Addressing Challenges in Inhaled Antifungal Drug Development

Moderated by Dr. Richard Moss, Dr. Kieren Marr

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Remote Proceeding

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A P P E A R A N C E S

List of Attendees:

Dr. Barbara Alexander, Duke University
Dr. David Andes, University of Wisconsin-Madison
Dr. Darius Armstrong-James, Imperial College, London
Dr. Rohit Bazaz, University of Manchester, UK
Dr. Lance Berman, Pulmocide, Inc.
Dr. Radu Botgros, European Medicines Agency
Dr. Dale Christensen, TFF Pharmaceuticals
Dr. Cornelius Clancy, University of Pittsburgh
Dr. Russell Clayton, Pulmatrix, Inc.
Dr. David Corry, Baylor College of Medicine
Dr. Shampa Das, University of Liverpool
Dr. David Denning, University of Manchester
Dr. Anthony Durmowicz, Cystic Fibrosis Foundation
Dr. Paul Greenberger, Northwestern University, Feinberg School of Medicine
Dr. Shahid Husain, University of Toronto
Dr. Charlotte Keywood, Zambon
Dr. Kieren Marr, Johns Hopkins
Dr. Richard Moss, Stanford University

A P P E A R A N C E S (Cont'd)

List of Attendees:

Dr. Luis Ostrosky-Zeichner, University of Texas Health Science Center at Houston
Dr. John Perfect, Duke University
Dr. Donald Sheppard, McGill University
Dr. William Steinbach, Duke University School of Medicine
Dr. David Stevens, Stanford University
Dr. Thomas Walsh, Weill Cornell Medicine of Cornell University and New York Presbyterian Hospital
Dr. Peter Wark, John Hunter Hospital, Australia
Dr. Shukal Bala, FDA
Dr. Timothy Bensman, FDA
Dr. Brandon Blakely, FDA
Dr. Irene Chan, FDA
Dr. Phil Colangelo, FDA
Dr. Cheryl Dixon, FDA
Dr. John Farley, FDA
Dr. Caroline Jjingo, FDA

A P P E A R A N C E S (Cont'd)

List of Attendees:

Dr. Yongman Kim, FDA
Dr. Robert Lim, FDA
Dr. Owen McMaster, FDA
Dr. Sumati Nambiar, FDA
Dr. Mark Needles, FDA
Dr. Khalid Puthawala, FDA
Dr. Thomas Smith, FDA
Dr. Christopher St. Clair, FDA

C O N T E N T S

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P R O C E E D I N G S

RECORDING: Audio-recording for this meeting has begun.

DR. FARLEY: Good morning, everyone. Shall we begin? Great. Good morning. This is John Farley, the director of the Office of Infectious Diseases at the Center for Drugs at FDA, and I want to welcome everyone to this virtual live workshop entitled Addressing Challenges in Inhaled Antifungal Drug Development.

This is our third virtual workshop this year, actually in the last few months, focused on coming together as a community to facilitate antifungal drug development.

We planned this workshop in response to the recent interest in development of inhaled antifungal products to address the needs of patients with allergic bronchopulmonary aspergillosis, which you'll hear during the day referred to as ABPA, and invasive pulmonary aspergillosis, which you may hear referred to as IPA.

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With no FDA-approved antifungal products, it is clear that a broad scientific discussion will be helpful as development programs are designed.

Today brings together an interdisciplinary team from the FDA, which include specialists in infectious disease, pulmonary medicine, device development, pharmacology, toxicology, clinical pharmacology, clinical microbiology, biostatistics and outcome assessments joining together with academic and industry thought and patients.

We want to thank all of our speakers and panelists for their efforts preparing for the workshop today. In particular, we thank those international thought leaders who are with us today, as well as our colleague from European Medicines Agency.

Just a bit of housekeeping as we get started, we ask that folks speak clearly, stick to their allotted time so that we can stay on time today and ensure that we have adequate time for discussion.

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For the audience, the speaker slides, transcripts and recordings will be available on the public webpage for this meeting in the coming days.

For the highest quality audio for participants, speakers and panelists will be moved to presenter status and be able to connect their phone for both speaking and listening functions as the time for their session approaches. You will know that has happened because the phone icon will appear in the upper left-hand corner of your screen. You can then click on that phone icon and request the meeting software to call you.

Otherwise, speakers and panelists will need to use their computer speaker for listening function only.

Please use the comment box if any technical assistance is needed.

At this point, I'm going to turn the program over to Doctors David Andes and Shampa Das. Dr. Andes is a faculty member and Chief of the Division of Infectious Disease within the Department

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of Medicine at the University of Wisconsin-Madison. And Dr. Das is a senior lecturer in the Antimicrobial Pharmacodynamics and Therapeutics Group at the University of Liverpool.

So thank you very much and Dr. Andes and Dr. Das, please take it away and begin session one. Thank you.

DR. ANDES: Thank you. Our first speaker, Dr. Richard Moss, who is Professor Emeritus Pediatrics at Stanford University, Center for Excellence in Pulmonary Biology. His recent work is focused on allergic fungal lung disease. His talk is titled What Place for Inhaled Antifungals in Pulmonary Medicine. Dr. Moss?

DR. MOSS: Hello. Can you hear me okay?

DR. ANDES: Yes.

DR. MOSS: I hope so. Okay. Great. So I've been asked to give an introductory overview of today's topic. And the way I thought I would approach this is to start by using aspergillosis as the prime

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example of fungal disease. And in fact, that is the focus of the drug development we're talking about.

And starting by pointing out that we all inhale spores from aspergillosis as well as other molds. And normally, we do not have any illness from that. We know that the host determines the risk of illness by in large for this particular set of problems. And on the bottom of this first slide, you see a number of different phenotypes or syndromes that have been recognized.

And I'll be talking firstly -- briefly about the immunocompromised hosts who can develop invasive pulmonary aspergillosis sometimes with disseminated disease. And then later, the immunocompetent patient who -- especially those that are atopic that would develop allergic disease.

So to start with the immunocompromised patient, we know that there are certain high-risk situations that have been identified and these tend to fall into a couple of different buckets. One main one is people that are neutropenic either as a result of

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induction chemotherapy for hematologic malignancy, or those who are receiving stem cell transplantation. And we know that the risk there, as you see in this slide, is elevated.

The other group amongst patients who have received organ transplants, we know that the lung is the main risk factor, although disease can occur in these other solid organs. And you'll note that mortality across the board still remains distressingly high.

So how might one think about approaching this from an inhalational viewpoint? Of course you have to start with the preclinical situation in animal models to test out the possibilities. And this is an illustrative study that was done at the University of Texas, San Antonio, in Tom Patterson's lab in which inhaled voriconazole, using the intravenous solution which is what clinicians may be using -- and we'll talk more about that with regards to amphotericin in particular. This is given two days before an aerosol challenge with

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aspergillus. I don't know why that went back. Okay. And in immunosuppressed mice, and you can see that it was compared to systemic, in this case intraperitoneal amphotericin B deoxycholate, or a vehicle that was given as treatment starting one day after the challenge. And what's clear is that the inhalational voriconazole was actually more effective than the systemic amphotericin either when assessed during the treatment period on the left or afterwards on the right. So this gives kind of an example of the kind of animal models that can be helpful in assessing that.

And then in terms of looking at particular novel products that are being developed, I put a couple of different studies here. On the upper left, you see a study that was also done in San Antonio, in this case with immunosuppressed guinea pigs who received a novel amphotericin B inhalational powder that was developed initially by Nectar and picked up by Novartis. Which four doses were given one day before an aspergillus aerosol challenge and

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compared with oral voriconazole, two doses, starting one day after the challenge. And at least one of the doses of the amphotericin B powder is shown to be relatively effective in proving survival to roughly 50 percent in this particular model. And that's comparable to the optimal dose of voriconazole given systemically as shown in the second panel there on the left.

Moving to the right-hand side, we see a study that was done by Pulmatrix and presented at the Academy of Allergy meeting in 2018, in immunosuppressed guinea pigs. And this was a situation where they're a Pulmatrix novel product, which is an inhalational form of itraconazole PUR1900 was given by nasal -- was given starting one day after a challenge with a nasal inhalation of aspergillus for a period of 10 days. And what you see there is that in comparison to systemic itraconazole, it appeared to be more effective in prolonging survival.

And interestingly, there's a dissociation that's seen in the top there between the

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microbiologic effect, which does not appear to have an effect on fungal burden, versus the survival effect. And this has been seen in a number of different studies. So we have to remember that endpoints don't necessarily reflect clinical outcome measures if -- if one is focused solely on microbiology.

And finally, on the bottom, we see a study from the Pulmocide group that was reported last year in immunocompromised mice who were given daily intranasal PC945, which is a novel azole inhalational product, and compared to oral Posaconazole, or in this case, a combination of the two.

And the -- this was done from one day after the challenge for six days and showed that in this particular model, combination therapy was superior in preserving survival compared to either the inhalational novel agent or the conventional systemic agent.

In reviewing the literature, I think a couple of broad conclusions are pertinent. First of all, antifungal prophylaxis and lung transplantation

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is something that has been reported on for many years using off-label use of IV formulations, mainly nebulized amphotericin B. There are a few case reports in the literature with inhalational voriconazole, also the IV solution.

And this is usually aimed at aspergillosis and -- and many of these clinical situations, combined with an oral anti-candid agent, fluconazole.

These studies have shown that liposomal amphotericin B is better tolerated versus the traditional or older deoxycholic micelle formulation.

And overall, the studies differ somewhat, but they show at least similar and in many cases reduced incidents of invasive disease with an unclear effect on anastomotic lung disease in lung transplant recipients.

And unfortunately, I couldn't find any direct comparative trials with oral azoles.

The second situation where I think these antifungals may play a role in immunocompromised

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patients are add-on treatments to systemic treatments for resistant or recalcitrant infections which are mainly concerning emergent fungi that are multi-resistant and often difficult to treat, even in combination therapy. For example, pseudocamarosporium, zygomycetes or fusarium.

And the -- area that I think is important is the prophylaxis with inhaled amphotericin in hematologic disease. These studies are usually highly targeted to patients with anticipated extended neutropenia. And these are high-risk patients often selected where oral azole prophylaxis, which is the recommended treatment, is problematic.

Those studies have shown a relative risk reduction of roughly 50 percent versus no prophylaxis in a few randomized controlled trials, but no direct comparisons to oral azoles.

And again, a better toleration of the niosomal formulation than the deoxycholate.

There is a fairly high discontinuation rate due to adverse effects of about 10 percent in the

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clinical experience due to induction of cough or bronchospasm, bad taste and nausea.

So current recommendations by the IDSA do include patients with hematologic malignancy and stem cell transplants. In areas of high azole resistance -- which is especially true in several areas of Northern Europe, but is a worldwide phenomenon -- or patients with contraindications to oral azole prophylaxis.

So turning from the immunocompromised patient to the immunocompetent patient, we have the issue of fungal asthma and its more severe phenotype, ABPA.

The basis of this I believe is the ability of the fungus to grow in the bronchial lumen in mucous plugs in people who have underlying muco-obstructive disease. So this includes not only asthma, but importantly cystic fibrosis and increasingly perhaps various forms of COPD. And the key factor is that one can detect luminal fungal growth that's shown here in the branching hyphae of

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aspergillus fumigatus, and the presence of endobronchial inflammation which you can see there in the inset as represented with -- epithelial cells and granule acidic infiltration.

I think that there is an extended phenotype here which several syndromes can be distinguished from each other, beginning with simple asthma.

Moving to a more chronic asthma associated with fungal sensitization on a chronic basis. A more severe form in which the asthma is phenotypically severe, accompanied by fungal sensitization, so called SAS. And then ABPA of which two different forms have been recognized, depending on the presence or absence of central bronchiectasis.

And you can see there on the bottom that this is a common problem in asthma with very high numbers represented that actually dwarf those with the various infective forms of aspergillosis in terms of worldwide burden.

Now how can we -- how can we hone down

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on fungal sensitivity as an associated problem? One way to look at that is through epidemiologic studies, like this one from a cohort in Sweden of 830 patients who use three different definitions of severe asthma, and looked at the prevalence of sensitivity to any allergen, non-mold allergens and mold allergens. And in terms of the association with severe asthma, we see a clear, significant different with mold sensitivity being a prominent associated finding. And looking at specific molds amongst the common mold allergens we see that aspergillus fumigatus shows by far the highest relationship with roughly 10 to 20 percent of severe asthmatics showing fungal sensitivity to this particular agent.

Now this is also true in pediatrics. And this is a study from New York, and there's a very similar one from London, both are cited there, which look at kids. In this case, around age 10, and describing the characteristics of those with or without fungal sensitivity. And in addition, those that might be sensitized to non-fungal allergens. And

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the key point here is that besides the biomarker IGE being a good reflection of the fungal sensitivity, we see lower lung function and less asthma control in the group with fungal sensitivities. And the interesting feature of this SAS, whether it's adult or pediatric, is that it is usually multi-fungal in relationship to particular agents, such as aspergillus which is the most common, but also Alternaria, Cladosporium, candida and some other prominent, known aeroallergens.

So this has led to the idea that one might use anti-infective therapy for asthma, which is not intuitively obvious, in those with fungal sensitivity. And there have been two randomized controlled studies of this in the UK. On the left you see a study from Manchester from David Denning's group which used itraconazole. You can see the sensitivities of their group. And this was a -- basically a half-year study with a significant primary endpoint result of improved asthma quality of life as -- as measured by the AQLQ score, as well as some other changes which suggest that efficacy, such as

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change in some lung function measurements. However, the follow-up study using voriconazole in Leicester, the -- study on the right, failed to show any difference in a 12-week randomized controlled trial.

So my conclusion is that at this point, we don't know the role of azoles in SAS and we need a better -- further clinical trials to see if this approach could be used, and therefore then adapted for use with antifungals since this is a chronic therapy. And the whole -- one of the -- rationales is to avoid toxicity and side effects as well as enhance local concentrations.

Now turning to ABPA, we see that up to five percent of those with severe asthma have been found to have ABPA. In cystic fibrosis and other at-risk groups, it's higher. It's about eight percent in adults and registry figures. Again, representing a large cohort of patients with an unmet need in terms of effective therapy.

Current therapy, which goes back now to the '60s, is oral glucocorticoid steroids which are

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still the mainstay of therapy, but these are -- these are long-term treatments of months rather than a few days. And can result, and in many cases do result, in significant toxicity. And that's pushed the development of alternatives, including monthly pulse IV steroids which are being used in some patients to spare the toxicity.

Since the early '90s oral azoles active against aspergillus starting with itraconazole have also been used and validated in several placebo-controlled trials. But again, the long-term treatment increases the possibility of toxicity, and in addition, depending on the azole we're speaking of, there are issues with absorption, metabolism, drug/drug interactions, which together really mandate therapeutic drug level monitoring, which is both expensive and troublesome.

And importantly, azole resistance is clearly increasing on a worldwide basis, especially in areas where antifungals are widely used in agriculture. And that's driven over decades the off-

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label use of nebulized amphotericin B. And in the last 10 to 15 years, the advent of biologic agents, mostly with omalizumab, the monoclonal anti-IGE, which has been validated at both in open label and placebo-controlled situations. But is expensive and requires observation in an office or a clinic. And most recently, other T2 high response biologicals have been adapted for early use in ABPA, and reports of those are in the literature.

The amphotericin B aerosol therapy unfortunately has issues related to the four different IV preparations which are used. All of these are used off-label, so they've not been specifically studied and approved in a -- in the usual fashion for a regulatory vetting.

We do think that the lipid formulations are better here as they seem to be in invasive immunocompromised disease patients. One of the problems in all these studies and systems is the wide variety of delivery devices. So there's no vetted drug delivery combo that has clearly defined

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characteristics. So there are wide ranges of dosing and dose regimes used. But nevertheless, this is something that is out there.

So an example of the study which looked at this is this particular one for new patients, adult patients with asthma and ABPA, that was conducted in India which compared the amphotericin B deoxycholate formulation in combination with budesonide to a control arm. So it's an active control study using budesonide as the control. And in comparison to the steroid-only arm, the patients who received the antifungal had a significantly decreased number of exacerbations after one year, and a trend towards reduced -- towards an extended time to first exacerbation.

Hopefully we'll get better data from a multicenter study in France with liposomal amphotericin B, which is ongoing with enrollment completed. So hopefully that will add to our knowledge about that.

This has also been applied to cystic

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fibrosis which you see there on table two on this slide. A number of studies have been done. Note the very small number of patients. These are basically case series or individual studies. A few others exist in the literature. Now obviously, there is a publication bias that may be involved here, but the case reports do suggest positive clinical outcomes in these patients with biomarker responses such as reduction in IGE on the therapy.

So turning to actual development of new drugs, we now have at least the first published study in healthy volunteers with the Pulmatrix dry powder formulation of itraconazole which is shown here. And as expected, what we see is a markedly higher sputum level as compared to oral itraconazole. And a markedly lower plasma level as compared to oral itraconazole. So the plasma exposure is up to 400 times lower with sputum concentrations up to 70 times higher, versus the oral formulation. And as shown in the bottom left figure there, you can see that in some cases, 24 to 48 hours, the MIC90 is still exceeded for

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aspergillus using this intervention.

Similarly, Pulmocide has also, with their PC945 formulation, starting to generate some data clinically. This is just an example which I was kindly provided by Pulmocide to show a patient with ABPA where there was, on top of systemic therapy, resolution to the pulmonary infiltrates and a positive change in the biomarkers particular IGE with the addition of the PC945 to the treatment program.

And in terms of the immunocompromised patient, there also may be a clinical application as this case report which was presented last year in the UK, again using PC945 in a patient with anastomotic disease where the inhalational azole agent was added to a conventional combination systemic therapy resulting in clinical improvement.

And finally, I just want to point out what I think is a neat system, the in vitro alveolus model which is a cellular bilayer model in which the upper chamber is coated with epithelial cells tied to pneumocytes, then there's a semipermeable membrane,

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and below it, a coating of the systemic side with pulmonary endothelial cells, recapitulating the air/liquid interface. And what we see on the top is that one can then add the conidia and the drug if you want. And then on the bottom, measurement of fungal penetration through the bilayer and -- and growth into hyphae as measured by the readout with galactomannan.

So in this particular study which was published last year, this model was used to show that combination therapy was much more effective than either the monotherapy with the inhalational route of the PC945 that is on the top layer, or the systemic route with the addition of Posaconazole on the endothelial side on the bottom layer.

So in summary, I would conclude that because of favorable pharmacokinetics, pharmacodynamics and toxicology specific respiratory developed drugs and device combinations may find validated roles in a number of different situations. I think prophylaxis of aspergillosis in lung transplant recipients and patients with hematologic

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malignancies with neutropenia, adjunctive treatment of resistant or recalcitrant multidrug resistant fungal lung infections, and in the allergic patient, treatment of allergic pulmonary aspergillosis, and possibly treatment of severe asthma with fungal sensitization. And I'll conclude there. Thanks for your attention.

DR. DAS: Hi. I would like to -- thank you very much, Professor Richard Moss for that excellent presentation. I believe all questions will be addressed in the panel session at the end.

I would like to now introduce Dr. Owen McMaster. Dr. McMaster is a pharmacology and toxicology reviewer in the Division of Pharmacology and Toxicology for infectious diseases in the Office of New Drugs at the FDA. And he has review experience planning antifungals and antivirals.

I'd like to hand over to Dr. McMaster now.

DR. MCMASTER: Hi. My name is Owen McMaster. Good morning. This is Owen McMaster. I'm

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a pharm/tox reviewer in the Division of Pharm/Tox for infectious diseases.

As the content of this presentation represent my own opinion and not the official position of this CDER or FDA. And I have no conflicts to declare.

Now this morning, my brief presentation is intended to provide an overview of the pharmacology and toxicology data that are typically submitted during the I&D process.

As I go through the presentation, I'll address any special procedures or modifications relevant to the development of an inhaled antifungal. And I'll finish by touching on what we might do in the future to improve predictability of these evaluations.

So as mentioned in the previous talk, a quick search of the public literature reveals interest in inhalation formulations of previously approved antifungal drugs, like voriconazole, Posaconazole and itraconazole, but also drugs like PC945 which is being specifically developed as an inhaled treatment for

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pulmonary aspergillosis.

The regulatory basis for the pharmacology and toxicology package comes from 21CFR312.23, which indicates that I&D's just contain adequate information about the pharmacology and toxicology studies of the drug. The regulation also directs sponsors to the FDA for guidance on how these requirements might be met.

This slide shows two guidance documents relevant to the development of inhaled antifungals. The first is ICH guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization to pharmaceuticals M3. This describes the non-clinical safety studies recommended to support human clinical trials -- scope and duration, as well as marketing authorization for pharmaceuticals.

The second is FDA's non-clinical safety evaluation of reformulated products and products intended for administration by an alternate route, guidance for industry and staff. I provide a link to

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these documents below.

This slide describes the non-clinical studies referenced in ICHM3. I must point out that the primary pharmacology or pharmacodynamic studies which evaluate the mode of action or effects of a drug in relation to its desired therapeutic effects, are not reviewed by the pharm/tox team, but by my colleagues in the clinical microbiology and clinical pharmacology groups. You'll hear from them later in the day.

Other studies recommended by ICHM3 include secondary pharmacology, safety pharmacology, pharmacokinetics, acute and repetos toxicity studies, genetic reproductive carcinogenicity, immunotoxicity, phototoxicity and abuse liability studies -- combination -- studies were necessary.

FDA's non-clinical reformulation guidance addresses the additional testing that would be expected if a drug is being studied for inhalation administration as a new route of administration.

Drugs being repurposed for use by

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inhalation should undergo a short-term -- two to four week -- inhalation toxicity testing in two species. If the drug is to be chronically administered, this should be followed by a longer inhalation study, for up to six months, in the most appropriate species.

Studies of new routes should not only contain a vehicle control, but also a -- control group as well, especially if novel excipients are used.

Experimental inhalation exposures take many forms in the lab, including nose-only, oropharyngeal, oronasal, head-only and whole body exposures.

This slide shows the rats being exposed to drugs by nose-only exposure.

I also want to point out that dosimetry for inhalation toxicology studies is not as straightforward as, say, intravenous or oral device studies where a specific measured quantity of drug can be reliably delivered to the test animal.

For inhalation toxicology studies, exposures are estimated by the formula shown above

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which is -- considers the delivered dose as being calculated by multiplying the aerosol drug concentration by the respiratory minute volume of the animal, multiplied by the duration of daily exposure, multiplied by the inhaled fraction of particles between one and five microns, and then divided by the body weight of the animal. Obviously, inaccuracies in any of these factors will impact the estimate of the amount of drug administered to the animal.

The delivered dose is different from the dose, which is actually deposited to the innermost regions of the lung. This pulmonary deposited dose is determined by multiplying the delivered dose by a deposition factor, which varies by species. So for particles between one and five microns, the deposition factor is .1 for mice and rats, .25 for dogs and monkeys, and assumed to be 1 for humans.

Pulmonary deposition varies across species and depends on the size of the drug containing particles. This slide compares a pulmonary deposition in nose-breathing rats and dogs and in nose-breathing

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and mouth-breathing humans. Deposition in larger species such as dogs and monkeys is more similar to -- to that in humans than for rats.

This slide shows the deposition curves for an adult human as we extend the scale of particle sizes down into the nano range. Of those -- data were not corrected for inhalabilities also clear, the deposition weight varies widely as we compare the nasal/oropharyngeal region, to the trachea/bronchia region and then to the pulmonary region.

So back to the tox studies -- pharmacology studies evaluating the cardiovascular, CNF and respiratory effects are expected during the development of an inhalation antifungal. This is a reformulation. The safety pharmacology may already be complete using the oral route of administration. If not, safety evaluations may be incorporated into general toxicity studies, which should be conducted prior to human exposure.

I've added a link to the ICH safety pharmacology guidance below.

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Prior to human trials, in vitro, metabolic and plasma protein -- data for animals and humans are expected, along with in vitro pulmonary and systemic exposure data in test species. Prior to phase three, more extensive data will be expected.

Repeat those inhalation toxicity studies should be conducted in two species with durations equaling or exceeding the proposed duration of the clinical trial. Ideally, both species should be dosed by inhalation mode of administration, provided that this route of administration results in systemic exposure in at least one species sufficient to assess toxicity compared to the anticipated clinical exposure.

A full panel of -- pathology evaluations is expected with new molecular entities being developed for inhalation administration.

Reversibility arms should be included as needed to evaluate if observed toxicities resolve or get worse at the end of dosing.

These studies can also be used to

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qualify novel excipients or impurities which may be associated with this formulation.

This shows a typical study design, and I just want to point out the inclusion of the air control groups which are important if we have novel excipients, to distinguish between excipients effects versus the drug effects. And also that the -- there's a column for target and achieved doses because often they are significantly different from each other.

In vitro results from the genotoxicity testing are expected prior to human trials. And in vivo results are expected prior to phase two.

Fertility and embryo -- development studies should be conducted prior to phase three and post -- pre and post-natal development studies should be submitted by the time the NDA is submitted.

The sponsor should conduct these studies using a route of administration that results in systemic exposure and exposure to the reproductive organs. So for example, if adequate systemic exposure is not achieved by the inhalation route, reproductive

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toxicology evaluation should be conducted using the oral or intravenous route.

Carcinogenicity studies will be needed as the expected clinical use of the drug is at least six months. The details may be can -- the studies may be conducted by the inhalation route and should include one long-term rodent carcinogenicity study, plus a short or medium term in vivo rodent -- such as a transgenic mice or a second long-term rodent carcinogenicity study.

Additional studies should be conducted on a case by case basis. Combination studies may be needed if the inhalation drug is co-packaged with another drug, or if there's limited clinical information regarding one or both the drugs in the combination -- studies may be needed if the pediatric population is the primary population for this drug, or -- and/or if the existing animal data have identified potential developmental concerns for target organs, such as joints.

Immunotoxicity studies should be

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considered if there are immune-related signals in standard toxicity studies. Studies with abuse potential should be considered for drugs based on CNS activity, similarity of chemical structure to known drugs of abuse, receptor binding profile, behavioral clinical signs from the non-clinical studies.

Impurities, metabolites and leachables should be studied also as indicated.

So what are the gaps in existence we need to extrapolate from non-clinical data to inform clinical trials and drug development. The first obvious difference is in device designs. Since animals are tested using equipment that is very different from the devices that end up being used in the clinic. There are also obvious anatomical differences in the respiratory tracts across the various animal species used compared to humans.

There's also the fact that the doses administered in inhalation toxicity studies are not directly measured, but estimated based on assumptions and calculations, which may or may not be accurate.

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And finally, there's use of -- in healthy animals in toxicity studies, the interaction between an inhaled drug and healthy tissue to be quite different from the interaction with diseased lung tissue, exposing infected lung tissue to an inhaled antifungal may lead to greater or -- or less systemic exposures compared to the healthy lung.

Toxicology studies which incorporate the use of infected animals will be more complicated to conduct, but may actually provide data that are more relevant to inhaled antifungal use in patients.

So the non-clinical pharmacology and toxicology studies recommend to characterize the toxicity of inhaled antifungals that are described in ICHM3. These data help define clinical doses, inclusion, exclusion criteria and inform safety monitoring.

Understanding the limitations of these animal models relating to test article administration, pharmacokinetics evaluation into species allows a more realistic characterization of the risk to expand this

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in subjects and patients. Now with toxicity studies such as toxicology studies in animals with fungal infections could enhance the predictability of toxicology testing in these agents. Thank you.

DR. ANDES: Thanks, Dr. McMaster. Our next presentation is from Dr. Tim Benson [ph] -- Bensman, excuse me. Who is a clinical pharmacology reviewer in the Division of Infectious Disease Pharmacology in the Office of Clinical Pharmacology at the FDA. His review portfolio includes inhaled drug products for infectious diseases. And his presentation is titled Orally Inhaled Antifungal Drug Development, Clinical Pharmacology Perspective.

DR. BENSMAN: Thank you, Dr. Das. Thank you, Dr. Andes.

All right. Good morning, everyone. I'll take the next 15 minutes to talk about orally inhaled antifungal drug -- from a clinical pharmacology regulatory perspective. But I wanted to quickly acknowledge the contribution that Dr. Saluja [ph] has made to this presentation, specifically

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around inhaler device consideration.

In addition, this presentation will reflect my own views drawn from review experience and not represent policy of the FDA.

So the scope of this talk is to discuss the factors for consideration that are germane to developing an acceptable orally inhaled antifungal drug product, with particular attention to three. The device considerations, clinical pharmacokinetics, and dose finding.

Well, the rationale -- rationale behind orally inhaled drug products is the ability of directly targeting the infected airway, achieving high local drug concentration to the most systemic concentration. And this is illustrated in the schematic located at the bottom left corner of this slide. The individual on the left is administered an oral drug tablet and the individual on the right is administered an aerosol drug. The red indicates high drug concentration and pink indicates low drug concentration.

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So the theoretical advantages of the orally inhaled drug compared to the preferential oral drug is improving efficacy, reducing the amount administered to the patient and minimizing adverse effects that are associated with the preferential or -- drug.

