to patients to understand what is important to 9 measure. But also, you know, for you to sort of 10 factor in what your intervention is expected to 11 improve. 12 The next component is to define the 13 context of use. Context of use includes things like 14 the clinical trial design, the patient population in 15 which the COAs will be used, how they will be used, 16 such as whether the COAs are intended to support 17 labeling claims. And if so, what do those claims look 18 like? 19 So with the concepts of interest and 20 the context of use in mind, the next question is, 21 well, what kind of COAs are most appropriate for your</p>	<p style="text-align: right;">Page 84</p> <p>1 can plan ahead on how to gather the evidence needed to 2 support your intended labeling claims. But there are 3 good measurement principles that apply more broadly 4 and they're described in the FDA PRO guidance that I 5 reference here. And I highly recommend referring to 6 that guidance. 7 So when we review COAs, we look at 8 numerous characteristics that are outlined in the PRO 9 guidance. But on a high level, some important 10 characteristics include content validity and then 11 other measurement properties, and interpretation of 12 COA scores including clinically meaningful within 13 patient change. 14 Establishing content for -- content 15 validity for COA is fundamentally important. Content 16 validity is evidence that the content of the COA 17 instrument itself represents the important aspects of 18 a given concept for its intended use and its target 19 population. So content validity's basically whether 20 you're measuring the right things. It's important, 21 again, to get input from the relevant stakeholders</p>
<p style="text-align: right;">Page 83</p> <p>1 specific situation? It depends. And you may decide 2 to include multiple types of COAs in your -- for 3 multiple perspectives. It's important to keep in mind 4 that the observer reported assessment should rely only 5 on observable signs or behaviors. Symptoms and 6 disease impacts that are not inherently observable 7 would be best measure to a patient-reported outcome, 8 provided that the patients enrolled in your trial are 9 cognitively able to validly and reliably self-report 10 on their experience. 11 So what does FDA look at when we review 12 COAs? Well, we look at every COA measurement strategy 13 in its specific context of use. So for each drug 14 development program, we're looking at the COAs in the 15 context of the exact study objectives, the exact 16 clinical trial design, study population and the 17 intended labeling claims. 18 So in other words, there is really no 19 such thing as a COA being validated for all purposes. 20 So I really recommend starting these conversations 21 early with FDA in your drug development process so you</p>	<p style="text-align: right;">Page 85</p> <p>1 such as by talking with patients or caregivers, and to 2 submit that information to the FDA as evidence of 3 content validity that we can review. 4 COA instruments that are not developed 5 with input from the relevant stakeholders can have 6 some serious issues. So for example, if the 7 stakeholders are not involved in its development, then 8 the instrument might omit important or relevant 9 concepts, or it might include irrelevant content. It 10 could have poorly understood instructions or questions 11 or response options. So again, really important to 12 get input from the end users of the instruments. You 13 know, the patients, the caregivers and so on depending 14 on the type of COA. 15 Aside from content validity, other 16 measurement properties we look at include reliability, 17 which is how it reproduces. Construct validity, which 18 is whether the COA has quantitative associations with 19 other variables that we would expect, and ability for 20 the COA to detect change. And if possible, it is wise 21 to look at these measurement properties prior to phase</p>

<p style="text-align: right;">Page 86</p> <p>1 three to detect any potential issues with the COA and 2 allow for modifications, if needed, prior to phase 3 three.</p> <p>4 So lastly here, we have to interpret 5 the COA data and ultimately one thing we need to know 6 is whether changes in COA scores are meaningful. And 7 that's -- to say that statistical significance alone 8 does not indicate whether an individual patient has 9 experienced a meaningful "benefit" from the patient's 10 perspective.</p> <p>11 We recommend using anchor based methods 12 to facilitate interpretation of what kind of COA score 13 change represents a meaningful within patient change. 14 And selection of the anchor scales themselves is also 15 very important in order to ultimately provide clear 16 and interpretable information. So the PRO guidance is 17 also useful source of information on the topic of 18 anchor based methods that I would refer you to.</p> <p>19 So in closing, every drug development 20 program really has its unique considerations. So come 21 talk to FDA early and regularly throughout drug</p>	<p style="text-align: right;">Page 88</p> <p>1 and unmute your computer speakers after the video is 2 finished.</p> <p>3 I think they'll be loading this video 4 up here shortly.</p> <p>5 MR. BIRRELL: My name is Malcom 6 Birrell. I'm a 63-year-old retired pharmacist and I 7 live in the UK just south of Manchester.</p> <p>8 My experience of allergic 9 bronchopulmonary aspergillosis, ABPA, began in early 10 2014, when I was first diagnosed with the condition. 11 Up to that point, I was unaware of aspergillosis in 12 any of its forms. The diagnosis occurred somewhat by 13 chance.</p> <p>14 Around Christmas 2013, I contracted 15 pneumococcal pneumonia and esophageal sepsis, 16 resulting in a period of time in intensive care. 17 After I left the hospital, my GP doing some follow-up 18 was concerned that I'd incurred some permanent damage 19 to my lungs, specifically bronchiectasis.</p> <p>20 I was referred to the Northwest Lung 21 Centre at Wythenshawe Hospital in South Manchester.</p>
<p style="text-align: right;">Page 87</p> <p>1 development so we can discuss these topics with you in 2 detail. And as you prepare to meet with us, we 3 recommend submitting exact copies of any COAs that 4 you're proposing to use in your studies, including 5 copies of those anchor scales to help facilitate 6 productive discussions regarding your COAs.</p> <p>7 The PRO guidance as well as the patient 8 focus drug development guidance series are really, 9 really useful sources of information that I recommend 10 becoming familiar with, and some of those guidances 11 are listed here. So thank you so much for your 12 attention.</p> <p>13 DR. ANDES: Thanks, Dr. St. Clair, for 14 this excellent presentation. Next presentation, we're 15 privileged to have patient perspective from Malcom 16 Birrell, who's a retired pharmacist and is living with 17 allergic bronchopulmonary aspergillosis. One 18 housekeeping technical issue is this is going to be a 19 video. So if you're -- you'll listen to this video 20 through your computer speakers, so please put your 21 phones on mute. Then you can go back to your phones</p>	<p style="text-align: right;">Page 89</p> <p>1 As luck would have it, this is also the location of 2 the National Aspergillosis Center.</p> <p>3 While the lung center was able to 4 reassure me that I had not suffered any permanent lung 5 damage, ABPA was identified and hence, I became a 6 patient in Professor Denning's clinic.</p> <p>7 ABPA was diagnosed from blood tests and 8 sputum samples confirm the presence of aspergillus 9 growing in my lungs.</p> <p>10 In terms of symptoms, I did not feel 11 that my breathing was particularly impaired, but I did 12 have a persistent and productive cough. Being in my 13 company at this time was probably both noisy and a bit 14 distressing.</p> <p>15 I'd suffered with a cough for some 16 time, but I assumed that it was linked to changes in 17 my inhaled asthma medication.</p> <p>18 The other problem which I came to 19 realize was an impact of ABPA was as a recurrent 20 bacterial chest -- somewhere in the order of four or 21 five infections per year, and this in turn undermined</p>

<p style="text-align: right;">Page 90</p> <p>1 my general health.</p> <p>2 My treatment for ABPA commenced with</p> <p>3 itraconazole taken as oral capsules. Then came the</p> <p>4 need for regular blood tests to monitor liver</p> <p>5 function. It was also necessary because of potential</p> <p>6 interaction to switch my regular statin from mature to</p> <p>7 pravastatin.</p> <p>8 After just over a year, I requested a</p> <p>9 break from treatment. Itraconazole had eradicated the</p> <p>10 fungal growth and therefore relieved my symptoms, but</p> <p>11 I had experienced side effects throughout the</p> <p>12 treatment of constant mild and altered sense of taste.</p> <p>13 And actually for me, not being able to enjoy a good</p> <p>14 cup of coffee, that was particularly difficult.</p> <p>15 Having stopped the treatment, of</p> <p>16 course, the growth of aspergillus in my lungs,</p> <p>17 unintended symptoms gradually returned.</p> <p>18 Itraconazole treatment was recommended</p> <p>19 in October 2016, unfortunately with the same side</p> <p>20 effects as before.</p> <p>21 In February 2017, a pan azole resistant</p>	<p style="text-align: right;">Page 92</p> <p>1 azithromycin, three times a week, which was commenced</p> <p>2 around three years ago.</p> <p>3 I would like however to reiterate that</p> <p>4 nebulized -- practical impacts on daily life. Twice</p> <p>5 daily preparation, setting up, nebulizing, dismantling</p> <p>6 and cleaning of equipment is time consuming. It's</p> <p>7 also necessary to clean your teeth immediately after</p> <p>8 each session to avoid staining by the bright yellow</p> <p>9 liquid.</p> <p>10 Storage in the home is a further</p> <p>11 consideration. As you find that your fridge is full</p> <p>12 of injection vials and you have a wardrobe full of</p> <p>13 nebulizer equipment, water injections, sharps bins,</p> <p>14 syringes and needles. All of these things have an</p> <p>15 impact and shouldn't be discounted.</p> <p>16 Given my comments so far about my</p> <p>17 experience of ABPA and its treatment, it is I think</p> <p>18 easy to understand that I view the introduction of</p> <p>19 antifungal inhaler, or specific antifungal nebulas as</p> <p>20 very desirable.</p> <p>21 It could mean treatment which is easy</p>
<p style="text-align: right;">Page 91</p> <p>1 isolate was grown from my sputum and it became</p> <p>2 apparent to me for the first time that in reality,</p> <p>3 treatment options for aspergillosis were quite</p> <p>4 limited.</p> <p>5 Hence, my treatment was immediately</p> <p>6 changed to nebulized amphotericin B taken twice daily.</p> <p>7 The relative complexity of carrying out this treatment</p> <p>8 was something of a shock after taking oral medication.</p> <p>9 It involves making up amphotericin injection solution</p> <p>10 from powder vials using water for injections.</p> <p>11 Injecting some of this solution into the nebulizing</p> <p>12 chamber and adding further water for injections to the</p> <p>13 chamber, all of which of course is quite time</p> <p>14 consuming.</p> <p>15 Inhaling nebulized amphotericin is a</p> <p>16 little unpleasant, but I have continued with the</p> <p>17 treatment and I'm now in my fourth year. The</p> <p>18 treatment has been successful. I've been well with</p> <p>19 no, or very little, fungal growth and no cough. I've</p> <p>20 avoided bacterial chest infections -- by the addition</p> <p>21 of a prophylactic antibiotic treatment, namely</p>	<p style="text-align: right;">Page 93</p> <p>1 to administer and is virtually free some side effects</p> <p>2 and interactions, while also reducing some of the need</p> <p>3 for blood tests. In other words, a huge step forward</p> <p>4 from current oral and injectable therapies.</p> <p>5 I know from my own experience that lung</p> <p>6 and respiratory conditions are best managed by inhaled</p> <p>7 therapy. My asthma has been completely controlled by</p> <p>8 simple inhaled therapy throughout my adult life. And</p> <p>9 that contrasts sharply with my struggles with asthma</p> <p>10 as a child when there were no inhaled treatments and</p> <p>11 care seemed to rely on very few oral therapies which</p> <p>12 were ineffective and carried significant side effects.</p> <p>13 Inhaled therapies weren't introduced until I was in my</p> <p>14 middle-teens. From that point, my life was largely</p> <p>15 revolutionized.</p> <p>16 Even nebulized amphotericin with all</p> <p>17 its practical drawbacks has been successful for me in</p> <p>18 treating my ABPA and has been free from side effects.</p> <p>19 I should say at this point that throughout the</p> <p>20 treatment of my condition, I've been fortunate that I</p> <p>21 was attending clinic at Wythenshawe Hospital and</p>

<p style="text-align: right;">Page 94</p> <p>1 therefore had access to the National Aspergillosis 2 Centre. The patient group which is organized and run 3 there is a -- is a real help. When you suffer from a 4 condition which is actually not that common, all that 5 well known, and where there are real issues with the 6 treatments. The opportunity to talk for other 7 patients and to hear from expert speakers is a real 8 benefit when you're a long-term sufferer of a 9 condition like this.</p> <p>10 As a final point, I'd like to share my 11 belief that therapies which are as far as possible 12 free from side effects and interactions and convenient 13 to administer are especially important in treating 14 chronic conditions. This is because such treatments 15 encourage good patient compliance. A treatment cannot 16 be successful if patients are not prepared to take it. 17 In chronic disease, a high level of patient compliance 18 is required over the long-term. Thank you very much.</p> <p>19 DR. DAS: So our next speaker will be 20 Dr. Edwin -- our next speaker will be Dr. Edwin Rock 21 who's the Chief Medical Officer at Partner</p>	<p style="text-align: right;">Page 96</p> <p>1 investigational use as an adjunct to antifungal 2 therapy.</p> <p>3 Next slide, please.</p> <p>4 Data on aerosolized sargramostim 5 supported safety for investigational use.</p> <p>6 Inhalational sargramostim has been given chronically 7 to patients with pulmonary alveolar proteinosis, or 8 PAP. A lung disease caused by antibodies that block 9 GM-CSF function. Notably, patients with PAP are 10 susceptible to opportunistic infections, including 11 invasive aspergillosis. Likewise, GM-CSF neutralizing 12 antibody makes lethal experimental histoplasmic 13 capsulatum infections in mice, whereas GM-CSF 14 administration promotes fungal clearance.</p> <p>15 On the right here you see an Aerogen 16 ultra nebulizer device. Aerosolized sargramostim can 17 be given with standard handheld nebulizers such as 18 this one, which has been used in both pulmonary 19 alveolar proteinosis and COVID-19 trials.</p> <p>20 Next slide, please.</p> <p>21 Nonredundant antifungal mechanisms</p>
<p style="text-align: right;">Page 95</p> <p>1 Therapeutics. Dr. Rock will be talking about 2 sargramostim in the management of fungal infections.</p> <p>3 DR. ROCK: Good morning and thank you 4 to FDA for organizing this meeting, as well as to 5 Malcom Birrell for sharing his perspective.</p> <p>6 I'm looking for the button to advance 7 the slides. Thank you.</p> <p>8 Sargramostim, or Leukine, is 9 recombinant human GM-CSF made in yeast. It's approved 10 for sale by FDA in six disease indications for both 11 children and adults. These labeled indications all 12 build on sargramostim's capacity to stimulate myeloid 13 cell proliferation in the bone marrow and blood.</p> <p>14 Over half a million people have 15 received sargramostim since its market introduction in 16 1991. Although initially given intravenously, 17 subcutaneous and inhalational administration have also 18 been evaluated. As an example, aerosolized 19 sargramostim is being tested now in Europe and the US 20 for therapy of acute hypoxemia due to COVID-19 21 disease. Sargramostim is available now for</p>	<p style="text-align: right;">Page 97</p> <p>1 support further evaluation of sargramostim for 2 prevention and/or therapy of fungal diseases. In the 3 upper yellow box, you see overall anti-infectious 4 mechanisms of sargramostim whereas in the lower aqua 5 box, you see separate individual antifungal mechanisms 6 with supportive references. These five antifungal 7 effects include enhanced reactive oxygen species 8 generation -- and increased expression of fungal 9 pattern recognition receptor -- one, as well as 10 myeloperoxidase and neutrophil extracellular traps and 11 chitotriosidase. Proof of mechanism that GM-CSF may 12 be a useful adjunct to other antifungal therapies 13 comes from an immunosuppressed mouse model of 14 aspergillus in which intranasal GM-CSF led to a six- 15 fold reduction in pulmonary fungal burden.</p> <p>16 Also, anecdotal reports including by an 17 antifungal specialist on this afternoon's panel, 18 suggests that refractory fungal infections may be 19 treated successfully by addition of sargramostim to 20 other antifungal therapy.</p> <p>21 These data indicate that GM-CSF may not</p>

<p style="text-align: right;">Page 98</p> <p>1 by itself eliminate fungal infections, however, it may 2 be a useful adjunct in antifungal stewardship. While 3 antifungal therapy seeks to weaken the invading 4 fungus, GM-CSF compliments that therapy by 5 strengthening the host immune response. This effect 6 might be particularly useful to treat fungi that are 7 relatively insensitive to available drugs.</p> <p>8 Next slide, please.</p> <p>9 To summarize, sargramostim is an FDA 10 approved recombinant human GM-CSF made in yeast. It's 11 available now for investigational use as an adjunct to 12 antifungal therapy. Data on inhaled sargramostim 13 supported safety for investigational use and 14 nonredundant antifungal mechanisms support further 15 evaluation of it for prevention and/or therapy of 16 fungal diseases.</p> <p>17 At Partner Therapeutics, we're 18 interested to collaborate to evaluate further the 19 clinical utility of sargramostim in fungal and other 20 diseases. Our contact information is provided here. 21 We'll be glad to hear from you, including if you know</p>	<p style="text-align: right;">Page 100</p> <p>1 antifungal products.</p> <p>2 As you know, we've had a lot of 3 interest expressed recently in inhaled antifungal 4 products. A particular need for allergic 5 bronchopulmonary aspergillosis and invasive pulmonary 6 aspergillosis. There are no approved inhaled 7 antifungal products, but from regulatory standpoint, 8 the general principles for development of an inhaled 9 antifungal drug would be similar to those for inhaled 10 antibacterial drugs.</p> <p>11 Now the statutory standard for approval 12 of a drug is demonstration of substantial evidence, 13 which is evidence consisting of adequate and well- 14 controlled investigations.</p> <p>15 The characteristics of these 16 investigations are outlined in the code of federal 17 regulations, and some of the important characteristics 18 include a design that permits a valid comparison with 19 the control, and also that section contains 20 descriptions of various types of controls. Adequate 21 assurance that subjects have the disease or condition</p>
<p style="text-align: right;">Page 99</p> <p>1 of potential sites that may be interested in our 2 ongoing COVID-19 therapy trials. Thank you in any 3 case for your consideration.</p> <p>4 DR. ANDES: Thank you, Dr. Rock. We're 5 now scheduled for a lunchbreak. We're to return at 6 noon with the subsequent session starting at 12:10. 7 Thanks again to all the speakers for their excellent, 8 informative presentations. We'll be able to discuss 9 this further as a panel at the end of the day.</p> <p>10 (Off the record.)</p> <p>11 DR. DENNING: Can you -- are you 12 online, Dr. Smith?</p> <p>13 DR. SMITH: Yes, I am.</p> <p>14 DR. DENNING: All right. Do you want 15 to start your talk then? I think your slides are 16 there.</p> <p>17 MR. SMITH: Okay. Hi, this is Tom 18 Smith. I'm a clinical team leader in the Division of 19 Anti-Infectives at FDA. And I'd like to open our 20 afternoon session by discussing, from an FDA 21 standpoint, some regulatory considerations for inhaled</p>	<p style="text-align: right;">Page 101</p> <p>1 that's being studied, measures to minimize bias and 2 assure comparability of groups -- assessment of the -- 3 that are well defined and reliable, and an analysis of 4 results that's adequate to assess the effects of the 5 drug.</p> <p>6 Now the Modernization Act has clarified 7 that in certain circumstances, the agency may consider 8 data from one adequate and well-controlled 9 investigation and one with confirmatory evidence to 10 constitute substantial evidence. And this type of 11 supporting evidence in the past has included evidence 12 from nonclinical and in vitro studies, or from studies 13 in another indication. And one of our discussion 14 questions this afternoon is going to be discuss some 15 of the nonclinical and in vitro studies that might be 16 able to constitute support for approval for an inhaled 17 antifungal product.</p> <p>18 Regulatory pathways include traditional 19 approvals, which are based on an endpoint that 20 measures how a patient feels, functions or survives. 21 Or accelerated approval which is based on a surrogate</p>

<p style="text-align: right;">Page 102</p> <p>1 endpoint that's reasonably likely to predict clinical 2 benefit or in a clinical endpoint that you mentioned 3 earlier -- comorbidity and mortality. These 4 accelerated approvals require the confirmatory 5 clinical studies -- endpoints in antifungal trials for 6 systemic therapies included all cause mortality and 7 clinical success at a fixed timepoint, which is 6 to 8 12 weeks.</p> <p>9 As I mentioned earlier, the methods of 10 assessment of subject's responses should be well- 11 defined and reliable. The clinical endpoint directly 12 measures the therapeutic effect of a drug, which is an 13 effect on how a patient feels, functions or survives. 14 Whereas surrogate endpoints are markers such as a 15 laboratory measurement or other measurement that's 16 likely to predict a clinical benefit, but in itself is 17 not a measure of clinical benefit.</p> <p>18 We've had a number of advisory 19 committee meetings and workshops over the past several 20 years in the areas of inhaled antibacterial drugs for 21 conditions such as lung cystic fibrosis</p>	<p style="text-align: right;">Page 104</p> <p>1 typically for inhaled antibacterial drugs have been on 2 and off therapy used cyclically for conditions such as 3 non-CF bronchiectasis, which is similar to what's been 4 done with cystic fibrosis. And it isn't really clear 5 whether other approaches might be better.</p> <p>6 The optimum duration of therapy and 7 length of follow-up to determine a treatment benefit 8 hasn't been clear. The impact of therapies on 9 microbiologic floor due to long-term exposure and then 10 a subsequent development of resistant and replacement 11 with other microorganisms remains a concern.</p> <p>12 The references listed here are -- will 13 contain the transcripts of these advisory committee 14 meetings and workshops for further reference.</p> <p>15 Now the lessons that we've learned from 16 inhaled antibacterial therapies for conditions such as 17 non-CF bronchiectasis and non-TB mycobacterial lung 18 disease also apply to inhaled antifungal therapies. 19 It's important to select clinically meaningful 20 endpoints and not endpoints that are based solely on a 21 biomarker or a laboratory test.</p>
<p style="text-align: right;">Page 103</p> <p>1 bronchiectasis, non-tuberculosis mycobacterial lung 2 infections -- cystic fibrosis.</p> <p>3 And there are a number of challenges 4 that we have found in these programs which I think are 5 also applicable to the development of inhaled 6 antifungal drugs. These occur that the patient 7 populations are often very heterogenous in terms of 8 either underlying conditions or the severity of 9 illness, the microbiologic etiologies, the -- it's 10 been difficult to define clinically meaningful 11 endpoints. Unlike the situation with acute 12 infections, patients with some of these diseases have 13 persistent symptoms that are related to their 14 underlying condition. And they don't always respond 15 with what -- you know, complete resolution of their 16 condition.</p> <p>17 Also, as Dr. Moss pointed out earlier 18 today for the antifungal conditions, microbiologic 19 endpoints for some of the antibacterial conditions 20 don't necessarily correlate with clinical outcomes. 21 Treatment regimens have been either --</p>	<p style="text-align: right;">Page 105</p> <p>1 We emphasize the importance of adequate 2 development work, including phase two trials which 3 will help in determining some of the key design 4 elements for subsequent trials.</p> <p>5 Heterogeneity in the patient population 6 must be considered. Variability and treatment effect 7 can affect the trial results. And as we do with the 8 antibacterial -- inhaled antibacterial therapies, we 9 collaborate with our colleagues in the divisions of -- 10 Division of Pulmonary Allergy and Critical Care to 11 help in analyzing some of these endpoints and design - 12 - trial design elements.</p> <p>13 To move onto allergic bronchopulmonary 14 aspergillosis, there are no FDA approved drugs for 15 this condition. Infectious Disease Society of America 16 guidelines put antifungal therapy recommend 17 itraconazole as the primary treatment with 18 voriconazole or Posaconazole as alternatives. And 19 they mention inhaled amphotericin B as the treatment 20 for patients who fail or are intolerant to 21 itraconazole.</p>

<p style="text-align: right;">Page 106</p> <p>1 Some of our discussions regarding ABPA, 2 some of the -- the issues that have come up include 3 what the intended use of the product is. Whether it's 4 to replace oral itraconazole use, or to permit 5 reduction of oral steroids, to induce remission or to 6 be used as an adjunctive therapy.</p> <p>7 Patient population in terms of 8 underlying conditions, whether it's asthma, cystic 9 fibrosis, COPD, there are issues with documenting the 10 diagnosis of ABPA in out-staged and which of those 11 stages would be suitable for entering patients in the 12 trials. Identification of appropriate treatment 13 regimens, how to use adjunctive therapies, 14 particularly corticosteroids would be handled because 15 of the possible confounding efficacy assessments when 16 steroid therapy is weaned.</p> <p>17 There are endpoint issues, whether the 18 endpoint should be measures of lung function, patient 19 report -- measures, the number or severity of 20 exacerbations, the time to an exacerbation event, or 21 some composite of all of these. It's important to</p>	<p style="text-align: right;">Page 108</p> <p>1 IDSA guidelines recommend voriconazole as primary 2 treatment with liposomal amphotericin B -- as 3 alternatives -- therapy's recommended. And then they 4 do mention inhaled amphotericin B for tracheal 5 bronchial aspergillosis associated with -- injury and 6 lung transplant patients, or for antifungal 7 prophylaxis in lung transplantation.</p> <p>8 So the issues that have come up in 9 terms of therapies for IPA include the intended use, 10 whether it's the -- the therapy's deduced for 11 prophylaxis or for treatment. Whether it's to be an 12 adjunct to systemic therapy versus used as 13 monotherapy. And each of these considerations has 14 implications for trial design in terms of endpoints. 15 You know, whether the endpoint's going to be 16 occurrence of an infection, if it's a prophylactic 17 therapy versus some kind of clinical outcome 18 measurement or treatment.</p> <p>19 There are also implications in terms of 20 [virtual connectivity interruption]. There are also 21 issues in terms of superiority versus noninferiority</p>
<p style="text-align: right;">Page 107</p> <p>1 keep in mind that the endpoint has to be clinically 2 meaningful and not solely based on a biomarker or a 3 laboratory test.</p> <p>4 The evaluation of exacerbations, there 5 have been issues in terms of how to define the 6 beginning and end of an event, and how to determine 7 whether the event is due to asthma or some other 8 underlying lung condition versus ABPA.</p> <p>9 There are issues with how the 10 microbiologic assessments are to be interpreted when 11 the goal is reduction of a microbial burden rather 12 than eradication of an infection. And there are 13 issues in terms of the duration of trials.</p> <p>14 We're going to be discussing those 15 issues in the discussion period following 16 presentations.</p> <p>17 Then we'll move onto invasive pulmonary 18 aspergillosis. Again, here, there are some approved 19 drugs for systemic treatment. The azoles -- for 20 refractory intolerant -- patients who are intolerant 21 of the therapies, amphotericin B formulations. The</p>	<p style="text-align: right;">Page 109</p> <p>1 analyses. For instance, for an add-on therapy, the 2 expectation would be for a superiority trial versus 3 the possibility of noninferiority for other 4 monotherapies.</p> <p>5 Target population's important, whether 6 it's patients with hematologic malignancies, lung 7 transplantation, COPD. The endpoints for the 8 subpopulations under study could vary depending on 9 type of population that's being studied. These 10 endpoints could be clinical, microbiologic, radiologic 11 or some type of patient-reported outcome. And the 12 exact assessment of the response to therapy is -- is 13 also a potential issue.</p> <p>14 And then as we heard this morning, some 15 of the other important considerations are -- are from 16 -- that need to be addressed early on in development 17 include the device issues. We heard from our 18 colleagues in CDRH and from the Division of Medication 19 Error Prevention and Analysis. Patient labeling team 20 reviews instructions for use. We encourage early 21 interactions with -- to address chemistry issues.</p>