Now, concerning local drug exposure, if we look at the diagram on the right, you see this site of infection and the site of drug activity are located in the lung. And so clinical or pharmacodynamic measurement, sometimes fungal lung -- are sampled from the lung space to evaluate the therapeutic effects and described dose response relationship.

Concerning systemic drug exposure, the portals of entry are via the lungs and gastrointestinal organs. And they search and deliver drug throughout the body, following oral drug inhalation.

The sampling the blood compartment via PK studies provides us a way to except the levels of systemic drug exposure and their relationship to

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adverse effects.

Unfortunately, as the blood compartments downstream of the site of action as well as downstream of many dynamic PK processes, blood concentrations aren't considered surrogates for pulmonary concentration. And they're unlikely to describe the relationship between therapeutic lung effects and systemic drug exposure.

Now a distinguishing characteristic of orally inhaled products is the strong influence that drug, device and patient-related factors impact where the drug is deposited in the lung or by the deposition. It also impacts how fast or slow it could grow and how fast or slow it's cleared from the airway. Because of these intricate -- because of this intricate interface of drug, device and patient-related factors, you can get non-uniform lung exposure and get -- disease. And this makes interpreting lung concentrations made from sputum or epithelial lungs more difficult as it's likely compartmentalized as there's likely compartmentalization of drug throughout

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the lung, and especially in deep lung sites where fungal infection has caused obstruction or capitation.

The inhalation maneuver or technique is -- is one such challenge to lung deposition and distribution. A classic example for -- comes from metered dose inhalers, or MDIs. But the same consideration should be given to other inhaler devices, such as the dry powder inhaler, which is likely to be more used in this space.

In this example on the left, asthmatic patients inhaled what are labeled albuterol from a conventional press and breathe metered dose inhaler, before and after being trained to synchronize exhalation with inhalation. And a -- X-ray of MDI was evaluated in those who failed to coordinate.

As you can see in this figure, the deposited drug dose and distribution in the lungs was substantially different in patients using their own inhaler technique compared to a taught inhaler technique, or a breath actuated device that was triggered when the patient inhaled.

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In addition, physiological or pathophysiological factors are another such challenge to lung deposition and distribution. The lung -- on the right of this slide depicts two different individuals. The left lung is that of a healthy individual while the right lung is of a chronic obstructive lung disease with -- impaction and structural airway abnormalities that result in reduced lung function. Such abnormalities use an air turbulence, causing the drug to deposit at obstructed lung areas, as well as preferential airflow, and therefore more drugs to healthier lung regions that are able to expand.

Such factors, therefore, are not only impacting one drug distribution and drug deposition pattern variability between individuals, but they also -- also likely impact within an individual variability as inhaler technique probably varies, for example -- probably varies from day to day.

The effect of the device among deposition and efficacy is another important factor.

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An example from a phase two clinical trial compared two different inhaler devices delivering the same drug to the lungs. A device ranking component was conducted for the device one and compared to an approved dose in device two. Efficacy was deemed to be acceptable with the -- lowered dose with device one compared to device two, based on an FEV1 measurement or endpoint. But this underscores that both efficacy and safety are dependent on the device used, so the -- marketed inhalation drug product needs to be studied in clinical efficacy and safety trials.

As mentioned before, the clinical pharmacokinetic considerations for orally inhaled antifungal drug products are chiefly focused around addressing systemic drug exposure issues. So one needs to evaluate the safety/tolerability profile, identify the maximum tolerated dose, gain information on the drug's general body disposition and drug kinetics through single and multiple -- dose PK studies in healthy subjects as well as the targeted patient population.

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Now because of certain drug exposure of the orally inhaled antifungal drug product is expected to be low, in general, the lung has low drug metabolizing activity compared to the liver, in vitro approaches to evaluating drug/drug interaction potential is a good place to begin to determine whether there are potentially clinically significant drug/drug interaction. And such approaches are outlined in current FDA in vitro for drug interaction guidance.

Another noteworthy comment about this route of administration is that given that the site of action is upstream in the systemic -- exposure, a dosage -- in renal or hepatic impairment are not possible. And so it's deficient clinical experience at exposures that are achievable in such populations need to be considered in the drug development program.

Also, for antifungals with approved systemic formulation, the systemic orally inhaled antifungal drug, PK, can be used to bridge the systemic safety for that orally inhaled antifungal

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drug. However, for efficacy of the orally inhaled antifungal drug, bridging these and systemic PK to the approved systemically administered antifungal cannot be made. And that's the reason -- that has been discussed already.

Initial dose regimen selection is often times obtained from non-clinical or non-human animal models with fungal lung disease through the estimation of the clinical starting dose or dose regimen via the delivered dose as outlined by Dr. McMaster.

Lung PK -- targets for initial dose regimen selection are not common. However, the evaluation of the LF and -- drug concentrations do provide information on drug exposure and penetration in the lungs. And potentially, their association with clinical efficacy. However, there is a knowledge guess regarding the translation of the non-clinical lung PK/PD targets to humans and their link to clinical efficacy.

Also, in patients with invasive fungal lung infections, the interpretation of sputum and --

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antifungal drug concentrations are challenging. For one, there is a high degree of variability between individuals, especially for sputum where the relative variability is commonly around 100 percent.

Also, while it's generally rationalized that efficacy is due to high local concentration, with indirect approaches of -- different for the lung/drug concentrations may not reflect free-soluble drug concentrations at the lung target site infection. They also may result in different PK/PD values depending on which matrix is what. So poor inferences are -- are difficult.

Recognizing these complexities and dose response or dose findings should be an integral part of the phase two drug development program. And to form the phase three dose regimens, multiple ascending dose phase two trials -- the anticipated phase three inhaled clinical dose regimen as well as a range of dose regimen that are above and below it to evaluate efficacy and safety responses.

Also, given the significant influence

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of patient-related factors to orally inhaled antifungal drugs, it is also important to enroll patients that will reflect -- that will reflect the phase three target patient population.

So to summarize, there are many influential factors. Drug formulation, device, fungal lung disease severity and patient use, for example, that affect lung distribution and therefore lung pharmacokinetics of orally inhaled antifungal drugs. Plus the to be marketed orally inhaled drug product needs to be used in the phase two/three development program. Also, non-clinical animal models with fungal disease may be potentially informative, but at this time, phase two trials are needed to support the phase three dose regimen.

Certainly, there are a number of uncertainties that challenge us in this phase and I look forward to discussions throughout the day on how we can best consider them and consider -- so …

So to close, I wanted to acknowledge Doctors Colangelo, Soluja and Reynolds after their

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very fruitful discussions and comments. They were instrumental in putting this presentation together. Thank you.

DR. DAS: Thank you very much. I'd like to thank Dr. Tim Bensman. And then I'm going to introduce Dr. Brandon Blakely. Dr. Blakely is a biomedical engineer and acting team lead for the respiratory devices team at CDRH-FDA. Brandon's experience includes pulmonary diagnostic devices or nebulizers. He was taught -- about regulatory perspectives for device development for inhalation combination products.

DR. BLAKELY: Thank you. As the name of the talk suggests, I'm going to be going over the regulatory perspectives for devices in general and inhalation devices in particular, both CDER-led and CDRH-led.

So I'm going to give a brief summary of the classification system that medical device regulations are based on, then I will summarize the regulatory landscape for orally inhaled drug product

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device reviews specifically.

Devices are regulated in three risk-based classifications. Lower risk devices with well understood safety and effectiveness profiles are classified as class one devices where there is an assurance or safety and effectiveness through general controls.

General controls apply to all medical devices and include fundamental requirements regarding ensuring devices are not adulterated or misbranded, and that manufacturers follow our quality systems regulations for good manufacturing. Most of these devices are exempt from premarket notification requirements.

Moderate risk devices are considered class two for which safety and effectiveness can be assured through both the general controls and special controls.

Special controls are usually device-specific and can include things like performance or labeling requirements. These devices usually require

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a premarket clearance through the 510K process which requires demonstrating substantial equivalence to a predicate.

Finally, high-risk and generally novel devices, including implanted devices or those intended to sustain life, are class three devices which usually require a premarket approval or PMA. These devices require valid scientific evidence, generally in the form of well-controlled clinical studies, to demonstrate a reasonable assurance of safety and effectiveness.

As can be seen by the little cartoon here, CDRH-led devices for the delivery of drug for inhalation are generally regulated as class two devices.

So you can all reference the definition here, but you know, the basic idea is if a medical product requires two or more different types of regulated entities, for example a drug and a device, to achieve its intended use, that is considered a combination product. Review of combination products

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requires a coordination of multiple centers with one center acting as the lead and consulting the other center or centers as needed.

If a manufacturer wants feedback on which center would be the lead for their product, they can submit a request for designation, or RFD, to the Office of Combination Products or OCP. OCP will make their recommendation by determining the primary mode of action of the product. For example, if the product's primary mode of action is chemical action and metabolism, it would be led by CDRH.

There are two mechanisms to obtain OCP feedback. A formal RFD and a more flexible pre-RFD process. In the slide I am referencing the two relevant guidance documents that provide overviews of these types of interactions.

All right. Back to inhalation devices typical for orally inhaled drug products. There are roughly two broad classes: nebulizers and inhalers. Nebulizers are devices that, as the name suggests, nebulize liquid drug formulations into a mist for

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inhalation. Since nebulizers generally work with any appropriate liquid formulation of a drug, these are most often sold as general use nebulizers, which are regulated as devices by CDRH. This means that they are clear to be marketed to nebulizer any drug that is approved for nebulized solution route of administration in the orange book, and they are not co-packaged or cross labeled with a specific nebulizer. In some isolated cases, nebulizers have been designed and co-packaged specifically for one drug in which case those would be approved under the NDA for that drug.

Finally, there are inhalers which include metered dose inhalers or dry powder inhalers. These are typically co-packaged with the associated drug and are approved under the drug NDA submission. These combination products would be CDER-led, usually with consult from CDRH.

Here are some examples of drugs that are approved to be used with general purpose nebulizers. These are devices regulated solely by

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CDRH and are cleared for market through the 510K process.

For reference, here is the 510K database from the FDA website. You can search all 510K cleared devices which are organized by product code. The product code for nebulizers and nebulizers accessories for example is CAF. If you enter those three letters in the pro code field and search, you can find a comprehensive history of all 510K-cleared nebulizers. Most records should also include a 510K summary which is a publicly available overview of the device and the information, including performance data, that was provided in support of the submission.

For drugs intended for specific device combinations, there are two possible ways to obtain marketing approval or clearance. The most common path is including the device portion as part of the drug submission. In some cases, sponsors will clear a device for delivery through the 510K pathway if there's a predicate or another pathway is necessary. However, CDRH will only clear or approve devices

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intended to be delivered -- intended to deliver drugs, so long as the intended use of the device is consistent with the approved drug label.

As mentioned previously, the most common pathway for CDRH-led orally inhaled drug products is the 510K pathway. I'm going to quickly provide an overview of the 510K process which is based on demonstrating that the subject device is substantially -- to a predicate device. Many of the same review considerations also apply to NDAs or other drug submissions with device components. So the content presented here should also be informative of CDRH expectations when we consult for CDR-led combination products.

And an NDA for example, instead of evaluating the performance as compared to a predicate using our recognized consensus standards and guidances, we would be evaluating the safety and effectiveness of the device component of the NDA solely using our recognized consensus standards and guidances.

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In this slide, I am referencing the primary CDRH guidance on the 510K process. To obtain 510K clearance, a 510K submission must demonstrate that a newer modified device is substantially equivalent in its intended use in safety and effectiveness to a predicate device.

A predicate device is most often a legally marketed device that was cleared onto market by the 510K process. In order to be determined substantially equivalent to a predicate device, the subject device needs to demonstrate one of two things. Either it has the same intended use and the same technological characteristics, or it has the same intended use and different technological characteristic which do not raise use of questions of safety and effectiveness. And often through performance testing, can be demonstrated to be at least as safe and effective as the legally marketed predicate device.

The intended use is objectively determined from the content of the submission,

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including the labeling. The intended use encompasses the indications for use, which would be the specific patient population or disease the device is intended to treat or diagnose, intended users and the environment of use.

Here is a list of the common subject matter areas typically reviewed for device marketing submissions. From the device description intended use, CDRH evaluates topics related to the device's performance to ensure that it can fulfill the intended use, as well as issues related to basic safety from risks of physical hazards. Many of these basic safety topics are covered by various international consensus standards and FDA guidance documents, which I'll touch on briefly in the upcoming slides.

In terms of orally inhaled drug products delivery devices -- drug delivery devices, the primary performance metric we were interested in is the ability to deliver respirable aerosolized drug particles. Roughly speaking, a particle smaller than 5 microns in aerodynamic diameter are needed for long

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deposition. Larger particles largely impact the mouth or throat and do not reach the alveoli. Determining the aerodynamic distribution of the omitted particles from an orally inhaled drug product provides a quantitative assessment of the performance of the device and its capability to deliver a respirable dose.

The standard performance test to determine aerodynamic particle size distribution is cascade impaction. Cascade impactors separate particles and droplets by aerodynamic diameter, depending on inertial forces which are captured at various stages with different cutoff diameters.

CDRH evaluates cascade impactor testing to assess the performance of orally inhaled drug products. Generally, cascade impaction testing with at least six stages is required, including -- some reference to the relevant USP chapters that describe this testing.

When evaluating aerodynamic particle size distribution testing, it's important to measure

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various sources of variability. So we assess both the inter and intra device variability. So it is expected that you would do tests with multiple actuations of a particular device and with multiple devices.

In addition, if the device is intended to be used with various patient interfaces, for example, with spacers or with a mask or a mouthpiece, it's expected you would do the testing with all available interfaces to ensure consistent drug delivery.

Among the most important elements of basic safety in some of the most challenging is biocompatibility. Biocompatibility of a device means that the device's contact with tissue does not produce an adverse effect during its intended use. Biocompatibility evaluation is determined through a risk management process which accounts both for the type and duration of tissue contact.

For biocompatibility assessments, CDRH primarily relies on the ISO10993 series of standards. FDA has also issued guidance on the application of

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ISO10993 to the biocompatibility assessments of medical devices. In general, the expected number and types of in vitro and in vivo tests are outlined in this guidance.

In terms of the type of contact, orally inhaled drug products could have multiple types of contact as categorized by ISO10993.

For example, a face mask or mouthpiece would have direct intact skin contact, however, any device component, including anterior surfaces or ports over through or which gasses or liquids could be inspired by the patient, are considered externally tissue communicating-type contact.

Furthermore, there are specific biocompatibility hazards for gas pathway contacting devices not addressed by the ISO10993 series. Therefore, CDRH also recognizes the ISO18562 series which specifies both additional tests to ISO10993 and additional test approaches instead of some of the tests described by the ISO10993 series.

As I summarized already, there are many

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potentially complicated specifics to consider when evaluating biocompatibility of medical devices. For example, if you use an identical material to approved or cleared device, which includes the raw materials and manufacturing processes and other steps, you may under certain circumstances be able to provide a material certification statement as opposed to biocompatibility testing. There are additional biocompatibility endpoints for gas pathway contacting devices, such as particulate matter of volatile organic compound testing described in ISO18562.

Another important consideration is that some of the in vivo endpoints in the ISO10993 series can be substituted with a chemical characterization and toxicological risk assessment, depending on the intended use.

These tests are generally time consuming and expensive, so we strongly recommend that you interact with FDA early on in the product development process to ensure that the biocompatibility assessments are consistent with our

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review expectations.

Besides biocompatibility hazards, there are other hazards we evaluate for the basic safety of medical devices. The general safety standard for medical devices is published by the International Electrotechnical Commission, or IEC, and is the primary document of the IEC60601 series of basic safety standards for medical devices.

The IEC60601-1 standard is the primary or general standard that describes basic safety requirements applicable to most electrically powered medical devices.

Basic safety includes freedom from unacceptable risks from a range of potential hazards, including electrical and mechanical hazards, as covered by the requirements of IEC60601-1.

In addition to the electrical safety general standard, there are collateral standards to the 60601-1 general standard. One of the most common applicable to almost any electric device is IEC60601-1-2, which describes the requirements for emissions

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and immunity from electromagnetic radiation. So essentially that the device does not -- is not -- the performance of the device is not impacted by electromagnetic radiation from other devices and that it does not adversely impact other devices.

Finally, an increasingly important aspect of medical device development and review, including combination products and other drug delivery devices is software. Safety and effectiveness is often dependent on functioning software. There are industry standard designed verification and validation activities to ensure that device software conforms to user needs and the intended use of the device.

We have a guidance that describes the minimum software information needed in support of premarketing submission, depending on the level of concern.

Additionally, there are software verification and validation requirements per IEC60601-1 that I referenced earlier. And there is an FDA recognized consensus standard on the processes and

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activities related to the development and maintenance of medical device software.

So similar to CDR, CDRH encourages early communication interaction as you develop your product. Analogous to CDR is type A, type B, type C meetings. CDRH has a number of pre-submission or also known as Q-submission meetings, including informational meetings, pre-meetings or submission issue meetings that you can reference the guidance here.

For more details on the types of meetings available and the timelines for interactions, please refer to this 2019 Q-submission guidance document.

In conclusion, I hope I've summarized the importance of drug device synergy for safe and effective combination products and CDRH-led orally inhaled drug product reviews. We reviewed these devices using our regulations, guidances and recognized consensus standards under pen by risk-based approach. We aim to work with manufacturers to ensure

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that safe and effective devices are available to the public. Thank you.

DR. ANDES: Thank you, Dr. Blakely. Our next speaker is Irene Chan who currently serves as Deputy Director in the division Medication Error Prevention and Analysis at FDA and is currently involved in oversight of safety recommendations, such as labeling, packaging and product design. The title of her -- is Human Factors Considerations for Inhaled Antifungal Drug Development. Dr. Chan?

DR. CHAN: Hi. Does everyone hear me okay?

DR. ANDES: Yes.

DR. CHAN: Okay. Perfect. Thank you and welcome, everyone. I'm happy to be here. As mentioned, I will be talking about human factors considerations for inhaled antifungal drug development. I realized for some of you, there may not be as much familiarity with human factors, so I'll walk you through. If it comes up today, talk about, you know, what do we mean when we say human factors?

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What does that refer to? And we'll end with some specific considerations as it relates to the development of inhaled antifungal. General disclaimer.

So let's -- let's start with a definition. When we talk about human factors, or you may hear the term ergonomics sometimes used interchangeably, really what we're referring to is the scientific discipline that's concerned with the under -- of interactions among human beings and other elements of a system.

So when we say system, of course that can mean many things. For the purposes of our discussion, we're talking about medical products. That can include drug device combination products.

So there are many definitions that reside out there when it comes to human factors. I'm showing you another one that's actually derived from a national standard. And in this, the definition of human factors talks about the application of knowledge about human capabilities and limitations to the design

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and development of tools, devices, systems, environments and organization.

So really, to keep things simple when we're talking about human factors, what -- is the compatibility of a system that's been developed with people's needs, abilities and limitations. And what's important to keep in mind is where your product is going to be used. That use environment. The scenario under which that product will be used can influence an individual's needs, their abilities or limitations.

So let's talk about a different definition now. What is a medication error? Well, a medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer.

So the reason I mention this definition as well is when we think about medication error prevention and we think about human factors, it's very much a natural fit because at the end of the day, what we want to do is optimize human wellbeing. We want

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appropriate medication use. Ultimately, we want people to be able to use the products as they were intended.

So in terms of who looks at medication errors, that's where the Division of Medication Error Prevention and Analysis comes in. So we're aligned by therapeutic areas and we lead CDER's review as it pertains to medication error prevention and analysis, and the evaluation of human factors information within CDER.

So our mission is to increase the safety or drug products -- use error that is related to the naming, labeling, packaging or design of drug products.

So why do we care about human factors? Well, what it comes down to is we want you to optimize the user interface design of your medical product. And so when I use the term user interface, what I'm saying is a user interface is all those components of a product with which a user would interact. So that could include, for example, the labels and labeling,

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the packaging itself, the delivery device constituent part, as well as any associated controls and displays that come with that.

And why would we want to do that? Why would we want to optimize that user interface? Well, ultimately what we want to do is minimize errors. This is, you know, one example of something that we've seen that when you think about sort of proactive product design and -- and thinking about what user errors that could occur, what we've seen is -- is with this particular inhalational -- inhalational device, it's a product that requires a capsule to be pierced such that the contents can be inhaled.

However, when you think about normal mental modes and what people typically associate when they think about a capsule, what we've all been taught pretty much since we were, you know, seven, eight, nine years old is you swallow it. So it's probably no surprise to this audience that when this product is on the market, what happens is we start getting reports of people swallowing the capsule instead of utilizing

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the device as intended to inhale it.

So one thing that's important to note is of course your inhaled antifungal product is probably going to be a combination product. And my colleague, Dr. Blakely, touched on this definition in his presentation. Within the context of what we're talking about, we're talking really about drugs with devices even though a combination product could also be biologic with the device or a combination of all three of those components. They can be physically or chemically combined. They can be co-packaged in the kit, or they can be separate, cross-labeled products.

So this slide just presents some examples of combination products and certainly aerosol delivery devices or inhalational products are included in that list.

So what's our regulatory basis for evaluating human factors -- where the device constituent part is -- is concerned, we have certain regulations that apply. Specifically, my colleague had mentioned, quality system regulations. And so

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when we think about 21CFR820.30, there's specific language that speaks to the need to validate the device user interface.

The drug constituent side, fundamentally the Food, Drug and Cosmetic Act, focuses on the need to ensure prescription drug effectiveness and safety. And what we do is we seek to reduce risk from medication errors through improved product design, which can include focus on the packaging, the nomenclature of the labeling. And one of our PDUFA development goals was to ensure that drug safety is -- is established by prospectively designing a drug that minimizes the risk for errors made by intended end user.

There is also information that's contained in the quality system regulation preamble that speaks to the appropriateness of human factor studies, analyses and [virtual connectivity interruption] because you have tools available to you to consider how best to design your product throughout your development process.

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So what's important to emphasize is that designing a medical product, it's not just like following a recipe. There are a lot of design and safety standards that exist and certainly they need to be adhered to. But it isn't a box-checking exercise. Ultimately, what we want you to be doing is following a human factors engineering process. And the key point is that it is a process. It's not just completing a single study, though often times I think sometimes there's a lot of emphasis on conducting what's called a human factors validation study. But really, if you want to develop and design something that's safe and effective for your user, you want to think about it throughout your product development.

So this human factors engineering process is laid out here. I know this is a little bit of a busy slide, but what it comes down to is starting with understanding -- who are you designing this for? What does that person look like, or persons? Because often times, products have multiple users. What is that environment that it's going to be used in? How

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do we expect to use it? Why is it being used? You want to think about use-related hazards that can occur while using this product. You want to think about then how do you implement risk control so that you can decrease risk overall in the design of your product. And ultimately, to validate the use of that product and be able to demonstrate to the agency that any residual risk that -- that still exists after the design process is risk that's acceptable.

So as I mentioned, it is a process which means that this is something that you want to be thinking about throughout your drug development. And so that means as early as pre-I&D, you can already be thinking about, you know, what goes into design, doing your preliminary analyses, doing some focus work, doing ethnographic studies, etcetera, as you develop your product so that when you get to your marketing application, you have a set of data and you have a narrative story to help the agency understand what went into your design process. How did you arrive at this final -- oops. Apologies. Formatting issue

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here.

But ultimately, what this slide is intended to illustrate is that when you implement the human factors engineering process, the idea is that you want to take -- continually refine it and in that way, you're able to optimize your design and lower risk.

As we know, healthcare is increasingly complex. We're certainly getting into an era where there's a lot of intersection with digital health. There's a lot of interest in terms of -- I guess you could say special tool software, apps, other things that exist that really are intended to enhance that user experience and also help that end user use their product. But with that can come complexity. So the more complex products are, of course, the more opportunities that may be introduced for errors to occur.

So when errors occur, these consequences of course can be devastating. We want to eliminate the hazards, if possible, in the design of

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these products and that way we can prevent hazardous situations that can ultimately lead to harm.

In some cases, even if we can't completely eliminate a specific hazard, we try to minimize the risk through implementation of risk mitigation strategies that I eluded to earlier.

So, you know, in conclusion, when we're thinking about designing specifically antifungal inhalational products, I think there are some special considerations that -- that need to be taken into account. I think it's important to think about comorbidities in this space, especially likely comorbidities that can impact your understanding of what your user needs. Their capabilities as well as their limitations.

Also, depending on the product that's being developed, the dosing that may be required. There may be issues related to that that can actually restrict which platforms that you choose for your product or what type of a design that can be feasibly made to actually deliver the intended dose.

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Some delivery device platforms are also optimized to deliver to essential lung regions, for example. They may not reach other regions of the lung. So these are things that you want to consider early when you're thinking about lung deposition, when you're thinking about, you know, distribution.

And there can also be some challenges. So when you think about solubility considerations, this can also impact ultimately the end user because if there's additional tasks that are introduced that that end user will need to complete in order to ultimately administer that drug product, then that has to be considered as well in the overall complexity of the product design. Thank you very much for listening.

DR. DAS: Thank you very much. We'll be now going to a 10-minute break. I believe that we'll be resuming at 10:40, and there should be a timer displayed on your screen.

(Off the record.)

DR. DAS: I'd like to welcome everyone

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back. Thank you to all the speakers for an excellent session this morning. The session's going to continue now with Dr. Christopher St. Clair. Dr. St. Clair is a reviewer in the Division of Clinical Outcome Assessment in the Office of New Drugs at the FDA where he provides expertise on development, validation and interpretation of clinical outcome assessments. And he'll be talking about considerations for clinical outcome assessment development.

DR. ST. CLAIR: Thank you and good morning. This is Chris St. Clair. So today, I'm going to be outlining some considerations for selection or -- assessments, which I'm going to abbreviate as COA's from here on for use in clinical trials.

The general disclaimer here that I've used in this presentation here are mine.

So in the course of my talk today, I'm going to go over some definitions for COAs and then give some thoughts related to the development of them. And then I'm going to close with FDA review

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considerations for COAs.

So first, some definitions here. COAs measure or describe how a patient feels, functions or survives. And COAs are different from biomarkers, of course. We generally think of four major categories of COAs. The first one here are the patient reported outcome assessor, naturally the patient itself reporting on their own experience. And then we have clinician reported outcome assessments, which are of course conducted and scored by a clinician who's trained to do the assessment. Then we have observer reported outcome assessments, and one example of this would be an assessment completed by caregiver based on observable finds from the patient. And then we have performance outcome assessments which measure the patient's performance on a standardized task -- though not listed here, digital health technologies are emerging in importance and they can be used to capture clinical outcomes such as mobility and sleep. And that's something we're still -- still exploring and learning more about.

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So a patient -- for a clinical trial really requires a good understanding of the disease or condition being studied, as well as the possible clinical benefits of the intervention and what is important to patients and caregivers. So knowledge in these areas will help you select which COAs to use in a clinical trial. So we're going to go into these aspects in more detail here.

So when you think about the disease or condition, think about its natural history. Think about possible heterogeneity in its clinical presentation. And similarly, consider any patient subgroups that may be important to account for in your measurement strategy, as well as standards of care that may affect how you approach measurement.

The patient perspective is so important in many ways. So talk to patients, talk to caregivers, interview the focus groups. These are good ways to get this information and find out how the disease impacts patients -- how patients feel, how they function, and also what kind of clinical benefit

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would be meaningful from the patient perspective. What does clinical benefit look like to them?

And that leads into my next point which is for you to conceptualize what clinical -- for your intervention. The first component here is to identify the concepts of interest, which are the things that are important to measure. And again, it's important to talk to patients to understand what is important to measure. But also, you know, for you to sort of factor in what your intervention is expected to improve.

The next component is to define the context of use. Context of use includes things like the clinical trial design, the patient population in which the COAs will be used, how they will be used, such as whether the COAs are intended to support labeling claims. And if so, what do those claims look like?

So with the concepts of interest and the context of use in mind, the next question is, well, what kind of COAs are most appropriate for your

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specific situation? It depends. And you may decide to include multiple types of COAs in your -- for multiple perspectives. It's important to keep in mind that the observer reported assessment should rely only on observable signs or behaviors. Symptoms and disease impacts that are not inherently observable would be best measure to a patient-reported outcome, provided that the patients enrolled in your trial are cognitively able to validly and reliably self-report on their experience.

So what does FDA look at when we review COAs? Well, we look at every COA measurement strategy in its specific context of use. So for each drug development program, we're looking at the COAs in the context of the exact study objectives, the exact clinical trial design, study population and the intended labeling claims.

So in other words, there is really no such thing as a COA being validated for all purposes. So I really recommend starting these conversations early with FDA in your drug development process so you

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can plan ahead on how to gather the evidence needed to support your intended labeling claims. But there are good measurement principles that apply more broadly and they're described in the FDA PRO guidance that I reference here. And I highly recommend referring to that guidance.

So when we review COAs, we look at numerous characteristics that are outlined in the PRO guidance. But on a high level, some important characteristics include content validity and then other measurement properties, and interpretation of COA scores including clinically meaningful within patient change.