<p style="text-align: right;">Page 110</p> <p>1 And just finally, to sum up, we 2 recognize the need for development of safe and 3 effective antifungal products to treat allergic 4 pulmonary -- bronchopulmonary aspergillosis and IPA. 5 However, trials that are done must be feasible and 6 interpretable with clinically meaningful endpoints. 7 We recommend phase two trials to evaluate possible 8 endpoints, assess treatment effects and determine 9 other important design elements for trials, and we 10 look forward to continue -- continued work with 11 sponsors on trial development and appropriate data 12 packages that would support approval. 13 We look forward to a productive rest of 14 the afternoon. Thank you very much. 15 DR. DENNING: -- who's moved with EMA 16 from London to Amsterdam, thanks to Brexit. And he's 17 going to talk about -- give us a European perspective 18 on this. 19 DR. BOTGROS: Hello. Thank you very 20 much, Professor Denning. Can you all hear me? 21 DR. DENNING: Yes, we can.</p>	<p style="text-align: right;">Page 112</p> <p>1 antifungals, or of antifungals in general, as many of 2 you will know, we have in Europe a guideline on the 3 development of antifungal agents. And I have to say 4 that this guidance does not specifically address the 5 development on inhaled agents as it's primarily 6 concerned with the content of clinical development 7 programs to address the safety and efficacy of 8 antifungal agents administered by oral or parenteral 9 routes for the treatment and prophylaxis of invasive 10 fungal disease. But still, the main principles 11 outlined in the guideline do apply at least for 12 medicines in the treatment of prophylaxis or invasive 13 fungal infections, in particular invasive 14 aspergillosis. And here I'm talking about the inhaled 15 -- the ones -- the ones we are discussing today. 16 So the clinical trials expectations for 17 Europe are that they -- the trials would need to be 18 designed in the same way as described in the guidance. 19 Of course the situation is somewhat 20 different for medicines developed for the so called 21 chronic conditions, like ABPA. And I will try to</p>
<p style="text-align: right;">Page 111</p> <p>1 DR. BOTGROS: Thank you. So thanks 2 very much and thanks to the FDA for inviting me to 3 this workshop to present our perspective on 4 development on inhaled antifungal medicines. 5 As you notice, I don't have slides for 6 this. Apologies. The slot has been agreed slightly 7 later than the other ones, but I think the good news 8 is that we seem to have a similar thinking in the US 9 compared to what we heard today from our FDA 10 colleagues when it comes to development of 11 inhalational antifungal drugs. 12 I have to say that we also have -- saw 13 some recent interest in the -- for developing this 14 kind of products. Albeit not too high an interest 15 until now. And therefore, our exposure in Europe to 16 development for this type of product is still rather 17 limited, I would say. 18 As is in the case in the United States, 19 we also do not have approved inhaled antifungals in 20 Europe for allergic bronchopulmonary aspergillosis. 21 And when it comes to the development of inhaled</p>	<p style="text-align: right;">Page 113</p> <p>1 point out a few particular aspects in the next few 2 minutes. 3 In terms of for clinical development, 4 and we heard this morning the excellent presentation 5 by our FDA colleague, Dr. McMaster, we are concurrent 6 with the provisions of the ICHM3 or revision two 7 guidance, and of the other regulatory requirements for 8 nonclinical development. 9 So apart from the standard nonclinical 10 package that was already outlined by FDA colleagues, 11 we also support conducting inhalation toxicity studies 12 for this types of products as well as also mentioned 13 this morning. So in the interest of time, I won't -- 14 the details on this. 15 With regard to the clinical 16 development, I think we are also quite aligned with 17 our FDA colleagues in terms of regulatory requirements 18 for approval. We generally request conducting phase 19 one studies in healthy volunteers followed by -- by a 20 single ascending and multiple ascending dose studies 21 in patients.</p>

<p style="text-align: right;">Page 114</p> <p>1 I think a very important aspect of the 2 development is that the proposed dose regimen and 3 frequency of administration should and need to be well 4 justified. The -- the sponsor should carefully 5 consider the patient population to be enrolled in 6 phase two and three trials. And as an example, in 7 principle asthma patients and CF patients should be 8 studied in separate trials, as the underlying diseases 9 are different. The comedication is different. So 10 this may have a potential impact on safety and so on. 11 We are of course safety -- we are of 12 course happy to discuss with applicants about the 13 feasibility of that kind of approach, but that is in 14 principle the starting point. 15 For late clinical development, as well 16 as also mentioned minutes ago by my FDA colleague, 17 it's very important that adequate diagnosis and 18 staging of the subjects is made, and that is 19 critically important. 20 We are also of the view that any 21 regulatory approval of an inhaled antifungal should be</p>	<p style="text-align: right;">Page 116</p> <p>1 is clinically meaningful and that it takes into 2 account an adequate length of treatment, which also 3 may need to be discussed. 4 And as mentioned for the so called 5 chronic condition, like ABPA, we have no product 6 approved in Europe. We have -- we know and we have 7 the azoles parenteral that are recommended by 8 therapeutic guidelines. As we also heard earlier 9 today from Professor Moss. So there's a need to 10 discuss the design of the studies and whether they 11 should be either add-on or comparative. So this -- 12 these are things that will need to -- to discuss in a 13 scientific advice process. 14 I need to therefore stress again that 15 we strongly recommend that for developments of inhaled 16 antifungals, the sponsor applies for the MA scientific 17 advice to discuss all the aspects. Quality, 18 nonclinical and clinical aspects. In particular, if 19 the situation is such that the proposal pertains to a 20 drug device combination. And here I need to remind 21 you that we are assessing the device performance in</p>
<p style="text-align: right;">Page 115</p> <p>1 based on results generated in adequate randomized 2 clinical trials that are controlled. Which is of 3 course the appropriate standard for approving medicine 4 based on the assessment of its benefit risk balance. 5 Single pivotal trials are in general 6 acceptable, but I think I need to point out the fact 7 that the results need to be robust in the sense that 8 between phase two and three, there should be a 9 consistent magnitude of the treatment effect that 10 superiority over placebo should be shown in both type 11 of studies, and the safety provide should be benign. 12 If -- if any of this criteria does not apply, I 13 suppose that there will be a need to conduct a second 14 before to trial. 15 In terms of primary endpoint, it should 16 indeed be carefully chosen to reflect the clinical 17 benefit of the patient. And here we concur with the 18 fact that a biomarker may not be sufficient. We are 19 open to discuss of course with sponsor and the 20 framework of our EMA scientific advice, but we need to 21 be convinced that the endpoint -- the primary endpoint</p>	<p style="text-align: right;">Page 117</p> <p>1 our assessment, but we do not license the device in 2 Europe. 3 In terms of regulator azoles, we have a 4 few available. And I think we can employ those that 5 are suitable to address the setting -- and this are 6 settings of a medical need. 7 For instance, in case we can be 8 convinced that for example an earlier timepoint can 9 provide adequate initial evidence, we could consider a 10 condition of marketing authorization. But of course, 11 it's too early to -- to -- to say we willing to see 12 the development of the product one by one. 13 And in addition, we have as you may 14 know applicants for -- designations which bears some 15 incentives in Europe for drugs developed for rare 16 conditions. We have the -- the priority medicine 17 programs scheme that also can be discussed with the 18 EMA. 19 With that, in the interest of time, I 20 will stop here and not be forward thinking again. 21 Thank you colleagues for having invited me to this</p>

<p style="text-align: right;">Page 118</p> <p>1 important workshop. Thank you very much.</p> <p>2 DR. MARR: Thank you, Dr. Botgros.</p> <p>3 This is Kieren Marr, I'm co-chairing the session with</p> <p>4 Dr. Denning. I'd like to just remind everyone to</p> <p>5 please use the question and answer box for typing in</p> <p>6 questions as you go. We will have a robust discussion</p> <p>7 period at the end, but not after the individual talks.</p> <p>8 With that, I'll introduce Dr. Rohit</p> <p>9 Bazaz, who is a consultant in Infectious Disease in</p> <p>10 the National Aspergillosis Centre, Manchester</p> <p>11 University, NHS Foundation Trust and an honorary</p> <p>12 senior clinical -- at the University of Manchester.</p> <p>13 DR. BAZAZ: Good afternoon. Hopefully</p> <p>14 you can hear me. Yeah. So I'm going to give an</p> <p>15 overview of diseases that fall under the label of</p> <p>16 allergic fungal airways disease. And in particular,</p> <p>17 ABPA and -- and severe asthma -- fungal sensitization.</p> <p>18 I'm also going to just describe my -- my experience of</p> <p>19 being site PI for Manchester for the -- the AFAB [ph]</p> <p>20 trial of the IL-33 receptor antagonist, and explore</p> <p>21 the issues that we had for recruiting for that trial.</p>	<p style="text-align: right;">Page 120</p> <p>1 the left-hand side, you -- you have patients with</p> <p>2 asthma without any fungal sensitization. But moving</p> <p>3 along the spectrum, you have patients who have asthma</p> <p>4 associated with fungal sensitization, but in whom --</p> <p>5 seems to have a little or no effect on their asthma</p> <p>6 control. Moving further along the spectrum, you have</p> <p>7 closely related conditions of fast and seropositive</p> <p>8 ABPA. That's ABPA without bronchiectasis. But unlike</p> <p>9 SAS [ph], ABPA can go on to -- to cause</p> <p>10 bronchiectasis.</p> <p>11 So aspergillus sensitization is a -- is</p> <p>12 a term that obviously of course refers to production</p> <p>13 of aspergillus specific IGE antibodies following</p> <p>14 exposure to the fungus. And it can be detected either</p> <p>15 by skin prick test, leading to a cutaneous</p> <p>16 hypersensitivity reaction or more commonly by</p> <p>17 measuring serum aspergillus specific IGE</p> <p>18 concentration.</p> <p>19 Although inhaled fungal spores, fungal</p> <p>20 candida are normally removed from the airways by</p> <p>21 various mechanisms, including mucociliary clearance or</p>
<p style="text-align: right;">Page 119</p> <p>1 This -- this figure acts as a reminder</p> <p>2 that aspergillosis is a spectrum of diseases. And</p> <p>3 other exposure to aspergillus airborne spores through</p> <p>4 inhalation is -- is common. Only a minority of those</p> <p>5 exposed will develop lung disease. And in those who</p> <p>6 develop disease, the -- the manifestation of</p> <p>7 aspergillosis -- aspergillus disease largely depends</p> <p>8 on the immune response of the host. And if there's</p> <p>9 interplay between pathogen or host immune response</p> <p>10 that determines the -- the clinical syndrome that --</p> <p>11 that develops.</p> <p>12 I'm having a slight problem here. All</p> <p>13 right.</p> <p>14 So allergic reactions of course</p> <p>15 represent a deranged TH2 response to allergens and</p> <p>16 allergic fungal airways disease itself constitutes a</p> <p>17 spectrum of disease processes with the clinical</p> <p>18 features dependent very much on the extent of the</p> <p>19 derangement of this TH2 immune response. Most</p> <p>20 patients with asthma are not sensitized to</p> <p>21 aspergillus, so at the one end of this spectrum, on</p>	<p style="text-align: right;">Page 121</p> <p>1 alveola macrophages, effective clearance in patients</p> <p>2 with asthma and cystic fibrosis allow germination of</p> <p>3 these conidia into hyphae and that then triggers an</p> <p>4 allergic response within the airways. And it's used</p> <p>5 in production of pro-inflammatory cytokines then</p> <p>6 responsible for the clinical phenotypes that we see.</p> <p>7 And the reason that most fungal</p> <p>8 allergens are released only after spores germinate,</p> <p>9 after the spores are covered with a hydrophobic,</p> <p>10 protective layer made up of hydrophobic protein. And</p> <p>11 that protects the spores and enables invasion of the</p> <p>12 immune system.</p> <p>13 As you can see, there's reports of</p> <p>14 significant prevalence of sensitization to aspergillus</p> <p>15 in patients with -- with asthma and cystic fibrosis.</p> <p>16 And also, it's increasingly being recognized in</p> <p>17 patients with COPD. Although the implication of this</p> <p>18 on COPD progression requires further investigation.</p> <p>19 And it's not just aspergillus species</p> <p>20 that we inhale. In fact everyone inhales a very</p> <p>21 complex mixture of hyphal fragments, fungal spores and</p>

<p style="text-align: right;">Page 122</p> <p>1 yeast on a daily basis. And the species composition 2 varies depending on the day and the season and can 3 include species such as Alternaria and Cladosporium. 4 The highest concentrations of spores in the 5 environment are seen in the late summer and early 6 autumn, when over 50,000 fungal spores per cubic meter 7 of air per day can be present. Patients can become 8 sensitized to these fungi -- to -- to all these fungi 9 and studies have shown that the person can become co- 10 sensitized to multiple fungal allergens. 11 Moving specifically onto ABPA. ABPA, 12 as I mentioned, is an exaggerated immune response to 13 inhalation of -- of aspergillus. It's a complication 14 primarily of patients with asthma and cystic fibrosis. 15 It can rarely occur in -- outside of those conditions. 16 As a complication of asthma, it's thought to affect 17 around 2.5 percent of patients with -- with asthma. 18 And prevalence in children is thought to be less, but 19 reports vary, anything from one to eight percent 20 worldwide. 21 And estimates of the global prevalence</p>	<p style="text-align: right;">Page 124</p> <p>1 cells. 2 ABPA itself can be considered to be a 3 severe endotype of TH -- of T2-high asthma. And 4 looking at the mechanism in a bit more detail, what is 5 thought to happen is exposure to fungal allergens 6 induces airway epithelial cells to release 7 inflammatory -- such as IL-33 and IL-25. And these 8 activate enabling for type 2 cells and go on to 9 produce large quantities of type 2 cytokines, 10 including IL-5 and IL-13. And these cytokines drive, 11 as I said, differentiation of B cells to promote the 12 release of IGE. And that leads to sensitization of 13 mass cells -- allergic -- and at the same time 14 attracting and activating eosinophils. These 15 cytokines IL-33 and IL-25 also acts upon the intratec 16 [ph] and naïve T-cells to drive this -- this TH2 17 differentiation. And ultimately, you're left with a - 18 - a robust TH2 inflammatory response that has various 19 negative effects, including airway and mucous 20 production, hyperresponsiveness and bronchiectasis. 21 And over time, when persistent information leads to</p>
<p style="text-align: right;">Page 123</p> <p>1 and ABPA suggest it has a potentially significant 2 global burden disease is caused by ABPA. An estimated 3 4.8 million people worldwide effected. With regard to 4 clinical features, it's characterized by worsening 5 respiratory symptoms, cough and thick sputum. 6 So the model of asthma's being a single 7 entity has changed over time. It's now clear that 8 there are different clinical phenotypes that fall 9 under the umbrella of the term asthma. And these 10 different phenotypes are underpinned by different 11 mechanisms. In broad terms, they can be divided into 12 T2 high and T -- and non-T2 high groups. Allergic 13 fungal airways disease is clearly a predominantly T2 14 high disease. This is primarily, in terms of 15 pathogenesis, caused by dysregulation of the airway's 16 epithelial barrier allowing access by the stromal 17 tissue -- sorry, access to the stromal tissue by 18 allergens. And this -- cytokines by epithelial cells, 19 eventually leads to an inflammatory cascade inducing 20 the differentiation of naïve T cells and TH2 cells. 21 And eventually leading to IGE production from plasma</p>	<p style="text-align: right;">Page 125</p> <p>1 bronchiectasis, the -- how it drives is advanced ABPA. 2 So moving onto the clinical features of 3 ABPA, I think it's fair to say that ABPA's probably 4 still underrecognized. And in terms of the diagnostic 5 clues, clearly in terms of patients with asthma, one 6 of the key features included is poor asthma control 7 despite optimization of therapy. And clues from the 8 history are history of recurrent pneumonias and -- and 9 -- and -- and from symptoms, coughing up a thick, 10 tenacious sputum is another clue. 11 There is -- there is no one test that 12 we can do to diagnose ABPA. It is really a 13 consolation of -- of symptoms and clinical features. 14 And because of -- of that, that there have been 15 attempts to create diagnostic criteria over the years. 16 The first attempt being in 1977. You can see on the 17 left-hand side of the slide. But as I understand -- 18 diagnostic has improved slightly, then obviously the 19 diagnostic criteria have changed over time. And I 20 think it's fair to say probably the most used 21 diagnostic criteria at the moment is the issue --</p>

<p style="text-align: right;">Page 126</p> <p>1 working group criteria which you can hopefully see on 2 the -- the right-hand side of the slide there. And 3 requirement of the predisposing conditions. Bronchial 4 asthma and cystic fibrosis. And requirement of an IGE 5 -- certain IGE level of over 1,000, and of course 6 requirement of evidence of sensitivity to aspergillus. 7 And here we have examples of this -- 8 the fleeting shadowing on chest X-rays. This is a 9 patient who during flares of ABPA, had infiltrates. 10 And -- and the case of 1999 on the left, the 11 infiltrates were on the -- in the right lung and -- 12 but in 2002, the infiltrates were in the left lung. 13 And -- and these are, as I said, flares disease. I 14 think it's important to remember that in many 15 patients, this is a relapsing and remitting condition. 16 They have flares of disease, when they have coughing 17 up lots of phlegm, short of breath, unwell with fever. 18 But then things can -- can settle down over time, 19 particularly with -- with steroid therapy. But 20 there's still fleeting shadowing on chest X-ray 21 changes, changing position of the infiltrates over</p>	<p style="text-align: right;">Page 128</p> <p>1 And as I said, while all these are 2 suggestive of the diagnosis, none of them are -- are 3 specific for it. 4 So what the potential complications of 5 ABPA though -- from the patient point of view is poor 6 asthma control despite optimization of therapy. And 7 there are specific complications related to the 8 development of bronchiectasis, in particular of course 9 recurrent chest infections, hemoptysis and respiratory 10 failure. And there is a risk of develop -- of ABPA 11 progressing into chronic pulmonary aspergillosis. And 12 even aspergilloma formation, and again, because of 13 this -- this persisting inflammatory response, 14 patients can develop pulmonary fibrosis which of 15 course can impact on lung function. And rarely, ABPA 16 can lead to invasive aspergillosis. Particularly the 17 risk factor would be patients who've been receiving 18 high -- high and prolonged doses of corticosteroids. 19 So you've got to go in therapy for 20 ABPA, and there's been lots of discussion about this 21 already. The aim of therapy is of course to control</p>
<p style="text-align: right;">Page 127</p> <p>1 time is quite characteristic. 2 As I've said also, there's -- there's 3 mucus plugging in here. You can see bronchoscopy 4 images of a patient with -- in the midst of an ABPA 5 flare with thick sputum that's -- that's cluding the 6 airways. And that can lead to actual collapse of the 7 lung in severe cases, as you can see in the X-ray at 8 the top right. 9 So there are characteristic CT scan 10 features for ABPA. None of these are specific, but 11 they are suggestive. They -- they can be seen in 12 other conditions, but clearly in the right clinical 13 context, they're highly suggestive of the diagnosis. 14 In particular, bronchiectasis, you can see in -- in CT 15 scan B. Central cystic bronchiectasis, which often 16 effects the upper lobes. Over time, as you can see in 17 images C, D and E, you get varying degrees of mucus 18 plugging and bronchial wall thickening, tree and blood 19 changes, the centrilobular nodules with -- with a 20 linear branching pattern as -- as the inflammation 21 progresses over time.</p>	<p style="text-align: right;">Page 129</p> <p>1 the acute inflammation and limit the lung injury 2 during -- particularly during flares of the disease. 3 And -- and as with any other condition, we do attempt 4 to individualize therapy to the patient's own clinical 5 symptoms. And of course taking into consideration any 6 other medication that they may be on. 7 I think it's fair to say that first 8 line therapy is with -- during a severe flare of ABPA 9 would be with oral corticosteroids. There's no clear 10 consensus on dosage -- dosing regimens used. But in 11 general, it would be a fairly high dose, for example 12 30 to 40 milligrams of prednisone, and this would then 13 be tapered down over time, over a period of three to 14 four months. And that would be first line option in 15 treating a flare. 16 Now where antifungals have a role to 17 play of course is largely the steroid sparing agent. 18 And would be considered -- so oral antifungal would be 19 considered in patients who, for example, were unable 20 to taper off steroids completely or were requiring 21 frequent courses of steroids over time.</p>

<p style="text-align: right;">Page 130</p> <p>1 Now David is going to actually talk 2 about this in -- in a bit more detail in terms of the 3 trial evidence for the use of all antifungals. So I'm 4 not going to touch upon it in too much detail. But 5 suffice it to say that there is some randomized 6 control trial evidence favoring the use of -- or 7 supporting the use of itraconazole and voriconazole in 8 -- in ABPA. And but of course we have to remember 9 that these drugs, while they may be effective, they do 10 have a significant side effect. Profile for 11 itraconazole for example, patients can develop edema 12 and cardiac failure. For both drugs, peripheral 13 neuropathy can be a problem. And with voriconazole, 14 of course, you've got photosensitivity of the skin. 15 So particularly in elderly patients, a lot of them 16 don't tolerate these drugs. So they are often unable 17 to continue these drugs for a long period. 18 In our own center, we do -- we have had 19 some success with using nebulized amphotericin B 20 fungicidal and there was a small -- of a patient who 21 have responded to that and remained on it for -- for</p>	<p style="text-align: right;">Page 132</p> <p>1 is usually a guideline -- a various guideline for -- 2 to characterize what is meant by severe asthma. And a 3 total IGE level, unlike ABPA, the total IGE level 4 should be less than 1,000, and while -- SAS does not. 5 So again, in general, the treatment -- 6 David is going to talk about this in a bit more detail 7 in terms of the trial evidence, but the general 8 principles are similar to ABPA so far as treatments 9 nearly consist of optimization of asthma, medication 10 and steroids, if necessary, and antifungals -- 11 specifically itraconazole or voriconazole -- can be 12 used as, again, a steroid sparing agent if necessary. 13 I'm just -- again, I was going to 14 briefly touch on my own experience of -- of being the 15 site PI for the -- the -- trial. This was a 16 randomized, double-blind placebo controlled trial 17 evaluating human immunoglobulin that -- that binds the 18 main one of the cell surface IL-33 receptor. So as we 19 mentioned earlier, IL-33 is a key inflammatory that 20 mediates the drives of allergic asthma. And clearly 21 the aim here is to block -- block the signaling, the</p>
<p style="text-align: right;">Page 131</p> <p>1 several years with a good response. But if you look 2 back at -- at our patient review, overall patients 3 who've attempted this is that very high dropout rate 4 of patients, when given this, many patients don't 5 tolerate it. So as a -- as a large scale treatment, 6 there's going to be a huge number of patients who 7 won't be able to -- to have this. 8 So again, I'm not going to touch on 9 this in too much detail because it's clearly -- there 10 have been other talks about these during the day. But 11 in regard to drugs that are currently being evaluated, 12 of course we have the -- the inhaled itraconazole and 13 the PC945 nebulized azole. Again, I'm not going to go 14 into this in too much detail because there's going to 15 be other talks I'm aware of -- to this in more detail. 16 Now moving on to SAS, there are 17 similarities with ABPA, but there are some key 18 differences as well. So requirement in terms of the - 19 - key diagnostic criteria. The patient requires to 20 have severe asthma, which isn't necessarily -- which 21 isn't needed necessarily for ABPA. So severe asthma</p>	<p style="text-align: right;">Page 133</p> <p>1 IL-33 signaling. This is a phase two trial. And the 2 primary objective is to evaluate the effectiveness of 3 three doses of the drug given intravenously every four 4 weeks, compared with -- with placebo. And in terms of 5 any points, the main endpoints that were being 6 evaluated were the change in blood eosinophils over 7 time and change in blood eosinophils over time and 8 change of fractional exhaled nitric oxide to the FeNO 9 over time, which of course a marker of airway 10 eosinophilic inflammation. There are of course other 11 outputs that were -- that were looked at, including 12 PKPD assessment safety evaluations and so on. 13 So with regards to the inclusion 14 criteria, fairly standard 18 years and above, moderate 15 or severe asthma, and there were certain criteria that 16 had to be met with screening visit -- visit one, 17 that's a FeNO of above 25, an asthma control 18 questionnaire score of above 1.5, and a blood 19 eosinophil count of over 300 cells per microliter. 20 And then of course there has to be evidence of 21 allergic fungal airways disease.</p>

<p style="text-align: right;">Page 134</p> <p>1 Similarly, exclusion criteria were 2 fairly standard and included other significant 3 respiratory diseases or non-respiratory diseases. 4 Important part of recruiting for the 5 clinical trial is being aware of the prohibits and 6 mediations. And particular notes here with this trial 7 was -- modularity suppressive drugs, which of course 8 is understandable. But this included long-term oral 9 corticosteroids. And of course, many of our patients, 10 as you an imagine having -- are requiring long-term 11 oral corticosteroids because of the -- the severity of 12 their disease. So that clearly was an issue with 13 regard to recruitment. As for the medication which 14 was prohibited with the caveat -- the important useful 15 caveat, that patients who had been on oral antifungals 16 for at least a month prior to screening were allowed 17 to be enrolled, provided they'd been on the same dose 18 of the drug throughout that time period. 19 So the recruitment targets worldwide 20 was 46. Now our local recruitment target was 5, which 21 we thought was eminently achievable. We're a national</p>	<p style="text-align: right;">Page 136</p> <p>1 significant inflammation at the time, you have to 2 respect the fact that on any given day, the -- the 3 level of inflammation may be higher or lower. And so 4 clearly it was changed then to be a bit more pragmatic 5 and allow a slightly lower cutoff, but with evidence 6 historically of -- of that higher, above 300 level of 7 eosinophils. 8 So we did screen eight patients. Four 9 failed due to too low FeNO, three due to too low 10 cynophile count and one due to smoking. It had 11 transpired that they had actually started smoking 12 again after we did a consent with them which we 13 weren't aware of. And so as I said, we do have a 14 large number of patients who have been diagnosed with 15 ABPA and SAS. So we're just exploring why those 16 patients weren't screened. As you can imagine -- 17 declined, but this was a very motivated patient -- 18 this is a patient group we're very much interested in, 19 in being part of clinical trials, as you can imagine, 20 precisely because we're relatively short of drug 21 options. A lot of them did -- did want to be</p>
<p style="text-align: right;">Page 135</p> <p>1 center. We have lots of patients referred to us from 2 around our region, around the country. However, 3 unfortunately the expectation did not meet reality. 4 And worldwide, I understand the worldwide recruitment 5 was only 18. And locally, we unfortunately did not 6 recruit -- enroll anyone into the trial, which was of 7 course very disappointing. 8 And because we clearly -- we had the 9 greenlight for this trial in 2018, it clearly became 10 clear over -- after a few months that we were 11 struggling to recruit. So this led to following 12 feedback to sponsor, that was led to a protocol 13 amendment and as I mentioned, the -- the prohibition 14 of uses of long-term steroids was a problem, and that 15 was then relaxed in patients who were on low-dose oral 16 corticosteroids were then allowed to be enrolled. And 17 similarly, it became clear that -- that the cutoff of 18 300 microliters of blood eosinophil at the time of 19 screening was also an issue. And again, you have to 20 remember this is a relapsing -- waxing and waning 21 condition. So while of course you want to have</p>	<p style="text-align: right;">Page 137</p> <p>1 involved. And -- and the main issue, as I said was -- 2 was comorbidities or -- medication. That was another 3 major reason why patients didn't proceed to 4 enrollment. 5 So similarly, at the moment for these 6 conditions, we have relatively limited treatment 7 options. And with regard to recruiting for clinical 8 trials, that does lead to an engaged and motivated 9 group of patients. I think that's only been my 10 experience. And with regard to enrollment, as with 11 many other trials, obviously -- medications can -- can 12 be a significant barrier to recruitment. There needs 13 to be a balance between, of course, wanting to look at 14 the undiluted effect of the drug, but also be 15 realistic with regard to the proportion of patients 16 that were on various medications in the patient group 17 you're interested in. Thank you. 18 DR. MARR: Thank you, Dr. Bazaz. And 19 now we'll have a lecture by Dr. Denning. He's an 20 infectious disease clinician with expertise in fungal 21 diseases. The professor of infectious disease in</p>

<p style="text-align: right;">Page 138</p> <p>1 global health, the University of Manchester. David?</p> <p>2 DR. DENNING: Great. Thank you very</p> <p>3 much, Kieren. So I'm going to take you through a few</p> <p>4 thoughts about endpoints which I know is sort of</p> <p>5 critical to engagement in this -- in this area.</p> <p>6 So as Rohit and Rick have indicated,</p> <p>7 ABPA patients may not have severe asthma. Although,</p> <p>8 the majority have moderate or severe asthma. An so</p> <p>9 the criteria that you use for evaluation will be a bit</p> <p>10 different. If you can use a severe asthma endpoint</p> <p>11 which has been used for a lot of monoclonals, which --</p> <p>12 which requires some consideration.</p> <p>13 So what might be your primary endpoint</p> <p>14 options? You may measure lung function, and that's</p> <p>15 been done in different ways. Walking distance is one,</p> <p>16 FEE-1 or FEC, and others have promoted the idea of a</p> <p>17 step test as a easier thing to do than walking</p> <p>18 distance. Patient reported outcomes, AQLQ is well</p> <p>19 accepted in many asthma studies. ACQ also. And</p> <p>20 there's the St. George's respiratory questionnaire</p> <p>21 which is not been used as much in asthma, but in lots</p>	<p style="text-align: right;">Page 140</p> <p>1 And you may also want to do a composite</p> <p>2 endpoint. So you may choose lung function, patient-</p> <p>3 reported outcomes of IGE. As three examples, plus or</p> <p>4 minus steroid reaction as -- as an opportunity there.</p> <p>5 So there have been a number of</p> <p>6 randomized studies done in this area for slight</p> <p>7 different sorts of patient groups. And I'll take you</p> <p>8 through some of these and inhaled mitomycin was not</p> <p>9 very successful. Very small study a long time ago.</p> <p>10 The others have got a bit more of a label. And the</p> <p>11 final study here, which I'll talk very briefly about,</p> <p>12 was actually without any fungal markers, but used in</p> <p>13 antifungal with itraconazole, steroid resistant severe</p> <p>14 asthma.</p> <p>15 So the first sort of major ICT in this</p> <p>16 area was done by my fellowship director and mentor,</p> <p>17 friend David Stevens, and he looked at a reduction of</p> <p>18 steroid dose by at least 50 percent, and that was oral</p> <p>19 steroids. A reduction in total IGE of less -- a</p> <p>20 reduction by 25 percent or more, and one of exercise</p> <p>21 tolerance improving, results of at least one in five</p>
<p style="text-align: right;">Page 139</p> <p>1 of other respiratory diseases. There are general</p> <p>2 outcomes as to those respiratory ones, and they have</p> <p>3 the advantage of allowing cross comparison without</p> <p>4 medical entities. Exacerbation's maybe a key</p> <p>5 endpoint. I'm going to come back to that. And</p> <p>6 corticosteroid usage or reduction as well. And that</p> <p>7 should probably take into account inhaled products,</p> <p>8 not just oral. And then you may have some -- points</p> <p>9 including radiology, resolution of infiltrates for</p> <p>10 example. Sputum markers, such as eosinophils of</p> <p>11 culture. QPCR for aspergillus or even these days a</p> <p>12 mycobiome which can be done and assessed, although</p> <p>13 there are obviously no approved methods for doing that</p> <p>14 in regulation terms.</p> <p>15 IGE and fungal specific IGE are easy to</p> <p>16 measure and useful. And then you can do a breath</p> <p>17 biopsy where exhaled breath condensate is another way</p> <p>18 of approaching that. And FeNO would be another one,</p> <p>19 although our experience is that many patients with</p> <p>20 ABPA don't have an elevated FeNO, so that may not be</p> <p>21 useful.</p>	<p style="text-align: right;">Page 141</p> <p>1 pulmonary function tests or reduction of infiltrates.</p> <p>2 So this was a clear conversive endpoint. And the</p> <p>3 patients were enrolled in two phases. One, again,</p> <p>4 placebo with a -- a bigger dose of itraconazole, and</p> <p>5 then a lower dose for a second 16 weeks. And they all</p> <p>6 got that. And that was if you like the prize for</p> <p>7 those who got the placebo in the first side. And when</p> <p>8 you look at the outcomes, there are several things to</p> <p>9 note. First of all, on the placebo arm, there was a</p> <p>10 20 percent response rate, and that's very</p> <p>11 characteristic of this asthma population. That</p> <p>12 there's a -- a good placebo response rate. But there</p> <p>13 was a better response rate with antifungals which were</p> <p>14 significant. And then in the second phase, you had</p> <p>15 additional -- the patients who had been in the placebo</p> <p>16 arm but got itraconazole had a response rate as well.</p> <p>17 And overall, that led to a 60 percent response rate.</p> <p>18 So I think it'd be nice to do even better than that,</p> <p>19 but that was important. And patients with</p> <p>20 bronchiectasis didn't respond quite so well. But</p> <p>21 overall, the number needed to treat was only 3.58</p>

<p style="text-align: right;">Page 142</p> <p>1 which makes this a really quite successful treatment 2 for these patients.</p> <p>3 A similar study design in content in 4 terms of itraconazole for 16 weeks, but a very 5 different outcome measure with sputum cynophiles are 6 done in South Hampton in the UK. And you can see a 7 very marked reduction in their cynophile counts, and 8 this was marked as well with a -- they measured 9 eosinophil cationic protein at the same time. But 10 they also found a reduced exacerbation rate, but no 11 change in lung function in this study. But it wasn't 12 a very big study. It was only 29 patients.</p> <p>13 This is this study using fluconazole on 14 patients who have asthma of moderate severity, but 15 were allergic to trichophyton and had cutaneous skin 16 diseases. This is probably the -- the smallest ever 17 randomized study with a significant outcome with 11 18 patients treated for 5 months. And they had reduced 19 bronchial hypersensitivity and a marked reduction of 20 steroid requirements, and a peak flow improvement. I 21 think this is partly because the dermatophyte</p>	<p style="text-align: right;">Page 144</p> <p>1 exacerbation from a asthma exacerbation. And they -- 2 for exacerbations, they had a specific plan for all of 3 these, including looking for TB because they were in 4 India. And when you look at this at six weeks, you 5 can see that there's a really excellent response rate 6 to steroids as we know clinically, and a pretty good 7 response rate to itraconazole, 88 percent. And as you 8 got to three months, all the patients responded to one 9 or other of these agents. So all these patients 10 really got a lot of benefit. The IGE fell, and I'll 11 show you an example of that, and there were a small 12 number of patients who got exacerbations at one year 13 of therapy, after therapy and a slightly larger group 14 who had exacerbations at two years after therapy.</p> <p>15 So when you look at the IGE fall, you 16 can see that there was -- they were very high to begin 17 with, given the normal is up to about 100. And these 18 fell -- six weeks is quite a shock for -- and that 19 fall continued, but was maintained at three months. 20 And when you look at the secondary outcomes, which was 21 timed to the first exacerbation, you had on average to</p>
<p style="text-align: right;">Page 143</p> <p>1 infection was treated in patients with asthma who have 2 skin dermatophyte infections should probably be 3 checked and that should be addressed.</p> <p>4 So this much more recent study by 5 Ritesh Agarwal who's published a great deal in the 6 area of ABPA has really moved the field forward. 7 Again, looked at itraconazole of 400 milligrams a day 8 for four months, but compare this with steroids -- all 9 steroids. In what they call acute stage ABPA, which 10 is basically new patients coming through, haven't had 11 much treatment for the disease. And they used a 12 composite endpoint here again. They had a clinical 13 improvement scale of -- which -- of four points, and 14 they had to have some improvement -- 75 percent 15 improvement in that. Plus partial clearing of the 16 chest X-ray abnormalities and a serum IGE fall of at 17 least 25 percent.</p> <p>18 And helpfully, they distinguished ABPA 19 exacerbations from asthma exacerbations using a -- 20 particularly the IGE, but also the radiological 21 worsening to define ABPA -- or separated ABPA</p>	<p style="text-align: right;">Page 145</p> <p>1 wait in the steroid group for about a year and a 2 quarter. And similarly for -- with itraconazole. So 3 the frequency of exacerbation is low even after 4 stopping therapy. And the difference in FEV1 was not 5 significantly different between these two arms. And 6 the number of ABPA exacerbations you can see was not 7 statistically different than the number of asthma 8 exacerbations. Not statistically significant.</p> <p>9 And that's shared on this curve, or 10 graph, here where this is one year and this is two 11 years. So it takes a long time to exacerbate with -- 12 with this entity. So you have to -- if you're going 13 to study exacerbations, you need quite a lot of time.</p> <p>14 So we undertook an ICT in patients with 15 SAS, which Rohit has described the criteria for as 16 I've got here. But they also had negative IGE 17 antibody as well in the criteria there. And at four 18 months, you had a significant separation between 19 patients on active itraconazole, which again is 400 20 milligrams a day, versus a masked placebo. The -- 21 just crossed so we couldn't quite claim superiority.</p>

<p style="text-align: right;">Page 146</p> <p>1 They relaxed when they stopped therapy and -- but this 2 was significant in around just under 60 patients. 3 We took the analysis -- the primary 4 analysis was an MITT analysis, so they ran those. 5 Those who came off therapy in the first three months - 6 - in the first one month were not considered for the 7 main endpoint. And then we had to put a protocol 8 analysis at four months -- I'm sorry. At eight 9 months, actually. And this -- the improvement in the 10 AQLQ was pretty dramatic at .82, and a score out of 11 seven. And it got even greater when you look at the 12 longer period of time. 13 And when you compare that AQLQ score 14 with steroids in previous work that was done as part 15 of the omalizumab development, steroids give you an 16 improvement of .6. Omalizumab gave you a quality of 17 life improvement of .4, and itraconazole of .8 to 1.2. 18 So this was a really very profound improvement in the 19 -- in the quality of life of these patients, but as I 20 say, they were lapsed up frequently. 21 We also looked at their IGE and this</p>	<p style="text-align: right;">Page 148</p> <p>1 significant, but that primary endpoint was a 12-month 2 endpoint, but they only treated for three months. So 3 they were hoping that the voriconazole would carry 4 their patients for another nine months. And that 5 probably is somewhat unrealistic in terms of the -- of 6 the ability of a drug to do that. And certainly, we 7 showed early relapse. So this was one of the issues 8 around -- around this study. Voriconazole also has a 9 different set of side effects, and some patients 10 didn't tolerate it terribly well. 11 And then finally this rather remarkable 12 small study from Iran where they randomized patients 13 to prednisone [ph] or itraconazole and did assessments 14 at one month, because the steroids were only given for 15 one month, and then again at four months. And these 16 with steroid-resistant asthma. So these were patients 17 who were on high-dose steroids, but -- given inhaled 18 steroids, I'm sorry. But given more steroid on top of 19 that. And there was quite a bit of different in -- in 20 -- in these patients between how they improved, 21 particularly at four months here. And the -- when you</p>
<p style="text-align: right;">Page 147</p> <p>1 could be used. And so the active group of patients on 2 itraconazole had a fall of about 25 percent, whereas 3 the placebo group actually increased slightly. That 4 was highly significant. FEV1 didn't -- wasn't 5 different, but there was a slight improvement in 6 morning peak flow in these patients, which is 7 statistically significant and clinically valuable, but 8 not a massive change. 9 So this contrasts with the study that 10 was done in Leicester under Andy Warlaw's [ph] 11 direction where they looked at asthma patients of any 12 severity, but they had to have had two exacerbations 13 in the previous year, and they had to be sensitized to 14 aspergillus fumigatus. And they treated patients for 15 three months with itraconazole -- sorry -- 16 voriconazole or placebo and then followed them for 17 longer. And this was the quality of life measurements 18 here. And there was really no discernible difference 19 at three months between the two groups. And quite 20 contrast to the itraconazole, a SAS study. But they 21 then -- and the study was not statistically</p>	<p style="text-align: right;">Page 149</p> <p>1 look at the lung function, there was also a major gain 2 in lung function. So the FEV1 was around 1.6 to 1.8, 3 and by the time you got to four months, it was up at 4 3.1. If you look at FeNO, again, this was not very 5 high in these patients and didn't change very much, so 6 that wasn't very significant. And the eosinophile 7 counts were elevated and didn't fall very much. These 8 are the blood eosinophile counts. And the serum IGE 9 likewise didn't change very much. 10 So you've got a very different pattern 11 of responses in different sorts of patients. And 12 therefore, there isn't a -- a single one size fits all 13 in terms of endpoint. And these were just some 14 thoughts that I have about -- about this. So 15 precisely who you enroll in the study is really 16 important in terms of what you're going to measure and 17 what the outcome may be. And active, ongoing disease 18 is one of those key features. I'm -- the -- the 19 prevention of exacerbations for short period of 20 therapy, probably not going to be the best approach. 21 You have to show the exacerbations on therapy I think.</p>

<p style="text-align: right;">Page 150</p> <p>1 For the patients, improvement in 2 breathing and reduced coughing is very important. 3 They also want to be able to reduce their steroids 4 because of weight gain and -- and the long-term 5 consequences. There are modest changes in lung 6 function. There are significant changes in total IGE 7 in most of the studies. Overall, longer treatment 8 seems to do better. And the exacerbations need to be 9 thought about because you can have ABPA exacerbations, 10 asthma exacerbations or, as Malcom Birrell indicated, 11 bacterial exacerbations -- bronchiectasis. And for 12 the most part, particularly ABPA exacerbations are 13 generally infrequent. So you need a longer duration 14 to be able to -- to assess all of these different 15 things. With that, I shall stop. Thank you very 16 much.</p> <p>17 So we'll now move to a different topic 18 area which is what is the potential role for inhaled 19 antifungals in invasive lung infections. And Kieren 20 Marr who is a professor of medicine, highly 21 experienced infectious disease physician who's led</p>	<p style="text-align: right;">Page 152</p> <p>1 the -- the spectrum of clinical manifestations 2 according to type of or severity of immune deficiency. 3 And if you consider what I'm going to be talking about 4 today, it's at the far left. And in people who are 5 predominantly very immunosuppressed, then have 6 predominantly acute infections.</p> <p>7 I think it's very important to note 8 that disease is dependent on not only the severity of 9 immune suppression, but type of immune suppression. 10 And much -- much of the diseases that we are talking 11 about today have a -- a common early pathogenesis 12 which involves for clearance of inhaled conidia. 13 However, what I'm going to be talking about 14 predominantly today is where poor clearance of inhaled 15 conidia and dramatic immunosuppression of secondary 16 disease can lead more prominently to acute infection.</p> <p>17 The goal of airway drug delivery is of 18 course then dependent on the host and the stage of 19 disease, and encompasses both prevention as well as 20 therapy. And I'll just start with some caveats, which 21 is that the literature predominantly does contain</p>
<p style="text-align: right;">Page 151</p> <p>1 several studies in invasive aspergillosis is going to 2 take us through the potential in this area.</p> <p>3 DR. MARR: Thank you, David. So in way 4 of an outline, I'm going to largely focus as, we have 5 previously, in pulmonary mold infections. And much of 6 what I will talk about is pertinent to aspergillosis 7 specifically.</p> <p>8 I will talk about some of the 9 heterogeneity in infections as well as the hosts. And 10 this talk will focus predominantly on hematologic 11 malignancies, subsets of people who also have 12 underwent allogeneic stem cell transplants. And I'll 13 also mention briefly post-viral lung disease 14 associated aspergillosis as a component of people in 15 ICUs. Notably, Dr. Husain, after this lecture, will 16 be talking about lung transplant.</p> <p>17 I will specifically address the roles 18 of inhaled antifungals with a large focus on 19 prophylaxis where a lot of the data lie. And also 20 mention, adjunctive therapy.</p> <p>21 So this slide on the right really shows</p>	<p style="text-align: right;">Page 153</p> <p>1 reports of nebulized or aerosolized amphotericin 2 formulations, but there are -- have been different 3 formulations studied, different devices used and 4 different treatment algorithms. And because of this, 5 I'm -- I'm not really going to attempt to draw any 6 comparative conclusions from the data that have been 7 presented today, but rather overview the disease and 8 clinical use, not really discuss specific drugs.</p> <p>9 This slide is a schematic that reminds 10 me to -- to really emphasize that even acute invasive 11 aspergillosis can be a heterogeneous-type of disease 12 with mixed in multiple potential manifestations that 13 involve fungal growth, and specifically germination 14 into hyphae that evokes inflammation and invasion into 15 the airway. Disease can be both predominantly 16 involving the airway, which also evokes mucus 17 production and inflammation, and it can also be 18 invasive to the point of -- of potentiating 19 angioinvasion as well.</p> <p>20 So when you consider this in many 21 different types of host contexts, the phenotype can be</p>

<p style="text-align: right;">Page 154</p> <p>1 predominantly driven by invasive angio aspergillosis, 2 especially invasive disease that involves 3 dissemination by vasculature. But there are diseases 4 that also manifest in these hosts as well, but involve 5 predominantly tracheal bronchial disease. And when 6 you think about these infections, it's really 7 important to also remember that some of the clinical 8 manifestations that we observe are because of 9 obstruction-type of complications that can also be 10 associated with bacterial pneumonias as well. And so 11 while we can talk about invasive aspergillosis, I 12 think it's important to understand that there are 13 mixed and multiple manifestations that can lead to the 14 clinical phenotype.</p> <p>15 The hematology/oncology population is 16 the population that we have studied most robustly over 17 several decades to understand invasive mold 18 infections, and they certainly have unique needs. The 19 -- as I mentioned before, the primary manifestation of 20 inhaled conidia escaping both first and secondary line 21 defenses can ultimately lead to invasion into the lung</p>	<p style="text-align: right;">Page 156</p> <p>1 prevent these complications. Both because of the 2 attributable mortality associated with invasive 3 aspergillosis, but also because that enables us to 4 more aggressively and for a longer more durable period 5 of time, treat malignancies.</p> <p>6 To address that azoles have become our 7 mainstay -- and this started in the early 1990s with 8 pivotal trials showing that fluconazole prevents 9 candidiasis. And subsequently, less so with 10 itraconazole, voriconazole, but then Posaconazole is 11 of course approved for prophylaxis in allo BMT 12 patients with graft vs. host disease as well as in 13 neutropenic patients with myelodysplastic syndromes or 14 acute myelogenous leukemia.</p> <p>15 So this is important to remember that 16 we are trying to prevent invasive mold infections, but 17 these patients retain risks for candida infections as 18 well. And so there -- even if we are going to an 19 inhaled strategy, we will potentially be needing to 20 also preserve candida prevention as well.</p> <p>21 I'll also add in detail that there are</p>
<p style="text-align: right;">Page 155</p> <p>1 as well as potentially angioinvasion. But when you 2 actually see these patients in a clinical context, it 3 becomes very clear that radiographically, they can 4 present many different ways. The -- the figure here 5 shows classic nodular manifestations as well as more 6 inflammatory, larger nodules with secondary necrosis 7 inhabitation. But we do see a lot of people that can 8 have a predominantly air space manifestations with 9 consolidations. And that can as well involve 10 different parts of the lung, including the pleura, to 11 also evoke pleural effusions.</p> <p>12 It's very difficult to treat these 13 people successfully. It's important to remember that 14 we are at the same time trying to effectively treat 15 hematologic malignancies. And so these can be 16 competing forces for certain, and these infections can 17 be difficult to diagnose. Although, we've had great 18 strides over the last 20 years in applying biomarkers 19 both to bronchoalveolar lavage fluids as well as to 20 blood compartments to assist as an aid to diagnose.</p> <p>21 One of our primary goals has been to</p>	<p style="text-align: right;">Page 157</p> <p>1 new therapies for hematologic malignancies that have 2 presented some unmet needs when considering our -- our 3 -- being azole antifungal drugs.</p> <p>4 And certainly, turning to a more 5 detailed discussion of inhaled amphotericin products, 6 there's plenty of proof of concept that has been shown 7 that these products can potentially be useful to 8 prevent development of progressive, invasive 9 aspergillosis in animal models, I think nicely 10 summarized in this metanalyses from five years ago.</p> <p>11 Most of the literature evaluating the clinical 12 application of inhaled amphotericin B have -- were 13 started in the 1990s. And the first studies by 14 Connelly [ph], a cohort study evaluating neutropenic 15 oncology and BMT patients showed --</p> <p>16 David, I think that -- can you mute 17 yourself, please?</p> <p>18 Showed that there were fewer infections 19 in the treatment group. And then multiple other 20 cohorts using historic controls or use of oral 21 amphotericin B that is of course rather akin to</p>

<p style="text-align: right;">Page 158</p> <p>1 prophylaxis in this setting showed at least strong 2 trends to fewer infections with the inhaled 3 amphotericin product.</p> <p>4 The Schwartz study was the largest 5 study that was done in neutropenic leukemia and BMT 6 patients. Predominantly that did show, again, a trend 7 from seven percent to four percent of invasive 8 infections in the active treatment group. But 9 subsequently, largely in the early 2000s, the field 10 moved to applying and evaluating the use of lipid 11 formulations of amphotericin B and two of the classic 12 -- and -- and have predominantly focused on two 13 different drugs, that being ABLC and liposomal 14 amphotericin B. And I'll go into a little bit more 15 depth on those formulations.</p> <p>16 The Duke group, and specifically led by 17 Barbara Alexander, published their noncomparative 18 evaluations of inhaled ABLC in 2006 in a small cohort 19 of 40 patients who were treated for up to 13 weeks, 20 who also received fluconazole. And they are reported 21 that there were few infections that were confirmed</p>	<p style="text-align: right;">Page 160</p> <p>1 aerosolized during the first and second cycle of 2 chemotherapy, compared to historic controls. These 3 authors reported decrease in documented invasive 4 pulmonary aspergillosis, fewer use of systemic 5 antifungal therapies and some cough savings. I -- I 6 want -- I put up this table to -- in order to outline 7 an important concept which is that these are people 8 who received sequential therapies for induction and 9 then maintenance treatment for leukemia. And their 10 risks are across certain different episodes, there was 11 at least a higher number of infections diagnosed in 12 that first chemotherapy cycle, but a trend to 13 protection as well during the second chemotherapy 14 cycle. These are details to be thinking about with 15 regards to the -- the type of trial designed to 16 evaluate prevention in this kind of context.</p> <p>17 And I'll also highlight a retrospective 18 allogeneic BMT study in which drug was administered in 19 the setting specifically to -- for graft vs. host 20 disease. And that it was started with onset of 21 corticosteroids. This was, again, an inhaled</p>
<p style="text-align: right;">Page 159</p> <p>1 during that period of time. Importantly to note a lot 2 of these patients had come off of that therapy or 3 received empirical systemic antifungals because of 4 suspected disease. That report also disclosed that 5 cough was common as well as some patients developing a 6 decrease in FEV1 at least once after administration of 7 drug. The largest study that has been performed is by 8 Renders [ph] of 271 neutropenic malignancy patients 9 who were treated over 407 episodes in a randomized 10 fashion. Importantly, there's a date there -- here. 11 These were patients that were enrolled between 2000 12 and 2007. I apologize for that mistake. They 13 received twice weekly liposomal amphotericin B by 14 nebulized route, compared to a placebo. And this 15 study showed certainly decreased incidents in invasive 16 fungal infections albeit with more cough in the active 17 amphotericin arm.</p> <p>18 There have been as well some nice 19 studies. I'll focus on this one by Chong [ph] 20 reporting real life outcomes. This was a study with 21 127 AML patients who received liposomal amphotericin B</p>	<p style="text-align: right;">Page 161</p> <p>1 amphotericin study with fluconazole and they reported 2 a decrease in incidents of invasive aspergillosis 3 during the latter time here as shown in the figure. 4 Importantly, these studies, especially ones that are 5 variable over time, are really limited by the 6 differences in the patient population. There of 7 course were differences in conditioning therapies that 8 led to risks for infections by virtue of their risks 9 for other underlying diseases, relapse as well as 10 graft vs. host disease. And there were differences in 11 the way that the investigators were diagnosing 12 aspergillosis.</p> <p>13 Importantly, this is a population that 14 has now a growing amount of unmet needs because of the 15 use of antineoplastic agents that are complicated by 16 concurrent azole use. The classic scenario is with -- 17 application in people with ALL. More and more 18 commonly, centers are using a different agents for 19 treatment of AML, especially BCL2 inhibitors with 20 regimens containing venetoclax. Concurrent use of 21 azoles can alter the -- the amount of this active drug</p>

<p style="text-align: right;">Page 162</p> <p>1 leading to toxicities, or on the other end with a too 2 aggressive dose application potential compromise in 3 activity against the EML [ph]. There's also people 4 with CLL and other lymphoid malignancies that are 5 increasingly receiving ibrutinib, as well as multiple 6 other agents like IDH1 or IDH2 inhibitors for AML. 7 So these are settings in which there 8 are clear unmet needs because of our deficiencies in - 9 - in ability to give mold active azoles and -- and in 10 many of these settings, they retain very high-risk for 11 invasive aspergillosis. 12 I want to touch briefly on adjunctive 13 therapy. And I just pulled out a couple reports from 14 the literature in order to illustrate a couple 15 important concepts. There are several agents that 16 have been evaluated, not only nebulized amphotericin B 17 products, but nebulized voriconazole. And reports of 18 successful therapy for concurrent tracheal bronchial 19 disease that is typically in the context of structural 20 lung disease. So there's a lot of reporting bias 21 here, but importantly, it also has implications with</p>	<p style="text-align: right;">Page 164</p> <p>1 where it's most needed. And it also illustrates the 2 potential deficiencies of some of the systemic drug 3 getting back into the airway. 4 The last case -- the last case that I 5 want to talk about here for adjunctive therapy is a 6 case of disease that developed in the context of 7 severe influenza, structural lung disease. The graph 8 at the bottom is very complex and I'm putting it up 9 here for a reason, and that is to show the length of 10 duration that some of these people can have 11 complications associated with aspergillosis for a 12 very, very long time, becoming more of a chronic 13 invasive infection. And the numerous types of 14 therapies that they go on and off of for both systemic 15 disease as well as tracheal bronchial disease. 16 Evaluating therapy in that context could be rather 17 complicated for sure. 18 I also want to say briefly that there 19 is, in the literature, multiple reports of adjunctive 20 inhaled therapy being applied for resistant infections 21 or structurally resistant infections. In other words,</p>
<p style="text-align: right;">Page 163</p> <p>1 regards to our ability to develop these clinical 2 studies. 3 This figure on the top is an example of 4 a patient who had a fistula that was developed after a 5 lung resection for a tumor -- so a lung cancer -- and 6 a hole that was made in his lung that was -- that had 7 a fistula into the airway. And this was pretty clean, 8 although you can see the hole by a bronchoscopy. 9 Ultimately, over the course of time, this person 10 developed an empyema that was complicated with 11 aspergillus. Within the airway you can see in the 12 figures subpanels C and D with inflammation and ground 13 glass within the lung itself. And then after systemic 14 voriconazole, there was some improvement as seen in F 15 and E, especially improvement in the lung parenchyma, 16 but not as much within the airway itself. This is a 17 context where inhaled amphotericin B was given and it 18 effectively cleared the airways much more successfully 19 as shown in panel -- the last panel on the right. 20 And so this is kind of the -- the 21 setting where we're putting the drug into the place</p>	<p style="text-align: right;">Page 165</p> <p>1 those caused by ones that are relatively protected 2 from systemic exposure because of their anatomy or 3 presence in necrosis. Commonly, a situation that 4 occurs with mucormycosis or even drug resistance -- 5 drug resistant organisms that are successfully 6 treated. Again, a lot of reporting bias occurs in 7 that kind of a setting. 8 I want to end with a brief conversation 9 of influenza associated aspergillosis and COVID-19 10 associated aspergillosis. And I think that many do 11 understand that at this point in time, we've had many 12 cohort studies done all over the world that emphasize 13 that this is a real entity that occurs in a 14 significant number of people that have very severe 15 disease that's caused by influenza. I summarize 16 cohort studies that have been done since 2015. And 17 you can see that the reported rates my vary, but when 18 the diagnostics are used very aggressively, of course 19 they do go up. There is as well some geographic and 20 seasonal variation that may be associated with the 21 influenza strain itself.</p>

<p style="text-align: right;">Page 166</p> <p>1 More recently, and in fact this month, 2 a new report came out from a French retrospective 3 study that was done over nine years and it had 4 important findings in it that I want to highlight. 5 This was a nine-year retrospective study that reported 6 21 percent incidents of invasive pulmonary 7 aspergillosis that developed in the context of 8 influenza infection. They reported a rather high rate 9 of concurrent tracheal bronchitis. They did do 10 aggressive bronchoscopies with almost 30 percent of 11 people that did develop tracheal bronchitis, and they 12 described importantly organisms that spoliated in the 13 airway, became invasive, can be radiographically 14 variable. But in the context of this disease with 15 tracheal bronchitis, there were higher markers that 16 included galactomannan and -- and beta D glucan in 17 blood that I think was a little bit surprising for 18 many of us, but important to recognize the potential 19 differences between tracheal bronchitis and invasive 20 aspergillosis in that context. 21 And I'll stop just by mentioning that</p>	<p style="text-align: right;">Page 168</p> <p>1 associated aspergillosis as well. There is some 2 suggestion of therapeutic efficacy especially in 3 context of airway complications in -- in concurrent 4 invasive disease. I'll thank you for your time. 5 Okay. If David's not going to come on, 6 I can go ahead and introduce the next speaker who is 7 Dr. Shahid Husain. He's the director of transplant 8 infectious disease at the University Health Network in 9 Toronto. Professor of medicine at the University of 10 Toronto. His research is directed towards antifungal 11 prophylaxis in solid organ transplant recipients. Dr. 12 Husain? Dr. Husain, are you there? 13 DR. DENNING: He's on mine, but he's 14 not on here. 15 DR. HUSAIN: Oh, sorry. Sorry. Can 16 you hear me now? 17 DR. DENNING: Yes. 18 DR. HUSAIN: Okay. Sorry. So I was 19 saying that I'm really excited to be part of this 20 workshop, especially about the fungal infection 21 because I think this has gone into backburner with</p>
<p style="text-align: right;">Page 167</p> <p>1 increasingly, we have become aware of the entity 2 called CAPA, or COVID-associated pulmonary 3 aspergillosis, not well described in reports from 4 China. This is a graphic that I put together that -- 5 that describes the emergence, if you will, or the 6 descriptions that occurred over time. The most 7 definitive ones have been three prospective studies 8 that were reported from Italy, the Netherlands and the 9 UK that reported rates ranging from 14 percent to 10 upwards of 30 percent in people with severe COVID. 11 These were studies that used aggressive biomarker-type 12 of screening strategies as well as some closed circuit 13 bronchoscopy to assist diagnosis. So this is another 14 entity where there is potentially a mix of tracheal 15 bronchial manifestations and invasive manifestations 16 that can complicate systemic therapy. 17 And I will conclude here. Inhaled 18 antifungals have been compelling for prevention of 19 invasive fungal infections in the context of 20 hematologic malignancies. And certainly there's 21 potential utility for severe viral infection</p>	<p style="text-align: right;">Page 169</p> <p>1 COVID and everything that here nowadays is related to 2 COVID. So I'm very excited to talk about fungi with 3 fun people around. And I'm going to talk about 4 antifungal prophylaxis and treatment in solid organ 5 transplant, particularly -- or lung transplant. 6 So just to -- when I talk, is in two 7 parts. And the first part I will present some data to 8 show that the endpoint, what I'm suggesting, what is 9 the importance of this endpoint on the basis of the 10 current literature. And I'll try to -- up a framework 11 for the endpoints for the studies of invasive fungal 12 infections in lung transplant. 13 So we -- we all know this Seminole 14 study which was done by -- which has well written the 15 incidents of invasive fungal infection in solid organ 16 transplants. And you can see the lung transplant 17 recipients are the second highest in sold organ 18 transplants to have invasive fungal infections. 19 And this has the consistent -- on the 20 left you can see the -- study from France, and where's 21 the green dotted line is the lung transplants showing</p>