Establishing content for -- content validity for COA is fundamentally important. Content validity is evidence that the content of the COA instrument itself represents the important aspects of a given concept for its intended use and its target population. So content validity's basically whether you're measuring the right things. It's important, again, to get input from the relevant stakeholders

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such as by talking with patients or caregivers, and to submit that information to the FDA as evidence of content validity that we can review.

COA instruments that are not developed with input from the relevant stakeholders can have some serious issues. So for example, if the stakeholders are not involved in its development, then the instrument might omit important or relevant concepts, or it might include irrelevant content. It could have poorly understood instructions or questions or response options. So again, really important to get input from the end users of the instruments. You know, the patients, the caregivers and so on depending on the type of COA.

Aside from content validity, other measurement properties we look at include reliability, which is how it reproduces. Construct validity, which is whether the COA has quantitative associations with other variables that we would expect, and ability for the COA to detect change. And if possible, it is wise to look at these measurement properties prior to phase

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three to detect any potential issues with the COA and allow for modifications, if needed, prior to phase three.

So lastly here, we have to interpret the COA data and ultimately one thing we need to know is whether changes in COA scores are meaningful. And that's -- to say that statistical significance alone does not indicate whether an individual patient has experienced a meaningful "benefit" from the patient's perspective.

We recommend using anchor based methods to facilitate interpretation of what kind of COA score change represents a meaningful within patient change. And selection of the anchor scales themselves is also very important in order to ultimately provide clear and interpretable information. So the PRO guidance is also useful source of information on the topic of anchor based methods that I would refer you to.

So in closing, every drug development program really has its unique considerations. So come talk to FDA early and regularly throughout drug

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development so we can discuss these topics with you in detail. And as you prepare to meet with us, we recommend submitting exact copies of any COAs that you're proposing to use in your studies, including copies of those anchor scales to help facilitate productive discussions regarding your COAs.

The PRO guidance as well as the patient focus drug development guidance series are really, really useful sources of information that I recommend becoming familiar with, and some of those guidances are listed here. So thank you so much for your attention.

DR. ANDES: Thanks, Dr. St. Clair, for this excellent presentation. Next presentation, we're privileged to have patient perspective from Malcom Birrell, who's a retired pharmacist and is living with allergic bronchopulmonary aspergillosis. One housekeeping technical issue is this is going to be a video. So if you're -- you'll listen to this video through your computer speakers, so please put your phones on mute. Then you can go back to your phones

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and unmute your computer speakers after the video is finished.

I think they'll be loading this video up here shortly.

MR. BIRRELL: My name is Malcom Birrell. I'm a 63-year-old retired pharmacist and I live in the UK just south of Manchester.

My experience of allergic bronchopulmonary aspergillosis, ABPA, began in early 2014, when I was first diagnosed with the condition. Up to that point, I was unaware of aspergillosis in any of its forms. The diagnosis occurred somewhat by chance.

Around Christmas 2013, I contracted pneumococcal pneumonia and esophageal sepsis, resulting in a period of time in intensive care. After I left the hospital, my GP doing some follow-up was concerned that I'd incurred some permanent damage to my lungs, specifically bronchiectasis.

I was referred to the Northwest Lung Centre at Wythenshawe Hospital in South Manchester.

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As luck would have it, this is also the location of the National Aspergillosis Center.

While the lung center was able to reassure me that I had not suffered any permanent lung damage, ABPA was identified and hence, I became a patient in Professor Denning's clinic.

ABPA was diagnosed from blood tests and sputum samples confirm the presence of aspergillus growing in my lungs.

In terms of symptoms, I did not feel that my breathing was particularly impaired, but I did have a persistent and productive cough. Being in my company at this time was probably both noisy and a bit distressing.

I'd suffered with a cough for some time, but I assumed that it was linked to changes in my inhaled asthma medication.

The other problem which I came to realize was an impact of ABPA was as a recurrent bacterial chest -- somewhere in the order of four or five infections per year, and this in turn undermined

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my general health.

My treatment for ABPA commenced with itraconazole taken as oral capsules. Then came the need for regular blood tests to monitor liver function. It was also necessary because of potential interaction to switch my regular statin from mature to pravastatin.

After just over a year, I requested a break from treatment. Itraconazole had eradicated the fungal growth and therefore relieved my symptoms, but I had experienced side effects throughout the treatment of constant mild and altered sense of taste. And actually for me, not being able to enjoy a good cup of coffee, that was particularly difficult.

Having stopped the treatment, of course, the growth of aspergillus in my lungs, unintended symptoms gradually returned.

Itraconazole treatment was recommended in October 2016, unfortunately with the same side effects as before.

In February 2017, a pan azole resistant

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isolate was grown from my sputum and it became apparent to me for the first time that in reality, treatment options for aspergillosis were quite limited.

Hence, my treatment was immediately changed to nebulized amphotericin B taken twice daily. The relative complexity of carrying out this treatment was something of a shock after taking oral medication. It involves making up amphotericin injection solution from powder vials using water for injections. Injecting some of this solution into the nebulizing chamber and adding further water for injections to the chamber, all of which of course is quite time consuming.

Inhaling nebulized amphotericin is a little unpleasant, but I have continued with the treatment and I'm now in my fourth year. The treatment has been successful. I've been well with no, or very little, fungal growth and no cough. I've avoided bacterial chest infections -- by the addition of a prophylactic antibiotic treatment, namely

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azithromycin, three times a week, which was commenced around three years ago.

I would like however to reiterate that nebulized -- practical impacts on daily life. Twice daily preparation, setting up, nebulizing, dismantling and cleaning of equipment is time consuming. It's also necessary to clean your teeth immediately after each session to avoid staining by the bright yellow liquid.

Storage in the home is a further consideration. As you find that your fridge is full of injection vials and you have a wardrobe full of nebulizer equipment, water injections, sharps bins, syringes and needles. All of these things have an impact and shouldn't be discounted.

Given my comments so far about my experience of ABPA and its treatment, it is I think easy to understand that I view the introduction of antifungal inhaler, or specific antifungal nebules as very desirable.

It could mean treatment which is easy

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to administer and is virtually free some side effects and interactions, while also reducing some of the need for blood tests. In other words, a huge step forward from current oral and injectable therapies.

I know from my own experience that lung and respiratory conditions are best managed by inhaled therapy. My asthma has been completely controlled by simple inhaled therapy throughout my adult life. And that contrasts sharply with my struggles with asthma as a child when there were no inhaled treatments and care seemed to rely on very few oral therapies which were ineffective and carried significant side effects. Inhaled therapies weren't introduced until I was in my middle-teens. From that point, my life was largely revolutionized.

Even nebulized amphotericin with all its practical drawbacks has been successful for me in treating my ABPA and has been free from side effects. I should say at this point that throughout the treatment of my condition, I've been fortunate that I was attending clinic at Wythenshawe Hospital and

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therefore had access to the National Aspergillosis Centre. The patient group which is organized and run there is a -- is a real help. When you suffer from a condition which is actually not that common, all that well known, and where there are real issues with the treatments. The opportunity to talk for other patients and to hear from expert speakers is a real benefit when you're a long-term sufferer of a condition like this.

As a final point, I'd like to share my belief that therapies which are as far as possible free from side effects and interactions and convenient to administer are especially important in treating chronic conditions. This is because such treatments encourage good patient compliance. A treatment cannot be successful if patients are not prepared to take it. In chronic disease, a high level of patient compliance is required over the long-term. Thank you very much.

DR. DAS: So our next speaker will be Dr. Edwin -- our next speaker will be Dr. Edwin Rock who's the Chief Medical Officer at Partner

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Therapeutics. Dr. Rock will be talking about sargramostim in the management of fungal infections.

DR. ROCK: Good morning and thank you to FDA for organizing this meeting, as well as to Malcom Birrell for sharing his perspective.

I'm looking for the button to advance the slides. Thank you.

Sargramostim, or Leukine, is recombinant human GM-CSF made in yeast. It's approved for sale by FDA in six disease indications for both children and adults. These labeled indications all build on sargramostim's capacity to stimulate myeloid cell proliferation in the bone marrow and blood.

Over half a million people have received sargramostim since its market introduction in 1991. Although initially given intravenously, subcutaneous and inhalational administration have also been evaluated. As an example, aerosolized sargramostim is being tested now in Europe and the US for therapy of acute hypoxemia due to COVID-19 disease. Sargramostim is available now for

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investigational use as an adjunct to antifungal therapy.

Next slide, please.

Data on aerosolized sargramostim supported safety for investigational use. Inhalational sargramostim has been given chronically to patients with pulmonary alveolar proteinosis, or PAP. A lung disease caused by antibodies that block GM-CSF function. Notably, patients with PAP are susceptible to opportunistic infections, including invasive aspergillosis. Likewise, GM-CSF neutralizing antibody makes lethal experimental histoplasmic capsulatum infections in mice, whereas GM-CSF administration promotes fungal clearance.

On the right here you see an Aerogen ultra nebulizer device. Aerosolized sargramostim can be given with standard handheld nebulizers such as this one, which has been used in both pulmonary alveolar proteinosis and COVID-19 trials.

Next slide, please.

Nonredundant antifungal mechanisms

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support further evaluation of sargramostim for prevention and/or therapy of fungal diseases. In the upper yellow box, you see overall anti-infectious mechanisms of sargramostim whereas in the lower aqua box, you see separate individual antifungal mechanisms with supportive references. These five antifungal effects include enhanced reactive oxygen species generation -- and increased expression of fungal pattern recognition receptor -- one, as well as myeloperoxidase and neutrophil extracellular traps and chitotriosidase. Proof of mechanism that GM-CSF may be a useful adjunct to other antifungal therapies comes from an immunosuppressed mouse model of aspergillus in which intranasal GM-CSF led to a six-fold reduction in pulmonary fungal burden.

Also, anecdotal reports including by an antifungal specialist on this afternoon's panel, suggests that refractory fungal infections may be treated successfully by addition of sargramostim to other antifungal therapy.

These data indicate that GM-CSF may not

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by itself eliminate fungal infections, however, it may be a useful adjunct in antifungal stewardship. While antifungal therapy seeks to weaken the invading fungus, GM-CSF compliments that therapy by strengthening the host immune response. This effect might be particularly useful to treat fungi that are relatively insensitive to available drugs.

Next slide, please.

To summarize, sargramostim is an FDA approved recombinant human GM-CSF made in yeast. It's available now for investigational use as an adjunct to antifungal therapy. Data on inhaled sargramostim supported safety for investigational use and nonredundant antifungal mechanisms support further evaluation of it for prevention and/or therapy of fungal diseases.

At Partner Therapeutics, we're interested to collaborate to evaluate further the clinical utility of sargramostim in fungal and other diseases. Our contact information is provided here. We'll be glad to hear from you, including if you know

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of potential sites that may be interested in our ongoing COVID-19 therapy trials. Thank you in any case for your consideration.

DR. ANDES: Thank you, Dr. Rock. We're now scheduled for a lunchbreak. We're to return at noon with the subsequent session starting at 12:10. Thanks again to all the speakers for their excellent, informative presentations. We'll be able to discuss this further as a panel at the end of the day.

(Off the record.)

DR. DENNING: Can you -- are you online, Dr. Smith?

DR. SMITH: Yes, I am.

DR. DENNING: All right. Do you want to start your talk then? I think your slides are there.

MR. SMITH: Okay. Hi, this is Tom Smith. I'm a clinical team leader in the Division of Anti-Infectives at FDA. And I'd like to open our afternoon session by discussing, from an FDA standpoint, some regulatory considerations for inhaled

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antifungal products.

As you know, we've had a lot of interest expressed recently in inhaled antifungal products. A particular need for allergic bronchopulmonary aspergillosis and invasive pulmonary aspergillosis. There are no approved inhaled antifungal products, but from regulatory standpoint, the general principles for development of an inhaled antifungal drug would be similar to those for inhaled antibacterial drugs.

Now the statutory standard for approval of a drug is demonstration of substantial evidence, which is evidence consisting of adequate and well-controlled investigations.

The characteristics of these investigations are outlined in the code of federal regulations, and some of the important characteristics include a design that permits a valid comparison with the control, and also that section contains descriptions of various types of controls. Adequate assurance that subjects have the disease or condition

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that's being studied, measures to minimize bias and assure comparability of groups -- assessment of the -- that are well defined and reliable, and an analysis of results that's adequate to assess the effects of the drug.

Now the Modernization Act has clarified that in certain circumstances, the agency may consider data from one adequate and well-controlled investigation and one with confirmatory evidence to constitute substantial evidence. And this type of supporting evidence in the past has included evidence from nonclinical and in vitro studies, or from studies in another indication. And one of our discussion questions this afternoon is going to be discuss some of the nonclinical and in vitro studies that might be able to constitute support for approval for an inhaled antifungal product.

Regulatory pathways include traditional approvals, which are based on an endpoint that measures how a patient feels, functions or survives. Or accelerated approval which is based on a surrogate

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endpoint that's reasonably likely to predict clinical benefit or in a clinical endpoint that you mentioned earlier -- comorbidity and mortality. These accelerated approvals require the confirmatory clinical studies -- endpoints in antifungal trials for systemic therapies included all cause mortality and clinical success at a fixed timepoint, which is 6 to 12 weeks.

As I mentioned earlier, the methods of assessment of subject's responses should be well-defined and reliable. The clinical endpoint directly measures the therapeutic effect of a drug, which is an effect on how a patient feels, functions or survives. Whereas surrogate endpoints are markers such as a laboratory measurement or other measurement that's likely to predict a clinical benefit, but in itself is not a measure of clinical benefit.

We've had a number of advisory committee meetings and workshops over the past several years in the areas of inhaled antibacterial drugs for conditions such as lung cystic fibrosis

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bronchiectasis, non-tuberculosis mycobacterial lung infections -- cystic fibrosis.

And there are a number of challenges that we have found in these programs which I think are also applicable to the development of inhaled antifungal drugs. These occur that the patient populations are often very heterogenous in terms of either underlying conditions or the severity of illness, the microbiologic etiologies, the -- it's been difficult to define clinically meaningful endpoints. Unlike the situation with acute infections, patients with some of these diseases have persistent symptoms that are related to their underlying condition. And they don't always respond with what -- you know, complete resolution of their condition.

Also, as Dr. Moss pointed out earlier today for the antifungal conditions, microbiologic endpoints for some of the antibacterial conditions don't necessarily correlate with clinical outcomes.

Treatment regimens have been either --

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typically for inhaled antibacterial drugs have been on and off therapy used cyclically for conditions such as non-CF bronchiectasis, which is similar to what's been done with cystic fibrosis. And it isn't really clear whether other approaches might be better.

The optimum duration of therapy and length of follow-up to determine a treatment benefit hasn't been clear. The impact of therapies on microbiologic floor due to long-term exposure and then a subsequent development of resistant and replacement with other microorganisms remains a concern.

The references listed here are -- will contain the transcripts of these advisory committee meetings and workshops for further reference.

Now the lessons that we've learned from inhaled antibacterial therapies for conditions such as non-CF bronchiectasis and non-TB mycobacterial lung disease also apply to inhaled antifungal therapies. It's important to select clinically meaningful endpoints and not endpoints that are based solely on a biomarker or a laboratory test.

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We emphasize the importance of adequate development work, including phase two trials which will help in determining some of the key design elements for subsequent trials.

Heterogeneity in the patient population must be considered. Variability and treatment effect can affect the trial results. And as we do with the antibacterial -- inhaled antibacterial therapies, we collaborate with our colleagues in the divisions of -- Division of Pulmonary Allergy and Critical Care to help in analyzing some of these endpoints and design -- trial design elements.

To move onto allergic bronchopulmonary aspergillosis, there are no FDA approved drugs for this condition. Infectious Disease Society of America guidelines put antifungal therapy recommend itraconazole as the primary treatment with voriconazole or Posaconazole as alternatives. And they mention inhaled amphotericin B as the treatment for patients who fail or are intolerant to itraconazole.

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Some of our discussions regarding ABPA, some of the -- the issues that have come up include what the intended use of the product is. Whether it's to replace oral itraconazole use, or to permit reduction of oral steroids, to induce remission or to be used as an adjunctive therapy.

Patient population in terms of underlying conditions, whether it's asthma, cystic fibrosis, COPD, there are issues with documenting the diagnosis of ABPA in out-staged and which of those stages would be suitable for entering patients in the trials. Identification of appropriate treatment regimens, how to use adjunctive therapies, particularly corticosteroids would be handled because of the possible confounding efficacy assessments when steroid therapy is weaned.

There are endpoint issues, whether the endpoint should be measures of lung function, patient report -- measures, the number or severity of exacerbations, the time to an exacerbation event, or some composite of all of these. It's important to

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keep in mind that the endpoint has to be clinically meaningful and not solely based on a biomarker or a laboratory test.

The evaluation of exacerbations, there have been issues in terms of how to define the beginning and end of an event, and how to determine whether the event is due to asthma or some other underlying lung condition versus ABPA.

There are issues with how the microbiologic assessments are to be interpreted when the goal is reduction of a microbial burden rather than eradication of an infection. And there are issues in terms of the duration of trials.

We're going to be discussing those issues in the discussion period following presentations.

Then we'll move onto invasive pulmonary aspergillosis. Again, here, there are some approved drugs for systemic treatment. The azoles -- for refractory intolerant -- patients who are intolerant of the therapies, amphotericin B formulations. The

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IDSA guidelines recommend voriconazole as primary treatment with liposomal amphotericin B -- as alternatives -- therapy's recommended. And then they do mention inhaled amphotericin B for tracheal bronchial aspergillosis associated with -- injury and lung transplant patients, or for antifungal prophylaxis in lung transplantation.

So the issues that have come up in terms of therapies for IPA include the intended use, whether it's the -- the therapy's deduced for prophylaxis or for treatment. Whether it's to be an adjunct to systemic therapy versus used as monotherapy. And each of these considerations has implications for trial design in terms of endpoints. You know, whether the endpoint's going to be occurrence of an infection, if it's a prophylactic therapy versus some kind of clinical outcome measurement or treatment.

There are also implications in terms of [virtual connectivity interruption]. There are also issues in terms of superiority versus noninferiority

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analyses. For instance, for an add-on therapy, the expectation would be for a superiority trial versus the possibility of noninferiority for other monotherapies.

Target population's important, whether it's patients with hematologic malignancies, lung transplantation, COPD. The endpoints for the subpopulations under study could vary depending on type of population that's being studied. These endpoints could be clinical, microbiologic, radiologic or some type of patient-reported outcome. And the exact assessment of the response to therapy is -- is also a potential issue.

And then as we heard this morning, some of the other important considerations are -- are from -- that need to be addressed early on in development include the device issues. We heard from our colleagues in CDRH and from the Division of Medication Error Prevention and Analysis. Patient labeling team reviews instructions for use. We encourage early interactions with -- to address chemistry issues.

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And just finally, to sum up, we recognize the need for development of safe and effective antifungal products to treat allergic pulmonary -- bronchopulmonary aspergillosis and IPA. However, trials that are done must be feasible and interpretable with clinically meaningful endpoints. We recommend phase two trials to evaluate possible endpoints, assess treatment effects and determine other important design elements for trials, and we look forward to continue -- continued work with sponsors on trial development and appropriate data packages that would support approval.

We look forward to a productive rest of the afternoon. Thank you very much.

DR. DENNING: -- who's moved with EMA from London to Amsterdam, thanks to Brexit. And he's going to talk about -- give us a European perspective on this.

DR. BOTGROS: Hello. Thank you very much, Professor Denning. Can you all hear me?

DR. DENNING: Yes, we can.

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DR. BOTGROS: Thank you. So thanks very much and thanks to the FDA for inviting me to this workshop to present our perspective on development on inhaled antifungal medicines.

As you notice, I don't have slides for this. Apologies. The slot has been agreed slightly later than the other ones, but I think the good news is that we seem to have a similar thinking in the US compared to what we heard today from our FDA colleagues when it comes to development of inhalational antifungal drugs.

I have to say that we also have -- saw some recent interest in the -- for developing this kind of products. Albeit not too high an interest until now. And therefore, our exposure in Europe to development for this type of product is still rather limited, I would say.

As is in the case in the United States, we also do not have approved inhaled antifungals in Europe for allergic bronchopulmonary aspergillosis. And when it comes to the development of inhaled

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antifungals, or of antifungals in general, as many of you will know, we have in Europe a guideline on the development of antifungal agents. And I have to say that this guidance does not specifically address the development on inhaled agents as it's primarily concerned with the content of clinical development programs to address the safety and efficacy of antifungal agents administered by oral or parenteral routes for the treatment and prophylaxis of invasive fungal disease. But still, the main principles outlined in the guideline do apply at least for medicines in the treatment of prophylaxis or invasive fungal infections, in particular invasive aspergillosis. And here I'm talking about the inhaled -- the ones -- the ones we are discussing today.

So the clinical trials expectations for Europe are that they -- the trials would need to be designed in the same way as described in the guidance.

Of course the situation is somewhat different for medicines developed for the so called chronic conditions, like ABPA. And I will try to

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point out a few particular aspects in the next few minutes.

In terms of for clinical development, and we heard this morning the excellent presentation by our FDA colleague, Dr. McMaster, we are concurrent with the provisions of the ICHM3 or revision two guidance, and of the other regulatory requirements for nonclinical development.

So apart from the standard nonclinical package that was already outlined by FDA colleagues, we also support conducting inhalation toxicity studies for this types of products as well as also mentioned this morning. So in the interest of time, I won't -- the details on this.

With regard to the clinical development, I think we are also quite aligned with our FDA colleagues in terms of regulatory requirements for approval. We generally request conducting phase one studies in healthy volunteers followed by -- by a single ascending and multiple ascending dose studies in patients.

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I think a very important aspect of the development is that the proposed dose regimen and frequency of administration should and need to be well justified. The -- the sponsor should carefully consider the patient population to be enrolled in phase two and three trials. And as an example, in principle asthma patients and CF patients should be studied in separate trials, as the underlying diseases are different. The comedication is different. So this may have a potential impact on safety and so on.

We are of course safety -- we are of course happy to discuss with applicants about the feasibility of that kind of approach, but that is in principle the starting point.

For late clinical development, as well as also mentioned minutes ago by my FDA colleague, it's very important that adequate diagnosis and staging of the subjects is made, and that is critically important.

We are also of the view that any regulatory approval of an inhaled antifungal should be

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based on results generated in adequate randomized clinical trials that are controlled. Which is of course the appropriate standard for approving medicine based on the assessment of its benefit risk balance.

Single pivotal trials are in general acceptable, but I think I need to point out the fact that the results need to be robust in the sense that between phase two and three, there should be a consistent magnitude of the treatment effect that superiority over placebo should be shown in both type of studies, and the safety provide should be benign. If -- if any of this criteria does not apply, I suppose that there will be a need to conduct a second before to trial.

In terms of primary endpoint, it should indeed be carefully chosen to reflect the clinical benefit of the patient. And here we concur with the fact that a biomarker may not be sufficient. We are open to discuss of course with sponsor and the framework of our EMA scientific advice, but we need to be convinced that the endpoint -- the primary endpoint

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is clinically meaningful and that it takes into account an adequate length of treatment, which also may need to be discussed.

And as mentioned for the so called chronic condition, like ABPA, we have no product approved in Europe. We have -- we know and we have the azoles parenteral that are recommended by therapeutic guidelines. As we also heard earlier today from Professor Moss. So there's a need to discuss the design of the studies and whether they should be either add-on or comparative. So this -- these are things that will need to -- to discuss in a scientific advice process.

I need to therefore stress again that we strongly recommend that for developments of inhaled antifungals, the sponsor applies for the MA scientific advice to discuss all the aspects. Quality, nonclinical and clinical aspects. In particular, if the situation is such that the proposal pertains to a drug device combination. And here I need to remind you that we are assessing the device performance in

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our assessment, but we do not license the device in Europe.

In terms of regulator azoles, we have a few available. And I think we can employ those that are suitable to address the setting -- and this are settings of a medical need.

For instance, in case we can be convinced that for example an earlier timepoint can provide adequate initial evidence, we could consider a condition of marketing authorization. But of course, it's too early to -- to -- to say we willing to see the development of the product one by one.

And in addition, we have as you may know applicants for -- designations which bears some incentives in Europe for drugs developed for rare conditions. We have the -- the priority medicine programs scheme that also can be discussed with the EMA.

With that, in the interest of time, I will stop here and not be forward thinking again. Thank you colleagues for having invited me to this

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important workshop. Thank you very much.
DR. MARR: Thank you, Dr. Botgros. This is Kieren Marr, I'm co-chairing the session with Dr. Denning. I'd like to just remind everyone to please use the question and answer box for typing in questions as you go. We will have a robust discussion period at the end, but not after the individual talks.
With that, I'll introduce Dr. Rohit Bazaz, who is a consultant in Infectious Disease in the National Aspergillosis Centre, Manchester University, NHS Foundation Trust and an honorary senior clinical -- at the University of Manchester.
DR. BAZAZ: Good afternoon. Hopefully you can hear me. Yeah. So I'm going to give an overview of diseases that fall under the label of allergic fungal airways disease. And in particular, ABPA and -- and severe asthma -- fungal sensitization. I'm also going to just describe my -- my experience of being site PI for Manchester for the -- the AFAB [ph] trial of the IL-33 receptor antagonist, and explore the issues that we had for recruiting for that trial.

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This -- this figure acts as a reminder that aspergillosis is a spectrum of diseases. And other exposure to aspergillus airborne spores through inhalation is -- is common. Only a minority of those exposed will develop lung disease. And in those who develop disease, the -- the manifestation of aspergillosis -- aspergillus disease largely depends on the immune response of the host. And if there's interplay between pathogen or host immune response that determines the -- the clinical syndrome that -- that develops.
I'm having a slight problem here. All right.
So allergic reactions of course represent a deranged TH2 response to allergens and allergic fungal airways disease itself constitutes a spectrum of disease processes with the clinical features dependent very much on the extent of the derangement of this TH2 immune response. Most patients with asthma are not sensitized to aspergillus, so at the one end of this spectrum, on

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the left-hand side, you -- you have patients with asthma without any fungal sensitization. But moving along the spectrum, you have patients who have asthma associated with fungal sensitization, but in whom -- seems to have a little or no effect on their asthma control. Moving further along the spectrum, you have closely related conditions of fast and seropositive ABPA. That's ABPA without bronchiectasis. But unlike SAS [ph], ABPA can go on to -- to cause bronchiectasis.
So aspergillus sensitization is a -- is a term that obviously of course refers to production of aspergillus specific IGE antibodies following exposure to the fungus. And it can be detected either by skin prick test, leading to a cutaneous hypersensitivity reaction or more commonly by measuring serum aspergillus specific IGE concentration.
Although inhaled fungal spores, fungal candida are normally removed from the airways by various mechanisms, including mucociliary clearance or

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alveola macrophages, effective clearance in patients with asthma and cystic fibrosis allow germination of these conidia into hyphae and that then triggers an allergic response within the airways. And it's used in production of pro-inflammatory cytokines then responsible for the clinical phenotypes that we see.
And the reason that most fungal allergens are released only after spores germinate, after the spores are covered with a hydrophobic, protective layer made up of hydrophobic protein. And that protects the spores and enables invasion of the immune system.
As you can see, there's reports of significant prevalence of sensitization to aspergillus in patients with -- with asthma and cystic fibrosis. And also, it's increasingly being recognized in patients with COPD. Although the implication of this on COPD progression requires further investigation.
And it's not just aspergillus species that we inhale. In fact everyone inhales a very complex mixture of hyphal fragments, fungal spores and

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yeast on a daily basis. And the species composition varies depending on the day and the season and can include species such as Alternaria and Cladosporium. The highest concentrations of spores in the environment are seen in the late summer and early autumn, when over 50,000 fungal spores per cubic meter of air per day can be present. Patients can become sensitized to these fungi -- to -- to all these fungi and studies have shown that the person can become co-sensitized to multiple fungal allergens.

Moving specifically onto ABPA. ABPA, as I mentioned, is an exaggerated immune response to inhalation of -- of aspergillus. It's a complication primarily of patients with asthma and cystic fibrosis. It can rarely occur in -- outside of those conditions. As a complication of asthma, it's thought to affect around 2.5 percent of patients with -- with asthma. And prevalence in children is thought to be less, but reports vary, anything from one to eight percent worldwide.

And estimates of the global prevalence

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and ABPA suggest it has a potentially significant global burden disease is caused by ABPA. An estimated 4.8 million people worldwide effected. With regard to clinical features, it's characterized by worsening respiratory symptoms, cough and thick sputum.

So the model of asthma's being a single entity has changed over time. It's now clear that there are different clinical phenotypes that fall under the umbrella of the term asthma. And these different phenotypes are underpinned by different mechanisms. In broad terms, they can be divided into T2 high and T -- and non-T2 high groups. Allergic fungal airways disease is clearly a predominantly T2 high disease. This is primarily, in terms of pathogenesis, caused by dysregulation of the airway's epithelial barrier allowing access by the stromal tissue -- sorry, access to the stromal tissue by allergens. And this -- cytokines by epithelial cells, eventually leads to an inflammatory cascade inducing the differentiation of naïve T cells and TH2 cells. And eventually leading to IGE production from plasma

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cells.

ABPA itself can be considered to be a severe endotype of TH -- of T2-high asthma. And looking at the mechanism in a bit more detail, what is thought to happen is exposure to fungal allergens induces airway epithelial cells to release inflammatory -- such as IL-33 and IL-25. And these activate enabling for type 2 cells and go on to produce large quantities of type 2 cytokines, including IL-5 and IL-13. And these cytokines drive, as I said, differentiation of B cells to promote the release of IGE. And that leads to sensitization of mass cells -- allergic -- and at the same time attracting and activating eosinophils. These cytokines IL-33 and IL-25 also acts upon the intratec [ph] and naïve T-cells to drive this -- this TH2 differentiation. And ultimately, you're left with a -- a robust TH2 inflammatory response that has various negative effects, including airway and mucous production, hyperresponsiveness and bronchiectasis. And over time, when persistent information leads to

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bronchiectasis, the -- how it drives is advanced ABPA.

So moving onto the clinical features of ABPA, I think it's fair to say that ABPA's probably still underrecognized. And in terms of the diagnostic clues, clearly in terms of patients with asthma, one of the key features included is poor asthma control despite optimization of therapy. And clues from the history are history of recurrent pneumonias and -- and -- and -- and from symptoms, coughing up a thick, tenacious sputum is another clue.

There is -- there is no one test that we can do to diagnose ABPA. It is really a consolation of -- of symptoms and clinical features. And because of -- of that, that there have been attempts to create diagnostic criteria over the years. The first attempt being in 1977. You can see on the left-hand side of the slide. But as I understand -- diagnostic has improved slightly, then obviously the diagnostic criteria have changed over time. And I think it's fair to say probably the most used diagnostic criteria at the moment is the issue --

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working group criteria which you can hopefully see on the -- the right-hand side of the slide there. And requirement of the predisposing conditions. Bronchial asthma and cystic fibrosis. And requirement of an IGE -- certain IGE level of over 1,000, and of course requirement of evidence of sensitivity to aspergillus.

And here we have examples of this -- the fleeting shadowing on chest X-rays. This is a patient who during flares of ABPA, had infiltrates. And -- and the case of 1999 on the left, the infiltrates were on the -- in the right lung and -- but in 2002, the infiltrates were in the left lung. And -- and these are, as I said, flares disease. I think it's important to remember that in many patients, this is a relapsing and remitting condition. They have flares of disease, when they have coughing up lots of phlegm, short of breath, unwell with fever. But then things can -- can settle down over time, particularly with -- with steroid therapy. But there's still fleeting shadowing on chest X-ray changes, changing position of the infiltrates over

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time is quite characteristic.

As I've said also, there's -- there's mucus plugging in here. You can see bronchoscopy images of a patient with -- in the midst of an ABPA flare with thick sputum that's -- that's cluding the airways. And that can lead to actual collapse of the lung in severe cases, as you can see in the X-ray at the top right.

So there are characteristic CT scan features for ABPA. None of these are specific, but they are suggestive. They -- they can be seen in other conditions, but clearly in the right clinical context, they're highly suggestive of the diagnosis. In particular, bronchiectasis, you can see in -- in CT scan B. Central cystic bronchiectasis, which often effects the upper lobes. Over time, as you can see in images C, D and E, you get varying degrees of mucus plugging and bronchial wall thickening, tree and blood changes, the centrilobular nodules with -- with a linear branching pattern as -- as the inflammation progresses over time.

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And as I said, while all these are suggestive of the diagnosis, none of them are -- are specific for it.

So what the potential complications of ABPA though -- from the patient point of view is poor asthma control despite optimization of therapy. And there are specific complications related to the development of bronchiectasis, in particular of course recurrent chest infections, hemoptysis and respiratory failure. And there is a risk of develop -- of ABPA progressing into chronic pulmonary aspergillosis. And even aspergilloma formation, and again, because of this -- this persisting inflammatory response, patients can develop pulmonary fibrosis which of course can impact on lung function. And rarely, ABPA can lead to invasive aspergillosis. Particularly the risk factor would be patients who've been receiving high -- high and prolonged doses of corticosteroids.

So you've got to go in therapy for ABPA, and there's been lots of discussion about this already. The aim of therapy is of course to control

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the acute inflammation and limit the lung injury during -- particularly during flares of the disease. And -- and as with any other condition, we do attempt to individualize therapy to the patient's own clinical symptoms. And of course taking into consideration any other medication that they may be on.

I think it's fair to say that first line therapy is with -- during a severe flare of ABPA would be with oral corticosteroids. There's no clear consensus on dosage -- dosing regimens used. But in general, it would be a fairly high dose, for example 30 to 40 milligrams of prednisone, and this would then be tapered down over time, over a period of three to four months. And that would be first line option in treating a flare.

Now where antifungals have a role to play of course is largely the steroid sparing agent. And would be considered -- so oral antifungal would be considered in patients who, for example, were unable to taper off steroids completely or were requiring frequent courses of steroids over time.

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Now David is going to actually talk about this in -- in a bit more detail in terms of the trial evidence for the use of all antifungals. So I'm not going to touch upon it in too much detail. But suffice it to say that there is some randomized control trial evidence favoring the use of -- or supporting the use of itraconazole and voriconazole in -- in ABPA. And but of course we have to remember that these drugs, while they may be effective, they do have a significant side effect. Profile for itraconazole for example, patients can develop edema and cardiac failure. For both drugs, peripheral neuropathy can be a problem. And with voriconazole, of course, you've got photosensitivity of the skin. So particularly in elderly patients, a lot of them don't tolerate these drugs. So they are often unable to continue these drugs for a long period.

In our own center, we do -- we have had some success with using nebulized amphotericin B fungicidal and there was a small -- of a patient who have responded to that and remained on it for -- for

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several years with a good response. But if you look back at -- at our patient review, overall patients who've attempted this is that very high dropout rate of patients, when given this, many patients don't tolerate it. So as a -- as a large scale treatment, there's going to be a huge number of patients who won't be able to -- to have this.

So again, I'm not going to touch on this in too much detail because it's clearly -- there have been other talks about these during the day. But in regard to drugs that are currently being evaluated, of course we have the -- the inhaled itraconazole and the PC945 nebulized azole. Again, I'm not going to go into this in too much detail because there's going to be other talks I'm aware of -- to this in more detail.

Now moving on to SAS, there are similarities with ABPA, but there are some key differences as well. So requirement in terms of the -- key diagnostic criteria. The patient requires to have severe asthma, which isn't necessarily -- which isn't needed necessarily for ABPA. So severe asthma

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is usually a guideline -- a various guideline for -- to characterize what is meant by severe asthma. And a total IGE level, unlike ABPA, the total IGE level should be less than 1,000, and while -- SAS does not.

So again, in general, the treatment -- David is going to talk about this in a bit more detail in terms of the trial evidence, but the general principles are similar to ABPA so far as treatments nearly consist of optimization of asthma, medication and steroids, if necessary, and antifungals -- specifically itraconazole or voriconazole -- can be used as, again, a steroid sparing agent if necessary.

I'm just -- again, I was going to briefly touch on my own experience of -- of being the site PI for the -- the -- trial. This was a randomized, double-blind placebo controlled trial evaluating human immunoglobulin that -- that binds the main one of the cell surface IL-33 receptor. So as we mentioned earlier, IL-33 is a key inflammatory that mediates the drives of allergic asthma. And clearly the aim here is to block -- block the signaling, the

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IL-33 signaling. This is a phase two trial. And the primary objective is to evaluate the effectiveness of three doses of the drug given intravenously every four weeks, compared with -- with placebo. And in terms of any points, the main endpoints that were being evaluated were the change in blood eosinophils over time and change in blood eosinophils over time and change of fractional exhaled nitric oxide to the FeNO over time, which of course a marker of airway eosinophilic inflammation. There are of course other outputs that were -- that were looked at, including PKPD assessment safety evaluations and so on.

So with regards to the inclusion criteria, fairly standard 18 years and above, moderate or severe asthma, and there were certain criteria that had to be met with screening visit -- visit one, that's a FeNO of above 25, an asthma control questionnaire score of above 1.5, and a blood eosinophil count of over 300 cells per microliter. And then of course there has to be evidence of allergic fungal airways disease.

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Similarly, exclusion criteria were fairly standard and included other significant respiratory diseases or non-respiratory diseases.

Important part of recruiting for the clinical trial is being aware of the prohibits and mediations. And particular notes here with this trial was -- modularity suppressive drugs, which of course is understandable. But this included long-term oral corticosteroids. And of course, many of our patients, as you an imagine having -- are requiring long-term oral corticosteroids because of the -- the severity of their disease. So that clearly was an issue with regard to recruitment. As for the medication which was prohibited with the caveat -- the important useful caveat, that patients who had been on oral antifungals for at least a month prior to screening were allowed to be enrolled, provided they'd been on the same dose of the drug throughout that time period.

So the recruitment targets worldwide was 46. Now our local recruitment target was 5, which we thought was eminently achievable. We're a national

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center. We have lots of patients referred to us from around our region, around the country. However, unfortunately the expectation did not meet reality. And worldwide, I understand the worldwide recruitment was only 18. And locally, we unfortunately did not recruit -- enroll anyone into the trial, which was of course very disappointing.

And because we clearly -- we had the greenlight for this trial in 2018, it clearly became clear over -- after a few months that we were struggling to recruit. So this led to following feedback to sponsor, that was led to a protocol amendment and as I mentioned, the -- the prohibition of uses of long-term steroids was a problem, and that was then relaxed in patients who were on low-dose oral corticosteroids were then allowed to be enrolled. And similarly, it became clear that -- that the cutoff of 300 microliters of blood eosinophil at the time of screening was also an issue. And again, you have to remember this is a relapsing -- waxing and waning condition. So while of course you want to have

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significant inflammation at the time, you have to respect the fact that on any given day, the -- the level of inflammation may be higher or lower. And so clearly it was changed then to be a bit more pragmatic and allow a slightly lower cutoff, but with evidence historically of -- of that higher, above 300 level of eosinophils.

So we did screen eight patients. Four failed due to too low FeNO, three due to too low cynophile count and one due to smoking. It had transpired that they had actually started smoking again after we did a consent with them which we weren't aware of. And so as I said, we do have a large number of patients who have been diagnosed with ABPA and SAS. So we're just exploring why those patients weren't screened. As you can imagine -- declined, but this was a very motivated patient -- this is a patient group we're very much interested in, in being part of clinical trials, as you can imagine, precisely because we're relatively short of drug options. A lot of them did -- did want to be

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involved. And -- and the main issue, as I said was -- was comorbidities or -- medication. That was another major reason why patients didn't proceed to enrollment.

So similarly, at the moment for these conditions, we have relatively limited treatment options. And with regard to recruiting for clinical trials, that does lead to an engaged and motivated group of patients. I think that's only been my experience. And with regard to enrollment, as with many other trials, obviously -- medications can -- can be a significant barrier to recruitment. There needs to be a balance between, of course, wanting to look at the undiluted effect of the drug, but also be realistic with regard to the proportion of patients that were on various medications in the patient group you're interested in. Thank you.

DR. MARR: Thank you, Dr. Bazaz. And now we'll have a lecture by Dr. Denning. He's an infectious disease clinician with expertise in fungal diseases. The professor of infectious disease in

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global health, the University of Manchester. David?

DR. DENNING: Great. Thank you very much, Kieren. So I'm going to take you through a few thoughts about endpoints which I know is sort of critical to engagement in this -- in this area.

So as Rohit and Rick have indicated, ABPA patients may not have severe asthma. Although, the majority have moderate or severe asthma. An so the criteria that you use for evaluation will be a bit different. If you can use a severe asthma endpoint which has been used for a lot of monoclonals, which -- which requires some consideration.

So what might be your primary endpoint options? You may measure lung function, and that's been done in different ways. Walking distance is one, FEE-1 or FEC, and others have promoted the idea of a step test as a easier thing to do than walking distance. Patient reported outcomes, AQLQ is well accepted in many asthma studies. ACQ also. And there's the St. George's respiratory questionnaire which is not been used as much in asthma, but in lots

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of other respiratory diseases. There are general outcomes as to those respiratory ones, and they have the advantage of allowing cross comparison without medical entities. Exacerbation's maybe a key endpoint. I'm going to come back to that. And corticosteroid usage or reduction as well. And that should probably take into account inhaled products, not just oral. And then you may have some -- points including radiology, resolution of infiltrates for example. Sputum markers, such as eosinophils of culture. QPCR for aspergillus or even these days a mycobiome which can be done and assessed, although there are obviously no approved methods for doing that in regulation terms.

IGE and fungal specific IGE are easy to measure and useful. And then you can do a breath biopsy where exhaled breath condensate is another way of approaching that. And FeNO would be another one, although our experience is that many patients with ABPA don't have an elevated FeNO, so that may not be useful.

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And you may also want to do a composite endpoint. So you may choose lung function, patient-reported outcomes of IGE. As three examples, plus or minus steroid reaction as -- as an opportunity there.

So there have been a number of randomized studies done in this area for slight different sorts of patient groups. And I'll take you through some of these and inhaled mitomycin was not very successful. Very small study a long time ago. The others have got a bit more of a label. And the final study here, which I'll talk very briefly about, was actually without any fungal markers, but used in antifungal with itraconazole, steroid resistant severe asthma.

So the first sort of major ICT in this area was done by my fellowship director and mentor, friend David Stevens, and he looked at a reduction of steroid dose by at least 50 percent, and that was oral steroids. A reduction in total IGE of less -- a reduction by 25 percent or more, and one of exercise tolerance improving, results of at least one in five

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pulmonary function tests or reduction of infiltrates. So this was a clear conversive endpoint. And the patients were enrolled in two phases. One, again, placebo with a -- a bigger dose of itraconazole, and then a lower dose for a second 16 weeks. And they all got that. And that was if you like the prize for those who got the placebo in the first side. And when you look at the outcomes, there are several things to note. First of all, on the placebo arm, there was a 20 percent response rate, and that's very characteristic of this asthma population. That there's a -- a good placebo response rate. But there was a better response rate with antifungals which were significant. And then in the second phase, you had additional -- the patients who had been in the placebo arm but got itraconazole had a response rate as well. And overall, that led to a 60 percent response rate. So I think it'd be nice to do even better than that, but that was important. And patients with bronchiectasis didn't respond quite so well. But overall, the number needed to treat was only 3.58

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which makes this a really quite successful treatment for these patients.

A similar study design in content in terms of itraconazole for 16 weeks, but a very different outcome measure with sputum cynophiles are done in South Hampton in the UK. And you can see a very marked reduction in their cynophile counts, and this was marked as well with a -- they measured eosinophil cationic protein at the same time. But they also found a reduced exacerbation rate, but no change in lung function in this study. But it wasn't a very big study. It was only 29 patients.

This is this study using fluconazole on patients who have asthma of moderate severity, but were allergic to trichophyton and had cutaneous skin diseases. This is probably the -- the smallest ever randomized study with a significant outcome with 11 patients treated for 5 months. And they had reduced bronchial hypersensitivity and a marked reduction of steroid requirements, and a peak flow improvement. I think this is partly because the dermatophyte

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infection was treated in patients with asthma who have skin dermatophyte infections should probably be checked and that should be addressed.

So this much more recent study by Ritesh Agarwal who's published a great deal in the area of ABPA has really moved the field forward. Again, looked at itraconazole of 400 milligrams a day for four months, but compare this with steroids -- all steroids. In what they call acute stage ABPA, which is basically new patients coming through, haven't had much treatment for the disease. And they used a composite endpoint here again. They had a clinical improvement scale of -- which -- of four points, and they had to have some improvement -- 75 percent improvement in that. Plus partial clearing of the chest X-ray abnormalities and a serum IGE fall of at least 25 percent.

And helpfully, they distinguished ABPA exacerbations from asthma exacerbations using a -- particularly the IGE, but also the radiological worsening to define ABPA -- or separated ABPA

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exacerbation from a asthma exacerbation. And they -- for exacerbations, they had a specific plan for all of these, including looking for TB because they were in India. And when you look at this at six weeks, you can see that there's a really excellent response rate to steroids as we know clinically, and a pretty good response rate to itraconazole, 88 percent. And as you got to three months, all the patients responded to one or other of these agents. So all these patients really got a lot of benefit. The IGE fell, and I'll show you an example of that, and there were a small number of patients who got exacerbations at one year of therapy, after therapy and a slightly larger group who had exacerbations at two years after therapy.

So when you look at the IGE fall, you can see that there was -- they were very high to begin with, given the normal is up to about 100. And these fell -- six weeks is quite a shock for -- and that fall continued, but was maintained at three months. And when you look at the secondary outcomes, which was timed to the first exacerbation, you had on average to

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wait in the steroid group for about a year and a quarter. And similarly for -- with itraconazole. So the frequency of exacerbation is low even after stopping therapy. And the difference in FEV1 was not significantly different between these two arms. And the number of ABPA exacerbations you can see was not statistically different than the number of asthma exacerbations. Not statistically significant.

And that's shared on this curve, or graph, here where this is one year and this is two years. So it takes a long time to exacerbate with -- with this entity. So you have to -- if you're going to study exacerbations, you need quite a lot of time.

So we undertook an ICT in patients with SAS, which Rohit has described the criteria for as I've got here. But they also had negative IGE antibody as well in the criteria there. And at four months, you had a significant separation between patients on active itraconazole, which again is 400 milligrams a day, versus a masked placebo. The -- just crossed so we couldn't quite claim superiority.

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They relaxed when they stopped therapy and -- but this was significant in around just under 60 patients.

We took the analysis -- the primary analysis was an MITT analysis, so they ran those. Those who came off therapy in the first three months -- - in the first one month were not considered for the main endpoint. And then we had to put a protocol analysis at four months -- I'm sorry. At eight months, actually. And this -- the improvement in the AQLQ was pretty dramatic at .82, and a score out of seven. And it got even greater when you look at the longer period of time.

And when you compare that AQLQ score with steroids in previous work that was done as part of the omalizumab development, steroids give you an improvement of .6. Omalizumab gave you a quality of life improvement of .4, and itraconazole of .8 to 1.2. So this was a really very profound improvement in the -- in the quality of life of these patients, but as I say, they were lapsed up frequently.

We also looked at their IGE and this

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could be used. And so the active group of patients on itraconazole had a fall of about 25 percent, whereas the placebo group actually increased slightly. That was highly significant. FEV1 didn't -- wasn't different, but there was a slight improvement in morning peak flow in these patients, which is statistically significant and clinically valuable, but not a massive change.

So this contrasts with the study that was done in Leicester under Andy Warlaw's [ph] direction where they looked at asthma patients of any severity, but they had to have had two exacerbations in the previous year, and they had to be sensitized to aspergillus fumigatus. And they treated patients for three months with itraconazole -- sorry -- voriconazole or placebo and then followed them for longer. And this was the quality of life measurements here. And there was really no discernible difference at three months between the two groups. And quite contrast to the itraconazole, a SAS study. But they then -- and the study was not statistically

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significant, but that primary endpoint was a 12-month endpoint, but they only treated for three months. So they were hoping that the voriconazole would carry their patients for another nine months. And that probably is somewhat unrealistic in terms of the -- of the ability of a drug to do that. And certainly, we showed early relapse. So this was one of the issues around -- around this study. Voriconazole also has a different set of side effects, and some patients didn't tolerate it terribly well.

And then finally this rather remarkable small study from Iran where they randomized patients to prednisone [ph] or itraconazole and did assessments at one month, because the steroids were only given for one month, and then again at four months. And these with steroid-resistant asthma. So these were patients who were on high-dose steroids, but -- given inhaled steroids, I'm sorry. But given more steroid on top of that. And there was quite a bit of different in -- in -- in these patients between how they improved, particularly at four months here. And the -- when you

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look at the lung function, there was also a major gain in lung function. So the FEV1 was around 1.6 to 1.8, and by the time you got to four months, it was up at 3.1. If you look at FeNO, again, this was not very high in these patients and didn't change very much, so that wasn't very significant. And the eosinophile counts were elevated and didn't fall very much. These are the blood eosinophile counts. And the serum IGE likewise didn't change very much.

So you've got a very different pattern of responses in different sorts of patients. And therefore, there isn't a -- a single one size fits all in terms of endpoint. And these were just some thoughts that I have about -- about this. So precisely who you enroll in the study is really important in terms of what you're going to measure and what the outcome may be. And active, ongoing disease is one of those key features. I'm -- the -- the prevention of exacerbations for short period of therapy, probably not going to be the best approach. You have to show the exacerbations on therapy I think.

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For the patients, improvement in breathing and reduced coughing is very important. They also want to be able to reduce their steroids because of weight gain and -- and the long-term consequences. There are modest changes in lung function. There are significant changes in total IGE in most of the studies. Overall, longer treatment seems to do better. And the exacerbations need to be thought about because you can have ABPA exacerbations, asthma exacerbations or, as Malcom Birrell indicated, bacterial exacerbations -- bronchiectasis. And for the most part, particularly ABPA exacerbations are generally infrequent. So you need a longer duration to be able to -- to assess all of these different things. With that, I shall stop. Thank you very much.

So we'll now move to a different topic area which is what is the potential role for inhaled antifungals in invasive lung infections. And Kieren Marr who is a professor of medicine, highly experienced infectious disease physician who's led

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several studies in invasive aspergillosis is going to take us through the potential in this area.

DR. MARR: Thank you, David. So in way of an outline, I'm going to largely focus as, we have previously, in pulmonary mold infections. And much of what I will talk about is pertinent to aspergillosis specifically.

I will talk about some of the heterogeneity in infections as well as the hosts. And this talk will focus predominantly on hematologic malignancies, subsets of people who also have underwent allogeneic stem cell transplants. And I'll also mention briefly post-viral lung disease associated aspergillosis as a component of people in ICUs. Notably, Dr. Husain, after this lecture, will be talking about lung transplant.

I will specifically address the roles of inhaled antifungals with a large focus on prophylaxis where a lot of the data lye. And also mention, adjunctive therapy.

So this slide on the right really shows

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the -- the spectrum of clinical manifestations according to type of or severity of immune deficiency. And if you consider what I'm going to be talking about today, it's at the far left. And in people who are predominantly very immunosuppressed, then have predominantly acute infections.

I think it's very important to note that disease is dependent on not only the severity of immune suppression, but type of immune suppression. And much -- much of the diseases that we are talking about today have a -- a common early pathogenesis which involves for clearance of inhaled conidia. However, what I'm going to be talking about predominantly today is where poor clearance of inhaled conidia and dramatic immunosuppression of secondary disease can lead more prominently to acute infection.

The goal of airway drug delivery is of course then dependent on the host and the stage of disease, and encompasses both prevention as well as therapy. And I'll just start with some caveats, which is that the literature predominantly does contain

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reports of nebulized or aerosolized amphotericin formulations, but there are -- have been different formulations studied, different devices used and different treatment algorithms. And because of this, I'm -- I'm not really going to attempt to draw any comparative conclusions from the data that have been presented today, but rather overview the disease and clinical use, not really discuss specific drugs.

This slide is a schematic that reminds me to -- to really emphasize that even acute invasive aspergillosis can be a heterogeneous-type of disease with mixed in multiple potential manifestations that involve fungal growth, and specifically germination into hyphae that evokes inflammation and invasion into the airway. Disease can be both predominantly involving the airway, which also evokes mucus production and inflammation, and it can also be invasive to the point of -- of potentiating angioinvasion as well.

So when you consider this in many different types of host contexts, the phenotype can be

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predominantly driven by invasive angio aspergillosis, especially invasive disease that involves dissemination by vasculature. But there are diseases that also manifest in these hosts as well, but involve predominantly tracheal bronchial disease. And when you think about these infections, it's really important to also remember that some of the clinical manifestations that we observe are because of obstruction-type of complications that can also be associated with bacterial pneumonias as well. And so while we can talk about invasive aspergillosis, I think it's important to understand that there are mixed and multiple manifestations that can lead to the clinical phenotype.

The hematology/oncology population is the population that we have studied most robustly over several decades to understand invasive mold infections, and they certainly have unique needs. The -- as I mentioned before, the primary manifestation of inhaled conidia escaping both first and secondary line defenses can ultimately lead to invasion into the lung

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as well as potentially angioinvasion. But when you actually see these patients in a clinical context, it becomes very clear that radiographically, they can present many different ways. The -- the figure here shows classic nodular manifestations as well as more inflammatory, larger nodules with secondary necrosis inhabitation. But we do see a lot of people that can have a predominantly air space manifestations with consolidations. And that can as well involve different parts of the lung, including the pleura, to also evoke pleural effusions.

It's very difficult to treat these people successfully. It's important to remember that we are at the same time trying to effectively treat hematologic malignancies. And so these can be competing forces for certain, and these infections can be difficult to diagnose. Although, we've had great strides over the last 20 years in applying biomarkers both to bronchoalveolar lavage fluids as well as to blood compartments to assist as an aid to diagnose.

One of our primary goals has been to

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prevent these complications. Both because of the attributable mortality associated with invasive aspergillosis, but also because that enables us to more aggressively and for a longer more durable period of time, treat malignancies.

To address that azoles have become our mainstay -- and this started in the early 1990s with pivotal trials showing that fluconazole prevents candidiasis. And subsequently, less so with itraconazole, voriconazole, but then Posaconazole is of course approved for prophylaxis in allo BMT patients with graft vs. host disease as well as in neutropenic patients with myelodysplastic syndromes or acute myelogenous leukemia.

So this is important to remember that we are trying to prevent invasive mold infections, but these patients retain risks for candida infections as well. And so there -- even if we are going to an inhaled strategy, we will potentially be needing to also preserve candida prevention as well.

I'll also add in detail that there are

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new therapies for hematologic malignancies that have presented some unmet needs when considering our -- our -- being azole antifungal drugs.

And certainly, turning to a more detailed discussion of inhaled amphotericin products, there's plenty of proof of concept that has been shown that these products can potentially be useful to prevent development of progressive, invasive aspergillosis in animal models, I think nicely summarized in this metanalyses from five years ago. Most of the literature evaluating the clinical application of inhaled amphotericin B have -- were started in the 1990s. And the first studies by Connelly [ph], a cohort study evaluating neutropenic oncology and BMT patients showed --

David, I think that -- can you mute yourself, please?

Showed that there were fewer infections in the treatment group. And then multiple other cohorts using historic controls or use of oral amphotericin B that is of course rather akin to

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prophylaxis in this setting showed at least strong trends to fewer infections with the inhaled amphotericin product.

The Schwartz study was the largest study that was done in neutropenic leukemia and BMT patients. Predominantly that did show, again, a trend from seven percent to four percent of invasive infections in the active treatment group. But subsequently, largely in the early 2000s, the field moved to applying and evaluating the use of lipid formulations of amphotericin B and two of the classic -- and -- and have predominantly focused on two different drugs, that being ABLC and liposomal amphotericin B. And I'll go into a little bit more depth on those formulations.

The Duke group, and specifically led by Barbara Alexander, published their noncomparative evaluations of inhaled ABLC in 2006 in a small cohort of 40 patients who were treated for up to 13 weeks, who also received fluconazole. And they are reported that there were few infections that were confirmed

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during that period of time. Importantly to note a lot of these patients had come off of that therapy or received empirical systemic antifungals because of suspected disease. That report also disclosed that cough was common as well as some patients developing a decrease in FEV1 at least once after administration of drug. The largest study that has been performed is by Renders [ph] of 271 neutropenic malignancy patients who were treated over 407 episodes in a randomized fashion. Importantly, there's a date there -- here. These were patients that were enrolled between 2000 and 2007. I apologize for that mistake. They received twice weekly liposomal amphotericin B by nebulized route, compared to a placebo. And this study showed certainly decreased incidents in invasive fungal infections albeit with more cough in the active amphotericin arm.

There have been as well some nice studies. I'll focus on this one by Chong [ph] reporting real life outcomes. This was a study with 127 AML patients who received liposomal amphotericin B

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aerosolized during the first and second cycle of chemotherapy, compared to historic controls. These authors reported decrease in documented invasive pulmonary aspergillosis, fewer use of systemic antifungal therapies and some cough savings. I -- I want -- I put up this table to -- in order to outline an important concept which is that these are people who received sequential therapies for induction and then maintenance treatment for leukemia. And their risks are across certain different episodes, there was at least a higher number of infections diagnosed in that first chemotherapy cycle, but a trend to protection as well during the second chemotherapy cycle. These are details to be thinking about with regards to the -- the type of trial designed to evaluate prevention in this kind of context.

And I'll also highlight a retrospective allogeneic BMT study in which drug was administered in the setting specifically to -- for graft vs. host disease. And that it was started with onset of corticosteroids. This was, again, an inhaled

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amphotericin study with fluconazole and they reported a decrease in incidents of invasive aspergillosis during the latter time here as shown in the figure. Importantly, these studies, especially ones that are variable over time, are really limited by the differences in the patient population. There of course were differences in conditioning therapies that led to risks for infections by virtue of their risks for other underlying diseases, relapse as well as graft vs. host disease. And there were differences in the way that the investigators were diagnosing aspergillosis.