<p style="text-align: right;">Page 170</p> <p>1 the higher rate of mold infections as compared to 2 other solid organ transplants. And the right is -- 3 study from Switzerland where it's shown the rate of 4 mold infections in solid organ transplants. 5 And surprisingly, like we were talking 6 about almost two decades here in the setting of -- 7 prophylaxis among transplant, but the incident -- more 8 or less has -- 9 And then when you look at what kind of 10 fungal infection these solid organ transplant 11 recipients get, you can say -- you can see here the 12 majority of these infections are indeed candida 13 infections, with the exception of two -- transplants 14 that is lung and heart where they're invasive 15 aspergillus infections is noted with higher frequency. 16 And when you look at them all invasive 17 mold and invasive aspergillus infections in this 18 slide, what I've done is I've combined all the -- of 19 the -- studies done to date in lung transplant to look 20 at what kind of aspergillus species are predominantly 21 noted. And you can see irrespective of the various</p>	<p style="text-align: right;">Page 172</p> <p>1 over at -- and they are showing and -- majority of the 2 lung transplants will receive -- prophylaxis. Almost 3 60 percent of them will get an aerosol prophylaxis. 4 Any lung transplant with aspergillus colonization will 5 get antifungal prophylaxis. And majority of cystic 6 fibrosis patients undergoing lung transplant will get 7 invasive aspergillosis. 8 I am not going to discuss the various 9 prophylactic strategies and their efficacy because 10 most of them are observational studies. 11 So I'd like to show the slide about the 12 importance of colonization of aspergillus in the 13 airways of the lung transplant. The two studies here 14 are the studies which show the natural course. These 15 studies were published in the absence of any sort of 16 antifungal prophylaxis and lung transplant. And you 17 can see there are two distant patterns that emerge. 18 So for non-cystic fibrosis patients -- transplant 19 colonization with aspergillus is noted in one-third of 20 the individuals. And of these, one-quarter will go on 21 to develop invasive aspergillosis.</p>
<p style="text-align: right;">Page 171</p> <p>1 studies in the continent, majority of the fungal 2 infection or aspergillus infection lung transplants 3 are aspergillus fumigatus infections. 4 Now the next point that I want to 5 address is time to onset of mold infection in lung 6 transplants. The -- lung infection in lung 7 transplant. And you can see majority of the 8 infections do tend to occur between 0 to 12 months. 9 There's a spike peaking around 6 months and goes down 10 to 12 months, and then it dwindles down, the green 11 horizontal bar is the oldest study that we did which 12 included more than 900 lung transplants across the 13 world. And you can see almost 60 percent of -- 14 aspergillosis cases tend to occur within 12 months. 15 So I like hematology -- the period of 16 neutropenia -- the risk period for the development of 17 mold -- invasive mold in general, and invasive 18 aspergillosis in particular a bit longer in lung 19 transplants. 20 What do people do in terms of dealing 21 with this issue? There are three surveys. Those are</p>	<p style="text-align: right;">Page 173</p> <p>1 While in patients with cystic fibrosis, 2 if it's a pre-transplant colonization, which is noted 3 in almost 40 percent of the individuals. And majority 4 of them will go on to -- one-quarter of them will go 5 on to develop tracheal bronchitis. So a post- 6 transplant colonization usually does not result in 7 significantly higher rate of invasive aspergillosis. 8 And in various studies, this -- center 9 is studying aspergillus colonization at one year, was 10 significant risk factors high as of this year, 2.11. 11 And here you can see aspergillosis culture positivity 12 of pre-transplant. The aspergillus culture positivity 13 was associated with the significant risk of disease. 14 It's not only the development of 15 invasive aspergillosis -- colonization, but also 16 subsequent development of what is called CLAD -- that 17 is chronic lung allograft dysfunction -- which was 18 previously called as the -- it's a very nice study 19 from -- that the risk was higher if you're colonized 20 with the small -- aspergillosis species of which -- is 21 prime example.</p>

<p style="text-align: right;">Page 174</p> <p>1 But another study from the other side 2 of the Atlantic, from Madrid, they did not find any 3 association with CLAD. However, you know, they do not 4 differentiate between small and large -- in their 5 study. 6 So as I mentioned before that -- 7 preferential of inhaled amphotericin B has been used, 8 and especially the liquid formulations because they 9 tend to stay longer in their particular -- as is 10 evidence in this slide that concentration is above the 11 MIC and it can stay up till 160 hours. And in this 12 slide, I'm comparing both the lipid complex as well as 13 liposomal amphotericin B. This is after four days of 14 consecutive doses, people has indeed used, inhaled 15 amphotericin B. Various corporations as shown in the 16 summary slide have with more than 1,000 patients and - 17 - formulation for amphotericin B, deoxycholate and 18 liposomal amphotericin B and lipid complex have been 19 studied. 20 The issue of -- those are being used 21 for this study's various regimen that have been used</p>	<p style="text-align: right;">Page 176</p> <p>1 from Spain in which they compared the aspergillosis 2 sensitivities before they started doing, you know, 3 some prophylaxis that was before 2009 and after. You 4 can see initially, only 38 percent of the aspergillus 5 isolates were resistant to the amphotericin. But 6 after starting the liposomal amphotericin B, almost 60 7 percent of these isolates became resistant to 8 amphotericin B. 9 It's not only the resistant 10 amphotericin B isolates that lead to aspergillus, but 11 there was allergen of non-aspergillus mold as 12 highlighted here with the orangish bar. 13 I have refrained from discussing the 14 definitions because they are standardized in terms of 15 the -- of pulmonary diseases -- but I want to spend 16 some time briefly about colonization definition that 17 will be a unique feature in lung transplant patients. 18 So eradication of fungal colonization 19 is defined by negative fungal culture respiratory 20 specimens. It can be a single negative culture from 21 the DEL [ph]. Two negative sputum cultures recurrent</p>
<p style="text-align: right;">Page 175</p> <p>1 in these studies, and in the duration. The reported 2 efficacy is important in the extreme -- and I'll let 3 you be the judge, but these are all observational 4 studies. 5 In the morning, it was mentioned that 6 these drugs do result in side effects -- inhaled side 7 effects. And we heard testimony from the patient who 8 was talking about how difficult it is to take the 9 amphotericin B. And indeed, at least in the 10 literature, beside the fact -- amphotericin B and 11 deoxycholate -- lipid complex amphotericin B. But I 12 would like to -- you to look at the decline in -- in 13 one second -- liposomal -- but clearly, 1 in 10 14 patients do or go onto develop this decline in -- and 15 almost 1 in 10 will discontinue the amphotericin B 16 drug, deoxycholate. Or if the rate is much less with 17 lipid complex and it was liposomal amphotericin B. 18 The other thing that we have to be 19 aware of the fact is that the continent's used often 20 yield preferential results in the change of the micro 21 -- and this is very nicely documented in this study</p>	<p style="text-align: right;">Page 177</p> <p>1 is the isolation of the same fungal during the follow- 2 up at least a month after the completion of the first 3 course of prophylaxis. While -- is a different fungal 4 species from the baseline colonization at least a 5 month after. 6 And persistent colonization is ongoing 7 isolation of the same fungal species defined at the 8 baseline. And this was very nice to outline this 9 study from -- Australia. 10 So in summary, what is different from 11 mold infection? So key is you have to take it -- when 12 you are designing a clinical trial. So risk period is 13 clearly longer as compared to hematological 14 malignancy. It is up till a year in lung transplant - 15 - period and almost three months in heart transplant. 16 I didn't show you too much data on heart transplant 17 because they are far and few between. 18 There are some unique clinical 19 presentations, especially the mold colonization which 20 has not only -- disease, but also indirect 21 consequences in terms of CLAD. Tracheal bronchitis</p>

<p style="text-align: right;">Page 178</p> <p>1 which is more common, and bronchial nestum otic 2 infections.</p> <p>3 Data on the clinical risk factors in 4 heart transplant is not well defined and -- and the 5 data in lung transplant is slightly better, but it's 6 not the best. We know there are differential 7 characteristics of biomarkers in solid organ 8 transplant, especially lack of sensitivity of sound 9 seen on --</p> <p>10 And more importantly, the long-term 11 safety of inhaled drugs are not known and this becomes 12 a prime concern in terms of lung transplant recipients 13 who have around about 50 percent rate of CLAD at five 14 years of transplantation.</p> <p>15 So but this -- how do I pull it 16 together and -- and these are just my cards to 17 initiate the discussion. Based on the -- guidelines 18 that we developed about four -- four or five years 19 ago. On the literature -- the base of the literature 20 we thought if you know it's a prophylactic had to be 21 employed, it should be -- nearly be a duration of</p>	<p style="text-align: right;">Page 180</p> <p>1 the observation studies where we looked at antifungal 2 prophylaxis study they have looked at one year. So it 3 is development of the probable or proven invasive 4 disease, colonization of brachial fungal infection are 5 the primary endpoints. And I think the quality of 6 life, there are few specific lung transplant quality 7 of life measurements. There are one which is called 8 QLPP from the University of Burgh [ph] -- Pittsburgh 9 by -- and that's a very nice one. And all cause 10 mortality at one year along with lymphatic 11 antifungals. Time to diagnose is at a -- rate.</p> <p>12 So for preemptive therapy, it is -- at 13 least for the literature, it is directed by positive - 14 - greater than 1, or aspergillus cultures questionable 15 PCR -- but without radiological bronchoscopy evidence 16 of disease during the -- transplantation. Recommended 17 duration is three to four months and the primary 18 endpoint here would be -- aspergillus culture at the 19 end of the therapy. While the proven -- while the 20 population of patients with mold colonization probable 21 or proven fungal infection, and I have combined the</p>
<p style="text-align: right;">Page 179</p> <p>1 first and -- four to six months. The primary 2 endpoint, it will still be the heart -- endpoint of 3 the development of invasive disease at six months 4 post-transplant -- for six months. It will be at the 5 end of the therapy. But also, we need to assess the 6 population of patients with more colonization at six 7 months post-transplant. Secondly, endpoints of the 8 efficacy of the left side, we can see the symptoms, 9 those are -- study and I think these are the valid 10 endpoints. And on the right are the lab -- that need 11 to discuss -- FEV1 we see. And we have to be, 12 ourselves, at least doing therapy all within 30 days 13 of -- therapy.</p> <p>14 Bottomline function test in lung 15 transplant, they need to be more -- time of initiation 16 of baseline and subsequently up to a year, and indeed, 17 tolerance is a huge issue. But with -- that needs to 18 be assessed.</p> <p>19 When you look at the secondary endpoint 20 for the efficacy, we need to extend the time period up 21 till a year for these -- most of these studies, even</p>	<p style="text-align: right;">Page 181</p> <p>1 clinical syndromes together -- at six months of post- 2 sufficient therapy.</p> <p>3 Secondly, essential endpoints are 4 essentially the same for safety and the secondary 5 endpoint for efficacy also go up to a year -- up to a 6 year. However, in case of comparison between the 7 preemptive -- two preemptive arms, I think the outcome 8 should be assessed a year post-initiation of therapy. 9 And as -- population, one year is very pertinent for 10 lung transplant because this is the period where they 11 get repeated episodes of rejection and higher 12 immunosuppression. Once they cross one-year hump, 13 they literally do much better.</p> <p>14 For heart transplantation, there's no 15 need for routine prophylaxis. It has been employed 16 only in the cases where a program has looked -- has 17 any episode of IEA and could not determine the source 18 of the outbreak. Or when for some reason you found 19 aspergillus under the heart, here the outcome would be 20 -- should be assessed at four weeks post -- of 21 therapy, which is usually six to three months. Second</p>

<p style="text-align: right;">Page 182</p> <p>1 endpoints are essentially the same for all inhalation 2 drugs. And then efficacy endpoints are slightly 3 shorter than the lung transplant by six months, but 4 the rest are essentially the same. 5 I know at least three or four speakers 6 have previously, including Dr. Marr, has discussed the 7 use of inhaled antifungals in the drug, but as a 8 standard of care, they are not recommended. Indeed, 9 they are -- of newer inhaled antifungal drugs and 10 inhaled amphotericin B -- there's lack of human data - 11 - detailed human data and the -- and the worry of 12 systemic fungal disease. The advantage of nebulized 13 drug is that it is in the highest concentration where 14 it is needed, but the disadvantage is that it does not 15 have systemic effect. So it's like Las Vegas. What 16 happens there, stays there, and that may have some 17 consequences. But I think the two clinical syndromes 18 that might benefit are the tracheal bronchitis and 19 bronchial -- infection. And adjunct with the systemic 20 antifungals probably in the resistance cases. But 21 here, the endpoints have to have both microbiological</p>	<p style="text-align: right;">Page 184</p> <p>1 Good afternoon to our US colleagues. Can you hear me? 2 DR. MARR: Yes, we can. 3 DR. BERMAN: Okay. I don't see the 4 slides up yet. All right. Let me begin while the 5 slides come up. Well, good afternoon to the -- our US 6 colleagues and good evening to our European 7 colleagues. As Dr. Marr said, I'm Lance Berman. I'm 8 the incoming chief medical officer at Pulmocide. And 9 just before we begin, on behalf of my colleagues at 10 Pulmocide, I would like to thank the organizers for 11 inviting us to participate in these proceedings. 12 I'll provide some details in the 13 company's novel inhaled antifungal agent, PC945. And 14 will then present some clinical experience with the 15 drug that I hope will illustrate some of the important 16 challenges that we face when building a clinical 17 development program to ultimately ensure that this 18 drug one day reaches patients. 19 At Pulmocide, we are developing PC945 20 for the management of pulmonary diseases caused by 21 fungal infections. We are a small company with an</p>
<p style="text-align: right;">Page 183</p> <p>1 cure at the end of the therapy, as well as -- if I can 2 remember the term -- endoscopic care, or at least 3 normal looking bronchial airways and anastomosis. 4 With that, I will stop. Happy to take 5 any questions afterwards. I'm looking forward to the 6 discussion. 7 DR. DENNING: Thank you very much, 8 Shahid. We're going to take a break now. We're just 9 running a little bit late. Can I suggest we -- we 10 convene at -- on the hour? That gives a 12-minute 11 break which will slightly reduce our final discussion. 12 But I think it's appropriate to have a break before we 13 enter into the -- the contributions from industry. 14 So we'll -- we'll be back in 12 15 minutes, okay? 16 (Off the record.) 17 DR. MARR: Okay. Welcome back to the 18 session on industry perspectives. Our first speaker 19 will be Dr. Lance Berman, who's the chief medical 20 officer of Pulmocide. 21 DR. BERMAN: All right. Thank you.</p>	<p style="text-align: right;">Page 185</p> <p>1 office in the UK and the US. And we were formed by 2 the former head of GSK -- PC945 is a novel inhaled -- 3 which has been specifically designed for use in the 4 lung. And its potential uses could therefore -- 5 treatments in various forms of pulmonary aspergillosis 6 and prophylaxis in a range of patients at risk. 7 Our available clinical data to date 8 demonstrates an apparent -- patients not responding to 9 standard of care with good tolerability, very low 10 systemic exposure and no report of drug/drug 11 interaction via the inhalation route with three 12 important characteristics. The first is that the mean 13 particle size is approximately 3.5 microns with a 14 range of about 1 to 4 microns, which is typical of 15 inhaled medicines. Which is similar to the size of 16 aspergillus spores. And so the drug should reach the 17 deepest, smaller airways. 18 The second is that -- solubility is low 19 and the distillation rate is slow, which results in 20 minimal uptake into the -- by the paracellular route. 21 And consequently, very low systemic concentration in</p>

<p style="text-align: right;">Page 186</p> <p>1 the thickogram and more range. Which will have 2 certain safety intolerability advantages, most notably 3 cardiac, nephron and -- and -- and a very low risk 4 then -- for drug interaction. 5 And in the first characteristic is that 6 the drug accumulates. And so it has a long residence 7 time in airway cells such as the alveola macrophages 8 and bronchial and alveola epithelial cells. We 9 believe this could enhance the ability of the host 10 cells to clear the fungus given that macrophages is 11 our first line of defense from this disease. PC945 12 works as expected by inhibiting the ergosterol 13 synthesis which causes disruption of the fungal 14 membrane integrity. The drug's antifungal effect has 15 been demonstrated in vitro, in vivo and in humans, and 16 it's been found to inhibit the growth of approximately 17 96 different fumigates, clinical isolates and is 18 potent again for other aspergillus species such as 19 flavi, nigri and terrei, among others. 20 It's also been demonstrated to inhibit 21 the growth of other fungi including candida, most</p>	<p style="text-align: right;">Page 188</p> <p>1 preemptive study in colonized lung transplant 2 patients. Unfortunately, these three studies had to 3 be terminated early due to the COVID pandemic during 4 which screening activities were essentially halted and 5 patients were shielded from returning to the clinic -- 6 So most of the clinical experience with 7 PC945 comes from the special needs program in the 8 United Kingdom which is a program that's regulated by 9 the MHRA, in which -- supply of an unlicensed 10 medication to meet the needs of individuals or 11 patients where there is no equipment or license for 12 medicinal product. 13 This product is -- this program, I beg 14 your pardon, is ongoing. And so far, PC945 -- to a 15 total of 10 patients. Nine of these are in the 16 treatment -- either with invasive pulmonary 17 aspergillosis or with allergic bronchopulmonary 18 aspergillosis. And one in the secondary prophylaxis 19 setting. 20 Briefly, safety and tolerability data 21 from the clinical development and special needs</p>
<p style="text-align: right;">Page 187</p> <p>1 notably candida auris as well as -- and so on. The 2 drug product is a ready to use vial containing a 3 single dose of 14.8 milligrams of room temperature 4 stable solution and it's delivered using an off the 5 shelf nebulizer. The administration is twice daily of 6 10-minute nebulizations. And in contrast of the 7 experience that was described earlier today by Mr. 8 Birrell, the administration process is much easier 9 than what he described with nebulized amphotericin B. 10 One simply shakes the vial, pours the liquid into the 11 chamber and begins the nebulization. 12 We've done, in terms of the clinical 13 development program, four clinical studies. The phase 14 one study included healthy volunteers in mild 15 asthmatics. These were a single dose, rising dose and 16 multiple dose study. These were followed by three 17 phase two studies. Two conducted in patients with 18 aspergillus fungal bronchitis. One in subjects with 19 moderate to severe asthma or other chronic respiratory 20 disease, and the other in patients with cystic 21 fibrosis. And the third phase two study was a</p>	<p style="text-align: right;">Page 189</p> <p>1 program have been favorable with no significant drug 2 related adverse events, and no significant bronchial 3 hyperactivity or bronchospasm wave changes in lung 4 function. These pulmonary assessments were based on 5 pre and post monitoring frequent -- 6 Patients tolerated nebulizations very 7 well and have reported -- taste or smell, which is 8 usually associated with nebulized amphotericin B. 9 There have been no reported drug 10 interactions so far in the special needs program. 11 This is based on feedback from the treating centers 12 who conduct routine immunosuppressant and antifungal 13 drug thereof, and who reported not needing to adjust 14 immunosuppressant doses when inhaled PC945 was either 15 started or stopped. 16 And as predicted, systemic exposures 17 have been extremely low in the -- range. 18 Since most of the clinical experience 19 comes from the special needs program, I thought it 20 would be -- to share an overview of the program and 21 then show you some patient cases as these demonstrate</p>

<p style="text-align: right;">Page 190</p> <p>1 the challenges faced when treating refractory ICA, and 2 the potential benefit that PC945 could have.</p> <p>3 This table summarizes the patients 4 predisposing backgrounds with numbers of patients per 5 background -- the range of antifungal treatments prior 6 to starting the inhaled PC945, and then the observed 7 overall response assessed after three months.</p> <p>8 So of the nine patients treated with 9 945, eight had invasive pulmonary aspergillosis who 10 had failed or were intolerant of systemic antifungal 11 therapies. And of those eight patients, seven were 12 post-lung transplant patients and one was an ICU 13 patient. And in the nine patients in the program had 14 ABPA which also not responded to antifungal therapies.</p> <p>15 Favorable responses which were based on 16 clinical, mycological and radiological assessments 17 were observed in seven out of these nine treated 18 patients. And of those seven, four were complete 19 responses and three were partial responses.</p> <p>20 One patient showed stable disease, and 21 it's suspected that the subject may not have had</p>	<p style="text-align: right;">Page 192</p> <p>1 has ranged from six weeks through to over a year, with 2 five patients still -- still receiving treatment.</p> <p>3 These are images of a patient actually 4 that Dr. Moss showed you briefly at the beginning of 5 the proceeding, but I'll give you some more details on 6 this patient. This is a 29-year-old woman with a 7 history of cystic fibrosis who developed invasive 8 aspergillosis one month after a bilateral lung 9 transplant with severe tracheal bronchitis and a large 10 fungal mass over her unhealed anastomosis site. 11 Aspergillus fumigatus was cultured at the time of her 12 diagnosis. She was treated for two months on multiple 13 antifungals, initially itraconazole and then 14 Posaconazole, followed by -- and nebulized 15 amphotericin B. And eventually -- was also added as a 16 last ditch attempt because the team was essentially 17 struggling to manage her infection. Her treating 18 physician was particularly concerned that the 19 anastomosis would be -- due to fungal invasion of her 20 bronchi cartilage. So the patient was started on 21 inhaled PC945 while she remained on Posaconazole and</p>
<p style="text-align: right;">Page 191</p> <p>1 aspergillosis when PC945 was initiated. And that what 2 was observed on bronchoscopy was probably in fact 3 granulomatous disease.</p> <p>4 And another patient showed disease 5 progression. This patient was determined to have a -- 6 azole resistant fumigator string. And in fact, both 7 of these patients had bronchial stents in -- in phase 8 two.</p> <p>9 Before I go to the next slide, I would 10 like to point one patient in this table whose data is 11 particularly interesting. We can't present her -- her 12 images because at this point, we -- consent to do so 13 is still pending. But this is a young woman with 14 mucus-induced hemophagocytic syndrome, who developed 15 - aspergillus bronchitis. And this form of invasive 16 pulmonary aspergillosis, as you know, is associated 17 with a very high mortality rate. This patient was 18 assessed as having a complete response six weeks after 19 treating with inhaled PC945, and she's remained well 20 since stopping PC945.</p> <p>21 Across the program, treatment duration</p>	<p style="text-align: right;">Page 193</p> <p>1 terbinafine. In about two weeks after she initiated 2 treatment, her infection started showing signs of 3 resolving. So that after two months, no fungus was 4 visible at the site of the infection, which you can 5 see on the image on -- on the right. Mycologically, 6 her lavage fungal cultures and her lavage 7 galactomannan were negative after our treatment. 8 Well, it should be said that these were also negative 9 before 945 was initiated, despite having had positive 10 cultures at the time of the initial diagnosis.</p> <p>11 She was treating in total for about 12 three months and was assessed as a complete response 13 by the clinical team. Her anastomosis has since 14 healed and she's remained infection-free now for 10 15 months after stopping PC945.</p> <p>16 The next patient a 63-year-old man who 17 received a single lung transplant 15 years ago for 18 idiopathic pulmonary fibrosis. About five years ago, 19 he developed CLAD in the transplanted lung and 20 underwent a single second lung transplant. Following 21 this second transplant, he developed an intractable</p>

<p style="text-align: right;">Page 194</p> <p>1 parenchymal fumigatus infection in his second 2 transplanted lung, which was -- which was essentially 3 his remaining viable lung. The first image on the 4 left is a CT scan showing his -- his viable right lung 5 riddled with aspergillosis, parenchymal nodules and 6 his fibrotic shriveled up nonviable left lung. He was 7 treated with several systemic antifungals and 8 nebulized amphotericin B, but infection persisted, 9 continuing positive cultures in galactomannan. This 10 patient had a very difficult clinical course and had 11 been requesting hospitalization approximately every 12 two weeks for intravenous caspofungin whenever his 13 symptoms became intolerable or if he developed 14 recurrent exacerbations. He was also having recurrent 15 therapeutic bronchoscopies to review the -- lung. So 16 he was -- levels. After that six months of treatment, 17 his cough had gone and he was no longer waking at 18 night. He described his life as having been 19 transformed. And improvement in lung function was 20 observed and an increase in his FEV1 was approximately 21 415 mL. So since initiating treatment with PC945,</p>	<p style="text-align: right;">Page 196</p> <p>1 transverse myelitis to an azole, neurological symptoms 2 to caspofungin and an acute kidney injury to IV 3 liposomal amphotericin B, and she could not tolerate 4 the nebulized form of amphotericin B. She was started 5 on PC945, and after one month her radiological 6 response was assessed as a -- as a partial response, 7 but significantly improved, showing clearing of the 8 consolidation of the mucus impaction. There were no 9 subsequent CT scans available at the time of the last 10 update, but this is the information we have right now. 11 Her clinical response is observed as partial, but also 12 significantly improved as she no longer had heavy 13 sputum load and no more mucus plugging. In fact, 14 about a month after starting treatment, she needed the 15 help of a physical therapist in order to extract 16 sputum from -- which was a significant change for her. 17 There's been a significant improvement of her general 18 wellbeing, her quality of life and her exercise 19 tolerance, all of which have continued to improve over 20 the following months. Her mycological assessment a 21 month after she started treatment was assessed as a</p>
<p style="text-align: right;">Page 195</p> <p>1 he had no exacerbations and no longer required 2 hospitalization for intravenous caspofungin. At this 3 stage, we do not have any data on his mycological 4 responses. His follow-up bronchoscopies have been 5 postponed pending the outcome of the pandemic. As 6 we've been informed that his recent CT scan showed 7 radiological improvement, but we don't have these 8 images yet. So at this time, he's continuing on PC945 9 and is doing well.</p> <p>10 The last patient that I have time to 11 present is an image that I think Dr. Moss showed you 12 as well at the beginning of the proceedings. This 13 woman is in her mid-50s with a lung history of severe 14 steroid dependent asthma and ABPA with a high sputum 15 burden, mucus plugging, chronic wheezing, malaise and 16 frequent exacerbations. In addition to oral steroids, 17 she also received one week of intravenous steroids 18 which requires hospitalization and she usually does 19 this every two months. Over a 12-year period, she had 20 been treated with various systemic antifungals and 21 nebulized amphotericin B, but she developed a</p>	<p style="text-align: right;">Page 197</p> <p>1 complete response with a negative lavage sputum 2 cultures which have remained negative throughout 3 treatment. Her total IGE levels fell as well, but we 4 understand that recently, there may have been some -- 5 in a recent exacerbation, which we continue to follow- 6 up on. So at the moment, she remains on PC945 and has 7 had no hospitalizations for intravenous steroids, nor 8 has she received any -- any other antifungal since 9 starting PC945 over a year ago.</p> <p>10 And so as we explore the further 11 clinical development in IPA, and in particular, in 12 those not responding to existing antifungal therapies, 13 one of the major overarching challenges which I 14 believe we heard about earlier in the proceedings from 15 the clinical trials -- heterogeneity of patients who 16 succumb to this disease. And this heterogeneity, 17 which is particularly challenging to do with given how 18 rare these patients are and how hard it is to recruit 19 a -- that might otherwise be able to absorb some of 20 this heterogeneity, and the variability that this 21 introduces into analyses.</p>