Importantly, this is a population that has now a growing amount of unmet needs because of the use of antineoplastic agents that are complicated by concurrent azole use. The classic scenario is with -- application in people with ALL. More and more commonly, centers are using a different agents for treatment of AML, especially BCL2 inhibitors with regimens containing venetoclax. Concurrent use of azoles can alter the -- the amount of this active drug

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leading to toxicities, or on the other end with a too aggressive dose application potential compromise in activity against the EML [ph]. There's also people with CLL and other lymphoid malignancies that are increasingly receiving ibrutinib, as well as multiple other agents like IDH1 or IDH2 inhibitors for AML.

So these are settings in which there are clear unmet needs because of our deficiencies in -- - in ability to give mold active azoles and -- and in many of these settings, they retain very high-risk for invasive aspergillosis.

I want to touch briefly on adjunctive therapy. And I just pulled out a couple reports from the literature in order to illustrate a couple important concepts. There are several agents that have been evaluated, not only nebulized amphotericin B products, but nebulized voriconazole. And reports of successful therapy for concurrent tracheal bronchial disease that is typically in the context of structural lung disease. So there's a lot of reporting bias here, but importantly, it also has implications with

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regards to our ability to develop these clinical studies.

This figure on the top is an example of a patient who had a fistula that was developed after a lung resection for a tumor -- so a lung cancer -- and a hole that was made in his lung that was -- that had a fistula into the airway. And this was pretty clean, although you can see the hole by a bronchoscopy. Ultimately, over the course of time, this person developed an empyema that was complicated with aspergillus. Within the airway you can see in the figures subpanels C and D with inflammation and ground glass within the lung itself. And then after systemic voriconazole, there was some improvement as seen in F and E, especially improvement in the lung parenchyma, but not as much within the airway itself. This is a context where inhaled amphotericin B was given and it effectively cleared the airways much more successfully as shown in panel -- the last panel on the right.

And so this is kind of the -- the setting where we're putting the drug into the place

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where it's most needed. And it also illustrates the potential deficiencies of some of the systemic drug getting back into the airway.

The last case -- the last case that I want to talk about here for adjunctive therapy is a case of disease that developed in the context of severe influenza, structural lung disease. The graph at the bottom is very complex and I'm putting it up here for a reason, and that is to show the length of duration that some of these people can have complications associated with aspergillosis for a very, very long time, becoming more of a chronic invasive infection. And the numerous types of therapies that they go on and off of for both systemic disease as well as tracheal bronchial disease. Evaluating therapy in that context could be rather complicated for sure.

I also want to say briefly that there is, in the literature, multiple reports of adjunctive inhaled therapy being applied for resistant infections or structurally resistant infections. In other words,

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those caused by ones that are relatively protected from systemic exposure because of their anatomy or presence in necrosis. Commonly, a situation that occurs with mucormycosis or even drug resistance -- drug resistant organisms that are successfully treated. Again, a lot of reporting bias occurs in that kind of a setting.

I want to end with a brief conversation of influenza associated aspergillosis and COVID-19 associated aspergillosis. And I think that many do understand that at this point in time, we've had many cohort studies done all over the world that emphasize that this is a real entity that occurs in a significant number of people that have very severe disease that's caused by influenza. I summarize cohort studies that have been done since 2015. And you can see that the reported rates my vary, but when the diagnostics are used very aggressively, of course they do go up. There is as well some geographic and seasonal variation that may be associated with the influenza strain itself.

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More recently, and in fact this month, a new report came out from a French retrospective study that was done over nine years and it had important findings in it that I want to highlight. This was a nine-year retrospective study that reported 21 percent incidents of invasive pulmonary aspergillosis that developed in the context of influenza infection. They reported a rather high rate of concurrent tracheal bronchitis. They did do aggressive bronchoscopies with almost 30 percent of people that did develop tracheal bronchitis, and they described importantly organisms that spoliated in the airway, became invasive, can be radiographically variable. But in the context of this disease with tracheal bronchitis, there were higher markers that included galactomannan and -- and beta D glucan in blood that I think was a little bit surprising for many of us, but important to recognize the potential differences between tracheal bronchitis and invasive aspergillosis in that context.

And I'll stop just by mentioning that

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increasingly, we have become aware of the entity called CAPA, or COVID-associated pulmonary aspergillosis, not well described in reports from China. This is a graphic that I put together that -- that describes the emergence, if you will, or the descriptions that occurred over time. The most definitive ones have been three prospective studies that were reported from Italy, the Netherlands and the UK that reported rates ranging from 14 percent to upwards of 30 percent in people with severe COVID. These were studies that used aggressive biomarker-type of screening strategies as well as some closed circuit bronchoscopy to assist diagnosis. So this is another entity where there is potentially a mix of tracheal bronchial manifestations and invasive manifestations that can complicate systemic therapy.

And I will conclude here. Inhaled antifungals have been compelling for prevention of invasive fungal infections in the context of hematologic malignancies. And certainly there's potential utility for severe viral infection

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associated aspergillosis as well. There is some suggestion of therapeutic efficacy especially in context of airway complications in -- in concurrent invasive disease. I'll thank you for your time.

Okay. If David's not going to come on, I can go ahead and introduce the next speaker who is Dr. Shahid Husain. He's the director of transplant infectious disease at the University Health Network in Toronto. Professor of medicine at the University of Toronto. His research is directed towards antifungal prophylaxis in solid organ transplant recipients. Dr. Husain? Dr. Husain, are you there?

DR. DENNING: He's on mine, but he's not on here.

DR. HUSAIN: Oh, sorry. Sorry. Can you hear me now?

DR. DENNING: Yes.

DR. HUSAIN: Okay. Sorry. So I was saying that I'm really excited to be part of this workshop, especially about the fungal infection because I think this has gone into backburner with

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COVID and everything that here nowadays is related to COVID. So I'm very excited to talk about fungi with fun people around. And I'm going to talk about antifungal prophylaxis and treatment in solid organ transplant, particularly -- or lung transplant.

So just to -- when I talk, is in two parts. And the first part I will present some data to show that the endpoint, what I'm suggesting, what is the importance of this endpoint on the basis of the current literature. And I'll try to -- up a framework for the endpoints for the studies of invasive fungal infections in lung transplant.

So we -- we all know this Seminole study which was done by -- which has well written the incidents of invasive fungal infection in solid organ transplants. And you can see the lung transplant recipients are the second highest in sold organ transplants to have invasive fungal infections.

And this has the consistent -- on the left you can see the -- study from France, and where's the green dotted line is the lung transplants showing

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the higher rate of mold infections as compared to other solid organ transplants. And the right is -- study from Switzerland where it's shown the rate of mold infections in solid organ transplants.

And surprisingly, like we were talking about almost two decades here in the setting of -- prophylaxis among transplant, but the incident -- more or less has --

And then when you look at what kind of fungal infection these solid organ transplant recipients get, you can say -- you can see here the majority of these infections are indeed candida infections, with the exception of two -- transplants that is lung and heart where they're invasive aspergillus infections is noted with higher frequency.

And when you look at them all invasive mold and invasive aspergillus infections in this slide, what I've done is I've combined all the -- of the -- studies done to date in lung transplant to look at what kind of aspergillus species are predominantly noted. And you can see irrespective of the various

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studies in the continent, majority of the fungal infection or aspergillus infection lung transplants are aspergillus fumigatus infections.

Now the next point that I want to address is time to onset of mold infection in lung transplants. The -- lung infection in lung transplant. And you can see majority of the infections do tend to occur between 0 to 12 months. There's a spike peaking around 6 months and goes down to 12 months, and then it dwindles down, the green horizontal bar is the oldest study that we did which included more than 900 lung transplants across the world. And you can see almost 60 percent of -- aspergillosis cases tend to occur within 12 months.

So I like hematology -- the period of neutropenia -- the risk period for the development of mold -- invasive mold in general, and invasive aspergillosis in particular a bit longer in lung transplants.

What do people do in terms of dealing with this issue? There are three surveys. Those are

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over at -- and they are showing and -- majority of the lung transplants will receive -- prophylaxis. Almost 60 percent of them will get an aerosol prophylaxis. Any lung transplant with aspergillus colonization will get antifungal prophylaxis. And majority of cystic fibrosis patients undergoing lung transplant will get invasive aspergillosis.

I am not going to discuss the various prophylactic strategies and their efficacy because most of them are observational studies.

So I'd like to show the slide about the importance of colonization of aspergillus in the airways of the lung transplant. The two studies here are the studies which show the natural course. These studies were published in the absence of any sort of antifungal prophylaxis and lung transplant. And you can see there are two distant patterns that emerge. So for non-cystic fibrosis patients -- transplant colonization with aspergillus is noted in one-third of the individuals. And of these, one-quarter will go on to develop invasive aspergillosis.

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While in patients with cystic fibrosis, if it's a pre-transplant colonization, which is noted in almost 40 percent of the individuals. And majority of them will go on to -- one-quarter of them will go on to develop tracheal bronchitis. So a post-transplant colonization usually does not result in significantly higher rate of invasive aspergillosis.

And in various studies, this -- center is studying aspergillus colonization at one year, was significant risk factors high as of this year, 2.11. And here you can see aspergillosis culture positivity of pre-transplant. The aspergillus culture positivity was associated with the significant risk of disease.

It's not only the development of invasive aspergillosis -- colonization, but also subsequent development of what is called CLAD -- that is chronic lung allograft dysfunction -- which was previously called as the -- it's a very nice study from -- that the risk was higher if you're colonized with the small -- aspergillosis species of which -- is prime example.

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But another study from the other side of the Atlantic, from Madrid, they did not find any association with CLAD. However, you know, they do not differentiate between small and large -- in their study.

So as I mentioned before that -- preferential of inhaled amphotericin B has been used, and especially the liquid formulations because they tend to stay longer in their particular -- as is evidence in this slide that concentration is above the MIC and it can stay up till 160 hours. And in this slide, I'm comparing both the lipid complex as well as liposomal amphotericin B. This is after four days of consecutive doses, people has indeed used, inhaled amphotericin B. Various corporations as shown in the summary slide have with more than 1,000 patients and -- formulation for amphotericin B, deoxycholate and liposomal amphotericin B and lipid complex have been studied.

The issue of -- those are being used for this study's various regimen that have been used

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in these studies, and in the duration. The reported efficacy is important in the extreme -- and I'll let you be the judge, but these are all observational studies.

In the morning, it was mentioned that these drugs do result in side effects -- inhaled side effects. And we heard testimony from the patient who was talking about how difficult it is to take the amphotericin B. And indeed, at least in the literature, beside the fact -- amphotericin B and deoxycholate -- lipid complex amphotericin B. But I would like to -- you to look at the decline in -- in one second -- liposomal -- but clearly, 1 in 10 patients do or go onto develop this decline in -- and almost 1 in 10 will discontinue the amphotericin B drug, deoxycholate. Or if the rate is much less with lipid complex and it was liposomal amphotericin B.

The other thing that we have to be aware of the fact is that the continent's used often yield preferential results in the change of the micro -- and this is very nicely documented in this study

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from Spain in which they compared the aspergillosis sensitivities before they started doing, you know, some prophylaxis that was before 2009 and after. You can see initially, only 38 percent of the aspergillus isolates were resistant to the amphotericin. But after starting the liposomal amphotericin B, almost 60 percent of these isolates became resistant to amphotericin B.

It's not only the resistant amphotericin B isolates that lead to aspergillus, but there was allergen of non-aspergillus mold as highlighted here with the orangish bar.

I have refrained from discussing the definitions because they are standardized in terms of the -- of pulmonary diseases -- but I want to spend some time briefly about colonization definition that will be a unique feature in lung transplant patients.

So eradication of fungal colonization is defined by negative fungal culture respiratory specimens. It can be a single negative culture from the DEL [ph]. Two negative sputum cultures recurrent

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is the isolation of the same fungal during the follow-up at least a month after the completion of the first course of prophylaxis. While -- is a different fungal species from the baseline colonization at least a month after.

And persistent colonization is ongoing isolation of the same fungal species defined at the baseline. And this was very nice to outline this study from -- Australia.

So in summary, what is different from mold infection? So key is you have to take it -- when you are designing a clinical trial. So risk period is clearly longer as compared to hematological malignancy. It is up till a year in lung transplant -- period and almost three months in heart transplant. I didn't show you too much data on heart transplant because they are far and few between.

There are some unique clinical presentations, especially the mold colonization which has not only -- disease, but also indirect consequences in terms of CLAD. Tracheal bronchitis

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which is more common, and bronchial nestum otic infections.

Data on the clinical risk factors in heart transplant is not well defined and -- and the data in lung transplant is slightly better, but it's not the best. We know there are differential characteristics of biomarkers in solid organ transplant, especially lack of sensitivity of sound seen on --

And more importantly, the long-term safety of inhaled drugs are not known and this becomes a prime concern in terms of lung transplant recipients who have around about 50 percent rate of CLAD at five years of transplantation.

So but this -- how do I pull it together and -- and these are just my cards to initiate the discussion. Based on the -- guidelines that we developed about four -- four or five years ago. On the literature -- the base of the literature we thought if you know it's a prophylactic had to be employed, it should be -- nearly be a duration of

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first and -- four to six months. The primary endpoint, it will still be the heart -- endpoint of the development of invasive disease at six months post-transplant -- for six months. It will be at the end of the therapy. But also, we need to assess the population of patients with more colonization at six months post-transplant. Secondly, endpoints of the efficacy of the left side, we can see the symptoms, those are -- study and I think these are the valid endpoints. And on the right are the lab -- that need to discuss -- FEV1 we see. And we have to be, ourselves, at least doing therapy all within 30 days of -- therapy.

Bottomline function test in lung transplant, they need to be more -- time of initiation of baseline and subsequently up to a year, and indeed, tolerance is a huge issue. But with -- that needs to be assessed.

When you look at the secondary endpoint for the efficacy, we need to extend the time period up till a year for these -- most of these studies, even

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the observation studies where we looked at antifungal prophylaxis study they have looked at one year. So it is development of the probable or proven invasive disease, colonization of brachial fungal infection are the primary endpoints. And I think the quality of life, there are few specific lung transplant quality of life measurements. There are one which is called QLPP from the University of Burgh [ph] -- Pittsburgh by -- and that's a very nice one. And all cause mortality at one year along with lymphatic antifungals. Time to diagnose is at a -- rate.

So for preemptive therapy, it is -- at least for the literature, it is directed by positive - - greater than 1, or aspergillus cultures questionable PCR -- but without radiological bronchoscopy evidence of disease during the -- transplantation. Recommended duration is three to four months and the primary endpoint here would be -- aspergillus culture at the end of the therapy. While the proven -- while the population of patients with mold colonization probable or proven fungal infection, and I have combined the

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clinical syndromes together -- at six months of post-sufficient therapy.

Secondly, essential endpoints are essentially the same for safety and the secondary endpoint for efficacy also go up to a year -- up to a year. However, in case of comparison between the preemptive -- two preemptive arms, I think the outcome should be assessed a year post-initiation of therapy. And as -- population, one year is very pertinent for lung transplant because this is the period where they get repeated episodes of rejection and higher immunosuppression. Once they cross one-year hump, they literally do much better.

For heart transplantation, there's no need for routine prophylaxis. It has been employed only in the cases where a program has looked -- has any episode of IEA and could not determine the source of the outbreak. Or when for some reason you found aspergillus under the heart, here the outcome would be -- should be assessed at four weeks post -- of therapy, which is usually six to three months. Second

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endpoints are essentially the same for all inhalation drugs. And then efficacy endpoints are slightly shorter than the lung transplant by six months, but the rest are essentially the same.

I know at least three or four speakers have previously, including Dr. Marr, has discussed the use of inhaled antifungals in the drug, but as a standard of care, they are not recommended. Indeed, they are -- of newer inhaled antifungal drugs and inhaled amphotericin B -- there's lack of human data -- - detailed human data and the -- and the worry of systemic fungal disease. The advantage of nebulized drug is that it is in the highest concentration where it is needed, but the disadvantage is that it does not have systemic effect. So it's like Las Vegas. What happens there, stays there, and that may have some consequences. But I think the two clinical syndromes that might benefit are the tracheal bronchitis and bronchial -- infection. And adjunct with the systemic antifungals probably in the resistance cases. But here, the endpoints have to have both microbiological

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cure at the end of the therapy, as well as -- if I can remember the term -- endoscopic care, or at least normal looking bronchial airways and anastomosis.

With that, I will stop. Happy to take any questions afterwards. I'm looking forward to the discussion.

DR. DENNING: Thank you very much, Shahid. We're going to take a break now. We're just running a little bit late. Can I suggest we -- we convene at -- on the hour? That gives a 12-minute break which will slightly reduce our final discussion. But I think it's appropriate to have a break before we enter into the -- the contributions from industry.

So we'll -- we'll be back in 12 minutes, okay?

(Off the record.)

DR. MARR: Okay. Welcome back to the session on industry perspectives. Our first speaker will be Dr. Lance Berman, who's the chief medical officer of Pulmocide.

DR. BERMAN: All right. Thank you.

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Good afternoon to our US colleagues. Can you hear me?

DR. MARR: Yes, we can.

DR. BERMAN: Okay. I don't see the slides up yet. All right. Let me begin while the slides come up. Well, good afternoon to the -- our US colleagues and good evening to our European colleagues. As Dr. Marr said, I'm Lance Berman. I'm the incoming chief medical officer at Pulmocide. And just before we begin, on behalf of my colleagues at Pulmocide, I would like to thank the organizers for inviting us to participate in these proceedings.

I'll provide some details in the company's novel inhaled antifungal agent, PC945. And will then present some clinical experience with the drug that I hope will illustrate some of the important challenges that we face when building a clinical development program to ultimately ensure that this drug one day reaches patients.

At Pulmocide, we are developing PC945 for the management of pulmonary diseases caused by fungal infections. We are a small company with an

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office in the UK and the US. And we were formed by the former head of GSK -- PC945 is a novel inhaled -- which has been specifically designed for use in the lung. And its potential uses could therefore -- treatments in various forms of pulmonary aspergillosis and prophylaxis in a range of patients at risk.

Our available clinical data to date demonstrates an apparent -- patients not responding to standard of care with good tolerability, very low systemic exposure and no report of drug/drug interaction via the inhalation route with three important characteristics. The first is that the mean particle side is approximately 3.5 microns with a range of about 1 to 4 microns, which is typical of inhaled medicines. Which is similar to the size of aspergillus spores. And so the drug should reach the deepest, smaller airways.

The second is that -- solubility is low and the distillation rate is slow, which results in minimal uptake into the -- by the paracellular route. And consequently, very low systemic concentration in

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the thickogram and more range. Which will have certain safety intolerability advantages, most notably cardiac, nephron and -- and -- and a very low risk then -- for drug interaction.

And in the first characteristic is that the drug accumulates. And so it has a long residence time in airway cells such as the alveola macrophages and bronchial and alveola epithelial cells. We believe this could enhance the ability of the host cells to clear the fungus given that macrophages is our first line of defense from this disease. PC945 works as expected by inhibiting the ergosterol synthesis which causes disruption of the fungal membrane integrity. The drug's antifungal effect has been demonstrated in vitro, in vivo and in humans, and it's been found to inhibit the growth of approximately 96 different fumigates, clinical isolates and is potent again for other aspergillus species such as flavi, nigri and terrei, among others.

It's also been demonstrated to inhibit the growth of other fungi including candida, most

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notably candida auris as well as -- and so on. The drug product is a ready to use vial containing a single dose of 14.8 milligrams of room temperature stable solution and it's delivered using an off the shelf nebulizer. The administration is twice daily of 10-minute nebulizations. And in contrast of the experience that was described earlier today by Mr. Birrell, the administration process is much easier than what he described with nebulized amphotericin B. One simply shakes the vial, pours the liquid into the chamber and begins the nebulization.

We've done, in terms of the clinical development program, four clinical studies. The phase one study included healthy volunteers in mild asthmatics. These were a single dose, rising dose and multiple dose study. These were followed by three phase two studies. Two conducted in patients with aspergillus fungal bronchitis. One in subjects with moderate to severe asthma or other chronic respiratory disease, and the other in patients with cystic fibrosis. And the third phase two study was a

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preemptive study in colonized lung transplant patients. Unfortunately, these three studies had to be terminated early due to the COVID pandemic during which screening activities were essentially halted and patients were shielded from returning to the clinic --

So most of the clinical experience with PC945 comes from the special needs program in the United Kingdom which is a program that's regulated by the MHRA, in which -- supply of an unlicensed medication to meet the needs of individuals or patients where there is no equipment or license for medicinal product.

This product is -- this program, I beg your pardon, is ongoing. And so far, PC945 -- to a total of 10 patients. Nine of these are in the treatment -- either with invasive pulmonary aspergillosis or with allergic bronchopulmonary aspergillosis. And one in the secondary prophylaxis setting.

Briefly, safety and tolerability data from the clinical development and special needs

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program have been favorable with no significant drug related adverse events, and no significant bronchial hyperactivity or bronchospasm wave changes in lung function. These pulmonary assessments were based on pre and post monitoring frequent --

Patients tolerated nebulizations very well and have reported -- taste or smell, which is usually associated with nebulized amphotericin B.

There have been no reported drug interactions so far in the special needs program. This is based on feedback from the treating centers who conduct routine immunosuppressant and antifungal drug thereof, and who reported not needing to adjust immunosuppressant doses when inhaled PC945 was either started or stopped.

And as predicted, systemic exposures have been extremely low in the -- range.

Since most of the clinical experience comes from the special needs program, I thought it would be -- to share an overview of the program and then show you some patient cases as these demonstrate

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the challenges faced when treating refractory ICA, and the potential benefit that PC945 could have.

This table summarizes the patients predisposing backgrounds with numbers of patients per background -- the range of antifungal treatments prior to starting the inhaled PC945, and then the observed overall response assessed after three months.

So of the nine patients treated with 945, eight had invasive pulmonary aspergillosis who had failed or were intolerant of systemic antifungal therapies. And of those eight patients, seven were post-lung transplant patients and one was an ICU patient. And in the nine patients in the program had ABPA which also not responded to antifungal therapies.

Favorable responses which were based on clinical, mycological and radiological assessments were observed in seven out of these nine treated patients. And of those seven, four were complete responses and three were partial responses.

One patient showed stable disease, and it's suspected that the subject may not have had

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aspergillosis when PC945 was initiated. And that what was observed on bronchoscopy was probably in fact granulomatous disease.

And another patient showed disease progression. This patient was determined to have a -- azole resistant fumigator string. And in fact, both of these patients had bronchial stents in -- in phase two.

Before I go to the next slide, I would like to point one patient in this table whose data is particularly interesting. We can't present her -- her images because at this point, we -- consent to do so is still pending. But this is a young woman with mucus-induced hemophagocytic syndrome, who developed - aspergillus bronchitis. And this form of invasive pulmonary aspergillosis, as you know, is associated with a very high mortality rate. This patient was assessed as having a complete response six weeks after treating with inhaled PC945, and she's remained well since stopping PC945.

Across the program, treatment duration

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has ranged from six weeks through to over a year, with five patients still -- still receiving treatment.

These are images of a patient actually that Dr. Moss showed you briefly at the beginning of the proceeding, but I'll give you some more details on this patient. This is a 29-year-old woman with a history of cystic fibrosis who developed invasive aspergillosis one month after a bilateral lung transplant with severe tracheal bronchitis and a large fungal mass over her unhealed anastomosis site. Aspergillus fumigatus was cultured at the time of her diagnosis. She was treated for two months on multiple antifungals, initially itraconazole and then Posaconazole, followed by -- and nebulized amphotericin B. And eventually -- was also added as a last ditch attempt because the team was essentially struggling to manage her infection. Her treating physician was particularly concerned that the anastomosis would be -- due to fungal invasion of her bronchi cartilage. So the patient was started on inhaled PC945 while she remained on Posaconazole and

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terbinafine. In about two weeks after she initiated treatment, her infection started showing signs of resolving. So that after two months, no fungus was visible at the site of the infection, which you can see on the image on -- on the right. Mycologically, her lavage fungal cultures and her lavage galactomannan were negative after our treatment. Well, it should be said that these were also negative before 945 was initiated, despite having had positive cultures at the time of the initial diagnosis.

She was treating in total for about three months and was assessed as a complete response by the clinical team. Her anastomosis has since healed and she's remained infection-free now for 10 months after stopping PC945.

The next patient a 63-year-old man who received a single lung transplant 15 years ago for idiopathic pulmonary fibrosis. About five years ago, he developed CLAD in the transplanted lung and underwent a single second lung transplant. Following this second transplant, he developed an intractable

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parenchymal fumigatus infection in his second transplanted lung, which was -- which was essentially his remaining viable lung. The first image on the left is a CT scan showing his -- his viable right lung riddled with aspergillosis, parenchymal nodules and his fibrotic shriveled up nonviable left lung. He was treated with several systemic antifungals and nebulized amphotericin B, but infection persisted, continuing positive cultures in galactomannan. This patient had a very difficult clinical course and had been requesting hospitalization approximately every two weeks for intravenous caspofungin whenever his symptoms became intolerable or if he developed recurrent exacerbations. He was also having recurrent therapeutic bronchoscopies to review the -- lung. So he was -- levels. After that six months of treatment, his cough had gone and he was no longer waking at night. He described his life as having been transformed. And improvement in lung function was observed and an increase in his FEV1 was approximately 415 mils. So since initiating treatment with PC945,

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he had no exacerbations and no longer required hospitalization for intravenous caspofungin. At this stage, we do not have any data on his mycological responses. His follow-up bronchoscopies have been postponed pending the outcome of the pandemic. As we've been informed that his recent CT scan showed radiological improvement, but we don't have these images yet. So at this time, he's continuing on PC945 and is doing well.

The last patient that I have time to present is an image that I think Dr. Moss showed you as well at the beginning of the proceedings. This woman is in her mid-50s with a lung history of severe steroid dependent asthma and ABPA with a high sputum burden, mucus plugging, chronic wheezing, malaise and frequent exacerbations. In addition to oral steroids, she also received one week of intravenous steroids which requires hospitalization and she usually does this every two months. Over a 12-year period, she had been treated with various systemic antifungals and nebulized amphotericin B, but she developed a

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transverse myelitis to an azole, neurological symptoms to caspofungin and an acute kidney injury to IV liposomal amphotericin B, and she could not tolerate the nebulized form of amphotericin B. She was started on PC945, and after one month her radiological response was assessed as a -- as a partial response, but significantly improved, showing clearing of the consolidation of the mucus impaction. There were no subsequent CT scans available at the time of the last update, but this is the information we have right now. Her clinical response is observed as partial, but also significantly improved as she no longer had heavy sputum load and no more mucus plugging. In fact, about a month after starting treatment, she needed the help of a physical therapist in order to extract sputum from -- which was a significant change for her. There's been a significant improvement of her general wellbeing, her quality of life and her exercise tolerance, all of which have continued to improve over the following months. Her mycological assessment a month after she started treatment was assessed as a

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complete response with a negative lavage sputum cultures which have remained negative throughout treatment. Her total IGE levels fell as well, but we understand that recently, there may have been some -- in a recent exacerbation, which we continue to follow-up on. So at the moment, she remains on PC945 and has had no hospitalizations for intravenous steroids, nor has she received any -- any other antifungal since starting PC945 over a year ago.

And so as we explore the further clinical development in IPA, and in particular, in those not responding to existing antifungal therapies, one of the major overarching challenges which I believe we heard about earlier in the proceedings from the clinical trials -- heterogeneity of patients who succumb to this disease. And this heterogeneity, which is particularly challenging to do with given how rare these patients are and how hard it is to recruit a -- that might otherwise be able to absorb some of this heterogeneity, and the variability that this introduces into analyses.

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So for example, how do we plan for and handle the fact that post-lung transplant and hematology/oncology of stem cell transplant patients with IPA may come into the study with different mortality risk scenarios, when all cause mortality is considered as a treatment failure. And similarly, how should we think about defining standards of care with regard to background antifungal regimens and treatment durations for the purposes of objectifying study entry, and how should immunosuppression of the use of products like GM-CSF for background disease for example be standardized to minimize variability during the study?

Similarly, how should we think about -- heterogenous group, should it be combined or that -- and lastly, if an inhaled agent is added to a background of systemic standard of care or a range of systemic agents, as is the case in an IPA clinical trial, do we need to consider the potential for an additive, or potentially synergistic or potentially antagonistic effect. And if an effect such as this is

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believed to exist, how can we deal with this without necessarily further restricting study entry?

On that note, we are called for panel discussion. I hope the clinical experience and some of these questions raise the right precedent for what's to come. But before I finish, I'd like to thank the patient whose clinical journey we presented and for allowing us to include her images into this talk. As well as the following the physicians who were taking care of these patients. Dr. Anna Reed at Harefield Hospital and Dr. Darius Armstrong-James at Imperial College, but who I believe is still on the panel. Thank you very much.