<p style="text-align: right;">Page 198</p> <p>1 So for example, how do we plan for and 2 handle the fact that post-lung transplant and 3 hematology/oncology of stem cell transplant patients 4 with IPA may come into the study with different 5 mortality risk scenarios, when all cause mortality is 6 considered as a treatment failure. And similarly, how 7 should we think about defining standards of care with 8 regard to background antifungal regimens and treatment 9 durations for the purposes of objectifying study 10 entry, and how should immunosuppression of the use of 11 products like GM-CSF for background disease for 12 example be standardized to minimize variability during 13 the study? 14 Similarly, how should we think about -- 15 heterogenous group, should it be combined or that -- 16 and lastly, if an inhaled agent is added to a 17 background of systemic standard of care or a range of 18 systemic agents, as is the case in an IPA clinical 19 trial, do we need to consider the potential for an 20 additive, or potentially synergistic or potentially 21 antagonistic effect. And if an effect such as this is</p>	<p style="text-align: right;">Page 200</p> <p>1 where PFF Pharmaceuticals has a unique platform for 2 formulation of -- of drugs that create these -- this - 3 - what we call brittle matrix powder. And -- and 4 essentially, the process is shown on this -- on this 5 slide where we take a -- a drug solution, and this can 6 be -- we can work with poorly soluble drugs. And so 7 you can make an aqueous organic mixture. You can add 8 excipients for stabilization and we -- we then drip 9 that solution onto a cryocooled stainless steel drum 10 where it instantly freezes very rapidly. We then 11 collect the chips of ice that are created from that 12 cryocooling process, put them into a lyophilizer and 13 remove the solvents, leaving this brittle matrix 14 powder. That powder can either be put into vials or 15 capsules. In the case of inhaled drugs, we put it 16 into capsules and then we deliver it with a dry powder 17 inhaler using commercial devices. 18 What we end up doing is taking a 19 crystalline-type drug in most cases and converting it 20 to this brittle matrix powder that is shown on the 21 bottom right slide. And this -- this standing --</p>
<p style="text-align: right;">Page 199</p> <p>1 believed to exist, how can we deal with this without 2 necessarily further restricting study entry? 3 On that note, we are called for panel 4 discussion. I hope the clinical experience and some 5 of these questions raise the right precedent for 6 what's to come. But before I finish, I'd like to 7 thank the patient whose clinical journey we presented 8 and for allowing us to include her images into this 9 talk. As well as the following the physicians who 10 were taking care of these patients. Dr. Anna Reed at 11 Harefield Hospital and Dr. Darius Armstrong-James at 12 Imperial College, but who I believe is still on the 13 panel. Thank you very much. 14 DR. MARR: Thank you, Dr. Berman. The 15 next talk will be from Dr. Dale Christensen, who's the 16 director of development for PFF Pharmaceuticals. Dr. 17 Christensen? 18 DR. CHRISTENSEN: Thank you. I'd like 19 to start out today by thanking the FDA for putting on 20 this program and also for inviting PFF to participate. 21 What I'll be describing today is a development program</p>	<p style="text-align: right;">Page 201</p> <p>1 microscopic image shows that we've, you know -- that 2 rapid cooling process essentially traps the -- the 3 drug and excipients in a matrix that -- that when the 4 solvent is removed, creates a powder that has a very 5 high surface area to volume ratio. When it's 6 delivered through the commercial -- through the DPI 7 device, the sheer induced by the device creates 8 ideally respirable powders with anywhere from 60 to 9 we've seen up around 90 percent of the particles in 10 the one to five micron range with -- with a typical 11 MMAD around 2.2 to -- to 3. And so we are getting 12 very high efficiency delivery to the lung. 13 So what I'll be describing going 14 forward is the initial clinical trials where we've 15 used this process to make a voriconazole powder for 16 inhalation. And we have recently announced that we 17 completed a phase one clinical trial with the 18 voriconazole inhalation powder. It was a placebo 19 controlled single ascending dose followed by multiple 20 ascending dose. Typical phase one study, six plus two 21 placebo controlled with dose levels of 10, 20, 40 and</p>

<p style="text-align: right;">Page 202</p> <p>1 80 milligrams of voriconazole inhaled in the single 2 ascending doses. And then in the repeat dosage, we 3 also used those same doses, but delivered them twice 4 daily for 17 days, or 13 total doses. Where we looked 5 at blood sputum -- blood and sputum exposure on day 6 one and day seven in the -- following the single dose 7 on -- in the -- and we also looked at extensive 8 characterization of the pulmonary function, 9 tolerability, other safety signals. And when we 10 completed that study, we have looked at the PK. And 11 what I show here is a -- a graph showing single dose 12 PK and we'd recently received the repeat dose PK, but 13 I didn't have -- have time to get it incorporated in 14 this. But what you see from a single dose is that -- 15 and it's the -- the inhaled is on the -- are the lower 16 ones leading up to the 80 milligram dose that is the 17 blue line. And we see a -- of -- that is essentially 18 right after dosing. Our first collected time point 19 was 15 minutes following administration of the dose. 20 So we're seeing very rapid uptake into system 21 circulation. And clearance that it is typical of the</p>	<p style="text-align: right;">Page 204</p> <p>1 no ECG or liver -- liver or enzyme changes suggesting 2 that the inhaled powder is tolerated far better than 3 the dose limiting toxicities that occur from oral 4 dosing. 5 Moving onto how we're looking at 6 developing this further is really -- we are looking at 7 development of this to treat invasive pulmonary 8 aspergillosis patients as they transition from an 9 inpatient IV therapy into the normal point where they 10 would go onto the oral therapy to -- on an outpatient 11 basis. And, you know, we are looking at various 12 inclusion criteria, whether -- whether we would be 13 treating only those who microbiologically confirmed 14 disease, or whether it's -- whether it's culture or 15 PCR confirmed, or whether we would treat patients when 16 -- when it is diagnosed as a probable aspergillosis. 17 We will be looking at radiographic 18 evidence from chest CTs, biomarkers, galactomannan, 19 and ultimately as everybody in this conference has 20 discussed so far, we have a small -- small group of 21 patients who are -- tend to be very susceptible in the</p>
<p style="text-align: right;">Page 203</p> <p>1 voriconazole clearance. 2 In the multiple -- in the repeat dose 3 phase, we did see some accumulation and we are seeing 4 levels that are -- are clearer and present, but they 5 are also safe doses. And one of the key points here 6 is that just because we're delivering this to the 7 lung, doesn't mean that you go without systemic 8 coverage. 9 In terms of safety, we received a 10 letter -- a summary letter from our data safety 11 monitoring board. This trial was very closely 12 monitored by DSMB. Knowing the risks of the oral 13 voriconazole in terms of visual disturbances and the 14 various hepatic toxicity and others. And what we 15 noted is that, you know, in terms of the tolerability 16 from the inhalation and the lung -- or respiratory 17 perspective, there were no changes in FEV1 assessed at 18 any time point following single dosing, or at any time 19 point on day one, day -- day four, day seven following 20 repeat dosing. And so the drug is very well tolerated 21 in terms of respiratory function. We also saw no --</p>	<p style="text-align: right;">Page 205</p> <p>1 hematological malignancies -- bone marrow transplant, 2 lung transplant patients. 3 And so one of the key questions here 4 that -- that occurs is, you know, defining that 5 patient population. Because as we've heard 6 previously, there is a discussion about -- about what 7 is a representative population. And so, you know, we 8 -- we need to determine -- and this is something where 9 FDA input will be required in -- in determining how 10 many patients with hematological malignancies will be 11 required in a given cohort in order to provide that 12 broad approval. Or whether it needs to be a narrow 13 trial where we're only treating hematological 14 malignancy patients, and going for a limited 15 population approval in that group. 16 Certainly, you know, because we are 17 planning this as a monotherapy approach, we would be 18 trying to rule -- or we would rule out patients with 19 angioinvasive or evidence of systemic disease. And we 20 are doing this as a double-dummy design where all 21 patients would be getting either placebo inhale</p>

<p style="text-align: right;">Page 206</p> <p>1 capsules along with a background of oral -- or they 2 would be getting one of two doses of the inhaled 3 voriconazole and they would be getting an inhaled -- 4 or an oral placebo. So that the patients don't know 5 what they're getting, or which route they're getting 6 the voriconazole from. The physicians would know that 7 their patients are getting voriconazole, but they also 8 would not know what route they're getting it from.</p> <p>9 So in selecting our doses for this 10 study, we are -- we have been talking to key opinion 11 leaders and we are guided in part by this paper 12 published Hilger Getall [ph 42119] from Denmark where 13 they -- where they treated a -- they published three - 14 - three patients that were treated with 40 milligrams 15 three times a day for two weeks, and then they dropped 16 the dosing down to 40 milligrams twice daily. And 17 this was the nebulize -- they were nebulizing the 18 intravenous drug formulated -- or diluted down so they 19 could deliver it via nebulizer. And in this case, 20 they -- they used -- or these three patients that they 21 treated, they did a monotherapy, so there was no</p>	<p style="text-align: right;">Page 208</p> <p>1 know, stable disease. If we -- if we're seeing a 2 patient with no change in CT lesion growth. If their 3 FEV1 is stable, do we define that as a treatment -- 4 treatment failure, or is it a success? Because the 5 disease has not gotten worse.</p> <p>6 And importantly for this -- for our 7 approach, you know, because we are proposing a 8 monotherapy in comparing -- we would be looking for, 9 as was previously mentioned in the clinical 10 pharmacology discussion, we would be looking at 11 potential for superiority in the treatment arm in 12 terms of efficacy. But at least we would be looking 13 at noninferiority. But what we would expect due to 14 the lower levels of systemic drug here is, you know, 15 increased safety in terms of fewer patient withdrawals 16 due to adverse events. We also would expect that 17 there are fewer drug/drug interactions. In the case 18 of transplant, we would expect that by giving the 19 patient the -- the inhaled, that we would see less 20 requirement for changes to the dosing of their 21 supportive immunosuppressive therapies. And then</p>
<p style="text-align: right;">Page 207</p> <p>1 systemic antifungal that was being administered to 2 these subjects. And then they also -- they cleared 3 the aspergillosis in all three patients. They saw 4 improvement both radiographically, microbiologically 5 as well as in lung function for most of them. And 6 importantly, there was no systemic escape that was 7 reported for any of them when they only received 8 inhaled voriconazole treatment.</p> <p>9 So coming back to our trial design, we 10 are currently looking at, you know, defining the 11 outcomes. And this is again a case where, you know, 12 going back to that patient population as Dr. Berman 13 mentioned just previously. You know, if -- mortality 14 is a limiter, you know, if we're going into 15 hematological malignancy patients, how do we define 16 whether -- whether that mortality was from -- from 17 their cancer or whether it was from the aspergillosis. 18 And so those are some things that we need to very 19 carefully work with the FDA to define.</p> <p>20 And the other endpoints that have been 21 discussed, but again as Dr. Berman also mentioned, you</p>	<p style="text-align: right;">Page 209</p> <p>1 coming back, finally, you know, we have been 2 discussing, you know, enrollment rates. And, you 3 know, we're getting reports from some -- or we're 4 getting some estimates of a site being able to enroll 5 around one -- or one-tenth of a patient per month per 6 site. And so this creates a very large trial if we're 7 going into a large population -- that. And so we are 8 very interested in exploring the potential for a 9 limited population approval for -- for this drug.</p> <p>10 And to summarize, I believe that we 11 have the potential to document or demonstrate several 12 advantages of the TFF voriconazole formulation in that 13 we will be delivering the IDSA recommended first line 14 agent for aspergillosis, and delivering it directly to 15 the site of infection. We believe that based on our 16 results, that we'll be able to generate a higher local 17 concentration in order to get that greater efficacy 18 for the treatment of the pulmonary aspergillosis. And 19 then due to reduced systemic exposure, we have the 20 potential for lower toxicity and reduced potential for 21 drug/drug interactions.</p>

<p style="text-align: right;">Page 210</p> <p>1 And with that, I would like to thank 2 you all and look forward to the further discussions. 3 DR. MARR: Thank you, Dr. Christensen. 4 Our next speaker is Dr. Charlotte Keywood, who is 5 director of -- head of Global RND at Zambon. 6 Charlotte? 7 DR. KEYWOOD: Thank you very much. 8 Yes. Good afternoon and good evening to everyone, and 9 thank you very much for inviting me to give some 10 perspectives from the sponsor side on the challenges 11 for clinical development in ABPA. 12 Little bit of background about Zambon, 13 the company I work for. I'm head of Global RND there. 14 It's a family owned company with a headquarters in 15 Italy, and the company is 114 years old. More 16 recently, the focus of the RND pipeline has been in 17 severe respiratory infection and inflammation. 18 In Europe, we have on the market an 19 inhaled form of colistimethate sodium which is 20 nebulized through a handheld nebulizer. And that's 21 licensed for treating pseudomonas infection in cystic</p>	<p style="text-align: right;">Page 212</p> <p>1 heavily interested in acute -- or I'm sorry -- serious 2 lung infection. And so getting a good trial design 3 for any of these indications is clearly something that 4 we're interested in and that is important. 5 I think some of the things that we're 6 going to discuss have been touched on previously, but 7 I want to put them in the context of a sponsor trying 8 to design and then run a clinical trial. Clearly, 9 there's an unmet need for an effective agent for ABPA. 10 That's easy for patients to use a, as a patient 11 representative said. And also, hasn't got the side 12 effects associated with system azoles. I'm only 13 considering or how are we going to design the clinical 14 trial? What is in the clinical development program? 15 What is important to bring to the patient? 16 Well, clearly, we want to reduce the 17 frequency of the exacerbations. Reduce the use of 18 steroids. Reduce the systemicazole therapy. Reduce 19 the healthcare utilization so the patient doesn't have 20 to go to hospital or so any clinic visits. And hence, 21 improve patient function and quality of life.</p>
<p style="text-align: right;">Page 211</p> <p>1 fibrosis patients. 2 Now this product is also now being 3 developed in a global phase three program for 4 treatment of pseudomonas infection in lung cystic 5 fibrosis patients. And there may be some things that 6 we can learn from that program that we can apply going 7 forward in ABPA. 8 We also have a phase three program in 9 bronchiolitis obliterans syndrome using liposomal -- 10 And then at Zambon, we also have a 11 proprietary drive how to formulation platform called 12 the Edry platform. And this is looking at developing 13 inhaled anti-infected. But the new program is an 14 inhaled formulation of voriconazole which has very 15 good lung penetration. And we're developing that for 16 ABPA in asthma patients. 17 We hope to be able to follow that up 18 with Edry inhaled antibiotic for mycobacterial 19 infection. And then also we're looking at a potential 20 anti-inflammatory for acute lung injury. 21 So as you can see, Zambon is pretty</p>	<p style="text-align: right;">Page 213</p> <p>1 And bearing these objectives in mind we 2 have to try to ease them into the development program. 3 So at -- there's three areas of -- of 4 development challenges, which is sort of what 5 patients, what outcome measures, and then how do we 6 run the trial? 7 So in the first instance, let's look at 8 patient identification. And that's in itself an 9 initial challenge because the prevalence of ABPA is 10 not entirely clear. The number of patients in the 11 ABPA pool is unclear. The prevalence estimates are 12 currently derived largely from expert centers who tend 13 to see quite a number of these patients. And so the 14 prevalence may be overestimated and not easily applied 15 to the general asthma population. 16 Second challenge is at what stages ABPA 17 should be treated. Should we be treating acute ABPA 18 exacerbations, or shall we be looking at stable ABPA? 19 And then in which case, how do we diagnose and define 20 these? 21 At the moment, there's no one status</p>

<p style="text-align: right;">Page 214</p> <p>1 criteria for diagnosis and classification of severity 2 of ABPA. Now some criteria have been published, but 3 they're not necessary a hard and fast consensus. And 4 it's not known exactly right now how well they would 5 lend themselves to application in a clinical trial. 6 Of course, at the moment, there's no hard and fast 7 diagnostic criteria for patient entry into the 8 clinical trial. 9 If you're looking to bring patients 10 into a trial, how do we document the history of stable 11 ABPA? And then how do we go forward to define it for 12 entry into the trial? We can use the ISHAM criteria, 13 but then how best do we apply that to get our 14 homogenous patient population, but without making the 15 inclusion criteria so difficult that the trial becomes 16 unfeasible? 17 Moving onto light outcome measures. So 18 what do we measure? Well, at the moment as we know, 19 registration trials for ABPA haven't been done. It's 20 entirely new territory, so the endpoints have yet to 21 be clearly defined.</p>	<p style="text-align: right;">Page 216</p> <p>1 exacerbations? 2 Within ABPA patients, they tend to have 3 three types of exacerbation, and that could be like an 4 asthma attack, an ABPA exacerbation itself or even a 5 bronchiectasis exacerbations. Do we combine all three 6 in a single endpoint or do we try and separate them 7 out? These exacerbations do have different treatment 8 modalities, and so how do we then capture and analyze 9 that in a clinical trial? Should we be looking at 10 frequency or time to first exacerbation? There are 11 drawbacks to looking at time to first exacerbation due 12 to the fact that you lose data after the first 13 timepoint has been reached. 14 A big important aspect of treating ABPA 15 is to reduce steroid use and to reduce azole use. So 16 we need to capture that within a clinical trial. 17 Should that be a primary outcome measure or secondary? 18 How do we capture the steroid burden and the systemic 19 azole burden within the clinical trial? 20 And of course, we need to look at 21 quality life -- quality of life, patient</p>
<p style="text-align: right;">Page 215</p> <p>1 Some of the endpoints that have been 2 used in asthma and cystic fibrosis in the past may all 3 not really be applicable for this kind of population. 4 And in considering the endpoints, of course we have a 5 choice between our surrogate endpoint and our clinical 6 outcome measures. And which ones should we be using 7 when? The surrogate endpoints including laboratory 8 measures, such as IGE, galactomannan, imaging, chest 9 X-rays, high resolution CT and pulmonary function 10 testing. These well might be better to be used in the 11 early phases of development to be looking for signal 12 as to whether you're getting drug effect. And they 13 can also be used to perhaps support clinical outcome 14 measures which probably lend themselves better to the 15 later phase of development, where we need to show 16 patient benefit. 17 And in thinking about the outcome 18 measures, well, we want to reduce the amount of times 19 patients have bad events and their asthma gets worse. 20 So we can look at pulmonary exacerbations. But what 21 do we mean by that? How do we define and capture</p>	<p style="text-align: right;">Page 217</p> <p>1 functionality. So which of the PROs would really lend 2 themselves to measuring this in these clinical trials? 3 Finally, sort of how do we do the 4 trial? Now there's any number of development 5 challenges on how to design and conduct the trial, but 6 I just need to hit on a few that really sort of jumped 7 out at me. First of all, the selection of trial sites 8 -- I mean, this is a highly specialized area of -- of 9 research and patient treatment. There's no patient 10 registry for ABPA at the moment, so identifying 11 patients asthma community does present a challenge. 12 The trials themselves will be quite 13 complex to do, both in identifying patients and then 14 managing them through the trial. The trials will have 15 to be conducted at very specialized centers, and there 16 are a limited number of specialized centers for ABPA. 17 Duration of treatment. This was 18 touched on a little bit earlier. I mean, how long 19 should we treat for? Longer is probably better. 20 Should we be thinking about the way ABPA exacerbations 21 are normally treated with oral azoles? Should we have</p>

<p style="text-align: right;">Page 218</p> <p>1 treatments that go weeks long? Months long? Into -- 2 continuous? These are all things we need to think 3 about when we're trying to design the trial. And it 4 will affect the patient recruitment and retention in 5 the trial.</p> <p>6 As I mentioned a bit earlier, 7 identifying patients but not making the inclusion 8 criteria so difficult that we can't get patients into 9 the trial or we screen -- we really have to balance 10 the need to get a robust population, robust and 11 homogenous population to demonstrate drug effects, but 12 balance that with not excluding patients who may 13 benefit from the treatment, and making recruitment 14 very difficult and the trial essentially unfeasible.</p> <p>15 Capturing and managing the 16 exacerbations. For example, we need to look at the 17 type of exacerbation and then document the start and 18 duration of those exacerbations. Now when the types 19 of exacerbations are managed a little bit differently, 20 then they will have different durations. And so that 21 may present difficulties in looking to analyze the</p>	<p style="text-align: right;">Page 220</p> <p>1 underreporting.</p> <p>2 And then that brings me on to talking 3 about sample size estimation. Right now, there's no 4 precedent for ABPA trials, so we don't know how to 5 measure our -- our outcomes, or the frequency of the 6 outcome variable and what would be a clinically 7 significant improvement in that outcome. So if we're 8 thinking of frequency of exacerbation, how many 9 exacerbations per year could we expect patients to 10 have in the trial? And what would be a meaningful 11 outcome to reduce frequency? Can we use examples from 12 bronchiectasis trials? Would that help with -- there 13 is some overlap between these types of patients. But 14 on the other hand, they are distinct clinical 15 entities.</p> <p>16 So these are just some of the 17 challenges in the -- considering the clinical 18 development. And when we take this into account, we 19 also perhaps want to look at the regulatory pathway 20 considerations.</p> <p>21 The azoles that are being developed for</p>
<p style="text-align: right;">Page 219</p> <p>1 data.</p> <p>2 The test to support the diagnosis of an 3 exacerbation such as IGE and chest X-ray require 4 patients to come into hospital, be examined and take 5 time to report. So then again, that -- that presents 6 some logistic challenge in documenting exacerbations.</p> <p>7 When we're treating exacerbations, 8 whether it be an asthma or ABPA or bronchiectasis 9 exacerbation, we need to have a standardized treatment 10 regimen for patients in the trial so we can at least 11 compare and make conclusions on treatment efficacy.</p> <p>12 And it's also -- looking at the 13 bronchiectasis example, it may be that the need for 14 patients to come to hospital when they have an 15 exacerbation can sometimes lead to underreporting of 16 exacerbations. Possibly less likely in ABPA where 17 patients may well be much more severely ill and 18 they're more likely to come to hospital. But even so, 19 the need for patients to then come in and go through a 20 number of tests may present barriers for patients 21 reporting exacerbations in trials. It could lead to</p>	<p style="text-align: right;">Page 221</p> <p>1 inhalation in ABPA are already well known. We're 2 looking at voriconazole that has a long history of 3 human exposure. The systemic effects of voriconazole 4 are very well characterized. And so the safety 5 profile in humans is well known.</p> <p>6 Clearly, the inhalational safety will 7 be well studied in the preclinical and -- and clinical 8 studies. But also looking at the clinical development 9 challenges, we can see that these trials are very 10 difficult, and they're behaving very much like rare 11 disease trials. So recruiting patients for these 12 trials, we need to think of them in the context of a 13 rare disease-type trial.</p> <p>14 So knowing the safety profile of the 15 drug and knowing how difficult the trials could be, 16 what could be an appropriate number in size of study 17 for us to find NDA or an MAA? How can we -- can we 18 streamline the process to get these important 19 treatments to patients more rapidly? Should we 20 consider QIDP and fast track designations? This 21 probably qualifies for that sort of designation. And</p>

<p style="text-align: right;">Page 222</p> <p>1 like our previous speaker said, should we consider 2 LCAD for ABPA? Could there be a set of patients 3 within ABPA that could be considered for LCAD? 4 So these are just some of the 5 perspectives on the development and the challenges 6 that we have. Clearly, these challenges are well 7 worth meeting to try and bring these important 8 treatments to patients. And with that, I'd like to 9 say thank you very much for listening.</p> <p>10 DR. MARR: Thank you, Dr. Keywood. Our 11 last speaker in the industry session will be Dr. 12 Russell Clayton, who's an interim executive for 13 Pulmatrix.</p> <p>14 DR. CLAYTON: Thank you very much. And 15 I want to join my colleagues by thanking the Food and 16 Drug Administration for a very well planned and very 17 well executed workshop on this very important topic. 18 I'd also like to take a moment to congratulate all the 19 presenters today on -- on very pointed, relevant, 20 excellent presentations. So thank you very much. 21 I'm going to talk for a minute about</p>	<p style="text-align: right;">Page 224</p> <p>1 a single inhalation of 20 milligrams provided a 2 minimum inhibitory concentration against aspergillus 3 fumigatus for a -- a full 24 hours after a single 4 dose. And yet that same single dose had an 85-fold 5 lower systemic exposure than a single dose of a 200 6 milligram dose of the oral -- oral solution there. 7 There's a misprint on that slide. Oral itraconazole 8 for oral plasma exposure.</p> <p>9 So there really is a potential to 10 eradicate aspergillus fumigatus from the lung of 11 patients with ABPA. And it's been underscored several 12 times that one of the important goals is to reduce 13 corticosteroid exposure in this patient population and 14 ultimately shorten disease course, but at the same 15 time minimizing the risk that comes with systemic 16 azole therapy for -- for these types of products.</p> <p>17 So after the phase one studies were 18 completed, Pulmatrix launched a phase two study in 19 patients with asthma and ABPA. You see the design of 20 the study on the slide, basically four arms looking at 21 three different doses with a placebo control group.</p>
<p style="text-align: right;">Page 223</p> <p>1 Pulmatrix. The pleasure of working with Pulmatrix, 2 which is a Lexington, Massachusetts based company that 3 engineers a dry powder delivery vehicle with the goal 4 of developing inhalation medications for a -- you 5 know, therapies for a variety of diseases. The -- the 6 technology platform is the -- particle, which has the 7 potential to be used with a broad range of different 8 therapeutics. It has the ability to carry relatively 9 high payloads, but the real beauty here is the 10 potential to have a high dispersibility with a low 11 inspiratory flow. Considering that a lot of inhaled 12 medications are being delivered to patients with 13 respiratory disease, it may not be able to generate 14 high inspiratory flows there.</p> <p>15 One of the primary products in 16 development is POR1900, also referred to as pulmazole. 17 You have heard some of the speakers previously refer 18 to some of the phase one data. Pulmazole or POR1900 19 is being developed for the treatment of allergic 20 bronchopulmonary aspergillosis, or ABPA. And I think 21 we saw some data earlier today that demonstrated that</p>	<p style="text-align: right;">Page 225</p> <p>1 The primary objective to assess safety and 2 tolerability, but also to evaluate potential 3 endpoints. And we've heard a lot of about endpoints 4 and the uncertainty there. And also to hopefully 5 identify an optimal dose.</p> <p>6 You see what -- what we were trying to 7 recruit, basically males and females 18 to 75 years of 8 age, and they were being asked to perform once a day 9 dosing for 28 days.</p> <p>10 So what did we learn and how did this - 11 - how did this study proceed? We had over 25 sites in 12 five countries that were identified with a proven 13 track record of excellent performance in clinical 14 asthma studies. So going in felt very confident that 15 we'd be able to enroll this study. And it was a mix 16 of freestanding clinical study sites as well as 17 academic institutions. So we had what I think was -- 18 would be classified as the best of both worlds there.</p> <p>19 On the right-hand side, you'll see the 20 inclusion/exclusion criteria we -- we heard at -- by 21 Dr. Keywood very well illustrated some of the</p>

<p style="text-align: right;">Page 226</p> <p>1 challenges with regard to the inclusion/exclusion 2 criteria, and the limitations we have. Because if 3 your inclusion/exclusion criteria are too strict, 4 you're going to not be able to recruit your 5 population. Of course, if they're too wide, then you 6 have a very heterogenous population. 7 So this was thought by the planning 8 group to be a good mix of inclusion/exclusion 9 criteria. We did use the ISHAM criteria to diagnose 10 ABPA and limited it to stage 2, 4, 5A and 5B. So that 11 eliminated ABPA that was an acute or exacerbation 12 mode, or newly diagnosed ABPA. 13 And one of the key inclusion criteria 14 was at the time of enrollment, the subject had to have 15 a total serum IGE of greater than or equal to 1,000 -- 16 that's for ML. 17 Another key criteria with regard to 18 prohibited medications was the -- the subjects could 19 not have received any of the monoclonal antibody 20 therapies targeting asthma, or azole therapy in the 21 last six months. And we're going to return to that</p>	<p style="text-align: right;">Page 228</p> <p>1 respect very much said it was -- it was validated. 2 I'm -- I'm not so sure that that particular treatment 3 has been validated. There are basically a number of 4 small studies, case reports, that sort of thing. And 5 for that reason, we had to exclude these subjects 6 because we just weren't sure about the -- the safety 7 and efficacy of this particular product in ABPA. 8 But more importantly, this -- this 9 particular product is known for increasing serum to 10 the IGE levels. And we -- because we're concerned 11 that that would potentially mask an effect because we 12 were looking at IGE levels as one of our markers of 13 effect here. So we had that very significant barrier 14 because unfortunately, use of this product off label 15 in this population was -- was not uncommon. 16 What did we learn? We learned that 17 site selection is -- is a key factor here. You -- you 18 really need to go to sites that have a robust 19 population specific for -- for ABPA. And in that 20 particular vein, the academic sites tended to perform 21 better than the freestanding research units.</p>
<p style="text-align: right;">Page 227</p> <p>1 topic in -- in -- in a moment. 2 So how did this study proceed? Well, 3 similar to what Dr. Bazaz presented, there seemed to 4 be a shortage of -- of eligible subjects. There was a 5 relatively small pool. The -- each of the sites had a 6 multifaceted recruitment plan. They executed -- 7 qualified, but were over 75 years of age. Several 8 subjects could not meet our BMI cutoff of 35, and we 9 had quite a number of subjects whose current IGE level 10 was -- was far less than -- than 1,000. 11 And so that was one of the -- the 12 bigger sticking points here and -- and a cause of -- 13 with regard to whether or not, you know, how do you 14 know when it's no longer ABPA when their IGE is -- is 15 less than 1,000? So that's -- that's caused a little 16 bit of a concern there. 17 And then we had a number of subjects 18 that were -- that were disqualified because of 19 omalizumab use. And I wanted to -- to pause on that 20 point only because it was -- it was stated earlier 21 that this treatment -- I think the speaker who I</p>	<p style="text-align: right;">Page 229</p> <p>1 We also learned that the inclusion 2 criteria need to be rather wide, but of course not too 3 wide because then you start getting into a population 4 where you're going to have trouble interpreting the 5 data. 6 And importantly, you have to define a 7 relevant and realistic lower threshold for IGE. What 8 is the right number? What is -- what is the wrong 9 number for bringing patients into a study who are 10 diagnosed with ABPA, and yet they have an IGE level 11 below 1,000. 12 So what happened with this study? 13 Well, similarly to what we've heard previously, in 14 March, the study was suspended due to issue related to 15 -- to COVID-19. And a few months later, the decision 16 was made to -- to terminate the study basically due to 17 uncertainty, again, with regard to the COVID-19 18 pandemic. So as -- as of July of this year, this 19 study was -- was terminated. 20 I'm going to pause for a second to talk 21 about measures of effects. We were looking at several</p>

<p style="text-align: right;">Page 230</p> <p>1 different measures of effect in -- in this study. I 2 mentioned IGE which is very commonly used clinically 3 as an indicator of improvement. Many clinicians, we 4 use IGE as it decreases as a indicator to reduce, for 5 example, the dose of glucocorticoids. And so that -- 6 that is a measure of effect. But as we've heard, this 7 is a -- a laboratory biomarker, if I can even use the 8 term biomarker. And it's unlikely that this would of 9 and by itself be a -- a relevant clinical endpoint, or 10 valid clinical endpoint, without some sort of other 11 clinical endpoint supporting IGE as well. 12 In the phase two study, sputum 13 eosinophils was chosen as a measure effect. This was 14 modeled after Dr. Work's [ph] study which looked at 15 sputum eosinophils after 16 weeks of therapy with oral 16 itraconazole. But this is an endpoint that is -- or - 17 - that is technically challenging to say the least. 18 There were a number of our sites that frankly 19 struggled with the ability to -- to do the techniques 20 necessary to get an adequate count of sputum 21 eosinophils.</p>	<p style="text-align: right;">Page 232</p> <p>1 efficacy in this population. 2 So what does that leave us with? 3 Exacerbations. And we just heard from Dr. Keywood 4 that how do you define these exacerbations? Asthma 5 exacerbations, ABPA exacerbations? There has to be a 6 very clear definition that would be sufficiently 7 acceptable as registerable endpoints. And then the 8 other question is what's an appropriate observation 9 period? If ABPA goes into remission, is it really 10 relevant to go and take -- take an observation period 11 out for -- for 8 months or 12 months? After a certain 12 period of time, are you observing the patient's 13 frequency of asthma exacerbations of and by itself? 14 So that's -- you know, that was not -- 15 that's another point that's -- that's not extremely 16 clear. 17 If -- I'm sorry. I'm unable to advance 18 the slide. If you could go to the next slide, please? 19 So what -- what did we learn? So we -- 20 we learned that ABPA is an understudied entity. Now 21 that's -- that's a relative statement, but there are</p>
<p style="text-align: right;">Page 231</p> <p>1 Specific IGE was mentioned as -- as a 2 potential measure of effect, but it's -- it's not 3 clear as to what the correlation to disease for that. 4 Corticosteroid reduction mentioned previously is very 5 clinically meaningful. And one of the things that has 6 not been discussed a lot today is radiographic 7 evaluation. But -- but that of course requires 8 standardized criteria, and it's still not clear what 9 the correlation of the radiologic evaluation would be 10 to -- to disease. 11 So what do we default to? We default 12 to FED1, which is a standard endpoint for asthma 13 studies. Unfortunately, the variability of FED1 14 within an asthma population is only going to be 15 enhanced in patients with ABPA. 16 And as Dr. Denning pointed out in his 17 survey of ABPA studies, there's very few studies that 18 -- that are out there. And the few studies that are 19 out there demonstrate a very -- a relatively small 20 change in FED1. So it's -- it's unclear that this 21 particular endpoint would be robust enough to define</p>	<p style="text-align: right;">Page 233</p> <p>1 no large natural history studies. So we don't really 2 understand what the course of FED1 or -- or serum IGE, 3 or exacerbation frequency is in this -- in this 4 population. We don't really have a good handle on the 5 prevalence, as Dr. Keywood mentioned that 2.5 percent 6 number is really based on retrospective studies that - 7 - that are coming from centers that are seeing 8 patients with severe asthma. So it's -- it's not 9 likely applicable to -- to an entire asthma 10 population. And there are very few interventional 11 studies, and that underscores the -- the uncertainty 12 around endpoints. 13 The prevalence of ABPA is -- is likely 14 lower than currently assumed. I know that we've heard 15 statements to the contrary, but there are indications 16 at least through the conduct of clinical studies that 17 ABPA mimics studies in rare disease populations with 18 very low recruitment rates. And -- and that's going 19 to be a feasibility burden for -- for pivotal clinical 20 trials. 21 Site selection is a key, but site</p>

<p style="text-align: right;">Page 234</p> <p>1 identification is going to be very challenging because</p> <p>2 ABPA is -- is not necessarily a reported infectious</p> <p>3 disease. There are no existing registries, no</p> <p>4 advocacy groups. You've got to go and seek and find</p> <p>5 these sites and -- and hope that you've -- you've got</p> <p>6 the right criteria to choose these sites.</p> <p>7 If you're going to successfully recruit</p> <p>8 a study, the inclusion criteria has to be wide. But</p> <p>9 unfortunately, that makes for a heterogenous</p> <p>10 population. And then the question that I've asked</p> <p>11 previously, when is ABPA no longer ABPA? It's</p> <p>12 something that definitionally is very difficult to --</p> <p>13 to get to.</p> <p>14 And finally, as we've heard several</p> <p>15 times, the endpoints and tools to assess a therapeutic</p> <p>16 intervention are -- are -- are poorly defined. And,</p> <p>17 you know, which -- when is it appropriate to use</p> <p>18 asthma endpoints and -- or should there be ABPA</p> <p>19 endpoints?</p> <p>20 So if -- if we move to the left slide,</p> <p>21 please, because again, I cannot advance my own slides</p>	<p style="text-align: right;">Page 236</p> <p>1 prevalence of ABPA in these other recruitment issues</p> <p>2 to define -- to define the population, etcetera,</p> <p>3 creates tremendous feasibility burden to support</p> <p>4 standard clinical development program approach for a</p> <p>5 marketing authorization. It's unlikely that this</p> <p>6 entity is going to support the notion that two well</p> <p>7 controlled appropriately powered phase three studies</p> <p>8 are going to be feasible with anybody's -- within</p> <p>9 anyone's lifetime, in terms of proving efficacy and</p> <p>10 safety.</p> <p>11 And so as Dr. Keyword mentioned, and</p> <p>12 has been the subject from other speakers, this is</p> <p>13 likely to require a streamlined development program.</p> <p>14 And this certainly is -- is something that is -- is of</p> <p>15 interest to -- to all of our industry colleagues. And</p> <p>16 with that, I will end my part of the presentation.</p> <p>17 And again, thank -- thank you for listening.</p> <p>18 DR. MARR: Thanks very much. In the</p> <p>19 interest of time, we're going to minimize our break to</p> <p>20 five minutes. Please come back by 3:10 and we will</p> <p>21 start the question and answer period. Thank you.</p>
<p style="text-align: right;">Page 235</p> <p>1 unfortunately.</p> <p>2 What are the implications? I think the</p> <p>3 most important implication for ABPA is that industry</p> <p>4 sponsored intervention trials are -- are going to be a</p> <p>5 significant force in enlarging the understanding of</p> <p>6 ABPA. This -- this implies kind of a learn as you go-</p> <p>7 type of development program. You have to launch a</p> <p>8 development program with the idea that a lot of what</p> <p>9 you learn in your studies is going to contribute to</p> <p>10 the body of knowledge. But the implication there is</p> <p>11 that the endpoint definition may need to evolve. We</p> <p>12 may have loved the idea of -- of what the endpoint</p> <p>13 should be, but as the development program progresses,</p> <p>14 there -- there may need to be an acceptance of interim</p> <p>15 endpoints until we have the sufficient knowledge to</p> <p>16 define a -- a good endpoint.</p> <p>17 Second, there has to be -- we need to</p> <p>18 establish a standard criteria in defining ABPA, as</p> <p>19 well as the staging, as well as defining what</p> <p>20 remission means. That's in terms of IGE levels or</p> <p>21 other measures as well. And then finally, the low</p>	<p style="text-align: right;">Page 237</p> <p>1 (Off the record.)</p> <p>2 DR. WALSH: This is Dr. Walsh. Hello?</p> <p>3 Can you hear me?</p> <p>4 DR. MARR: Hey, Tom. We hear you.</p> <p>5 DR. WALSH: Great. Thank you.</p> <p>6 DR. MARR: Hey, Tom. Yeah, you're on.</p> <p>7 DR. STEVENS: It's David Stevens. Can</p> <p>8 -- can I be heard?</p> <p>9 DR. WALSH: Hi, David. We can hear</p> <p>10 you. This is Tom.</p> <p>11 DR. GREENBERGER: And Paul Greenberger</p> <p>12 here. Hear me?</p> <p>13 DR. WALSH: Hi, Dr. Greenberger.</p> <p>14 DR. GREENBERGER: Thank you.</p> <p>15 DR. SWEETS: Hi, Sweets [ph].</p> <p>16 DR. WALSH: Hi, Sweets. We can hear</p> <p>17 you.</p> <p>18 DR. MOSS: Hi, Rick Moss here. Can you</p> <p>19 hear me?</p> <p>20 DR. WALSH: Hi, Rick. We can hear you.</p> <p>21 DR. CLANCY: Not sure if I came through</p>

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<p>1 there. It's Neil Clancy.</p> <p>2 DR. WALSH: Hi, Neil. We can hear you.</p> <p>3 DR. CLANCY: Oh. Hey, Tom.</p> <p>4 DR. WALSH: How's it going?</p> <p>5 DR. MCMASTER: Hi. This is Owen</p> <p>6 McMaster. Can you hear me?</p> <p>7 DR. WALSH: Yes, Owen. We can hear</p> <p>8 you.</p> <p>9 DR. MCMASTER: Thanks.</p> <p>10 DR. MOSS: Rick Moss here. Coming</p> <p>11 through?</p> <p>12 DR. WALSH: Yes, Ricky. We can hear.</p> <p>13 DR. MOSS: Thanks.</p> <p>14 DR. CLANCY: Tom, just to give a heads</p> <p>15 up, I've got a commitment at 3:30. I'll silently</p> <p>16 disappear at that time. It's Neil, by the way.</p> <p>17 DR. WALSH: Okay. You'll be with us</p> <p>18 until --</p> <p>19 DR. CLANCY: Yeah. I will indeed.</p> <p>20 DR. HUSAIN: Tom, this is Shahid. Can</p> <p>21 you hear me?</p>	<p>1 starting. Just very briefly, we'll be wrapping up our</p> <p>2 preclinical discussion, although I wish it was more,</p> <p>3 at 3:20. Then we'll go onto David at 3:20-3:45 on</p> <p>4 endpoints, particularly for ABPA, but perhaps other</p> <p>5 entities as well. Kieren at 3:45 to 4:05, with</p> <p>6 endpoints in special populations -- the prophylaxis.</p> <p>7 And then I'll resume at 4:05 and finish at 4:20,</p> <p>8 patient reported outcomes. And then we will then hear</p> <p>9 from Sumati at 4:20, and we'll conclude at 4:30.</p> <p>10 So to begin, the first question is as</p> <p>11 development of an inhaled antifungal therapies will</p> <p>12 likely be based on streamlined development programs.</p> <p>13 What are the gaps in animal in vitro models that can</p> <p>14 be used to support these programs and how can they be</p> <p>15 addressed? And I would read into that -- one of our</p> <p>16 panelists, Don Sheppard, who's raised the question,</p> <p>17 what PKPD targets should we be aiming for? So I would</p> <p>18 open it up to this great audience and -- and please,</p> <p>19 feel free to -- to comment.</p> <p>20 DR. MARR: This is Kieren and if you</p> <p>21 are -- if you would just raise your hand, we can also</p>
<p>Page 239</p> <p>1 DR. WALSH: Yes, we can hear you.</p> <p>2 DR. HUSAIN: Thank you.</p> <p>3 DR. STEVENS: Can you hear me?</p> <p>4 DR. WALSH: We can hear.</p> <p>5 DR. ALEXANDER: Hi, Tom. It's Barbara</p> <p>6 Alexander.</p> <p>7 DR. WALSH: Hi, Barbara. Glad you</p> <p>8 could join us.</p> <p>9 DR. ALEXANDER: Sure thing.</p> <p>10 DR. WALSH: I think -- I think we're</p> <p>11 ready. Oh, let's see. We have one more minute. Oh,</p> <p>12 sorry. I lost you. I think we can start now. Is</p> <p>13 that okay? All right. Very well.</p> <p>14 We'll be looking at a somewhat</p> <p>15 truncated schedule. This is Tom -- Tom Walsh. I just</p> <p>16 want to welcome everyone here on the panel. It is an</p> <p>17 amazing cast of experts with some just tremendous</p> <p>18 experience in the field of medial mycology, and</p> <p>19 particularly in the area of pulmonary aspergillosis.</p> <p>20 Our schedule is somewhat more truncated</p> <p>21 this time. And so we're -- because of our timing of</p>	<p>Page 241</p> <p>1 call on you if you've got a question or comment, too.</p> <p>2 DR. WALSH: So if -- please feel free</p> <p>3 to -- yeah. To comment directly. If -- if not, I can</p> <p>4 just open up a few -- with a few comments that we --</p> <p>5 we've heard several different disease states and</p> <p>6 certainly in order to de-risk the -- the studies and</p> <p>7 in order to be able to have some sense of dose</p> <p>8 response relationship, it -- it behooves us to reflect</p> <p>9 that I think on at least the animal model systems</p> <p>10 potentially. One would be ABPA in which there are</p> <p>11 animal models that have been developed over the course</p> <p>12 of time. Arguably, not fully reflective of -- of our</p> <p>13 patient population, but still a reasonable</p> <p>14 approximation. There is then model -- there are</p> <p>15 models of chronic aspergillosis. Again, with some</p> <p>16 degree of limitations. And then finally, our class --</p> <p>17 invasive aspergillosis.</p> <p>18 So in that context, I would open the</p> <p>19 question again as to what endpoints might we consider?</p> <p>20 I would just raise the question -- looking at David</p> <p>21 Stevens' original study on Itra [ph] and then the work</p>

<p style="text-align: right;">Page 242</p> <p>1 -- elegant work done by David and -- and the fungal 2 allergic hypersensitivity asthma that clearly an 3 antifungal agent diminishing the presence of 4 aspergillus, or down -- the growth of aspergillus 5 really has a beneficial effect in ABPA. And probably 6 across all models I think as a reliable marker with 7 inhalational agents, you'd like to see a significant 8 impact reduction of -- of fungal -- residual fungal 9 burden. As simple as it is, modification could be by 10 culture, PCR, antigen, and then certainly measuring -- 11 BAL through ELS, and pulmonary alveola macrophages 12 gives us some sense of concentrations that we would 13 like to target.</p> <p>14 In a dose escalation cohort design, it 15 would be possible then to model these out, whether 16 it's in a chronic model, an ABPA model or acute 17 invasive aspergillosis model. Some of this work has 18 been done for some formulations, but I think there's a 19 long way to go. In that regard, I know that we have 20 to spend -- in developing appropriate animal models. 21 And certainly, chronic aspergillosis models and ABPA</p>	<p style="text-align: right;">Page 244</p> <p>1 have a successful outcome. And -- and that's very 2 relevant to -- to the issue of development of 3 resistance I think as well. It's having enough drug 4 on board consistently to -- to prevent that from 5 occurring.</p> <p>6 DR. WALSH: David, I -- I would agree 7 with that. But if we -- if we take the model from 8 sample four, exposures and time above MIC and data -- 9 for example, in resistant organisms where we sometimes 10 aim for high concentrations either in the lung or in 11 the plasma, there is a certain sense of having a 12 certain concentration above the MIC. Do you have a 13 set -- even if it is time dependent, PKPD, do you have 14 a certain -- do you have a sense as to how many times 15 above MIC you would like to see that over the course 16 of time?</p> <p>17 DR. DENNING: I -- I don't. Also, 18 there's a little bit of data, but not much. Some 19 aspergillus fumigatus strains which are apparently 20 tolerant. So they're inhibited at one concentration, 21 but a much, much higher concentration is required to</p>
<p style="text-align: right;">Page 243</p> <p>1 models really have a long way to go, and certainly 2 would be, I think tremendously helpful in helping us 3 to optimize and de-risk the clinical trials, 4 especially as we talk about streamlined designs.</p> <p>5 DR. DENNING: Yeah. So let me actually 6 make a comment.</p> <p>7 DR. WALSH: Yes, please. Please do so.</p> <p>8 DR. DENNING: One of the -- one of the 9 site challenges was azoles and aspergillus has been 10 dissecting whether it's an AUC [ph] -- excuse me. 11 Something in my throat. AUC or a time -- I see -- 12 concentration. My impression of the literature is 13 that because the azoles have a long half life and 14 therefore it's harder to sort it out, my impression 15 that it's time -- MIC rather than AUC -- for azoles 16 and aspergillus.</p> <p>17 And I wonder therefore whether in terms 18 of the phase one data, the -- did the persistence and 19 concentrations over time in the volunteers, and then 20 obviously subsequently in other patients, might be a 21 - a decent guide to whether -- what it's like if you</p>	<p style="text-align: right;">Page 245</p> <p>1 kill the organism. And where it illustrates the -- 2 the concentration that inhibits them and kills them is 3 very similar. So your question might be split into 4 two parts effectively because of this issue of -- of - 5 - probable issue of tolerance. Although that's yet to 6 be demonstrated in a -- in a more in vivo system 7 properly I think.</p> <p>8 DR. WALSH: I would agree. I would 9 agree. So I think that one could conclude that really 10 there is, especially for ABPA and chronic 11 aspergillosis, a dire need for -- for better models. 12 We -- I think we have very good systems for acute 13 pulmonary aspergillosis, but for inhalational ones, 14 still needs to really define the PKPD. Especially 15 given the experience we're seeing of probably this -- 16 this sense of time above MIC really being a critical 17 factor, particularly if you're going to have extended 18 durations or long intervals albeit once weekly, twice 19 weekly of inhalational treatments. I would agree.</p> <p>20 We could probably have an entire 21 symposium on -- on this subject, but it is 3:20 and I</p>

<p style="text-align: right;">Page 246</p> <p>1 want to try to stay on time. So, David, I will pass 2 the torch to you and you have the floor until 3:20. 3 DR. DENNING: Okay. So I think one of 4 the questions I'll ask is this issue of resistance. 5 Across the world, there is an increasing documentation 6 -- it may not be actually increasing incidents, but 7 certainly increasing documentation of itraconazole, 8 voriconazole and sometimes paranasal resistant -- in 9 the environment. Given that we all breathe these 10 organisms in, are we going to induce resistance during 11 therapy, or are we going to in patients treated over 12 the longer term, allow resistant organisms to survive 13 and then precipitate an immune response and 14 deterioration of ABPA or asthma? Because it'd be like 15 it's a super infection with a resistant pathogen. 16 So I think one of the questions here is 17 -- and it's really a question I think for the FDA. 18 And maybe we can suggest a possible proposal in this 19 area, is what sort of follow-up will be required of 20 these patients? In a relatively small phase three 21 study of two, three, 400 patients, you might have one</p>	<p style="text-align: right;">Page 248</p> <p>1 welcome. 2 DR. MOSS: I was just going to add that 3 -- this is Rick. Just coming from the experience of 4 CF, a pretty long history with inhalational 5 antimicrobial agents, the application of -- of 6 traditional breakpoints has really proven to be 7 completely obsolete in terms of clinical outcomes. 8 I'm just wondering -- it gets to the regulatory 9 question that David raised of what kind of follow-up 10 is necessary if you're using a reference point that is 11 essentially irrelevant to the population at hand. 12 DR. DENNING: Yeah. Sumati? You were 13 going to make a comment. 14 DR. NAMBIAR: Yeah. Certainly all the 15 points that have been made are all valid, and you 16 know, we don't have a lot of experience in this -- to 17 tell you exactly, you know, how we are going to 18 require monitoring post-approval. But I can certainly 19 tell you what we've done in the antibacterial space. 20 And the points raised about relevance of MIC receiving 21 -- therapy have certainly come up with antibacterial</p>
<p style="text-align: right;">Page 247</p> <p>1 or two that develop resistance in the space of six 2 months or a year, but you're not going to have enough 3 to -- probably to -- to really plot them out, how 4 common it is. Unless it's really, really common, 5 which is unlikely. But then when the drug is marketed 6 and you've got thousands of patients on treatment for 7 long periods of time, resistance is likely to emerge 8 but maybe at a low frequency or a high frequency. We 9 don't know. 10 So I would like to know I think what 11 the agency thinks about this and whether there's 12 anybody from the agency that would like to comment 13 about it? Maybe there's other people than me who are 14 listening who have a view about this? 15 DR. NAMBIAR: Hi, David? This is 16 Sumati. Can you hear me? 17 DR. DENNING: Yes, I can hear you. 18 Yes. 19 DR. NAMBIAR: Yeah. Dr. Walsh, is it 20 okay if I provide a quick response? 21 DR. WALSH: Oh, yes. Please do. We</p>	<p style="text-align: right;">Page 249</p> <p>1 drugs that have been approved for treatment of 2 patients with certain lung infections -- cystic 3 fibrosis patients. 4 So I think we, you know, exactly how we 5 are going to define and what kind of monitoring we do 6 I think is a -- subject to discussion, but systemic 7 antibacterials, you know, we have -- we have different 8 options. If -- if we see some concerning findings 9 during the conduct of the clinical trial, we do have 10 the authority to require post-marketing studies. 11 Besides that, currently, certain 12 antibacterial drugs are approved. We do require that 13 certain studies be conducted for a certain period of 14 time, whether it's five years or longer, to monitor 15 for resistance to the new drug one it's approved. 16 So I think, you know, depending on -- 17 on what the data are from the studies, how much 18 concern we have based on the information at hand, we 19 have the ability to require studies. The exact nature 20 of the study and the duration of that, I think is 21 something we're going to have to decide when we get to</p>

<p style="text-align: right;">Page 250</p> <p>1 that point.</p> <p>2 DR. DENNING: Okay. Just to add one</p> <p>3 further comment is that currently, most aspergilli</p> <p>4 that are cultured from the sputum samples are not</p> <p>5 tested for -- antifungals across the world. Some of</p> <p>6 the recommendations that we have suggested in some of</p> <p>7 the guidelines suggested that if you have an</p> <p>8 antifungal -- I'm sorry. If you grow an aspergillus</p> <p>9 in a patient on an antifungal, then you should --</p> <p>10 tested. This is of course if we have inhaled</p> <p>11 antifungals that comes significantly magnified I think</p> <p>12 in terms of its importance.</p> <p>13 So I think that maybe a -- within the -</p> <p>14 - microbiology community about that. And I wonder</p> <p>15 whether Kieren or Tom or -- or others, or Don Sheppard</p> <p>16 for example, have -- or Stevens have a view about</p> <p>17 that.</p> <p>18 DR. SHEPPARD: David, I have one</p> <p>19 comment. I'm sorry. This is Don.</p> <p>20 DR. WALSH: No, no. Please, go ahead.</p> <p>21 DR. SHEPPARD: I do have one comment</p>	<p style="text-align: right;">Page 252</p> <p>1 and we had the same two resistant strains, but all the</p> <p>2 rest were susceptible. In that situation, we haven't</p> <p>3 really created resistance. We've just unmasked the</p> <p>4 background noise, if you know what I'm getting at?</p> <p>5 DR. DENNING: Thank you. That was Don</p> <p>6 Sheppard from Montreal.</p> <p>7 DR. HUSAIN: Hi, this is Shahid. I</p> <p>8 don't -- very valid comment and indeed, there's always</p> <p>9 the issue -- this is reduced term. Happy in the panel</p> <p>10 or not, but this is one -- only one data that is</p> <p>11 shown. There is also a study in lung transplants from</p> <p>12 Alberta, which we're using -- prophylaxis. Dave</p> <p>13 quoted relatably our -- of aspergillus -- that.</p> <p>14 DR. WALSH: This is Tom. I would also</p> <p>15 like to raise the question to Barbara. Barbara, as</p> <p>16 you all know, has been with John -- at Duke</p> <p>17 University, has been using aerosolized ABLC in their</p> <p>18 lung transplant recipients as prophylaxis. And</p> <p>19 obviously given the broad spectrum, it raises the</p> <p>20 question and so far as whether they have seen</p> <p>21 organisms emerging resistant either environmentally</p>
<p style="text-align: right;">Page 251</p> <p>1 about what you had mentioned earlier, actually, with</p> <p>2 respect to this issue. And that is sorting out what</p> <p>3 we mean by resistance. Because for example, in</p> <p>4 Shahit's presentation, he was talking about the use of</p> <p>5 inhaled antifungals in -- in the lung transplant</p> <p>6 patients. The data that was presented in that paper</p> <p>7 and the way it's commonly presented is percent of</p> <p>8 isolates and resistance. And that doesn't actually</p> <p>9 tell us anything what the induction of resistance, it</p> <p>10 talks more about the selection for resistant species</p> <p>11 in the environment. You know, the classic question</p> <p>12 I'm asking is are you really just wiping out the --</p> <p>13 species and you're left with the background noise of</p> <p>14 resistance that was always there, or is there an</p> <p>15 actual increase in the amount of resistance measured</p> <p>16 on an absolute scale.</p> <p>17 So when we collect this data, we have</p> <p>18 to make sure we have the correct -- here. It doesn't</p> <p>19 do any good to know that there is a 50 percent</p> <p>20 resistance rate, if that is two strains. Whereas</p> <p>21 prior to the use of the drug, we had 50,000 strains</p>	<p style="text-align: right;">Page 253</p> <p>1 acquired or intrinsically within the house in that</p> <p>2 population in which I think amounts to well over 2,000</p> <p>3 patients at this point.</p> <p>4 Barbara, can you comment on selection</p> <p>5 of resistance in that population?</p> <p>6 DR. ALEXANDER: Yeah. Hey, Tom.</p> <p>7 Thanks. Yes. So we have over 1,500 lung transplant</p> <p>8 patients now that have been treated with inhaled</p> <p>9 amphotericin B lipid complex which we use as our</p> <p>10 standard prophylactic regiment at Duke. These are</p> <p>11 patients who've received this medication since around</p> <p>12 2000. And recently, we did retrospectively look at</p> <p>13 seven years' worth of data. And we did see</p> <p>14 breakthrough invasive fungal infections on -- in</p> <p>15 people who had received inhaled ABLC. Of note, many</p> <p>16 of those patients developed the infection 30 days, you</p> <p>17 know, after receipt of the drug. So it may be that</p> <p>18 the level of drug in the lung had gone down, and so</p> <p>19 the reason for the breakthrough was simply that the</p> <p>20 drug was no longer at adequate levels in the lung.</p> <p>21 But some of the pathogens that we did</p>