DR. MARR: Thank you, Dr. Berman. The next talk will be from Dr. Dale Christensen, who's the director of development for PFF Pharmaceuticals. Dr. Christensen?

DR. CHRISTENSEN: Thank you. I'd like to start out today by thanking the FDA for putting on this program and also for inviting PFF to participate. What I'll be describing today is a development program

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where PFF Pharmaceuticals has a unique platform for formulation of -- of drugs that create these -- this -- what we call brittle matrix powder. And -- and essentially, the process is shown on this -- on this slide where we take a -- a drug solution, and this can be -- we can work with poorly soluble drugs. And so you can make an aqueous organic mixture. You can add excipients for stabilization and we -- we then drip that solution onto a cryocooled stainless steel drum where it instantly freezes very rapidly. We then collect the chips of ice that are created from that cryocooling process, put them into a lyophilizer and remove the solvents, leaving this brittle matrix powder. That powder can either be put into vials or capsules. In the case of inhaled drugs, we put it into capsules and then we deliver it with a dry powder inhaler using commercial devices.

What we end up doing is taking a crystalline-type drug in most cases and converting it to this brittle matrix powder that is shown on the bottom right slide. And this -- this standing --

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microscopic image shows that we've, you know -- that rapid cooling process essentially traps the -- the drug and excipients in a matrix that -- that when the solvent is removed, creates a powder that has a very high surface area to volume ratio. When it's delivered through the commercial -- through the DPI device, the sheer induced by the device creates ideally respirable powders with anywhere from 60 to we've seen up around 90 percent of the particles in the one to five micron range with -- with a typical MMAD around 2.2 to -- to 3. And so we are getting very high efficiency delivery to the lung.

So what I'll be describing going forward is the initial clinical trials where we've used this process to make a voriconazole powder for inhalation. And we have recently announced that we completed a phase one clinical trial with the voriconazole inhalation powder. It was a placebo controlled single ascending dose followed by multiple ascending dose. Typical phase one study, six plus two placebo controlled with dose levels of 10, 20, 40 and

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80 milligrams of voriconazole inhaled in the single ascending doses. And then in the repeat dosage, we also used those same doses, but delivered them twice daily for 17 days, or 13 total doses. Where we looked at blood sputum -- blood and sputum exposure on day one and day seven in the -- following the single dose on -- in the -- and we also looked at extensive characterization of the pulmonary function, tolerability, other safety signals. And when we completed that study, we have looked at the PK. And what I show here is a -- a graph showing single dose PK and we'd recently received the repeat dose PK, but I didn't have -- have time to get it incorporated in this. But what you see from a single dose is that -- and it's the -- the inhaled is on the -- are the lower ones leading up to the 80 milligram dose that is the blue line. And we see a -- of -- that is essentially right after dosing. Our first collected time point was 15 minutes following administration of the dose. So we're seeing very rapid uptake into system circulation. And clearance that it is typical of the

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voriconazole clearance.

In the multiple -- in the repeat dose phase, we did see some accumulation and we are seeing levels that are -- are clearer and present, but they are also safe doses. And one of the key points here is that just because we're delivering this to the lung, doesn't mean that you go without systemic coverage.

In terms of safety, we received a letter -- a summary letter from our data safety monitoring board. This trial was very closely monitored by DSMB. Knowing the risks of the oral voriconazole in terms of visual disturbances and the various hepatic toxicity and others. And what we noted is that, you know, in terms of the tolerability from the inhalation and the lung -- or respiratory perspective, there were no changes in FEV1 assessed at any time point following single dosing, or at any time point on day one, day -- day four, day seven following repeat dosing. And so the drug is very well tolerated in terms of respiratory function. We also saw no --

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no ECG or liver -- liver or enzyme changes suggesting that the inhaled powder is tolerated far better than the dose limiting toxicities that occur from oral dosing.

Moving onto how we're looking at developing this further is really -- we are looking at development of this to treat invasive pulmonary aspergillosis patients as they transition from an inpatient IV therapy into the normal point where they would go onto the oral therapy to -- on an outpatient basis. And, you know, we are looking at various inclusion criteria, whether -- whether we would be treating only those who microbiologically confirmed disease, or whether it's -- whether it's culture or PCR confirmed, or whether we would treat patients when -- when it is diagnosed as a probable aspergillosis.

We will be looking at radiographic evidence from chest CTs, biomarkers, galactomannan, and ultimately as everybody in this conference has discussed so far, we have a small -- small group of patients who are -- tend to be very susceptible in the

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hematological malignancies -- bone marrow transplant, lung transplant patients.

And so one of the key questions here that -- that occurs is, you know, defining that patient population. Because as we've heard previously, there is a discussion about -- about what is a representative population. And so, you know, we -- we need to determine -- and this is something where FDA input will be required in -- in determining how many patients with hematological malignancies will be required in a given cohort in order to provide that broad approval. Or whether it needs to be a narrow trial where we're only treating hematological malignancy patients, and going for a limited population approval in that group.

Certainly, you know, because we are planning this as a monotherapy approach, we would be trying to rule -- or we would rule out patients with angioinvasive or evidence of systemic disease. And we are doing this as a double-dummy design where all patients would be getting either placebo inhale

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capsules along with a background of oral -- or they would be getting one of two doses of the inhaled voriconazole and they would be getting an inhaled -- or an oral placebo. So that the patients don't know what they're getting, or which route they're getting the voriconazole from. The physicians would know that their patients are getting voriconazole, but they also would not know what route they're getting it from.

So in selecting our doses for this study, we are -- we have been talking to key opinion leaders and we are guided in part by this paper published Hilger Getall [ph 42119] from Denmark where they -- where they treated a -- they published three -- three patients that were treated with 40 milligrams three times a day for two weeks, and then they dropped the dosing down to 40 milligrams twice daily. And this was the nebulize -- they were nebulizing the intravenous drug formulated -- or diluted down so they could deliver it via nebulizer. And in this case, they -- they used -- or these three patients that they treated, they did a monotherapy, so there was no

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systemic antifungal that was being administered to these subjects. And then they also -- they cleared the aspergillosis in all three patients. They saw improvement both radiographically, microbiologically as well as in lung function for most of them. And importantly, there was no systemic escape that was reported for any of them when they only received inhaled voriconazole treatment.

So coming back to our trial design, we are currently looking at, you know, defining the outcomes. And this is again a case where, you know, going back to that patient population as Dr. Berman mentioned just previously. You know, if -- mortality is a limiter, you know, if we're going into hematological malignancy patients, how do we define whether -- whether that mortality was from -- from their cancer or whether it was from the aspergillosis. And so those are some things that we need to very carefully work with the FDA to define.

And the other endpoints that have been discussed, but again as Dr. Berman also mentioned, you

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know, stable disease. If we -- if we're seeing a patient with no change in CT lesion growth. If their FEV1 is stable, do we define that as a treatment -- treatment failure, or is it a success? Because the disease has not gotten worse.

And importantly for this -- for our approach, you know, because we are proposing a monotherapy in comparing -- we would be looking for, as was previously mentioned in the clinical pharmacology discussion, we would be looking at potential for superiority in the treatment arm in terms of efficacy. But at least we would be looking at noninferiority. But what we would expect due to the lower levels of systemic drug here is, you know, increased safety in terms of fewer patient withdrawals due to adverse events. We also would expect that there are fewer drug/drug interactions. In the case of transplant, we would expect that by giving the patient the -- the inhaled, that we would see less requirement for changes to the dosing of their supportive immunosuppressive therapies. And then

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coming back, finally, you know, we have been discussing, you know, enrollment rates. And, you know, we're getting reports from some -- or we're getting some estimates of a site being able to enroll around one -- or one-tenth of a patient per month per site. And so this creates a very large trial if we're going into a large population -- that. And so we are very interested in exploring the potential for a limited population approval for -- for this drug.

And to summarize, I believe that we have the potential to document or demonstrate several advantages of the TFF voriconazole formulation in that we will be delivering the IDSA recommended first line agent for aspergillosis, and delivering it directly to the site of infection. We believe that based on our results, that we'll be able to generate a higher local concentration in order to get that greater efficacy for the treatment of the pulmonary aspergillosis. And then due to reduced systemic exposure, we have the potential for lower toxicity and reduced potential for drug/drug interactions.

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And with that, I would like to thank you all and look forward to the further discussions.

DR. MARR: Thank you, Dr. Christensen. Our next speaker is Dr. Charlotte Keywood, who is director of -- head of Global RND at Zambon. Charlotte?

DR. KEYWOOD: Thank you very much. Yes. Good afternoon and good evening to everyone, and thank you very much for inviting me to give some perspectives from the sponsor side on the challenges for clinical development in ABPA.

Little bit of background about Zambon, the company I work for. I'm head of Global RND there. It's a family owned company with a headquarters in Italy, and the company is 114 years old. More recently, the focus of the RND pipeline has been in severe respiratory infection and inflammation.

In Europe, we have on the market an inhaled form of colistimethate sodium which is nebulized through a handheld nebulizer. And that's licensed for treating pseudomonas infection in cystic

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fibrosis patients.

Now this product is also now being developed in a global phase three program for treatment of pseudomonas infection in lung cystic fibrosis patients. And there may be some things that we can learn from that program that we can apply going forward in ABPA.

We also have a phase three program in bronchiolitis obliterans syndrome using liposomal --

And then at Zambon, we also have a proprietary drive how to formulation platform called the Edry platform. And this is looking at developing inhaled anti-infected. But the new program is an inhaled formulation of voriconazole which has very good lung penetration. And we're developing that for ABPA in asthma patients.

We hope to be able to follow that up with Edry inhaled antibiotic for mycobacterial infection. And then also we're looking at a potential anti-inflammatory for acute lung injury.

So as you can see, Zambon is pretty

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heavily interested in acute -- or I'm sorry -- serious lung infection. And so getting a good trial design for any of these indications is clearly something that we're interested in and that is important.

I think some of the things that we're going to discuss have been touched on previously, but I want to put them in the context of a sponsor trying to design and then run a clinical trial. Clearly, there's an unmet need for an effective agent for ABPA. That's easy for patients to use a, as a patient representative said. And also, hasn't got the side effects associated with system azoles. I'm only considering or how are we going to design the clinical trial? What is in the clinical development program? What is important to bring to the patient?

Well, clearly, we want to reduce the frequency of the exacerbations. Reduce the use of steroids Reduce the systemic azole therapy. Reduce the healthcare utilization so the patient doesn't have to go to hospital or so any clinic visits. And hence, improve patient function and quality of life.

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And bearing these objectives in mind we have to try to ease them into the development program.

So at -- there's three areas of -- of development challenges, which is sort of what patients, what outcome measures, and then how do we run the trial?

So in the first instance, let's look at patient identification. And that's in itself an initial challenge because the prevalence of ABPA is not entirely clear. The number of patients in the ABPA pool is unclear. The prevalence estimates are currently derived largely from expert centers who tend to see quite a number of these patients. And so the prevalence may be overestimated and not easily applied to the general asthma population.

Second challenge is at what stages ABPA should be treated. Should we be treating acute ABPA exacerbations, or shall we be looking at stable ABPA? And then in which case, how do we diagnose and define these?

At the moment, there's no one status

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criteria for diagnosis and classification of severity of ABPA. Now some criteria have been published, but they're not necessary a hard and fast consensus. And it's not known exactly right now how well they would lend themselves to application in a clinical trial. Of course, at the moment, there's no hard and fast diagnostic criteria for patient entry into the clinical trial.

If you're looking to bring patients into a trial, how do we document the history of stable ABPA? And then how do we go forward to define it for entry into the trial? We can use the ISHAM criteria, but then how best do we apply that to get our homogenous patient population, but without making the inclusion criteria so difficult that the trial becomes unfeasible?

Moving onto light outcome measures. So what do we measure? Well, at the moment as we know, registration trials for ABPA haven't been done. It's entirely new territory, so the endpoints have yet to be clearly defined.

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Some of the endpoints that have been used in asthma and cystic fibrosis in the past may all not really be applicable for this kind of population. And in considering the endpoints, of course we have a choice between our surrogate endpoint and our clinical outcome measures. And which ones should we be using when? The surrogate endpoints including laboratory measures, such as IGE, galactomannan, imaging, chest X-rays, high resolution CT and pulmonary function testing. These well might be better to be used in the early phases of development to be looking for signal as to whether you're getting drug effect. And they can also be used to perhaps support clinical outcome measures which probably lend themselves better to the later phase of development, where we need to show patient benefit.

And in thinking about the outcome measures, well, we want to reduce the amount of times patients have bad events and their asthma gets worse. So we can look at pulmonary exacerbations. But what do we mean by that? How do we define and capture

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exacerbations?

Within ABPA patients, they tend to have three types of exacerbation, and that could be like an asthma attack, an ABPA exacerbation itself or even a bronchiectasis exacerbations. Do we combine all three in a single endpoint or do we try and separate them out? These exacerbations do have different treatment modalities, and so how do we then capture and analyze that in a clinical trial? Should we be looking at frequency or time to first exacerbation? There are drawbacks to looking at time to first exacerbation due to the fact that you lose data after the first timepoint has been reached.

A big important aspect of treating ABPA is to reduce steroid use and to reduce azole use. So we need to capture that within a clinical trial. Should that be a primary outcome measure or secondary? How do we capture the steroid burden and the systemic azole burden within the clinical trial?

And of course, we need to look at quality life -- quality of life, patient

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functionality. So which of the PROs would really lend themselves to measuring this in these clinical trials?

Finally, sort of how do we do the trial? Now there's any number of development challenges on how to design and conduct the trial, but I just need to hit on a few that really sort of jumped out at me. First of all, the selection of trial sites -- I mean, this is a highly specialized area of -- of research and patient treatment. There's no patient registry for ABPA at the moment, so identifying patients asthma community does present a challenge.

The trials themselves will be quite complex to do, both in identifying patients and then managing them through the trial. The trials will have to be conducted at very specialized centers, and there are a limited number of specialized centers for ABPA.

Duration of treatment. This was touched on a little bit earlier. I mean, how long should we treat for? Longer is probably better. Should we be thinking about the way ABPA exacerbations are normally treated with oral azoles? Should we have

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treatments that go weeks long? Months long? Into -- continuous? These are all things we need to think about when we're trying to design the trial. And it will affect the patient recruitment and retention in the trial.

As I mentioned a bit earlier, identifying patients but not making the inclusion criteria so difficult that we can't get patients into the trial or we screen -- we really have to balance the need to get a robust population, robust and homogenous population to demonstrate drug effects, but balance that with not excluding patients who may benefit from the treatment, and making recruitment very difficult and the trial essentially unfeasible.

Capturing and managing the exacerbations. For example, we need to look at the type of exacerbation and then document the start and duration of those exacerbations. Now when the types of exacerbations are managed a little bit differently, then they will have different durations. And so that may present difficulties in looking to analyze the

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data.

The test to support the diagnosis of an exacerbation such as IGE and chest X-ray require patients to come into hospital, be examined and take time to report. So then again, that -- that presents some logistic challenge in documenting exacerbations.

When we're treating exacerbations, whether it be an asthma or ABPA or bronchiectasis exacerbation, we need to have a standardized treatment regimen for patients in the trial so we can at least compare and make conclusions on treatment efficacy.

And it's also -- looking at the bronchiectasis example, it may be that the need for patients to come to hospital when they have an exacerbation can sometimes lead to underreporting of exacerbations. Possibly less likely in ABPA where patients may well be much more severely ill and they're more likely to come to hospital. But even so, the need for patients to then come in and go through a number of tests may present barriers for patients reporting exacerbations in trials. It could lead to

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underreporting.

And then that brings me on to talking about sample size estimation. Right now, there's no precedent for ABPA trials, so we don't know how to measure our -- our outcomes, or the frequency of the outcome variable and what would be a clinically significant improvement in that outcome. So if we're thinking of frequency of exacerbation, how many exacerbations per year could we expect patients to have in the trial? And what would be a meaningful outcome to reduce frequency? Can we use examples from bronchiectasis trials? Would that help with -- there is some overlap between these types of patients. But on the other hand, they are distinct clinical entities.

So these are just some of the challenges in the -- considering the clinical development. And when we take this into account, we also perhaps want to look at the regulatory pathway considerations.

The azoles that are being developed for

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inhalation in ABPA are already well known. We're looking at voriconazole that has a long history of human exposure. The systemic effects of voriconazole are very well characterized. And so the safety profile in humans is well known.

Clearly, the inhalational safety will be well studied in the preclinical and -- and clinical studies. But also looking at the clinical development challenges, we can see that these trials are very difficult, and they're behaving very much like rare disease trials. So recruiting patients for these trials, we need to think of them in the context of a rare disease-type trial.

So knowing the safety profile of the drug and knowing how difficult the trials could be, what could be an appropriate number in size of study for us to find NDA or an MAA? How can we -- can we streamline the process to get these important treatments to patients more rapidly? Should we consider QIDP and fast track designations? This probably qualifies for that sort of designation. And

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like our previous speaker said, should we consider LCAD for ABPA? Could there be a set of patients within ABPA that could be considered for LCAD?

So these are just some of the perspectives on the development and the challenges that we have. Clearly, these challenges are well worth meeting to try and bring these important treatments to patients. And with that, I'd like to say thank you very much for listening.

DR. MARR: Thank you, Dr. Keywood. Our last speaker in the industry session will be Dr. Russell Clayton, who's an interim executive for Pulmatrix.

DR. CLAYTON: Thank you very much. And I want to join my colleagues by thanking the Food and Drug Administration for a very well planned and very well executed workshop on this very important topic. I'd also like to take a moment to congratulate all the presenters today on -- on very pointed, relevant, excellent presentations. So thank you very much.

I'm going to talk for a minute about

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Pulmatrix. The pleasure of working with Pulmatrix, which is a Lexington, Massachusetts based company that engineers a dry powder delivery vehicle with the goal of developing inhalation medications for a -- you know, therapies for a variety of diseases. The -- the technology platform is the -- particle, which has the potential to be used with a broad range of different therapeutics. It has the ability to carry relatively high payloads, but the real beauty here is the potential to have a high dispersibility with a low inspiratory flow. Considering that a lot of inhaled medications are being delivered to patients with respiratory disease, it may not be able to generate high inspiratory flows there.

One of the primary products in development is POR1900, also referred to as pulmazole. You have heard some of the speakers previously refer to some of the phase one data. Pulmazole or POR1900 is being developed for the treatment of allergic bronchopulmonary aspergillosis, or ABPA. And I think we saw some data earlier today that demonstrated that

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a single inhalation of 20 milligrams provided a minimum inhibitory concentration against aspergillus fumigatus for a -- a full 24 hours after a single dose. And yet that same single dose had an 85-fold lower systemic exposure than a single dose of a 200 milligram dose of the oral -- oral solution there. There's a misprint on that slide. Oral itraconazole for oral plasma exposure.

So there really is a potential to eradicate aspergillus fumigatus from the lung of patients with ABPA. And it's been underscored several times that one of the important goals is to reduce corticosteroid exposure in this patient population and ultimately shorten disease course, but at the same time minimizing the risk that comes with systemic azole therapy for -- for these types of products.

So after the phase one studies were completed, Pulmatrix launched a phase two study in patients with asthma and ABPA. You see the design of the study on the slide, basically four arms looking at three different doses with a placebo control group.

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The primary objective to assess safety and tolerability, but also to evaluate potential endpoints. And we've heard a lot of about endpoints and the uncertainty there. And also to hopefully identify an optimal dose.

You see what -- what we were trying to recruit, basically males and females 18 to 75 years of age, and they were being asked to perform once a day dosing for 28 days.

So what did we learn and how did this -- how did this study proceed? We had over 25 sites in five countries that were identified with a proven track record of excellent performance in clinical asthma studies. So going in felt very confident that we'd be able to enroll this study. And it was a mix of freestanding clinical study sites as well as academic institutions. So we had what I think was -- would be classified as the best of both worlds there.

On the right-hand side, you'll see the inclusion/exclusion criteria we -- we heard at -- by Dr. Keywood very well illustrated some of the

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challenges with regard to the inclusion/exclusion criteria, and the limitations we have. Because if your inclusion/exclusion criteria are too strict, you're going to not be able to recruit your population. Of course, if they're too wide, then you have a very heterogenous population.

So this was thought by the planning group to be a good mix of inclusion/exclusion criteria. We did use the ISHAM criteria to diagnose ABPA and limited it to stage 2, 4, 5A and 5B. So that eliminated ABPA that was an acute or exacerbation mode, or newly diagnosed ABPA.

And one of the key inclusion criteria was at the time of enrollment, the subject had to have a total serum IGE of greater than or equal to 1,000 -- that's for ML.

Another key criteria with regard to prohibited medications was the -- the subjects could not have received any of the monoclonal antibody therapies targeting asthma, or azole therapy in the last six months. And we're going to return to that

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topic in -- in -- in a moment.

So how did this study proceed? Well, similar to what Dr. Bazaz presented, there seemed to be a shortage of -- of eligible subjects. There was a relatively small pool. The -- each of the sites had a multifaceted recruitment plan. They executed -- qualified, but were over 75 years of age. Several subjects could not meet our BMI cutoff of 35, and we had quite a number of subjects whose current IGE level was -- was far less than -- than 1,000.

And so that was one of the -- the bigger sticking points here and -- and a cause of -- with regard to whether or not, you know, how do you know when it's no longer ABPA when their IGE is -- is less than 1,000? So that's -- that's caused a little bit of a concern there.

And then we had a number of subjects that were -- that were disqualified because of omalizumab use. And I wanted to -- to pause on that point only because it was -- it was stated earlier that this treatment -- I think the speaker who I

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respect very much said it was -- it was validated. I'm -- I'm not so sure that that particular treatment has been validated. There are basically a number of small studies, case reports, that sort of thing. And for that reason, we had to exclude these subjects because we just weren't sure about the -- the safety and efficacy of this particular product in ABPA.

But more importantly, this -- this particular product is known for increasing serum to the IGE levels. And we -- because we're concerned that that would potentially mask an effect because we were looking at IGE levels as one of our markers of effect here. So we had that very significant barrier because unfortunately, use of this product off label in this population was -- was not uncommon.

What did we learn? We learned that site selection is -- is a key factor here. You -- you really need to go to sites that have a robust population specific for -- for ABPA. And in that particular vein, the academic sites tended to perform better than the freestanding research units.

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We also learned that the inclusion criteria need to be rather wide, but of course not too wide because then you start getting into a population where you're going to have trouble interpreting the data.

And importantly, you have to define a relevant and realistic lower threshold for IGE. What is the right number? What is -- what is the wrong number for bringing patients into a study who are diagnosed with ABPA, and yet they have an IGE level below 1,000.

So what happened with this study? Well, similarly to what we've heard previously, in March, the study was suspended due to issue related to -- to COVID-19. And a few months later, the decision was made to -- to terminate the study basically due to uncertainty, again, with regard to the COVID-19 pandemic. So as -- as of July of this year, this study was -- was terminated.

I'm going to pause for a second to talk about measures of effects. We were looking at several

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different measures of effect in -- in this study. I mentioned IGE which is very commonly used clinically as an indicator of improvement. Many clinicians, we use IGE as it decreases as a indicator to reduce, for example, the dose of glucocorticoids. And so that -- that is a measure of effect. But as we've heard, this is a -- a laboratory biomarker, if I can even use the term biomarker. And it's unlikely that this would of and by itself be a -- a relevant clinical endpoint, or valid clinical endpoint, without some sort of other clinical endpoint supporting IGE as well.

In the phase two study, sputum eosinophils was chosen as a measure effect. This was modeled after Dr. Work's [ph] study which looked at sputum eosinophils after 16 weeks of therapy with oral itraconazole. But this is an endpoint that is -- or -- that is technically challenging to say the least. There were a number of our sites that frankly struggled with the ability to -- to do the techniques necessary to get an adequate count of sputum eosinophils.

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Specific IGE was mentioned as -- as a potential measure of effect, but it's -- it's not clear as to what the correlation to disease for that. Corticosteroid reduction mentioned previously is very clinically meaningful. And one of the things that has not been discussed a lot today is radiographic evaluation. But -- but that of course requires standardized criteria, and it's still not clear what the correlation of the radiologic evaluation would be to -- to disease.

So what do we default to? We default to FED1, which is a standard endpoint for asthma studies. Unfortunately, the variability of FED1 within an asthma population is only going to be enhanced in patients with ABPA.

And as Dr. Denning pointed out in his survey of ABPA studies, there's very few studies that -- that are out there. And the few studies that are out there demonstrate a very -- a relatively small change in FED1. So it's -- it's unclear that this particular endpoint would be robust enough to define

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efficacy in this population.

So what does that leave us with? Exacerbations. And we just heard from Dr. Keywood that how do you define these exacerbations? Asthma exacerbations, ABPA exacerbations? There has to be a very clear definition that would be sufficiently acceptable as registerable endpoints. And then the other question is what's an appropriate observation period? If ABPA goes into remission, is it really relevant to go and take -- take an observation period out for -- for 8 months or 12 months? After a certain period of time, are you observing the patient's frequency of asthma exacerbations of and by itself?

So that's -- you know, that was not -- that's another point that's -- that's not extremely clear.

If -- I'm sorry. I'm unable to advance the slide. If you could go to the next slide, please?

So what -- what did we learn? So we -- we learned that ABPA is an understudied entity. Now that's -- that's a relative statement, but there are

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no large natural history studies. So we don't really understand what the course of FED1 or -- or serum IGE, or exacerbation frequency is in this -- in this population. We don't really have a good handle on the prevalence, as Dr. Keywood mentioned that 2.5 percent number is really based on retrospective studies that -- that are coming from centers that are seeing patients with severe asthma. So it's -- it's not likely applicable to -- to an entire asthma population. And there are very few interventional studies, and that underscores the -- the uncertainty around endpoints.

The prevalence of ABPA is -- is likely lower than currently assumed. I know that we've heard statements to the contrary, but there are indications at least through the conduct of clinical studies that ABPA mimics studies in rare disease populations with very low recruitment rates. And -- and that's going to be a feasibility burden for -- for pivotal clinical trials.

Site selection is a key, but site

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identification is going to be very challenging because ABPA is -- is not necessarily a reported infectious disease. There are no existing registries, no advocacy groups. You've got to go and seek and find these sites and -- and hope that you've -- you've got the right criteria to choose these sites.

If you're going to successfully recruit a study, the inclusion criteria has to be wide. But unfortunately, that makes for a heterogenous population. And then the question that I've asked previously, when is ABPA no longer ABPA? It's something that definitionally is very difficult to -- to get to.

And finally, as we've heard several times, the endpoints and tools to assess a therapeutic intervention are -- are -- are poorly defined. And, you know, which -- when is it appropriate to use asthma endpoints and -- or should there be ABPA endpoints?

So if -- if we move to the left slide, please, because again, I cannot advance my own slides

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unfortunately.

What are the implications? I think the most important implication for ABPA is that industry sponsored intervention trials are -- are going to be a significant force in enlarging the understanding of ABPA. This -- this implies kind of a learn as you go-type of development program. You have to launch a development program with the idea that a lot of what you learn in your studies is going to contribute to the body of knowledge. But the implication there is that the endpoint definition may need to evolve. We may have loved the idea of -- of what the endpoint should be, but as the development program progresses, there -- there may need to be an acceptance of interim endpoints until we have the sufficient knowledge to define a -- a good endpoint.

Second, there has to be -- we need to establish a standard criteria in defining ABPA, as well as the staging, as well as defining what remission means. That's in terms of IGE levels or other measures as well. And then finally, the low

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prevalence of ABPA in these other recruitment issues to define -- to define the population, etcetera, creates tremendous feasibility burden to support standard clinical development program approach for a marketing authorization. It's unlikely that this entity is going to support the notion that two well controlled appropriately powered phase three studies are going to be feasible with anybody's -- within anyone's lifetime, in terms of proving efficacy and safety.

And so as Dr. Keywood mentioned, and has been the subject from other speakers, this is likely to require a streamlined development program. And this certainly is -- is something that is -- is of interest to -- to all of our industry colleagues. And with that, I will end my part of the presentation. And again, thank -- thank you for listening.

DR. MARR: Thanks very much. In the interest of time, we're going to minimize our break to five minutes. Please come back by 3:10 and we will start the question and answer period. Thank you.

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(Off the record.)

DR. WALSH: This is Dr. Walsh. Hello? Can you hear me?

DR. MARR: Hey, Tom. We hear you.

DR. WALSH: Great. Thank you.

DR. MARR: Hey, Tom. Yeah, you're on.

DR. STEVENS: It's David Stevens. Can -- can I be heard?

DR. WALSH: Hi, David. We can hear you. This is Tom.

DR. GREENBERGER: And Paul Greenberger here. Hear me?

DR. WALSH: Hi, Dr. Greenberger.

DR. GREENBERGER: Thank you.

DR. SWEETS: Hi, Sweets [ph].

DR. WALSH: Hi, Sweets. We can hear you.

DR. MOSS: Hi, Rick Moss here. Can you hear me?

DR. WALSH: Hi, Rick. We can hear you.