<p style="text-align: right;">Page 254</p> <p>1 see break through, were organisms that are considered 2 intrinsically resistant to -- to amphotericin. So for 3 instance -- or aspergillus terreus. And so, you know, 4 one of the things I just -- back to is if you have a - 5 - a host that's appropriately immunosuppressed, and 6 they're continuously exposed to mold pathogens, 7 ultimately you're going to select for infection with a 8 pathogen that is resistant to the drug that you're 9 prophylaxing with. And we've seen this time and again 10 over the years, right? With the different drugs that 11 have been studied. Early when voriconazole came to 12 market, we saw reports of breakthrough mucormycosis on 13 -- on patients receiving voriconazole systemically for 14 prophylaxis. And so on some -- on some level, you 15 know, this is to be expected, right? 16 I -- I think it's really important 17 though that we, you know, are careful to try and get 18 baseline isolates. It's not uncommon to have lung 19 transplant patients colonized with mold. And so it'd 20 be really important to get the organisms that are 21 coming out of these patients. And then, you know,</p>	<p style="text-align: right;">Page 256</p> <p>1 DR. DURMOWICZ: This is Tony Durmowicz. 2 I'd like to make a couple comments on study design, 3 especially patient populations as it relates to cystic 4 fibrosis. And I think we heard this morning that the 5 prevalence of AVPANCF [ph] is very high. In adults, 6 it's eight percent. However, because it's a rare 7 disease, you know, it's very difficult to study a 8 meaningfully large study exclusive to people with CIA. 9 But I think it is important in our ABPA program to 10 include those patients. And as a result, I think 11 there could be a large study which strategies people 12 with CF included in it, at a number that would give at 13 least a somewhat meaningful indication of whether it 14 reacts differently than the general population, which 15 would mostly be asthma patients. You know, 16 alternatively, I suppose a post-marketing commitment 17 could be done to do a study in -- in people with CF if 18 that was felt to be needed. 19 One other thing. When we're developing 20 these kind of therapies, a lot of them are -- we're 21 talking about inhaled therapies today. And for CF,</p>
<p style="text-align: right;">Page 255</p> <p>1 looking at any breakthrough isolates that happen or 2 that occur from invasive disease and kind of see what 3 -- you know, what's happening over time. 4 DR. DENNING: Great. Thank you. 5 That's very helpful. And I wonder if there are any 6 other comments on this? Just one quick observation 7 we've seen in patients on oral itraconazole, we do 8 high volume -- to try and increase the yield of 9 strains that we commence that -- and we find a lot of 10 penicillium species coming up. And when we do MICs on 11 those, which we haven't properly reported because it's 12 quite difficult to report, they're often -- azole 13 resistant or -- azole resistant. And of course 14 penicillium antigenically similar to aspergillus and 15 may drive asthma. It's not quite ABPA, but it may 16 drive some of those immunological mechanisms. So it 17 may be more complex than simply fumigatus being 18 resistant a lot -- are there other comments that 19 people would like -- 20 DR. CLANCY: David? It's Neil Clancy. 21 DR. DENNING: Okay.</p>	<p style="text-align: right;">Page 257</p> <p>1 there's the burden of care. People with CF take a lot 2 of inhaled therapies. It usually a couple -- two to 3 four hours a day just on those therapies. And it's 4 not only the time to nebulization, but it's cleaning 5 and keeping, you know, clean if you will the -- the 6 nebulizers. And they use jet nebulizers, but more and 7 more they're -- they actually have to buy two 8 nebulizers. One a jet, one a vibrating mesh that 9 might be product specific. 10 So in that sense, dry powdered inhalers 11 become a -- a meaningful way to reduce the care 12 burden. And then finally, azoles seem to be, you 13 know, one of the focus -- post -- focus of our drug 14 development efforts as we've heard today. 15 People with CF now, the majority of 16 them in the US, and it will probably be likely in the 17 world are going to be going to CFTR modulator therapy. 18 A combination therapy. And -- and these drugs -- this 19 drug product -- these drugs in those combinations are 20 both effective by sip induction and sip inhibition. 21 And therefore, azoles would skew the levels. So in</p>

<p style="text-align: right;">Page 258</p> <p>1 that sense, in newer therapies that aren't -- aren't 2 azoles, you know, would be really helpful in that 3 population. So I just wanted to get that out there 4 from a CF perspective, what -- what the community 5 feels about the development of antifungal drugs. So 6 thank you.</p> <p>7 DR. DENNING: That's very helpful. And 8 one --</p> <p>9 DR. WALSH: This is Tom -- go ahead, 10 David, please.</p> <p>11 DR. DENNING: -- comment. Sorry about 12 that. If you go to -- CF actually, the teenage years 13 -- for ABPA. So actually, you might be extending the 14 age range down a little bit to be able to do that. At 15 least at some point.</p> <p>16 There's a handout from Neil Clancy as 17 well. Do you want to say something, Neil -- his 18 handout. Okay. Tom, you were going to say something?</p> <p>19 DR. WALSH: David?</p> <p>20 DR. DENNING: Yes?</p> <p>21 DR. WALSH: Hello? Yeah. David, just</p>	<p style="text-align: right;">Page 260</p> <p>1 okay?</p> <p>2 DR. DENNING: We can, yes.</p> <p>3 DR. GREENBERGER: I compliment everyone 4 on the presentations and -- and just being part of 5 this. So I have to first say about the total IGE 6 levels, the Northwestern University criteria have had 7 a upper boundary of normal of 417. So where as -- is 8 1,000. And the -- frankly, I mean 417 is about four 9 times the normal -- what the normal mean is of adults 10 and actually teenagers. But you miss -- the 11 sensitivity has improved to find the cases if you're 12 using 417. And there's a -- there's a discussion in 13 the literature on that one. But I would suggest an 14 open mind on having that 417.</p> <p>15 And the other is endpoints. Very, very 16 important. I think it was Dr. Clayton mentioned this 17 and I believe it. The radiologic endpoint to me is 18 one of the most important ones. The lack of 19 bronchiectasis or lack of new areas of bronchiectasis 20 is crucial. And that means not having new pulmonary 21 infiltrates with eosinophilia which leads, if not</p>
<p style="text-align: right;">Page 259</p> <p>1 raising -- raising the question in general and perhaps 2 to the audience, we've heard many different proposals 3 and concepts of endpoints of ABPA. And I'm wondering 4 if -- if the audience would like to contribute more. 5 In other words, if -- for the experts that we have in 6 our -- in the group, what would be a consensus, if at 7 all, on appropriate primary endpoint? Would it be a 8 composite or a single endpoint for ABPA?</p> <p>9 DR. DENNING: Very good question. 10 Dale's got his hand up. Did you want to talk about 11 that, Dale, or something else?</p> <p>12 DR. CHRISTENSEN: No. I was actually 13 wanting to ask a different question to get --</p> <p>14 DR. DENNING: Just hold it for a second 15 then. Let's --</p> <p>16 DR. WALSH: Please go ahead.</p> <p>17 DR. DENNING: -- Tom's point. So who 18 would like to -- we've got Paul Greenberger on the 19 line. He's been interested in this. Do you want to 20 respond to that, Paul?</p> <p>21 DR. GREENBERGER: Yes. Can you hear me</p>	<p style="text-align: right;">Page 261</p> <p>1 treated, to new areas of bronchiectasis. So a high 2 res CT scan's important to baseline and then whether 3 it's at three months for a study or perhaps longer. 4 And while -- while -- so I think on that endpoint, the 5 radiologic part is very, very important. And my own 6 view -- my own view --</p> <p>7 DR. DENNING: I'm sorry. Paul, do you 8 want to comment on the ideal primary endpoint or 9 whether you --</p> <p>10 DR. GREENBERGER: Yeah.</p> <p>11 DR. DENNING: -- composite? That would 12 be --</p> <p>13 DR. GREENBERGER: David, thank you. I 14 have one -- perhaps an ideal one would be the 15 radiographic findings on high res CTs focusing on 16 bronchiectasis and -- and presumably lack of any new 17 areas. That would be my ideal. And the second would 18 be using a composite like has been used in the 19 literature because I think that would be practical.</p> <p>20 DR. DENNING: Thank you. Would anyone 21 like to comment on endpoints before we run from that</p>

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<p>1 point? I know Dr. Stevens is on the call. He was 2 involved in that very pivotal study -- Dave, you want 3 to comment, David? I think he's on mute. Are you on 4 mute? There you are. Yes, David, can you comment? I 5 can't hear you. Yeah. Now we can hear you. Yeah. 6 DR. STEVENS: Okay. Can you hear me 7 now? 8 DR. DENNING: Yes. 9 DR. WALSH: Very clearly. 10 DR. STEVENS: Okay. Thank you. Yeah. 11 I -- I think it seems to be pretty well accepted that 12 oral itraconazole is useful in treatment of ABPA. And 13 based on our paper in the New England Journal of 14 MSG22. And I just wanted to point out, speaking about 15 composite endpoint, what our experience was. 16 We elected to go with a composite 17 endpoint that was defined before the study. And when 18 we presented our data, we presented each of the 19 components of the composite endpoint separately in 20 addition to the composite endpoint. And if you looked 21 at each of the components, that -- none of them alone</p>	<p>1 I'm -- I'm butting in. It's Neil. I've been out for 2 the past two or three minutes. 3 DR. DENNING: Okay. 4 DR. CLANCY: Sorry -- yeah. Yeah. 5 Sorry. 6 DR. DENNING: Go ahead. Yeah. 7 DR. ARMSTRONG: Oh, yeah. So -- yeah. 8 Just basically commenting on the basis of our 9 experience with the Pulmocide group. Frequency of 10 exacerbations -- usage, steroid usage, FEV1. Those 11 are simply grounds -- useful in monitoring response to 12 treatment with inhalants. And with a patient who has 13 presented today, one really interesting aspect was 14 that she had one of these iPhone help apps and she was 15 actually able to show that she had dramatically 16 increased exercise -- based on that. So we were not - 17 - monitoring, you know -- COVID, etcetera, might also 18 be helpful. I don't know. 19 DR. DENNING: Yeah. There's also now 20 an electronic cough monitor, which -- and actually 21 cough is a very important component for patients, even</p>
<p>Page 263</p> <p>1 would have made statistical significance. Or maybe 2 one out of five or something like that. So without 3 having used a composite endpoint, we would have come 4 up with -- emptyhanded in terms of whether 5 itraconazole is useful. And I think many of the 6 speakers addressed the problems of composite endpoint. 7 There's more of an emphasis now on patient-oriented 8 endpoints rather than biomarkers. But I just wanted 9 to point out -- go back to the data in that paper and 10 look at each of the individual components of the 11 composite endpoint and realize that had we dwelled on 12 only one of those, even if you want to argue that the 13 patient-oriented ones like the FEVs would have been 14 the best. It would have made -- it would not have 15 come to the same conclusion that it did. That's all I 16 wanted to say. 17 DR. DENNING: Thank you very much. 18 Darius Armstrong-James has put his hand up. Do you 19 want to say something, Darius? You're on silent at 20 the moment. 21 DR. CLANCY: Hey, guys. Real quick.</p>	<p>Page 265</p> <p>1 though it's a little bit hard to document without a 2 sort of formal cough monitor. So there might be 3 another approach to that as well. 4 DR. DENNING: Okay. Thank you very 5 much. 6 DR. ARMSTRONG: And just commenting on 7 resistance as well. I mean, if you've got a -- a high 8 sort of concentration azole going into the lung, as 9 well as your systemic azole, I mean, my -- my 10 impression from the -- the chronic patients is often 11 the systemic azole isn't going into the lung 12 appropriately. And that might be driving some of the 13 resistance of these. So presumably, if you -- 14 DR. CLANCY: Yeah. I'm very much, you 15 know, unhappy with Diana while fully acknowledging -- 16 DR. DENNING: Rick, you had your hand 17 up. 18 DR. MOSS: Yeah. Somebody else is 19 speaking I think that needs to mute. 20 DR. CLANCY: -- with Diana. What I've 21 always found with her is that --</p>

<p style="text-align: right;">Page 266</p> <p>1 DR. MARR: -- I think that's you. Can 2 you silence, please?</p> <p>3 DR. CLANCY: And, you know, if I felt 4 she overstepped herself with me or any of my people, 5 the best way --</p> <p>6 DR. MOSS: Yeah. There's too much 7 interference here.</p> <p>8 DR. MARR: Can the panel actually 9 silence?</p> <p>10 DR. CLANCY: With that, she always 11 responded and I often like --</p> <p>12 DR. MARR: Do you have the speaker? I 13 think it's Neil Clancy.</p> <p>14 DR. DENNING: Neil, can you turn your 15 microphone off? Yeah. There we go --</p> <p>16 DR. MOSS: Okay.</p> <p>17 DR. DENNING: Right. Rick, were you 18 going to say something? I think you --</p> <p>19 DR. MOSS: Yeah. Thanks. I agree with 20 the idea that a composite endpoint is probably going 21 to be the way to go in a pivotal ABPA trial, for the</p>	<p style="text-align: right;">Page 268</p> <p>1 should move onto invasive I think, in a minute. Dale, 2 do you want to pose your question?</p> <p>3 DR. CHRISTENSEN: Yes. And it does -- 4 it does start the transition to invasive. And that 5 is, you know, when considering going after invasive 6 disease, there is the -- the prophylaxis side and then 7 there is the therapeutic side. And as we heard just a 8 few minutes ago at Duke, as a standard, they prophylax 9 with liposomal amphotericin.</p> <p>10 And so my -- my question really gets 11 down to how would a center, you know -- because 12 liposomal amphotericin nebulized is not an approved 13 route of administration -- is not approved, so for 14 someone coming in with a -- with a dry powder 15 voriconazole, for example, how would that be, you know 16 -- what would the possibilities be? You know, would 17 those centers remove those patients from liposomal 18 amphotericin to enroll them in a study where they 19 would have to be compared to an approved route, ie: 20 oral Posaconazole versus the dry powder voriconazole, 21 instead of their current routine? You know, it --</p>
<p style="text-align: right;">Page 267</p> <p>1 reasons that David eluded to. And also, I think 2 since, you know, the early '90s when David was working 3 on that study, PROs have become much more important. 4 I think in the eyes of the agency, in terms of, you 5 know, clinically relevant endpoints, it's -- it's not 6 clear to me that just measuring FEV1 or even a 7 clearance of an infiltrate, radiographically, would 8 satisfy that criteria. The problem with a PRO is 9 there's nothing specific for ABPA. And the question 10 arises is is it adequate to use an asthma PRO in 11 which, you know, a number have been validated. And I 12 would -- I would hope the answer would be yes because 13 that would -- these are important. I just think in 14 terms of dealing with patients with this problem, what 15 they're most focused on is the toxicity of our 16 existing therapy which are -- the therapies are 17 effective, they're just not easily tolerated. And 18 that's, I think, a very important component that needs 19 to drive the discussion.</p> <p>20 DR. DENNING: Okay. Very good. So 21 should we move to Dale's new question? And then we</p>	<p style="text-align: right;">Page 269</p> <p>1 would that center just not consider taking part in a 2 trial or how would -- how would we be able to get that 3 trial enrolled it that is what many of these leading 4 centers do.</p> <p>5 DR. ALEXANDER: Hey. This is -- this 6 is Barb --</p> <p>7 DR. MARR: This is Kieren.</p> <p>8 DR. ALEXANDER: -- Alexander. Oh. Hi, 9 Kieren. So --</p> <p>10 DR. MARR: Oh, hey. I'm moderating 11 this and I was just going to turn it over to Barb. So 12 go ahead.</p> <p>13 DR. ALEXANDER: Sorry, Kieren. I think 14 that you have just hit your nail on the head with one 15 of the primary problems that we're going to face when 16 we try to find a study in inhaled product for 17 prophylaxis in the lung transplant population.</p> <p>18 You heard from Shahid this morning that 19 standard of care is to prophylax lung transplant 20 recipients because the risk of invasive fungal disease 21 is so high. And particularly high for invasive mold</p>

<p style="text-align: right;">Page 270</p> <p>1 infections. And in fact, we have international 2 guidelines now from the International Society for 3 Heart and Lung Transplant that recommend prophylaxis. 4 But the major transplant centers over the country, 5 while the majority of them prophylax, they use 6 different regimens. Different drugs, different 7 durations. And nothing is currently FDA cleared. 8 I think you're going to get the major 9 transplant centers happy to participate in a 10 prophylaxis study. We all want there to be an 11 approved prophylactic agent because currently, 12 patients are having to pay for these drugs out of 13 pocket. And they -- you know, they can't afford them. 14 There's a lot of issues around this. 15 So we -- we would really like to 16 participate. We want to participate. The problem is 17 going to be if you make us compare to placebo. 18 Because placebo is not standard of care. And so I 19 think we have to be creative in figuring out what the 20 comparison can be. 21 DR. WALSH: So I would just like to</p>	<p style="text-align: right;">Page 272</p> <p>1 skin cancers in lung transplant populations, or just 2 drug/drug interactions with the calcitor and 3 inhibitors, etcetera, that we're trying to use. Many 4 of the lung transplant patients have -- early on. 5 They're on amiodarone. There's just multiple, three- 6 way drug interactions that you can imagine. 7 So try and be -- to use an oral mold 8 active azole as the comparator. One, it's not 9 approved for prophylaxis and there's going to be a lot 10 of, you know -- there will be a lot of downsides to 11 that. So I guess, you know, could we use a historical 12 control group? Could we put something together? You 13 know, we could have a whole other conference just on 14 that topic, but I'll just stop there. And I'm very 15 interested to hear the agency's comments. 16 DR. DENNING: Sumati, do you want to 17 say anything about what -- what might be acceptable? 18 DR. NAMBIAR: Hi. This is Sumati. 19 David, I'm sorry. I didn't hear you clearly. Did you 20 ask me to respond or did you call on somebody else? 21 DR. DENNING: I think the fundamental</p>
<p style="text-align: right;">Page 271</p> <p>1 comment from -- from a historical standpoint, the 2 mycoses study group, both NIG, MSG and BAMSG, 3 wrestled with this question for virtually two decades. 4 And certainly came to the conclusion that a placebo 5 would not be appropriate given the standard of care. 6 But the challenge then becomes, and I would turn it to 7 Barbara -- Barbara, what do you think would be an 8 acceptable standard of care? And then going back to 9 the -- the agency, to -- or others, how would the 10 agency look upon a standard that was accepted by the 11 community, but would not have regulatory approval in 12 this population? 13 DR. ALEXANDER: You know, great 14 question. I've been struggling for a decade trying to 15 answer this. You know, we can try a systemic drug, 16 but you know, again, there -- there are a lot of 17 problems trying to compare an inhaled drug to a 18 systemic drug for prophylaxis. Particularly because 19 the mold active azoles either have, you know, 20 unacceptable side effects when we try to use them -- 21 use them long-term. For instance, voriconazole and</p>	<p style="text-align: right;">Page 273</p> <p>1 question is would a active comparator or a lung 2 transplant prophylaxis program, which is not approved 3 for prophylaxis, whether it's oral or inhaled, be an 4 acceptable comparative to the agency? Because there's 5 nothing that's approved at the moment. 6 DR. NAMBIAR: Right. Right. Yeah. I 7 think -- so it largely depends on the trial design. 8 If the trial design is one where the superiority of 9 the test drug is being demonstrated again, to whatever 10 is considered standard of care. I think that 11 certainly is much less problematic than if the trial 12 design is a noninferiority trial design where you're 13 comparing the test drug to an active comparator. In 14 that instance, you know -- ideally, we would like 15 products that are approved for the indication to be 16 used in noninferiority trial, but we do have 17 flexibility and we have exercise flexibility in many 18 instances. The products that may not have a labeled 19 indication, but are considered standard of care could 20 be used as comparative in a trial, but we would, you 21 know, like some information whether it's from -- it</p>

<p style="text-align: right;">Page 274</p> <p>1 could be from the literature, which supports that that 2 drug actually works in that particular indication. 3 Even for that particular condition, even if it doesn't 4 carry a labeled indication. 5 So I think a lot of details are needed 6 before I can comment to is it okay or not okay. 7 Primarily, the trial design, the patient population, 8 etcetera. 9 With regard to Dr. Alexander's question 10 about historic controls, I mean, I think that's, you 11 know, a topic which is really very complicated. And - 12 - and again, there are some particular or specific 13 situations where it might be -- sorry. It might be 14 acceptable to use historic controls. Again, it'll 15 depend on the patient population, the endpoint, the 16 disease that's being studied. 17 So unfortunately, I cannot give you a 18 straightforward answer, is it acceptable or not, but 19 if there is a good scientific rationale for why that 20 standard of care should be considered reasonable and 21 there's some evidence to support it, I think we're</p>	<p style="text-align: right;">Page 276</p> <p>1 don't have a requirement that you have to demonstrate 2 efficacy in the treatment indication before you do a 3 prophylaxis. I think that would be ideal. It -- it - 4 - it's -- date. That's a data package if you actually 5 have a treatment indication and -- document that was a 6 prophylaxis indication. But I think -- as you're 7 aware, I think there's -- that are approved, which 8 only carry the prophylaxis indication. 9 So there is some degree of mixability, 10 but I think it's fair to say that the best day the 11 package would be one where there is a treatment and a 12 prophylaxis indication. But again, depending on the - 13 - the specifics of the development program and the 14 molecule, I think we can make -- just for prophylaxis 15 if we have to. And I -- I think Radu has a slightly 16 different take on it, so I will let him provide MA 17 perspective. 18 DR. BOTGROS: Thank you. I -- I think 19 -- I think so much you guessed a little bit what I was 20 about to say. Indeed, you know, our guidance on 21 prophylaxis of invasive fungal disease mandates that</p>
<p style="text-align: right;">Page 275</p> <p>1 more than willing to consider that and make a 2 decision. So I hope I've answered your question. 3 DR. DENNING: Does Radu want to make a 4 comment on -- from Europe about that? 5 DR. BOTGROS: Yes. Thank you, David. 6 I think pretty much I echo what Sumati's saying 7 because indeed, if the -- if the design of the trial 8 is noninferiority, then it's very important to get the 9 comparator that will be used. You know, allows us to 10 conclude that the candida drug is better than placebo. 11 So I think this is why the choice of the comparator is 12 so important. So this, of course, in a superiority 13 setting, the approach could be -- well, a bit more 14 flexible I suppose. Thanks. 15 DR. MARR: This is Kieren. I've got a 16 related question for the regulators which -- which 17 also relates to question number three. And that is in 18 the context of an inhaled drug, would there be a 19 problem potentially in a prophylaxis indication 20 without a treatment indication? 21 DR. NAMBIAR: I think -- you know, we</p>	<p style="text-align: right;">Page 277</p> <p>1 studies in prophylaxis should only be conducted after 2 showing satisfactory clinical efficacy in the 3 treatment setting. So, you know, this is the -- the 4 starting point. And of course, you know, this is -- 5 this is what the guidance is saying. Of course, we 6 are -- we are willing to discuss, you know, with 7 sponsors, trying to understand, you know -- there -- 8 there is definitely something real flexibility, but I 9 wouldn't be able to tell you right now, you know, to 10 give a blank answer as to whether it would be 11 acceptable or not to -- of the fact that there's a -- 12 guidance mentions this. Thanks. 13 DR. MARR: Great. 14 DR. SHEPPARD: Can I make a quick 15 comment? 16 DR. MARR: Yes, please. 17 DR. SHEPPARD: Kieren, this is Don. 18 DR. MARR: Hey, Don. 19 DR. SHEPPARD: Since this is my -- my 20 one chance to make sure that both the FDA and the 21 Europeans hear this, just to point out that there's a</p>

<p style="text-align: right;">Page 278</p> <p>1 logical inconsistency in saying that a drug should 2 work the same in treatment in prophylaxis when you're 3 talking about the fungal diseases we're talking about. 4 By definition, prophylaxis is 5 preventing the initiation of infection, which is 6 caused by inhaled spores. And treatment is treating 7 hyphae in the lungs, which are fundamentally different 8 in their expression of genes, proteins, marthology, 9 polysaccharides and every other thing related to drug 10 targets. 11 So there's a very black and white 12 obvious reason why these are two different biological 13 states and that the treatments could be divergent for 14 prophylaxis and treatment of established disease. And 15 those who know me know I believe that. 16 DR. DENNING: Thank you, Don. 17 DR. MARR: Thank you, Don. This is 18 Kieren. I'll -- I'll add onto that in that 19 establishing a treatment indication for an exclusively 20 inhaled drug in a monotherapy paradigm, at least in 21 the hematology population, BMT population, and any</p>	<p style="text-align: right;">Page 280</p> <p>1 DR. PERFECT: Kieren, can you hear me? 2 DR. MARR: I certainly can, sir. 3 DR. PERFECT: I want to -- Don -- Don 4 made a very important statement here that we should 5 separate out prophylaxis in treatment. These are two 6 different issues and surely the FDA has done this in 7 the past and approved drugs for just prophylaxis. But 8 we should separate those out very, very carefully and 9 shouldn't be put under any restriction that you have 10 to do treatment before you do prophylaxis. It's a 11 different beast. 12 As far as other things and prophylaxis, 13 I just want to bring out something that's a little 14 different to talk about. Everybody's talking about 15 molds and stuff like that, but when I come to 16 prophylaxis, my issues is actually pneumocystis 17 prophylaxis. Actually, pneumocystis is a fungus, so 18 we're appropriately talking about it here. And maybe 19 a long-acting -- will work, but I would surely like to 20 have some enthusiasm or ideas about prophylaxis for 21 pneumocystis with particularly the -- particularly the</p>
<p style="text-align: right;">Page 279</p> <p>1 other population that is really severely ill enough to 2 see a -- a dramatic treatment effect is going to be 3 very, very difficult. 4 So it's precisely in that situation 5 where we can't really rule out systemic or invasive 6 disease. They have prolonged and deep 7 immunosuppression. There may be some unmet needs, but 8 we do have other systemic alternatives. So I think 9 that this is going to be a -- a topic that requires 10 more conversation as well and has a lot of different 11 issues that come up. 12 I'd like to get some of the panel's 13 feedback some more on what -- what do you envision for 14 treatments of invasive fungal infections for inhaled 15 formulations? And I see that Neil Clancy has his hand 16 up. I don't know if he's actually had his hand up for 17 a while or if he's wanting to chime in here? And if I 18 don't hear him, I'm going to ask Dr. John Perfect if 19 he's on the line to maybe comment on what would be an 20 appropriate population to establish a treatment 21 indication of -- for an inhaled drug?</p>	<p style="text-align: right;">Page 281</p> <p>1 cyst form, the trophozoite form. I'd like to see the 2 animal models be a little bit robust on this thing 3 because I will tell you on the on the wards, it is not 4 easy to use -- and they're really reaching out for 5 this thing and many of these type of patients for 6 prophylaxis. 7 And so I'm just putting another issue 8 out there for prophylaxis and the types of things that 9 we -- we need to think about. Not just the azole 10 compound. Not just the -- thank you. 11 DR. DENNING: Thanks, John. 12 DR. MARR: Thank you. 13 DR. DENNING: -- have a comment, 14 Kieren? 15 DR. MARR: Please. 16 DR. DENNING: The other -- just 17 extending the discussion slightly. The -- does the -- 18 one of the problems in lung transplant is obstructive 19 bronchiolitis, which comes later. And that's 20 associated with aspergillus colonization or the 21 infection.</p>

<p style="text-align: right;">Page 282</p> <p>1 So I -- but of course, inhaling a new 2 drug could lead to -- so I'm wondering what the -- 3 whether the panel -- any of the members of the panel 4 that regularly just have a view about longer term 5 survival of graft and the function of that graft as a 6 -- another longer-term endpoint and whether that's a 7 surveillance issue if the drug was approved for this 8 education. Maybe Shahid should comment on that first? 9 DR. HUSAIN: Sorry. Yes. Hi, there. 10 Thank you. Yes. I think the graft survival is -- is 11 an important -- and that should definitely be one of 12 the endpoints that need to be studied especially among 13 transplant recipients. Because at least from the data 14 -- there's no long-term data that I'm aware of. But, 15 like, especially short-term, there's clearly somewhat 16 an option in the pulmonary function test maybe 17 temporarily or they may have long-term consequences. 18 So I guess I answered your question or -- 19 DR. DENNING: Yes. I think so. 20 DR. HUSAIN: Hello? David, did I 21 answer your question?</p>	<p style="text-align: right;">Page 284</p> <p>1 chronic pulmonary aspergillosis if one has chronic 2 aspergillosis in patients with allergic -- with cystic 3 fibrosis. Many of these patients have airway disease 4 that would be with or without pulmonary infiltrates. 5 It would be quite amenable pathophysiologically as 6 well as in terms of equal poise and being ale to 7 provide an aerosol agent versus in a randomized trial 8 of systemic agent. We're clearly going after airway 9 disease where there's a legitimate opportunity for 10 hyphae organism. The very high and sustained 11 concentrations would really be the best target. 12 DR. MARR: Thanks, Tom. That was 13 exactly the -- the points that I was trying to bring 14 out and you just described them so cogently about 15 discerning really about where the infection is and the 16 degree of severity of disease in the host. 17 With that in mind, I just want to push 18 a little bit further. Is it possible? What do you 19 think about the feasibility of doing a treatment study 20 for purely airway disease in a non-organ transplant 21 host or non-lung transplant setting?</p>
<p style="text-align: right;">Page 283</p> <p>1 DR. DENNING: Yes. Yes, you did. 2 Thank you. That was fine. Very good. Thank you. I 3 just -- I'm not sure if there's a -- but maybe not. 4 Probably not. 5 DR. WALSH: David, this is -- this is 6 Tom. In addressing your question, I think one has to 7 really separate a part, the host very critically. In 8 profoundly persistent immunocompromised patients, for 9 example, profound persistent neutropenia, the biology 10 of the disease pathophysiologically is -- is very 11 different. You have typically deep infarctions, it 12 had -- necrosis, coagulative necrosis, that an angio - 13 - for which an aerosolized agent is hardly going to be 14 able to reach deeply into that process. And to open a 15 clinical trial for that kind of a step is -- with an 16 extremely high risk. Hematogenous delivery obviously 17 is -- would be the most logical. But if you were then 18 to take a step back away from that particular host 19 population and look toward more airway disease, 20 whether it's in tracheal bronchial disease in which 21 might be immunocompromised, whether one evaluates</p>	<p style="text-align: right;">Page 285</p> <p>1 DR. WALSH: I think one has to be very 2 careful. One has to first of all ascertain the 3 stability of the host with minimal -- with minimal 4 immune suppression, but clearly there are many patient 5 populations relatively stable. CPA is one. Chronic 6 macro triazine. Chronic cavity where aerosol -- 7 potentially inhaled drug delivery could make a major 8 benefit. The challenge is always -- and David Denning 9 who's done intensive work in this area of trying to 10 define endpoints in that population, but it certainly 11 -- even repeat bronchoscopy may be appropriate. And 12 then obviously patient-reported endpoints. 13 Which then brings us at 4:05 to our 14 question number four with your kind permission. 15 DR. MARR: Absolutely. I think -- 16 unless someone has a burning question on endpoints and 17 populations now, this has been a robust -- good, good. 18 Go ahead. 19 DR. WALSH: All right. Excellent. 20 Well, our question number four raises a drug question 21 for ABPA and invasive fungal infection, we're asked to</p>