DR. CLANCY: Not sure if I came through

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there. It's Neil Clancy.
DR. WALSH: Hi, Neil. We can hear you.
DR. CLANCY: Oh. Hey, Tom.
DR. WALSH: How's it going?
DR. MCMASTER: Hi. This is Owen McMaster. Can you hear me?
DR. WALSH: Yes, Owen. We can hear you.
DR. MCMASTER: Thanks.
DR. MOSS: Rick Moss here. Coming through?
DR. WALSH: Yes, Ricky. We can hear.
DR. MOSS: Thanks.
DR. CLANCY: Tom, just to give a heads up, I've got a commitment at 3:30. I'll silently disappear at that time. It's Neil, by the way.
DR. WALSH: Okay. You'll be with us until --
DR. CLANCY: Yeah. I will indeed.
DR. HUSAIN: Tom, this is Shahid. Can you hear me?

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DR. WALSH: Yes, we can hear you.
DR. HUSAIN: Thank you.
DR. STEVENS: Can you hear me?
DR. WALSH: We can hear.
DR. ALEXANDER: Hi, Tom. It's Barbara Alexander.
DR. WALSH: Hi, Barbara. Glad you could join us.
DR. ALEXANDER: Sure thing.
DR. WALSH: I think -- I think we're ready. Oh, let's see. We have one more minute. Oh, sorry. I lost you. I think we can start now. Is that okay? All right. Very well.
We'll be looking at a somewhat truncated schedule. This is Tom -- Tom Walsh. I just want to welcome everyone here on the panel. It is an amazing cast of experts with some just tremendous experience in the field of medial mycology, and particularly in the area of pulmonary aspergillosis.
Our schedule is somewhat more truncated this time. And so we're -- because of our timing of

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starting. Just very briefly, we'll be wrapping up our preclinical discussion, although I wish it was more, at 3:20. Then we'll go onto David at 3:20-3:45 on endpoints, particularly for ABPA, but perhaps other entities as well. Kieren at 3:45 to 4:05, with endpoints in special populations -- the prophylaxis. And then I'll resume at 4:05 and finish at 4:20, patient reported outcomes. And then we will then hear from Sumati at 4:20, and we'll conclude at 4:30.
So to begin, the first question is as development of an inhaled antifungal therapies will likely be based on streamlined development programs. What are the gaps in animal in vitro models that can be used to support these programs and how can they be addressed? And I would read into that -- one of our panelists, Don Sheppard, who's raised the question, what PKPD targets should we be aiming for? So I would open it up to this great audience and -- and please, feel free to -- to comment.
DR. MARR: This is Kieren and if you are -- if you would just raise your hand, we can also

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call on you if you've got a question or comment, too.
DR. WALSH: So if -- please feel free to -- yeah. To comment directly. If -- if not, I can just open up a few -- with a few comments that we -- we've heard several different disease states and certainly in order to de-risk the -- the studies and in order to be able to have some sense of dose response relationship, it -- it behooves us to reflect that I think on at least the animal model systems potentially. One would be ABPA in which there are animal models that have been developed over the course of time. Arguably, not fully reflective of -- of our patient population, but still a reasonable approximation. There is then model -- there are models of chronic aspergillosis. Again, with some degree of limitations. And then finally, our class -- invasive aspergillosis.
So in that context, I would open the question again as to what endpoints might we consider? I would just raise the question -- looking at David Stevens' original study on Itra [ph] and then the work

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-- elegant work done by David and -- and the fungal allergic hypersensitivity asthma that clearly an antifungal agent diminishing the presence of aspergillus, or down -- the growth of aspergillus really has a beneficial effect in ABPA. And probably across all models I think as a reliable marker with inhalational agents, you'd like to see a significant impact reduction of -- of fungal -- residual fungal burden. As simple as it is, modification could be by culture, PCR, antigen, and then certainly measuring -- BAL through ELS, and pulmonary alveola macrophages gives us some sense of concentrations that we would like to target.

In a dose escalation cohort design, it would be possible then to model these out, whether it's in a chronic model, an ABPA model or acute invasive aspergillosis model. Some of this work has been done for some formulations, but I think there's a long way to go. In that regard, I know that we have to spend -- in developing appropriate animal models. And certainly, chronic aspergillosis models and ABPA

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models really have a long way to go, and certainly would be, I think tremendously helpful in helping us to optimize and de-risk the clinical trials, especially as we talk about streamlined designs.

DR. DENNING: Yeah. So let me actually make a comment.

DR. WALSH: Yes, please. Please do so.

DR. DENNING: One of the -- one of the site challenges was azoles and aspergillus has been dissecting whether it's an AUC [ph] -- excuse me. Something in my throat. AUC or a time -- I see -- concentration. My impression of the literature is that because the azoles have a long half life and therefore it's harder to sort it out, my impression that it's time -- MIC rather than AUC -- for azoles and aspergillus.

And I wonder therefore whether in terms of the phase one data, the -- did the persistence and concentrations over time in the volunteers, and then obviously subsequently in other patients, might be a -- a decent guide to whether -- what it's like if you

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have a successful outcome. And -- and that's very relevant to -- to the issue of development of resistance I think as well. It's having enough drug on board consistently to -- to prevent that from occurring.

DR. WALSH: David, I -- I would agree with that. But if we -- if we take the model from sample four, exposures and time above MIC and data -- for example, in resistant organisms where we sometimes aim for high concentrations either in the lung or in the plasma, there is a certain sense of having a certain concentration above the MIC. Do you have a set -- even if it is time dependent, PKPD, do you have a certain -- do you have a sense as to how many times above MIC you would like to see that over the course of time?

DR. DENNING: I -- I don't. Also, there's a little bit of data, but not much. Some aspergillus fumigatus strains which are apparently tolerant. So they're inhibited at one concentration, but a much, much higher concentration is required to

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kill the organism. And where it illustrates the -- the concentration that inhibits them and kills them is very similar. So your question might be split into two parts effectively because of this issue of -- of -- probable issue of tolerance. Although that's yet to be demonstrated in a -- in a more in vivo system properly I think.

DR. WALSH: I would agree. I would agree. So I think that one could conclude that really there is, especially for ABPA and chronic aspergillosis, a dire need for -- for better models. We -- I think we have very good systems for acute pulmonary aspergillosis, but for inhalational ones, still needs to really define the PKPD. Especially given the experience we're seeing of probably this -- this sense of time above MIC really being a critical factor, particularly if you're going to have extended durations or long intervals albeit once weekly, twice weekly of inhalational treatments. I would agree.

We could probably have an entire symposium on -- on this subject, but it is 3:20 and I

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want to try to stay on time. So, David, I will pass the torch to you and you have the floor until 3:20.

DR. DENNING: Okay. So I think one of the questions I'll ask is this issue of resistance. Across the world, there is an increasing documentation -- it may not be actually increasing incidents, but certainly increasing documentation of itraconazole, voriconazole and sometimes paranasal resistant -- in the environment. Given that we all breathe these organisms in, are we going to induce resistance during therapy, or are we going to in patients treated over the longer term, allow resistant organisms to survive and then precipitate an immune response and deterioration of ABPA or asthma? Because it'd be like it's a super infection with a resistant pathogen.

So I think one of the questions here is -- and it's really a question I think for the FDA. And maybe we can suggest a possible proposal in this area, is what sort of follow-up will be required of these patients? In a relatively small phase three study of two, three, 400 patients, you might have one

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or two that develop resistance in the space of six months or a year, but you're not going to have enough to -- probably to -- to really plot them out, how common it is. Unless it's really, really common, which is unlikely. But then when the drug is marketed and you've got thousands of patients on treatment for long periods of time, resistance is likely to emerge but maybe at a low frequency or a high frequency. We don't know.

So I would like to know I think what the agency thinks about this and whether there's anybody from the agency that would like to comment about it? Maybe there's other people than me who are listening who have a view about this?

DR. NAMBIAR: Hi, David? This is Sumati. Can you hear me?

DR. DENNING: Yes, I can hear you. Yes.

DR. NAMBIAR: Yeah. Dr. Walsh, is it okay if I provide a quick response?

DR. WALSH: Oh, yes. Please do. We

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welcome.

DR. MOSS: I was just going to add that -- this is Rick. Just coming from the experience of CF, a pretty long history with inhalational antimicrobial agents, the application of -- of traditional breakpoints has really proven to be completely obsolete in terms of clinical outcomes. I'm just wondering -- it gets to the regulatory question that David raised of what kind of follow-up is necessary if you're using a reference point that is essentially irrelevant to the population at hand.

DR. DENNING: Yeah. Sumati? You were going to make a comment.

DR. NAMBIAR: Yeah. Certainly all the points that have been made are all valid, and you know, we don't have a lot of experience in this -- to tell you exactly, you know, how we are going to require monitoring post-approval. But I can certainly tell you what we've done in the antibacterial space. And the points raised about relevance of MIC receiving -- therapy have certainly come up with antibacterial

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drugs that have been approved for treatment of patients with certain lung infections -- cystic fibrosis patients.

So I think we, you know, exactly how we are going to define and what kind of monitoring we do I think is a -- subject to discussion, but systemic antibacterials, you know, we have -- we have different options. If -- if we see some concerning findings during the conduct of the clinical trial, we do have the authority to require post-marketing studies.

Besides that, currently, certain antibacterial drugs are approved. We do require that certain studies be conducted for a certain period of time, whether it's five years or longer, to monitor for resistance to the new drug one it's approved.

So I think, you know, depending on -- on what the data are from the studies, how much concern we have based on the information at hand, we have the ability to require studies. The exact nature of the study and the duration of that, I think is something we're going to have to decide when we get to

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that point.
DR. DENNING: Okay. Just to add one further comment is that currently, most aspergilli that are cultured from the sputum samples are not tested for -- antifungals across the world. Some of the recommendations that we have suggested in some of the guidelines suggested that if you have an antifungal -- I'm sorry. If you grow an aspergillus in a patient on an antifungal, then you should -- tested. This is of course if we have inhaled antifungals that comes significantly magnified I think in terms of its importance.
So I think that maybe a -- within the -- microbiology community about that. And I wonder whether Kieren or Tom or -- or others, or Don Sheppard for example, have -- or Stevens have a view about that.
DR. SHEPPARD: David, I have one comment. I'm sorry. This is Don.
DR. WALSH: No, no. Please, go ahead.
DR. SHEPPARD: I do have one comment

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about what you had mentioned earlier, actually, with respect to this issue. And that is sorting out what we mean by resistance. Because for example, in Shahit's presentation, he was talking about the use of inhaled antifungals in -- in the lung transplant patients. The data that was presented in that paper and the way it's commonly presented is percent of isolates and resistance. And that doesn't actually tell us anything what the induction of resistance, it talks more about the selection for resistant species in the environment. You know, the classic question I'm asking is are you really just wiping out the -- species and you're left with the background noise of resistance that was always there, or is there an actual increase in the amount of resistance measured on an absolute scale.
So when we collect this data, we have to make sure we have the correct -- here. It doesn't do any good to know that there is a 50 percent resistance rate, if that is two strains. Whereas prior to the use of the drug, we had 50,000 strains

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and we had the same two resistant strains, but all the rest were susceptible. In that situation, we haven't really created resistance. We've just unmasked the background noise, if you know what I'm getting at?
DR. DENNING: Thank you. That was Don Sheppard from Montreal.
DR. HUSAIN: Hi, this is Shahid. I don't -- very valid comment and indeed, there's always the issue -- this is reduced term. Happy in the panel or not, but this is one -- only one data that is shown. There is also a study in lung transplants from Alberta, which we're using -- prophylaxis. Dave quoted relatably our -- of aspergillus -- that.
DR. WALSH: This is Tom. I would also like to raise the question to Barbara. Barbara, as you all know, has been with John -- at Duke University, has been using aerosolized ABLC in their lung transplant recipients as prophylaxis. And obviously given the broad spectrum, it raises the question and so far as whether they have seen organisms emerging resistant either environmentally

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acquired or intrinsically within the house in that population in which I think amounts to well over 2,000 patients at this point.
Barbara, can you comment on selection of resistance in that population?
DR. ALEXANDER: Yeah. Hey, Tom. Thanks. Yes. So we have over 1,500 lung transplant patients now that have been treated with inhaled amphotericin B lipid complex which we use as our standard prophylactic regiment at Duke. These are patients who've received this medication since around 2000. And recently, we did retrospectively look at seven years' worth of data. And we did see breakthrough invasive fungal infections on -- in people who had received inhaled ABLC. Of note, many of those patients developed the infection 30 days, you know, after receipt of the drug. So it may be that the level of drug in the lung had gone down, and so the reason for the breakthrough was simply that the drug was no longer at adequate levels in the lung.
But some of the pathogens that we did

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see break through, were organisms that are considered intrinsically resistant to -- to amphotericin. So for instance -- or aspergillus terreus. And so, you know, one of the things I just -- back to is if you have a -- a host that's appropriately immunosuppressed, and they're continuously exposed to mold pathogens, ultimately you're going to select for infection with a pathogen that is resistant to the drug that you're prophylaxing with. And we've seen this time and again over the years, right? With the different drugs that have been studied. Early when voriconazole came to market, we saw reports of breakthrough mucormycosis on -- on patients receiving voriconazole systemically for prophylaxis. And so on some -- on some level, you know, this is to be expected, right?

I -- I think it's really important though that we, you know, are careful to try and get baseline isolates. It's not uncommon to have lung transplant patients colonized with mold. And so it'd be really important to get the organisms that are coming out of these patients. And then, you know,

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looking at any breakthrough isolates that happen or that occur from invasive disease and kind of see what -- you know, what's happening over time.

DR. DENNING: Great. Thank you. That's very helpful. And I wonder if there are any other comments on this? Just one quick observation we've seen in patients on oral itraconazole, we do high volume -- to try and increase the yield of strains that we commence that -- and we find a lot of penicillium species coming up. And when we do MICs on those, which we haven't properly reported because it's quite difficult to report, they're often -- azole resistant or -- azole resistant. And of course penicillium antigenically similar to aspergillus and may drive asthma. It's not quite ABPA, but it may drive some of those immunological mechanisms. So it may be more complex than simply fumigatus being resistant a lot -- are there other comments that people would like --

DR. CLANCY: David? It's Neil Clancy.

DR. DENNING: Okay.

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DR. DURMOWICZ: This is Tony Durmowicz. I'd like to make a couple comments on study design, especially patient populations as it relates to cystic fibrosis. And I think we heard this morning that the prevalence of AVPANCF [ph] is very high. In adults, it's eight percent. However, because it's a rare disease, you know, it's very difficult to study a meaningfully large study exclusive to people with CIA. But I think it is important in our ABPA program to include those patients. And as a result, I think there could be a large study which strategies people with CF included in it, at a number that would give at least a somewhat meaningful indication of whether it reacts differently than the general population, which would mostly be asthma patients. You know, alternatively, I suppose a post-marketing commitment could be done to do a study in -- in people with CF if that was felt to be needed.

One other thing. When we're developing these kind of therapies, a lot of them are -- we're talking about inhaled therapies today. And for CF,

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there's the burden of care. People with CF take a lot of inhaled therapies. It usually a couple -- two to four hours a day just on those therapies. And it's not only the time to nebulization, but it's cleaning and keeping, you know, clean if you will the -- the nebulizers. And they use jet nebulizers, but more and more they're -- they actually have to buy two nebulizers. One a jet, one a vibrating mesh that might be product specific.

So in that sense, dry powdered inhalers become a -- a meaningful way to reduce the care burden. And then finally, azoles seem to be, you know, one of the focus -- post -- focus of our drug development efforts as we've heard today.

People with CF now, the majority of them in the US, and it will probably be likely in the world are going to be going to CFTR modulator therapy. A combination therapy. And -- and these drugs -- this drug product -- these drugs in those combinations are both effective by sip induction and sip inhibition. And therefore, azoles would skew the levels. So in

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that sense, in newer therapies that aren't -- aren't azoles, you know, would be really helpful in that population. So I just wanted to get that out there from a CF perspective, what -- what the community feels about the development of antifungal drugs. So thank you.

DR. DENNING: That's very helpful. And one --

DR. WALSH: This is Tom -- go ahead, David, please.

DR. DENNING: -- comment. Sorry about that. If you go to -- CF actually, the teenage years -- for ABPA. So actually, you might be extending the age range down a little bit to be able to do that. At least at some point.

There's a handout from Neil Clancy as well. Do you want to say something, Neil -- his handout. Okay. Tom, you were going to say something?

DR. WALSH: David?

DR. DENNING: Yes?

DR. WALSH: Hello? Yeah. David, just

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raising -- raising the question in general and perhaps to the audience, we've heard many different proposals and concepts of endpoints of ABPA. And I'm wondering if -- if the audience would like to contribute more. In other words, if -- for the experts that we have in our -- in the group, what would be a consensus, if at all, on appropriate primary endpoint? Would it be a composite or a single endpoint for ABPA?

DR. DENNING: Very good question. Dale's got his hand up. Did you want to talk about that, Dale, or something else?

DR. CHRISTENSEN: No. I was actually wanting to ask a different question to get --

DR. DENNING: Just hold it for a second then. Let's --

DR. WALSH: Please go ahead.

DR. DENNING: -- Tom's point. So who would like to -- we've got Paul Greenberger on the line. He's been interested in this. Do you want to respond to that, Paul?

DR. GREENBERGER: Yes. Can you hear me

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okay?

DR. DENNING: We can, yes.

DR. GREENBERGER: I compliment everyone on the presentations and -- and just being part of this. So I have to first say about the total IGE levels, the Northwestern University criteria have had a upper boundary of normal of 417. So where as -- is 1,000. And the -- frankly, I mean 417 is about four times the normal -- what the normal mean is of adults and actually teenagers. But you miss -- the sensitivity has improved to find the cases if you're using 417. And there's a -- there's a discussion in the literature on that one. But I would suggest an open mind on having that 417.

And the other is endpoints. Very, very important. I think it was Dr. Clayton mentioned this and I believe it. The radiologic endpoint to me is one of the most important ones. The lack of bronchiectasis or lack of new areas of bronchiectasis is crucial. And that means not having new pulmonary infiltrates with eosinophilia which leads, if not

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treated, to new areas of bronchiectasis. So a high res CT scan's important to baseline and then whether it's at three months for a study or perhaps longer. And while -- while -- so I think on that endpoint, the radiologic part is very, very important. And my own view -- my own view --

DR. DENNING: I'm sorry. Paul, do you want to comment on the ideal primary endpoint or whether you --

DR. GREENBERGER: Yeah.

DR. DENNING: -- composite? That would be --

DR. GREENBERGER: David, thank you. I have one -- perhaps an ideal one would be the radiographic findings on high res CTs focusing on bronchiectasis and -- and presumably lack of any new areas. That would be my ideal. And the second would be using a composite like has been used in the literature because I think that would be practical.

DR. DENNING: Thank you. Would anyone like to comment on endpoints before we run from that

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point? I know Dr. Stevens is on the call. He was involved in that very pivotal study -- Dave, you want to comment, David? I think he's on mute. Are you on mute? There you are. Yes, David, can you comment? I can't hear you. Yeah. Now we can hear you. Yeah.

DR. STEVENS: Okay. Can you hear me now?

DR. DENNING: Yes.

DR. WALSH: Very clearly.

DR. STEVENS: Okay. Thank you. Yeah. I -- I think it seems to be pretty well accepted that oral itraconazole is useful in treatment of ABPA. And based on our paper in the New England Journal of MSG22. And I just wanted to point out, speaking about composite endpoint, what our experience was.

We elected to go with a composite endpoint that was defined before the study. And when we presented our data, we presented each of the components of the composite endpoint separately in addition to the composite endpoint. And if you looked at each of the components, that -- none of them alone

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would have made statistical significance. Or maybe one out of five or something like that. So without having used a composite endpoint, we would have come up with -- emptyhanded in terms of whether itraconazole is useful. And I think many of the speakers addressed the problems of composite endpoint. There's more of an emphasis now on patient-oriented endpoints rather than biomarkers. But I just wanted to point out -- go back to the data in that paper and look at each of the individual components of the composite endpoint and realize that had we dwelled on only one of those, even if you want to argue that the patient-oriented ones like the FEVs would have been the best. It would have made -- it would not have come to the same conclusion that it did. That's all I wanted to say.

DR. DENNING: Thank you very much. Darius Armstrong-James has put his hand up. Do you want to say something, Darius? You're on silent at the moment.

DR. CLANCY: Hey, guys. Real quick.

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I'm -- I'm butting in. It's Neil. I've been out for the past two or three minutes.

DR. DENNING: Okay.

DR. CLANCY: Sorry -- yeah. Yeah. Sorry.

DR. DENNING: Go ahead. Yeah.

DR. ARMSTRONG: Oh, yeah. So -- yeah. Just basically commenting on the basis of our experience with the Pulmocide group. Frequency of exacerbations -- usage, steroid usage, FEV1. Those are simply grounds -- useful in monitoring response to treatment with inhalants. And with a patient who has presented today, one really interesting aspect was that she had one of these iPhone help apps and she was actually able to show that she had dramatically increased exercise -- based on that. So we were not -- monitoring, you know -- COVID, etcetera, might also be helpful. I don't know.

DR. DENNING: Yeah. There's also now an electronic cough monitor, which -- and actually cough is a very important component for patients, even

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though it's a little bit hard to document without a sort of formal cough monitor. So there might be another approach to that as well.

DR. DENNING: Okay. Thank you very much.

DR. ARMSTRONG: And just commenting on resistance as well. I mean, if you've got a -- a high sort of concentration azole going into the lung, as well as your systemic azole, I mean, my -- my impression from the -- the chronic patients is often the systemic azole isn't going into the lung appropriately. And that might be driving some of the resistance of these. So presumably, if you --

DR. CLANCY: Yeah. I'm very much, you know, unhappy with Diana while fully acknowledging --

DR. DENNING: Rick, you had your hand up.

DR. MOSS: Yeah. Somebody else is speaking I think that needs to mute.

DR. CLANCY: -- with Diana. What I've always found with her is that --

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DR. MARR: -- I think that's you. Can you silence, please?
DR. CLANCY: And, you know, if I felt she overstepped herself with me or any of my people, the best way --
DR. MOSS: Yeah. There's too much interference here.
DR. MARR: Can the panel actually silence?
DR. CLANCY: With that, she always responded and I often like --
DR. MARR: Do you have the speaker? I think it's Neil Clancy.
DR. DENNING: Neil, can you turn your microphone off? Yeah. There we go --
DR. MOSS: Okay.
DR. DENNING: Right. Rick, were you going to say something? I think you --
DR. MOSS: Yeah. Thanks. I agree with the idea that a composite endpoint is probably going to be the way to go in a pivotal ABPA trial, for the

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reasons that David eluded to. And also, I think since, you know, the early '90s when David was working on that study, PROs have become much more important. I think in the eyes of the agency, in terms of, you know, clinically relevant endpoints, it's -- it's not clear to me that just measuring FEV1 or even a clearance of an infiltrate, radiographically, would satisfy that criteria. The problem with a PRO is there's nothing specific for ABPA. And the question arises is is it adequate to use an asthma PRO in which, you know, a number have been validated. And I would -- I would hope the answer would be yes because that would -- these are important. I just think in terms of dealing with patients with this problem, what they're most focused on is the toxicity of our existing therapy which are -- the therapies are effective, they're just not easily tolerated. And that's, I think, a very important component that needs to drive the discussion.
DR. DENNING: Okay. Very good. So should we move to Dale's new question? And then we

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should move onto invasive I think, in a minute. Dale, do you want to pose your question?
DR. CHRISTENSEN: Yes. And it does -- it does start the transition to invasive. And that is, you know, when considering going after invasive disease, there is the -- the prophylaxis side and then there is the therapeutic side. And as we heard just a few minutes ago at Duke, as a standard, they prophylax with liposomal amphotericin.
And so my -- my question really gets down to how would a center, you know -- because liposomal amphotericin nebulized is not an approved route of administration -- is not approved, so for someone coming in with a -- with a dry powder voriconazole, for example, how would that be, you know -- what would the possibilities be? You know, would those centers remove those patients from liposomal amphotericin to enroll them in a study where they would have to be compared to an approved route, ie: oral Posaconazole versus the dry powder voriconazole, instead of their current routine? You know, it --

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would that center just not consider taking part in a trial or how would -- how would we be able to get that trial enrolled it that is what many of these leading centers do.
DR. ALEXANDER: Hey. This is -- this is Barb --
DR. MARR: This is Kieren.
DR. ALEXANDER: -- Alexander. Oh. Hi, Kieren. So --
DR. MARR: Oh, hey. I'm moderating this and I was just going to turn it over to Barb. So go ahead.
DR. ALEXANDER: Sorry, Kieren. I think that you have just hit your nail on the head with one of the primary problems that we're going to face when we try to find a study in inhaled product for prophylaxis in the lung transplant population.
You heard from Shahid this morning that standard of care is to prophylax lung transplant recipients because the risk of invasive fungal disease is so high. And particularly high for invasive mold

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infections. And in fact, we have international guidelines now from the International Society for Heart and Lung Transplant that recommend prophylaxis. But the major transplant centers over the country, while the majority of them prophylax, they use different regimens. Different drugs, different durations. And nothing is currently FDA cleared.

I think you're going to get the major transplant centers happy to participate in a prophylaxis study. We all want there to be an approved prophylactic agent because currently, patients are having to pay for these drugs out of pocket. And they -- you know, they can't afford them. There's a lot of issues around this.

So we -- we would really like to participate. We want to participate. The problem is going to be if you make us compare to placebo. Because placebo is not standard of care. And so I think we have to be creative in figuring out what the comparison can be.

DR. WALSH: So I would just like to

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comment from -- from a historical standpoint, the mycoses study group, both NIG, MSG and BAMSG, wrestled with this question for virtually two decades. And certainly came to the conclusion that a placebo would not be appropriate given the standard of care. But the challenge then becomes, and I would turn it to Barbara -- Barbara, what do you think would be an acceptable standard of care? And then going back to the -- the agency, to -- or others, how would the agency look upon a standard that was accepted by the community, but would not have regulatory approval in this population?

DR. ALEXANDER: You know, great question. I've been struggling for a decade trying to answer this. You know, we can try a systemic drug, but you know, again, there -- there are a lot of problems trying to compare an inhaled drug to a systemic drug for prophylaxis. Particularly because the mold active azoles either have, you know, unacceptable side effects when we try to use them -- use them long-term. For instance, voriconazole and

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skin cancers in lung transplant populations, or just drug/drug interactions with the calcitor and inhibitors, etcetera, that we're trying to use. Many of the lung transplant patients have -- early on. They're on amiodarone. There's just multiple, three-way drug interactions that you can imagine.

So try and be -- to use an oral mold active azole as the comparator. One, it's not approved for prophylaxis and there's going to be a lot of, you know -- there will be a lot of downsides to that. So I guess, you know, could we use a historical control group? Could we put something together? You know, we could have a whole other conference just on that topic, but I'll just stop there. And I'm very interested to hear the agency's comments.

DR. DENNING: Sumati, do you want to say anything about what -- what might be acceptable?

DR. NAMBIAR: Hi. This is Sumati. David, I'm sorry. I didn't hear you clearly. Did you ask me to respond or did you call on somebody else?

DR. DENNING: I think the fundamental

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question is would a active comparator or a lung transplant prophylaxis program, which is not approved for prophylaxis, whether it's oral or inhaled, be an acceptable comparative to the agency? Because there's nothing that's approved at the moment.

DR. NAMBIAR: Right. Right. Yeah. I think -- so it largely depends on the trial design. If the trial design is one where the superiority of the test drug is being demonstrated again, to whatever is considered standard of care. I think that certainly is much less problematic than if the trial design is a noninferiority trial design where you're comparing the test drug to an active comparator. In that instance, you know -- ideally, we would like products that are approved for the indication to be used in noninferiority trial, but we do have flexibility and we have exercise flexibility in many instances. The products that may not have a labeled indication, but are considered standard of care could be used as comparative in a trial, but we would, you know, like some information whether it's from -- it

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could be from the literature, which supports that that drug actually works in that particular indication. Even for that particular condition, even if it doesn't carry a labeled indication.

So I think a lot of details are needed before I can comment to is it okay or not okay. Primarily, the trial design, the patient population, etcetera.

With regard to Dr. Alexander's question about historic controls, I mean, I think that's, you know, a topic which is really very complicated. And -- and again, there are some particular or specific situations where it might be -- sorry. It might be acceptable to use historic controls. Again, it'll depend on the patient population, the endpoint, the disease that's being studied.

So unfortunately, I cannot give you a straightforward answer, is it acceptable or not, but if there is a good scientific rationale for why that standard of care should be considered reasonable and there's some evidence to support it, I think we're

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more than willing to consider that and make a decision. So I hope I've answered your question.

DR. DENNING: Does Radu want to make a comment on -- from Europe about that?

DR. BOTGROS: Yes. Thank you, David. I think pretty much I echo what Sumati's saying because indeed, if the -- if the design of the trial is noninferiority, then it's very important to get the comparator that will be used. You know, allows us to conclude that the candida drug is better than placebo. So I think this is why the choice of the comparator is so important. So this, of course, in a superiority setting, the approach could be -- well, a bit more flexible I suppose. Thanks.