<p style="text-align: right;">Page 286</p> <p>1 discuss how we can advance facilitate the efforts to 2 develop patient-reported outcomes measures. 3 And so I would open that up. Obviously 4 there's been wonderful work especially done in the 5 area of ABPA. And we can start with ABPA and Dr. 6 Moss, Dr. Stevens, Dr. Denning or anyone who would 7 like to offer perspectives on what would be -- what 8 would be appropriate endpoints and -- or delegated 9 systems that we could choose for patient-reported 10 outcome measures. 11 DR. DENNING: Well, they -- they just - 12 - ACQ, the asthma control questionnaire, usually 13 without the FEV1 because that contaminates it. It's 14 been used in the -- study. I don't think it's a 15 primary endpoint, but it's a very useful and simple 16 thing. AQLQ has been used much more extensively and, 17 again, has not been used as a primary endpoint, but is 18 a broader set of questions of how patients feel on 19 therapy. And it's been used in some asthma studies. 20 I -- I personally would be quite keen to see some 21 clinical endpoints which aren't just respiratory</p>	<p style="text-align: right;">Page 288</p> <p>1 RECORDING: Your microphone has been 2 turned on. 3 DR. WALSH: I'm sorry, David. Either 4 my phone is deficient or I can't hear you. Hello? 5 DR. DENNING: Yes. Yes, Thomas. The 6 answer is yes, I think it would be helpful if -- 7 endpoint. Along with some microbiological or 8 immunological measures of response. And -- 9 DR. WALSH: David Stevens, could you 10 comment? David, you might be on mute. Let me check 11 the screen. Or Dr. Moss, are you there? 12 DR. DENNING: Rick Moss, he's on quiet, 13 too. He's on -- 14 DR. WALSH: Yeah. Please go. Did 15 somebody -- 16 DR. MOSS: I was going to respond from 17 the standpoint of the -- using a questionnaire, which 18 is available at multiple sites, and getting -- getting 19 meaningful information. It's a very good way to go. 20 In the study that we did, we tried to build into it 21 exercise factors and as has been stated by several of</p>
<p style="text-align: right;">Page 287</p> <p>1 function endpoints as the key measure of improvement. 2 Because that was our experience in the SAS study and 3 in our ABPA patients. The patients say they feel just 4 much better. They're stronger. They're less tired. 5 They can walk farther. They have more energy. It 6 isn't about, you know, whether they need more or less 7 inhaler -- 8 DR. SHEPPARD: -- so that is something 9 at least we're testing if there are CF patients in a 10 trial. 11 DR. DENNING: Okay. Yeah. 12 DR. WALSH: Okay. That's an excellent 13 point. To David -- to David's point, ABPA. David, do 14 you think the ACQ -- or AQLQ would be suitable as part 15 of a composite endpoint? Would you think it could 16 stand alone as a primary endpoint? 17 DR. DENNING: I think it would be a 18 very good path of a -- of a composite endpoint as 19 well. I think you do need some sort of biological 20 measure of -- of antifungal or immunological response. 21 But yes, I think it would be a good one.</p>	<p style="text-align: right;">Page 289</p> <p>1 the industry people, if a trial is going to come off 2 an ABPA, it's going to likely be a multi-center trial. 3 It was very difficult to get that standardized. Just 4 very difficult to get people to follow the same -- for 5 example, even a six-minute walk test or what -- 6 whatever type of physical exertion evaluation you 7 might choose. Very difficult to get that standardized 8 between sites. And so the use of a questionnaire 9 really has a lot of advantages. 10 DR. WALSH: Okay. Okay. Very good. 11 Very good. We do, in the limited time that we have, 12 have a question that hasn't been addressed thus far in 13 our discussion points, but was raised in a couple of 14 presentations. And that is the matter of safety. And 15 specifically, we have a question from Paul Manly [ph]. 16 Could the FDA comment on the merits of PROs in this 17 space? Specifically, what would they feel would be 18 appropriate? And I would add into that, how should we 19 incorporate safety as well into patient -- patient- 20 reported outcomes? Chris St. Clair, would you be able 21 to address those questions?</p>


<p style="text-align: right;">Page 290</p> <p>1 DR. ST. CLAIR: I think the safety 2 aspect, I'll defer to those. But in terms of maybe 3 more the -- the merits of PROs in general and what 4 types of things measure in PROs. You know, we've been 5 talking about respiratory symptoms. You know, 6 obviously that makes sense. I also think fatigue and 7 functioning, you know, sort of when we think of 8 quality of life, I'm -- I'm thinking along the lines 9 of, okay. How is the disease impacting the patient's 10 ability to engage in activities of daily living? So I 11 think questionnaires that are assessing the daily 12 functional capacity. You know, can they walk around 13 the back? Can they carry bags of groceries? Whatever 14 might be relevant to the exact patient population. I 15 think those types of assessments can be really 16 informative as well.</p> <p>17 DR. WALSH: So in that context, we -- 18 we heard that in our discussion that tolerability to 19 the existing agent, particularly systemic azoles, 20 which seems well-tolerated -- probably much less so. 21 And then the -- the terrible effects of long-term</p>	<p style="text-align: right;">Page 292</p> <p>1 Tony Durmowicz said about CF and the CFQR respiratory 2 domain. For those patients has been really very 3 valuable tool in terms of effective therapies. So if 4 those patients -- that's never been applied or 5 specifically validated for CF. So I -- I don't know 6 if -- you know, what its applicability might be. But 7 something along that line would be helpful.</p> <p>8 This -- some of the features are 9 similar to some of the asthma questionnaires, but some 10 are different also.</p> <p>11 DR. WALSH: Very good. Very good. Are 12 there any other tools that you would -- of patient- 13 reported outcomes that you think might be helpful? 14 We've heard of CFQR, we heard HEQ, HULQ. Are there 15 other validated instruments that we could adapt 16 particularly for ABPA?</p> <p>17 DR. DENNING: Just a general point, 18 Tom, that if you want to compare ABPA with other 19 diseases like multiple sclerosis or rheumatoid 20 arthritis, then you need a non-respiratory 21 questionnaire -- is pretty poor in this area. And</p>
<p style="text-align: right;">Page 291</p> <p>1 corticosteroid therapy. Do relate that to safety in 2 patient-reported outcomes.</p> <p>3 Chris, do you think that the patient- 4 reported outcomes could also weave-in elements of 5 safety and tolerability?</p> <p>6 DR. DENNING: I think they do.</p> <p>7 DR. ST. CLAIR: It's hard to -- advice, 8 but yeah. I'd like to hear from others as well.</p> <p>9 DR. WALSH: I'm sorry. It's hard to 10 hear. Forgive me. Chris?</p> <p>11 DR. DENNING: Yes. Tom, I think Paul - 12 - Rick Moss -- want to say something.</p> <p>13 DR. MOSS: Well, I do think it's very 14 important to include tolerability of which I think 15 there are some general validated instruments as part 16 of a PRO. Because again, I just come back to this 17 point, that I think from the patient's side, the 18 motivation to try new therapy like this would be 19 driven largely by tolerability issues with the 20 existing therapies, in terms of the allergic 21 aspergillosis group. And I also want to second what</p>	<p style="text-align: right;">Page 293</p> <p>1 that's helpful for reimbursement in terms of 2 negotiating the investment with agencies across the 3 world if they know what they values are compared to 4 other diseases. I don't think it would help very much 5 -- those would help as much with the -- with the prime 6 endpoint in a phase three person.</p> <p>7 DR. WALSH: Very good. And while we've 8 talked about ABPA, do we think to what degree might we 9 have patient-reported outcome measures in IFI? Such 10 as -- prevention? Actually, if I may, if I could be - 11 - defer that, because I think in the long run, 12 Barbara, you have probably the greatest experience at 13 Duke University. Do you have a sense of quality of 14 life on aerosolized ABLC or a sense of tolerability 15 given your best experience?</p> <p>16 DR. ALEXANDER: I think -- so quality 17 of life as it relates to receipt of inhaled ABLC. The 18 patients tend to tolerate the treatments well. You 19 heard from a patient advocate though that once you 20 leave the transplant center and it's not prepared and 21 given to you and made up for you, you know, the</p>

<p style="text-align: right;">Page 294</p> <p>1 logistics surrounding administration of inhaled 2 amphotericin products, you know, it's kind of a 3 downer. The good side is you only have to do it once 4 a week.</p> <p>5 In terms of tolerating the treatments 6 though, they do seem to tolerate the treatments very 7 well. The lipid formulations are not associated with 8 the bad taste and -- and as much bronchospasm and 9 cough as the -- as the amphotericin B deoxycholate.</p> <p>10 In terms of long-term quality of life, you know, I 11 think for the first year after lung transplant, there 12 are those people who do well and they go out and have 13 great quality of life. There are the others that get 14 into a vicious cycle of infection and rejection and 15 they are frequent -- frequently admitted to the 16 hospital and -- and a care system. But I don't know 17 that that's linked to the inhaled ABLC or inhaled 18 prophylaxis. That's more to do with just the nuts and 19 bolts of having had a lung transplant.</p> <p>20 I think one of the things that's going 21 to be really important in the lung transplant</p>	<p style="text-align: right;">Page 296</p> <p>1 in the next 10 minutes. I'm going to try to just 2 touch up on the highlights, you know, of -- from the 3 presentations we heard today -- excellent talks. And 4 my apologies up front. I -- if I miss some important 5 points, it's just hard to capture everything in these 6 few minutes, but the transcripts of the workshop will 7 be available and the slides will be available as well.</p> <p>8 So you will have all the -- online in a few days.</p> <p>9 So this morning, Dr. Moss got us 10 started with an excellent overview of inhaled 11 antifungal drug and their role in our therapeutic -- 12 he discuss the limitations and gaps in the data and 13 outlined some clinical conditions where they may play 14 a role. In immunocompromised patients for prophylaxis 15 or as adjunctive treatments -- I'm hearing a lot of 16 feedback. I think someone needs to mute their phone. 17 Adjunctive treatment for -- fungal lung infections. 18 And in patients with -- with the -- disease, I think 19 both with treatment of ABPA and treatment of severe 20 asthma with fungal sensitization.</p> <p>21 We then had a series of FDA I think</p>
<p style="text-align: right;">Page 295</p> <p>1 population specifically that's a little unique 2 compared to other populations where you try to study 3 any inhaled product is making sure that we're not 4 seeing increased risk of rejection. So --</p> <p>5 DR. WALSH: Very good. That's 6 tremendously helpful. Well, we're at 4:20 now and in 7 the spirit of staying right on time, first of all, we 8 want to -- on behalf of David and Kieren and myself 9 thank the panelists for their insightful discussions 10 as well as our FDA colleagues for their insights as 11 well on the regulatory aspects of this important class 12 of new agents. But at 4:20 now, I would like to turn 13 the microphone over to Sumati -- for a summary and 14 concluding -- summary and concluding remarks. Sumati?</p> <p>15 DR. MARR: Dr. Walsh, Sumati Nambiar is 16 the summary and closing remarks. So I hand it over to 17 her. Thank you.</p> <p>18 DR. NAMBIAR: Yeah. No problem. Thank 19 you, Dr. Walsh. So I really have the daunting task of 20 trying to summarize these proceedings, which lasted 21 about, you know, 10 hours of so and I have to do that</p>	<p style="text-align: right;">Page 297</p> <p>1 touching upon important aspects as they relate to drug 2 development. Dr. McMaster outlined the expected 3 pharmacology/toxicology package for an inhaled 4 antifungal drug, including the types of inhalation and 5 toxicology studies that are done to help define safe 6 clinical doses and -- safety monitoring in the clinic.</p> <p>7 The two key references that everyone should keep in 8 mind, the ICHN3 and the FDA's nonclinical safety 9 evaluation of -- products. I think Dr. McMaster also 10 noted that it's very important to understand the 11 limitations of these animal models as they relate to 12 the test article administration. Because there are 13 differences in device design and anatomical 14 differences between the nonclinical -- between animals 15 and humans. Limitations are -- kinetic evaluations 16 because they're not measured but estimated. And 17 understanding the test species of the healthier, 18 infected animals. I've been taking all this into 19 consideration and now it's a more realistic 20 characterization of the -- to humans.</p> <p>21 The next presentation was by Dr.</p>

<p style="text-align: right;">Page 298</p> <p>1 Timothy Bensman from Clinical Pharmacology. And Dr. 2 Bensman highlighted the impacted -- between drug 3 device and patient characteristics on the site of 4 absorption -- sorry. Deposition absorption and 5 clearance of the inhaled drug. I think Dr. Bensman 6 clearly emphasized the importance of phase two studies 7 in determining the appropriate doses in phase three 8 studies given some of the limitations with the 9 nonclinical studies, animal models and fungal lung 10 disease. Which can help in estimating the clinical 11 starting dose or dosing regimen, but certainly there 12 are limitations. I think the lung PKPD targets are 13 not commonly assessed and there are gaps -- and there 14 are gaps in our understanding of these targets and how 15 they translate to clinical efficacy. 16 Next, we heard from a colleague in 17 CDRH, Dr. Blakely, who discussed the key aspects from 18 a device standpoint. And he went through the device 19 review considerations for inhalational products. I 20 did want to note that we in the division work very 21 closely with colleagues in the CDRH on such programs</p>	<p style="text-align: right;">Page 300</p> <p>1 as all of these can impact safe use of the product. 2 Just as we interact with CDRH 3 colleagues very early in the drug development process, 4 we do interact with colleagues in DMEPA very early as 5 well, including at the pre I&D stage. 6 The last FDA presentation was from Dr. 7 St. Clair who discussed -- clinical outcome 8 assessments that can be used in clinical trials. And 9 the considerations in selecting or developing COAs, or 10 clinical outcome assessments. Dr. St. Clair noted 11 that we at the FDA evaluate the CEO instrument and the 12 context of its intended use, including study 13 objectives to patient population and the desired 14 labeling claims. As much as possible, I think the 15 advice from our COA colleagues is the measurement 16 properties be evaluated prior to embarking on phase 17 three studies to ensure that the COA's performing as 18 expected. Dr. St. Clair emphasized the importance of 19 other measurement properties and content validity, and 20 much like the other speakers, emphasized the 21 importance of early communications with the agency and</p>
<p style="text-align: right;">Page 299</p> <p>1 regarding device issues, and we engage in these 2 discussions -- product development. Dr. Blakely noted 3 that inhalation drug therapy, just as Dr. Bensman 4 mentioned, is really dependent on the -- between the 5 drug device and patient. He discussed how medical 6 devices are classified from -- standpoint. Noted that 7 most inhalation devices are considered class two. And 8 -- and he also emphasized the importance of early 9 communication with CDRH through the tree submission 10 process. 11 Next, we heard from Dr. Irene Chan from 12 the Division of Medication Error Prevention and 13 Analysis, DMEPA. And -- okay. So Dr. Chan covered 14 important aspects from a safe use and medication error 15 perspective, including the importance of optimizing 16 the user interface design. And she noted that 17 following a human -- engineering process is very 18 important. And there's need to -- for continued 19 refinement to minimize risk of -- product. There's 20 need to consider underlying comorbidities in patients 21 with elevated device platform and formulation changes</p>	<p style="text-align: right;">Page 301</p> <p>1 throughout the development process. And referred us 2 all to the FDA PRO guidance for important information. 3 We next heard from Mr. Birrell, and -- 4 thanks to Mr. Birrell for sharing his valuable 5 perspective as a patient with ABPA since he was 6 diagnosed about six years ago. His experience really 7 highlights the unmet need for safe and effective 8 therapies to address the needs of such patients. The 9 challenges with the chronic nature of the disease 10 issues regarding long-term oral therapies, including 11 side effects and issues with drug interactions, were 12 all highlighted in his presentation. Mr. Birrell's 13 experience also highlighted the practical difficulties 14 patients face with long-term nebulized therapy and its 15 impact on daily life. He also pointed out the 16 importance of treatment that encourage compliance, 17 particularly important for the management of chronic 18 disease. And also noted the value of having patient 19 groups to share -- to share one's experiences. Again, 20 our sincere thanks to Mr. Birrell for sharing his -- 21 his experience. We greatly appreciate it.</p>

<p style="text-align: right;">Page 302</p> <p>1 At the public comment session, Dr. 2 Edwin Rock from Partner Therapeutics discussed the 3 potential growth for evaluation of such grant -- in 4 the management of fungal infections. We then moved 5 onto session two where we discussed clinical trial 6 considerations for a new antifungal drug. 7 We started with a regulative 8 perspective where Dr. Smith provided perspectives from 9 the FDA and Dr. Radu Botgros presented the EMA 10 perspective. I think we did note that the Division of 11 Anti-Infectives works in close collaboration with 12 experts in Division of Pulmonary Allergy and Critical 13 Care in the design of these studies. 14 Dr. Smith emphasized that there were 15 important lessons learned from inhaled bacterial 16 therapies for conditions like non-CF bronchiectasis -- 17 lung disease which might have a bearing on development 18 of products for conditions like ABPA like we were 19 discussing today. I think he emphasized the 20 importance of selecting a clinically meaningful 21 endpoint and not one based solely on a biomarker. The</p>	<p style="text-align: right;">Page 304</p> <p>1 are available over the years with treatment of ABPA, 2 and we heard about the practical difficulties in 3 conducting a clinical trial in patients with SASS. 4 Dr. Denning provided some options for primary 5 endpoints, such as measures of lung function, patient- 6 reported outcomes either using respiratory domain or a 7 general domain. Noted the limitations of 8 exacerbations as an endpoint, given that the 9 infrequent -- would require longer term studies. 10 Emphasized the importance of reducing corticosteroid 11 usage from a patient's standpoint. And discussed some 12 supportive endpoints like radiology and sputum 13 markers, and also touched -- composite endpoints. For 14 -- fungal infections, Dr. Marr and Dr. Husain 15 discussed the role of inhaled antifungal therapies in 16 invasive fungal infections, but Dr. Marzook [ph] is 17 more hematologic medicines and Dr. Husain's 18 presentation on lung transplantation. 19 There's -- I think Dr. Marr has 20 identified that even though azole prophylaxis is 21 common -- is -- is main space of these patients during</p>
<p style="text-align: right;">Page 303</p> <p>1 need for adequate development work including phase two 2 trials, which would be very helpful in determining key 3 design elements of future trials. And heterogeneity 4 of patient population, which has come up during 5 multiple sessions this afternoon. 6 I think Dr. Botgros I think clearly, 7 you know, stated that in general, there's alignment 8 with FDA recommendations. Much like us, they have had 9 limited exposure so far with inhaled antifungal drug 10 development and there are no approved therapies in 11 Europe either for conditions like ABPA. The current 12 guidance in antifungal drug development does not cover 13 inhaled therapies, but some of the principles are 14 relevant to developing inhaled therapies as well. 15 We then moved onto a session on -- 16 first on ABPA specifically and next one on invasive 17 fungal infections. Dr. Bazaz and Dr. Denning covered 18 the topic of ABPA and broadly the allergic fungal 19 airway disease phenotypes. Underlying 20 immunopathogenesis, evolving diagnostic criteria, 21 etcetera. And discussed some clinical trial data that</p>	<p style="text-align: right;">Page 305</p> <p>1 their high-risk period, there is an unmet need because 2 of the growing list of drug interactions with azoles. 3 And that there might be potential roles of inhaled 4 antifungal drugs as adjunctive therapy for treatment 5 and also for patients with influenza or COVID- 6 associated fungal infections. 7 Dr. Husain sort of outlined some 8 potential clinical scenarios where these trials can be 9 done. Either the product could be used for universal 10 prophylaxis or -- or for preemptive therapy, or for 11 treatment of invasive fungal infections. And 12 suggested some potential endpoints that note that for 13 the treatment of invasive fungal infections, it's 14 probably nebulized drugs may not be able to use. I 15 mean, probably -- as well as therapy would need to be 16 in conjunction with other drugs. 17 We had a four industry speakers at the 18 next speaker -- at the next session. There were two 19 presentations each on products being developed for IFI 20 or allergic bronchopulmonary aspergillosis. I think 21 consistently across all the presentations, we heard</p>

<p style="text-align: right;">Page 306</p> <p>1 that there is a need for therapy for these conditions. 2 These products offer higher local concentrations and 3 no systemic toxicity and -- from a patient standpoint. 4 We heard about product -- that are designed for 5 inhaled therapy and features proposed devices to be 6 used. And some of which might reduce the patient 7 burden that we've heard about. I think we heard loud 8 and clear that these clinical trials are very 9 difficult to conduct. Defining patient population is 10 difficult. There's a lot of heterogeneity in the 11 patient population, and the heterogeneity can also 12 impact on the size of the treatment effect. Very 13 important consideration with the site selection. And 14 in defining the patient population, we have to strike 15 a balance between addressing heterogeneity and making 16 the trials -- as well. There's a lot of discussion 17 around lack of standardized endpoints or agreed to 18 endpoints because this is a new feed. And also 19 regarding the timing of the assessment. It's 20 certainly encouraging to see that some phase two 21 trials at least have been conducted or were attempted</p>	<p style="text-align: right;">Page 308</p> <p>1 approved or -- for inhaled therapies. So I think a 2 lot more scientific questions that need to be answered 3 in that context. 4 Question two is a discussion around 5 appropriate endpoints -- assessment, etcetera, for 6 ABPA trials. I think we -- we heard from the Cystic 7 Fibrosis Foundation about the importance of including 8 CF patients in these trials. I think important to 9 consider the burden of care because these patients are 10 on multiple other therapies, and so a product, which 11 is a dry powder inhaler, can certainly offer an 12 advantage in terms of burden. And I think an 13 important point was also brought up about potential 14 drug interaction with azoles because of the CFDR 15 modulating drugs that are used. The discussion around 16 potential endpoints, I don't think we came up with a 17 consensus endpoint, but there was suggestion that 18 radiologic resolution or improvement is important. CT 19 guided assessment of radiologic lesions, the 20 discussions around composite endpoints that have been 21 used in the prior -- study. And certainly some</p>
<p style="text-align: right;">Page 307</p> <p>1 to gain further insight into key aspects of trial 2 design. I think they did highlight some of the 3 practical challenges in doing these studies, and it's 4 very unfortunate to see that some of these studies 5 have been negatively impacted by the COVID pandemic. 6 I think there's also a -- need for 7 continued collaboration and interaction with 8 regulators. The possibility of using streamlined 9 development programs and approval under the -- sorry. 10 I know I've gone through a lot of 11 information in a short period of time. I'll quickly 12 summarize what I heard in the panel discussion. We 13 had four question. The first question really related 14 to gaps in animal model or in vitro models, but can be 15 used to support potential streamlined development 16 programs. I think there's a recognition that more 17 work needs to be done, particularly for ABPA chronic 18 aspergillosis model. For invasive aspergillosis, we 19 have reasonable models. And there's certainly a lot 20 of discussion about what development of resistance 21 means and how it can be monitored, should a product be</p>	<p style="text-align: right;">Page 309</p> <p>1 discussions around patient-reported outcomes. 2 For the third question about developing 3 inhaled therapies in invasive fungal infections and 4 prophylaxis, I think there's a clear message for us to 5 regulate those and separate them out. Treatment of 6 invasive fungal infections from prophylaxis, and 7 whether the, you know, the two need to be tied 8 together. I think there was also discussion around -- 9 for treatment particularly, the feasibility is an 10 issue and there might be a stable patient population, 11 like those with chronic -- disease or chronic 12 pulmonary aspergillosis where actually a treatment can 13 be assessed because in other patients with 14 immunocompromised patients with invasive fungal 15 infections, it might be a lot more challenging. 16 Certainly -- for antifungal drugs have a role in 17 prophylaxis in invasive fungal infections. 18 There's also discussion around, you 19 know, quality of life assessments in patients post- 20 transplant and the side effects of these inhaled 21 therapies and how that might impact on their life.</p>

<p style="text-align: right;">Page 310</p> <p>1 The last question related to patient-</p> <p>2 reported outcome measures, both for ABP and IFI.</p> <p>3 There were discussions around using some existing</p> <p>4 tools that certainly concerns raised that they may not</p> <p>5 be appropriate for primary endpoints. Some discussion</p> <p>6 around potentially using the CFQR for the CF</p> <p>7 population, and it has been used as an endpoint for</p> <p>8 regulatory approval in CF patients, not for fungal</p> <p>9 infections.</p> <p>10 I'm sure I didn't capture all the</p> <p>11 discussion points, but this is sort of -- that's a</p> <p>12 very high level summary of the panel discussion. So -</p> <p>13 - so really just some key points and next steps of</p> <p>14 where we go from here. I think we at the agency,</p> <p>15 along with all of you, share a common goal to have</p> <p>16 safe and effective treatment options for our patients</p> <p>17 with fungal infections, whether they fall in the</p> <p>18 spectrum of allergic pulmonary disease of invasive</p> <p>19 fungal infections. We also recognize that there are</p> <p>20 significant uncertainties at this time with regard to</p> <p>21 trial design endpoint, duration of therapy.</p>	<p style="text-align: right;">Page 312</p> <p>1 this workshop. And many thanks to our technical</p> <p>2 support team for ensuring the smooth conduct of this</p> <p>3 workshop. So with that, John -- I know I've gone</p> <p>4 through it really, really quickly. Maybe I can turn</p> <p>5 it over to you for a final -- okay. I'm just seeing a</p> <p>6 note from John. So he had to sign out. So I think on</p> <p>7 behalf of the Division of Anti-Infectives in the</p> <p>8 Office of Infectious Diseases, our sincere thanks and</p> <p>9 appreciation to each one of you for participating as a</p> <p>10 panelist or a speaker or just joining and -- and</p> <p>11 listening to the deliberations. Thank you very much</p> <p>12 and wish you all a good evening, good night, and many</p> <p>13 thanks to those on the other side of the Atlantic for</p> <p>14 staying this late. Apologies for the -- for the</p> <p>15 delayed conclusion of this meeting. Thank you.</p> <p>16 Okay. Shall we call it a day?</p> <p>17 DR. WALSH: Thank you.</p> <p>18 DR. NAMBIAR: Thank you so much.</p> <p>19 DR. MOSS: Thank you very much.</p> <p>20 (Whereupon, the meeting concluded at</p> <p>21 4:41 p.m.)</p>
<p style="text-align: right;">Page 311</p> <p>1 Moving forward, we hope that data that</p> <p>2 have been generated in ongoing programs with</p> <p>3 systematic data collection will play an important role</p> <p>4 in making advances in the field. There will be</p> <p>5 lessons learned along the way that will certainly help</p> <p>6 us refine our approaches. Cannot emphasize enough</p> <p>7 that it's important to define outcomes that are</p> <p>8 clinically relevant and meaningful to patients, and</p> <p>9 incorporating the voice of the patient will be very</p> <p>10 important as endpoints -- refined. As with all</p> <p>11 development programs, ensuring safety of patients is</p> <p>12 paramount in designing safety -- inhaled product with</p> <p>13 a patient population with chronic underlying lung</p> <p>14 condition can certainly be challenging.</p> <p>15 As the agency remains committed to</p> <p>16 working with all of you, that patient needs are being</p> <p>17 met, my sincere thanks to all speakers and panelists</p> <p>18 for your contribution to today's workshop. Again,</p> <p>19 thanks to Mr. Birrell for sharing his perspective. I</p> <p>20 think that was greatly appreciated. Certainly would</p> <p>21 like to thank Sumita -- and James -- for coordinating</p>	<p style="text-align: right;">Page 313</p> <p>1 CERTIFICATE OF NOTARY PUBLIC</p> <p>2 I, CARL HELLANDSJO, the officer before whom</p> <p>3 the foregoing proceedings were taken, do hereby</p> <p>4 certify that any witness(es) in the foregoing</p> <p>5 proceedings, prior to testifying, were duly sworn;</p> <p>6 that the proceedings were recorded by me and</p> <p>7 thereafter reduced to typewriting by a qualified</p> <p>8 transcriptionist; that said digital audio recording of</p> <p>9 said proceedings are a true and accurate record to the</p> <p>10 best of my knowledge, skills, and ability; that I am</p> <p>11 neither counsel for, related to, nor employed by any</p> <p>12 of the parties to the action in which this was taken;</p> <p>13 and, further, that I am not a relative or employee of</p> <p>14 any counsel or attorney employed by the parties</p> <p>15 hereto, nor financially or otherwise interested in the</p> <p>16 outcome of this action.</p> <p>17 </p> <p>18 CARL HELLANDSJO</p> <p>19 Notary Public in and for the</p> <p>20 State of Maryland</p> <p>21</p>

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