DR. MARR: This is Kieren. I've got a related question for the regulators which -- which also relates to question number three. And that is in the context of an inhaled drug, would there be a problem potentially in a prophylaxis indication without a treatment indication?

DR. NAMBIAR: I think -- you know, we

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don't have a requirement that you have to demonstrate efficacy in the treatment indication before you do a prophylaxis. I think that would be ideal. It -- it -- it's -- date. That's a data package if you actually have a treatment indication and -- document that was a prophylaxis indication. But I think -- as you're aware, I think there's -- that are approved, which only carry the prophylaxis indication.

So there is some degree of mixability, but I think it's fair to say that the best day the package would be one where there is a treatment and a prophylaxis indication. But again, depending on the -- the specifics of the development program and the molecule, I think we can make -- just for prophylaxis if we have to. And I -- I think Radu has a slightly different take on it, so I will let him provide MA perspective.

DR. BOTGROS: Thank you. I -- I think -- I think so much you guessed a little bit what I was about to say. Indeed, you know, our guidance on prophylaxis of invasive fungal disease mandates that

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studies in prophylaxis should only be conducted after showing satisfactory clinical efficacy in the treatment setting. So, you know, this is the -- the starting point. And of course, you know, this is -- this is what the guidance is saying. Of course, we are -- we are willing to discuss, you know, with sponsors, trying to understand, you know -- there -- there is definitely something real flexibility, but I wouldn't be able to tell you right now, you know, to give a blank answer as to whether it would be acceptable or not to -- of the fact that there's a -- guidance mentions this. Thanks.

DR. MARR: Great.

DR. SHEPPARD: Can I make a quick comment?

DR. MARR: Yes, please.

DR. SHEPPARD: Kieren, this is Don.

DR. MARR: Hey, Don.

DR. SHEPPARD: Since this is my -- my one chance to make sure that both the FDA and the Europeans hear this, just to point out that there's a

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logical inconsistency in saying that a drug should work the same in treatment in prophylaxis when you're talking about the fungal diseases we're talking about.

By definition, prophylaxis is preventing the initiation of infection, which is caused by inhaled spores. And treatment is treating hyphae in the lungs, which are fundamentally different in their expression of genes, proteins, marthology, polysaccharides and every other thing related to drug targets.

So there's a very black and white obvious reason why these are two different biological states and that the treatments could be divergent for prophylaxis and treatment of established disease. And those who know me know I believe that.

DR. DENNING: Thank you, Don.

DR. MARR: Thank you, Don. This is Kieren. I'll -- I'll add onto that in that establishing a treatment indication for an exclusively inhaled drug in a monotherapy paradigm, at least in the hematology population, BMT population, and any

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other population that is really severely ill enough to see a -- a dramatic treatment effect is going to be very, very difficult.

So it's precisely in that situation where we can't really rule out systemic or invasive disease. They have prolonged and deep immunosuppression. There may be some unmet needs, but we do have other systemic alternatives. So I think that this is going to be a -- a topic that requires more conversation as well and has a lot of different issues that come up.

I'd like to get some of the panel's feedback some more on what -- what do you envision for treatments of invasive fungal infections for inhaled formulations? And I see that Neil Clancy has his hand up. I don't know if he's actually had his hand up for a while or if he's wanting to chime in here? And if I don't hear him, I'm going to ask Dr. John Perfect if he's on the line to maybe comment on what would be an appropriate population to establish a treatment indication of -- for an inhaled drug?

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DR. PERFECT: Kieren, can you hear me?

DR. MARR: I certainly can, sir.

DR. PERFECT: I want to -- Don -- Don made a very important statement here that we should separate out prophylaxis in treatment. These are two different issues and surely the FDA has done this in the past and approved drugs for just prophylaxis. But we should separate those out very, very carefully and shouldn't be put under any restriction that you have to do treatment before you do prophylaxis. It's a different beast.

As far as other things and prophylaxis, I just want to bring out something that's a little different to talk about. Everybody's talking about molds and stuff like that, but when I come to prophylaxis, my issues is actually pneumocystis prophylaxis. Actually, pneumocystis is a fungus, so we're appropriately talking about it here. And maybe a long-acting -- will work, but I would surely like to have some enthusiasm or ideas about prophylaxis for pneumocystis with particularly the -- particularly the

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cyst form, the trophozoite form. I'd like to see the animal models be a little bit robust on this thing because I will tell you on the on the wards, it is not easy to use -- and they're really reaching out for this thing and many of these type of patients for prophylaxis.

And so I'm just putting another issue out there for prophylaxis and the types of things that we -- we need to think about. Not just the azole compound. Not just the -- thank you.

DR. DENNING: Thanks, John.

DR. MARR: Thank you.

DR. DENNING: -- have a comment, Kieren?

DR. MARR: Please.

DR. DENNING: The other -- just extending the discussion slightly. The -- does the -- one of the problems in lung transplant is obstructive bronchiolitis, which comes later. And that's associated with aspergillus colonization or the infection.

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So I -- but of course, inhaling a new drug could lead to -- so I'm wondering what the -- whether the panel -- any of the members of the panel that regularly just have a view about longer term survival of graft and the function of that graft as a -- another longer-term endpoint and whether that's a surveillance issue if the drug was approved for this education. Maybe Shahid should comment on that first?

DR. HUSAIN: Sorry. Yes. Hi, there. Thank you. Yes. I think the graft survival is -- is an important -- and that should definitely be one of the endpoints that need to be studied especially among transplant recipients. Because at least from the data -- there's no long-term data that I'm aware of. But, like, especially short-term, there's clearly somewhat an option in the pulmonary function test maybe temporarily or they may have long-term consequences. So I guess I answered your question or --

DR. DENNING: Yes. I think so.

DR. HUSAIN: Hello? David, did I answer your question?

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DR. DENNING: Yes. Yes, you did. Thank you. That was fine. Very good. Thank you. I just -- I'm not sure if there's a -- but maybe not. Probably not.

DR. WALSH: David, this is -- this is Tom. In addressing your question, I think one has to really separate a part, the host very critically. In profoundly persistent immunocompromised patients, for example, profound persistent neutropenia, the biology of the disease pathophysiologically is -- is very different. You have typically deep infarctions, it had -- necrosis, coagulative necrosis, that an angio - - for which an aerosolized agent is hardly going to be able to reach deeply into that process. And to open a clinical trial for that kind of a step is -- with an extremely high risk. Hematogenous delivery obviously is -- would be the most logical. But if you were then to take a step back away from that particular host population and look toward more airway disease, whether it's in tracheal bronchial disease in which might be immunocompromised, whether one evaluates

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chronic pulmonary aspergillosis if one has chronic aspergillosis in patients with allergic -- with cystic fibrosis. Many of these patients have airway disease that would be with or without pulmonary infiltrates. It would be quite amenable pathophysiologically as well as in terms of equal poise and being ale to provide an aerosol agent versus in a randomized trial of systemic agent. We're clearly going after airway disease where there's a legitimate opportunity for hyphae organism. The very high and sustained concentrations would really be the best target.

DR. MARR: Thanks, Tom. That was exactly the -- the points that I was trying to bring out and you just described them so cogently about discerning really about where the infection is and the degree of severity of disease in the host.

With that in mind, I just want to push a little bit further. Is it possible? What do you think about the feasibility of doing a treatment study for purely airway disease in a non-organ transplant host or non-lung transplant setting?

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DR. WALSH: I think one has to be very careful. One has to first of all ascertain the stability of the host with minimal -- with minimal immune suppression, but clearly there are many patient populations relatively stable. CPA is one. Chronic nacro triazine. Chronic cavitary where aerosol -- potentially inhaled drug delivery could make a major benefit. The challenge is always -- and David Denning who's done intensive work in this area of trying to define endpoints in that population, but it certainly -- even repeat bronchoscopy may be appropriate. And then obviously patient-reported endpoints.

Which then brings us at 4:05 to our question number four with your kind permission.

DR. MARR: Absolutely. I think -- unless someone has a burning question on endpoints and populations now, this has been a robust -- good, good. Go ahead.

DR. WALSH: All right. Excellent. Well, our question number four raises a drug question for ABPA and invasive fungal infection, we're asked to

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discuss how we can advance facilitate the efforts to develop patient-reported outcomes measures.

And so I would open that up. Obviously there's been wonderful work especially done in the area of ABPA. And we can start with ABPA and Dr. Moss, Dr. Stevens, Dr. Denning or anyone who would like to offer perspectives on what would be -- what would be appropriate endpoints and -- or delegated systems that we could choose for patient-reported outcome measures.

DR. DENNING: Well, they -- they just -- - ACQ, the asthma control questionnaire, usually without the FEV1 because that contaminates it. It's been used in the -- study. I don't think it's a primary endpoint, but it's a very useful and simple thing. AQLQ has been used much more extensively and, again, has not been used as a primary endpoint, but is a broader set of questions of how patients feel on therapy. And it's been used in some asthma studies. I -- I personally would be quite keen to see some clinical endpoints which aren't just respiratory

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function endpoints as the key measure of improvement. Because that was our experience in the SAS study and in our ABPA patients. The patients say they feel just much better. They're stronger. They're less tired. They can walk farther. They have more energy. It isn't about, you know, whether they need more or less inhaler --

DR. SHEPPARD: -- so that is something at least we're testing if there are CF patients in a trial.

DR. DENNING: Okay. Yeah.

DR. WALSH: Okay. That's an excellent point. To David -- to David's point, ABPA. David, do you think the ACQ -- or AQLQ would be suitable as part of a composite endpoint? Would you think it could standalone as a primary endpoint?

DR. DENNING: I think it would be a very good path of a -- of a composite endpoint as well. I think you do need some sort of biological measure of -- of antifungal or immunological response. But yes, I think it would be a good one.

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RECORDING: Your microphone has been turned on.

DR. WALSH: I'm sorry, David. Either my phone is deficient or I can't hear you. Hello?

DR. DENNING: Yes. Yes, Thomas. The answer is yes, I think it would be helpful if -- endpoint. Along with some microbiological or immunological measures of response. And --

DR. WALSH: David Stevens, could you comment? David, you might be on mute. Let me check the screen. Or Dr. Moss, are you there?

DR. DENNING: Rick Moss, he's on quiet, too. He's on --

DR. WALSH: Yeah. Please go. Did somebody --

DR. MOSS: I was going to respond from the standpoint of the -- using a questionnaire, which is available at multiple sites, and getting -- getting meaningful information. It's a very good way to go. In the study that we did, we tried to build into it exercise factors and as has been stated by several of

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the industry people, if a trial is going to come off an ABPA, it's going to likely be a multi-center trial. It was very difficult to get that standardized. Just very difficult to get people to follow the same -- for example, even a six-minute walk test or what -- whatever type of physical exertion evaluation you might choose. Very difficult to get that standardized between sites. And so the use of a questionnaire really has a lot of advantages.

DR. WALSH: Okay. Okay. Very good. Very good. We do, in the limited time that we have, have a question that hasn't been addressed thus far in our discussion points, but was raised in a couple of presentations. And that is the matter of safety. And specifically, we have a question from Paul Manly [ph]. Could the FDA comment on the merits of PROs in this space? Specifically, what would they feel would be appropriate? And I would add into that, how should we incorporate safety as well into patient -- patient-reported outcomes? Chris St. Clair, would you be able to address those questions?

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DR. ST. CLAIR: I think the safety aspect, I'll defer to those. But in terms of maybe more the -- the merits of PROs in general and what types of things measure in PROs. You know, we've been talking about respiratory symptoms. You know, obviously that makes sense. I also think fatigue and functioning, you know, sort of when we think of quality of life, I'm -- I'm thinking along the lines of, okay. How is the disease impacting the patient's ability to engage in activities of daily living? So I think questionnaires that are assessing the daily functional capacity. You know, can they walk around the back? Can they carry bags of groceries? Whatever might be relevant to the exact patient population. I think those types of assessments can be really informative as well.

DR. WALSH: So in that context, we -- we heard that in our discussion that tolerability to the existing agent, particularly systemic azoles, which seems well-tolerated -- probably much less so. And then the -- the terrible effects of long-term

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corticosteroid therapy. Do relate that to safety in patient-reported outcomes.

Chris, do you think that the patient-reported outcomes could also weave-in elements of safety and tolerability?

DR. DENNING: I think they do.

DR. ST. CLAIR: It's hard to -- advice, but yeah. I'd like to hear from others as well.

DR. WALSH: I'm sorry. It's hard to hear. Forgive me. Chris?

DR. DENNING: Yes. Tom, I think Paul -- Rick Moss -- want to say something.

DR. MOSS: Well, I do think it's very important to include tolerability of which I think there are some general validated instruments as part of a PRO. Because again, I just come back to this point, that I think from the patient's side, the motivation to try new therapy like this would be driven largely by tolerability issues with the existing therapies, in terms of the allergic aspergillosis group. And I also want to second what

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Tony Durmowicz said about CF and the CFQR respiratory domain. For those patients has been really very valuable tool in terms of effective therapies. So if those patients -- that's never been applied or specifically validated for CF. So I -- I don't know if -- you know, what its applicability might be. But something along that line would be helpful.

This -- some of the features are similar to some of the asthma questionnaires, but some are different also.

DR. WALSH: Very good. Very good. Are there any other tools that you would -- of patient-reported outcomes that you think might be helpful? We've heard of CFQR, we heard HEQ, HULQ. Are there other validated instruments that we could adapt particularly for ABPA?

DR. DENNING: Just a general point, Tom, that if you want to compare ABPA with other diseases like multiple sclerosis or rheumatoid arthritis, then you need a non-respiratory questionnaire -- is pretty poor in this area. And

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that's helpful for reimbursement in terms of negotiating the investment with agencies across the world if they know what they values are compared to other diseases. I don't think it would help very much -- those would help as much with the -- with the prime endpoint in a phase three person.

DR. WALSH: Very good. And while we've talked about ABPA, do we think to what degree might we have patient-reported outcome measures in IFI? Such as -- prevention? Actually, if I may, if I could be -- defer that, because I think in the long run, Barbara, you have probably the greatest experience at Duke University. Do you have a sense of quality of life on aerosolized ABLC or a sense of tolerability given your best experience?

DR. ALEXANDER: I think -- so quality of life as it relates to receipt of inhaled ABLC. The patients tend to tolerate the treatments well. You heard from a patient advocate though that once you leave the transplant center and it's not prepared and given to you and made up for you, you know, the

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logistics surrounding administration of inhaled amphotericin products, you know, it's kind of a downer. The good side is you only have to do it once a week.

In terms of tolerating the treatments though, they do seem to tolerate the treatments very well. The lipid formulations are not associated with the bad taste and -- and as much bronchospasm and cough as the -- as the amphotericin B deoxycholate. In terms of long-term quality of life, you know, I think for the first year after lung transplant, there are those people who do well and they go out and have great quality of life. There are the others that get into a vicious cycle of infection and rejection and they are frequent -- frequently admitted to the hospital and -- and a care system. But I don't know that that's linked to the inhaled ABLC or inhaled prophylaxis. That's more to do with just the nuts and bolts of having had a lung transplant.

I think one of the things that's going to be really important in the lung transplant

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population specifically that's a little unique compared to other populations where you try to study any inhaled product is making sure that we're not seeing increased risk of rejection. So --

DR. WALSH: Very good. That's tremendously helpful. Well, we're at 4:20 now and in the spirit of staying right on time, first of all, we want to -- on behalf of David and Kieren and myself thank the panelists for their insightful discussions as well as our FDA colleagues for their insights as well on the regulatory aspects of this important class of new agents. But at 4:20 now, I would like to turn the microphone over to Sumati -- for a summary and concluding -- summary and concluding remarks. Sumati?

DR. MARR: Dr. Walsh, Sumati Nambiar is the summary and closing remarks. So I hand it over to her. Thank you.

DR. NAMBIAR: Yeah. No problem. Thank you, Dr. Walsh. So I really have the daunting task of trying to summarize these proceedings, which lasted about, you know, 10 hours of so and I have to do that

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in the next 10 minutes. I'm going to try to just touch up on the highlights, you know, of -- from the presentations we heard today -- excellent talks. And my apologies up front. I -- if I miss some important points, it's just hard to capture everything in these few minutes, but the transcripts of the workshop will be available and the slides will be available as well. So you will have all the -- online in a few days.

So this morning, Dr. Moss got us started with an excellent overview of inhaled antifungal drug and their role in our therapeutic -- he discuss the limitations and gaps in the data and outlined some clinical conditions where they may play a role. In immunocompromised patients for prophylaxis or as adjunctive treatments -- I'm hearing a lot of feedback. I think someone needs to mute their phone. Adjunctive treatment for -- fungal lung infections. And in patients with -- with the -- disease, I think both with treatment of ABPA and treatment of severe asthma with fungal sensitization.

We then had a series of FDA I think

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touching upon important aspects as they relate to drug development. Dr. McMaster outlined the expected pharmacology/toxicology package for an inhaled antifungal drug, including the types of inhalation and toxicology studies that are done to help define safe clinical doses and -- safety monitoring in the clinic. The two key references that everyone should keep in mind, the ICHN3 and the FDA's nonclinical safety evaluation of -- products. I think Dr. McMaster also noted that it's very important to understand the limitations of these animal models as they relate to the test article administration. Because there are differences in device design and anatomical differences between the nonclinical -- between animals and humans. Limitations are -- kinetic evaluations because they're not measured but estimated. And understanding the test species of the healthier, infected animals. I've been taking all this into consideration and now it's a more realistic characterization of the -- to humans.

The next presentation was by Dr.

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Timothy Bensman from Clinical Pharmacology. And Dr. Bensman highlighted the impacted -- between drug device and patient characteristics on the site of absorption -- sorry. Deposition absorption and clearance of the inhaled drug. I think Dr. Bensman clearly emphasized the importance of phase two studies in determining the appropriate doses in phase three studies given some of the limitations with the nonclinical studies, animal models and fungal lung disease. Which can help in estimating the clinical starting dose or dosing regimen, but certainly there are limitations. I think the lung PKPD targets are not commonly assessed and there are gaps -- and there are gaps in our understanding of these targets and how they translate to clinical efficacy.

Next, we heard from a colleague in CDRH, Dr. Blakely, who discussed the key aspects from a device standpoint. And he went through the device review considerations for inhalational products. I did want to note that we in the division work very closely with colleagues in the CDRH on such programs

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regarding device issues, and we engage in these discussions -- product development. Dr. Blakely noted that inhalation drug therapy, just as Dr. Bensman mentioned, is really dependent on the -- between the drug device and patient. He discussed how medical devices are classified from -- standpoint. Noted that most inhalation devices are considered class two. And -- and he also emphasized the importance of early communication with CDRH through the tree submission process.

Next, we heard from Dr. Irene Chan from the Division of Medication Error Prevention and Analysis, DMEPA. And -- okay. So Dr. Chan covered important aspects from a safe use and medication error perspective, including the importance of optimizing the user interface design. And she noted that following a human -- engineering process is very important. And there's need to -- for continued refinement to minimize risk of -- product. There's need to consider underlying comorbidities in patients with elevated device platform and formulation changes

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as all of these can impact safe use of the product.

Just as we interact with CDRH colleagues very early in the drug development process, we do interact with colleagues in DMEPA very early as well, including at the pre I&D stage.

The last FDA presentation was from Dr. St. Clair who discussed -- clinical outcome assessments that can be used in clinical trials. And the considerations in selecting or developing COAs, or clinical outcome assessments. Dr. St. Clair noted that we at the FDA evaluate the CEO instrument and the context of its intended use, including study objectives to patient population and the desired labeling claims. As much as possible, I think the advice from our COA colleagues is the measurement properties be evaluated prior to embarking on phase three studies to ensure that the COA's performing as expected. Dr. St. Clair emphasized the importance of other measurement properties and content validity, and much like the other speakers, emphasized the importance of early communications with the agency and

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throughout the development process. And referred us all to the FDA PRO guidance for important information.

We next heard from Mr. Birrell, and -- thanks to Mr. Birrell for sharing his valuable perspective as a patient with ABPA since he was diagnosed about six years ago. His experience really highlights the unmet need for safe and effective therapies to address the needs of such patients. The challenges with the chronic nature of the disease issues regarding long-term oral therapies, including side effects and issues with drug interactions, were all highlighted in his presentation. Mr. Birrell's experience also highlighted the practical difficulties patients face with long-term nebulized therapy and its impact on daily life. He also pointed out the importance of treatment that encourage compliance, particularly important for the management of chronic disease. And also noted the value of having patient groups to share -- to share one's experiences. Again, our sincere thanks to Mr. Birrell for sharing his -- his experience. We greatly appreciate it.

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At the public comment session, Dr. Edwin Rock from Partner Therapeutics discussed the potential growth for evaluation of such grant -- in the management of fungal infections. We then moved onto session two where we discussed clinical trial considerations for a new antifungal drug.

We started with a regulative perspective where Dr. Smith provided perspectives from the FDA and Dr. Radu Botgros presented the EMA perspective. I think we did note that the Division of Anti-Infectives works in close collaboration with experts in Division of Pulmonary Allergy and Critical Care in the design of these studies.

Dr. Smith emphasized that there were important lessons learned from inhaled bacterial therapies for conditions like non-CF bronchiectasis -- lung disease which might have a bearing on development of products for conditions like ABPA like we were discussing today. I think he emphasized the importance of selecting a clinically meaningful endpoint and not one based solely on a biomarker. The

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need for adequate development work including phase two trials, which would be very helpful in determining key design elements of future trials. And heterogeneity of patient population, which has come up during multiple sessions this afternoon.

I think Dr. Botgros I think clearly, you know, stated that in general, there's alignment with FDA recommendations. Much like us, they have had limited exposure so far with inhaled antifungal drug development and there are no approved therapies in Europe either for conditions like ABPA. The current guidance in antifungal drug development does not cover inhaled therapies, but some of the principles are relevant to developing inhaled therapies as well.

We then moved onto a session on -- first on ABPA specifically and next one on invasive fungal infections. Dr. Bazaz and Dr. Denning covered the topic of ABPA and broadly the allergic fungal airway disease phenotypes. Underlying immunopathogenesis, evolving diagnostic criteria, etcetera. And discussed some clinical trial data that

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are available over the years with treatment of ABPA, and we heard about the practical difficulties in conducting a clinical trial in patients with SASS. Dr. Denning provided some options for primary endpoints, such as measures of lung function, patient-reported outcomes either using respiratory domain or a general domain. Noted the limitations of exacerbations as an endpoint, given that the infrequent -- would require longer term studies. Emphasized the importance of reducing corticosteroid usage from a patient's standpoint. And discussed some supportive endpoints like radiology and sputum markers, and also touched -- composite endpoints. For -- fungal infections, Dr. Marr and Dr. Husain discussed the role of inhaled antifungal therapies in invasive fungal infections, but Dr. Marzook [ph] is more hematologic medicines and Dr. Husain's presentation on lung transplantation.

There's -- I think Dr. Marr has identified that even though azole prophylaxis is common -- is -- is main space of these patients during

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their high-risk period, there is an unmet need because of the growing list of drug interactions with azoles. And that there might be potential roles of inhaled antifungal drugs as adjunctive therapy for treatment and also for patients with influenza or COVID-associated fungal infections.

Dr. Husain sort of outlined some potential clinical scenarios where these trials can be done. Either the product could be used for universal prophylaxis or -- or for preemptive therapy, or for treatment of invasive fungal infections. And suggested some potential endpoints that note that for the treatment of invasive fungal infections, it's probably nebulized drugs may not be able to use. I mean, probably -- as well as therapy would need to be in conjunction with other drugs.

We had a four industry speakers at the next speaker -- at the next session. There were two presentations each on products being developed for IFI or allergic bronchopulmonary aspergillosis. I think consistently across all the presentations, we heard

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that there is a need for therapy for these conditions. These products offer higher local concentrations and no systemic toxicity and -- from a patient standpoint. We heard about product -- that are designed for inhaled therapy and features proposed devices to be used. And some of which might reduce the patient burden that we've heard about. I think we heard loud and clear that these clinical trials are very difficult to conduct. Defining patient population is difficult. There's a lot of heterogeneity in the patient population, and the heterogeneity can also impact on the size of the treatment effect. Very important consideration with the site selection. And in defining the patient population, we have to strike a balance between addressing heterogeneity and making the trials -- as well. There's a lot of discussion around lack of standardized endpoints or agreed to endpoints because this is a new feed. And also regarding the timing of the assessment. It's certainly encouraging to see that some phase two trials at least have been conducted or were attempted

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to gain further insight into key aspects of trial design. I think they did highlight some of the practical challenges in doing these studies, and it's very unfortunate to see that some of these studies have been negatively impacted by the COVID pandemic.

I think there's also a -- need for continued collaboration and interaction with regulators. The possibility of using streamlined development programs and approval under the -- sorry.

I know I've gone through a lot of information in a short period of time. I'll quickly summarize what I heard in the panel discussion. We had four question. The first question really related to gaps in animal model or in vitro models, but can be used to support potential streamlined development programs. I think there's a recognition that more work needs to be done, particularly for ABPA chronic aspergillosis model. For invasive aspergillosis, we have reasonable models. And there's certainly a lot of discussion about what development of resistance means and how it can be monitored, should a product be

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approved or -- for inhaled therapies. So I think a lot more scientific questions that need to be answered in that context.

Question two is a discussion around appropriate endpoints -- assessment, etcetera, for ABPA trials. I think we -- we heard from the Cystic Fibrosis Foundation about the importance of including CF patients in these trials. I think important to consider the burden of care because these patients are on multiple other therapies, and so a product, which is a dry powder inhaler, can certainly offer an advantage in terms of burden. And I think an important point was also brought up about potential drug interaction with azoles because of the CFDR modulating drugs that are used. The discussion around potential endpoints, I don't think we came up with a consensus endpoint, but there was suggestion that radiologic resolution or improvement is important. CT guided assessment of radiologic legions, the discussions around composite endpoints that have been used in the prior -- study. And certainly some

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discussions around patient-reported outcomes.

For the third question about developing inhaled therapies in invasive fungal infections and prophylaxis, I think there's a clear message for us to regulate those and separate them out. Treatment of invasive fungal infections from prophylaxis, and whether the, you know, the two need to be tied together. I think there was also discussion around -- for treatment particularly, the feasibility is an issue and there might be a stable patient population, like those with chronic -- disease or chronic pulmonary aspergillosis where actually a treatment can be assessed because in other patients with immunocompromised patients with invasive fungal infections, it might be a lot more challenging. Certainly -- for antifungal drugs have a role in prophylaxis in invasive fungal infections.

There's also discussion around, you know, quality of life assessments in patients post-transplant and the side effects of these inhaled therapies and how that might impact on their life.

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The last question related to patient-reported outcome measures, both for ABP and IFI. There were discussions around using some existing tools that certainly concerns raised that they may not be appropriate for primary endpoints. Some discussion around potentially using the CFQR for the CF population, and it has been used as an endpoint for regulatory approval in CF patients, not for fungal infections.

I'm sure I didn't capture all the discussion points, but this is sort of -- that's a very high level summary of the panel discussion. So -- so really just some key points and next steps of where we go from here. I think we at the agency, along with all of you, share a common goal to have safe and effective treatment options for our patients with fungal infections, whether they fall in the spectrum of allergic pulmonary disease of invasive fungal infections. We also recognize that there are significant uncertainties at this time with regard to trial design endpoint, duration of therapy.

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Moving forward, we hope that data that have been generated in ongoing programs with systematic data collection will play an important role in making advances in the field. There will be lessons learned along the way that will certainly help us refine our approaches. Cannot emphasize enough that it's important to define outcomes that are clinically relevant and meaningful to patients, and incorporating the voice of the patient will be very important as endpoints -- refined. As with all development programs, ensuring safety of patients is paramount in designing safety -- inhaled product with a patient population with chronic underlying lung condition can certainly be challenging.

As the agency remains committed to working with all of you, that patient needs are being met, my sincere thanks to all speakers and panelists for your contribution to today's workshop. Again, thanks to Mr. Birrell for sharing his perspective. I think that was greatly appreciated. Certainly would like to thank Sumita -- and James -- for coordinating

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this workshop. And many thanks to our technical support team for ensuring the smooth conduct of this workshop. So with that, John -- I know I've gone through it really, really quickly. Maybe I can turn it over to you for a final -- okay. I'm just seeing a note from John. So he had to sign out. So I think on behalf of the Division of Anti-Infectives in the Office of Infectious Diseases, our sincere thanks and appreciation to each one of you for participating as a panelist or a speaker or just joining and -- and listening to the deliberations. Thank you very much and wish you all a good evening, good night, and many thanks to those on the other side of the Atlantic for staying this late. Apologies for the -- for the delayed conclusion of this meeting. Thank you.

Okay. Shall we call it a day?

DR. WALSH: Thank you.

DR. NAMBIAR: Thank you so much.

DR. MOSS: Thank you very much.

(Whereupon, the meeting concluded at 4:41 p.m.)

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I, CARL HELLANDSJO, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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