UNITED STATES

FOOD AND DRUG ADMINISTRATION

_____

PUBLIC WORKSHOP

DEVELOPMENT CONSIDERATIONS OF ANTIFUNGAL DRUGS TO ADDRESS UNMET MEDICAL NEED

_____

DATE: Thursday, August 4, 2020

TIME: 9:13 a.m.

LOCATION: Remote Proceeding - MD

Virtual Silver Spring, MD 20903

REPORTED BY: Janel Folsom, Notary Public

Job No. CS3856635

A P P E A R A N C E S

DR. JOHN FARLEY
DR. SUMATI NAMBIAR
DR. RADU BOTGROS
DR. ERIN ZEITUNI
DR. THOMAS WALSH
DR. JASON MOORE
DR. WILLIAM HOPE
DR. LAURA KOVANDA
DR. YULIYA YASINSKAYA
DR. KIEREN MARR
DR. JOHN REX
MATTHEW SCHUELER
DR. PETER PAPPAS
DR. CHERYL DIXON
DR. AARON DANE
DR. ASPASIA KATRAGKOU
DR. LUIS OSTROSKY-ZEICHNER
DR. TOM CHILLER
DR. HELEN BOUCHER
DR. BAOYING LIU

DR. MICHAEL HODGES
DR. DAVID ANGULO
DR. TAYLOR SANDISON
DR. GEORGE THOMPSON
DR. DAVID DENNING
DR. JOHN PERFECT
DR. THOMAS PATTERSON
DR. KAREN HIGGINS
DR. JOHN BENNETT
DR. SHAWN LOCKHART

P R O C E E D I N G S

DR. JOHN FARLEY: This is John Farley checking audio.

COURT REPORTER: Sounds good. We can hear you.

DR. JOHN FARLEY: Good. Shall I go ahead and start?

COURT REPORTER: Yes, you can start now.

DR. JOHN FARLEY: Okay. I'm very sorry for the delay, everyone. This is our first virtual workshop here in the Office of Infectious Disease. We've put in lots of preparation and weren't quite counting on doing this in the middle of a tropical storm, but we're hoping that the workshop goes smoothly today. In the event that you do lose Internet, please just log back in and join us.

I see that Tom Walsh is already losing connections but rejoining us right now. I want to welcome everybody this morning and thank particularly the speakers for the time that they've invested in preparing for this event.

We're here today to focus on the development of new therapies to address unmet medical need for the treatment of infections due to invasive molds and Candida auris. Discussions today will include the current state and clinical trial design considerations for developing new therapies for these infections.

Fungal diseases with unmet need occur in people who live in or travel to certain areas. An example of that is Valley Fever, which will be our focus tomorrow. And they also commonly affect people with weakened immune systems, and an example of that is Candida auris, which we'll be focusing on later today.

Similar to antibacterial drugs, antifungal resistance can severely limit treatment options. The science of preclinical development is hard and it's very important to establish feasible clinical trial designs that will lead to interpretable data.

Like antibacterial drugs, there are significant financial challenges. The key to making

Page 6

progress is coming together as a community. Government staffs, academic researchers, healthcare providers, patients and drug developers to frankly discuss the challenges and ideas for making progress together, and that's our main goal and our focus today.

Just a bit of housekeeping. We ask that folks speak clearly and stick to the time so that we can stay on time today and have time for some good discussion. For the audience, the speaker slides, transcripts and recordings will be available on the public webpage in the coming days.

So, at this point, I'm going to turn the program over to Sumati Nambiar and Erin Zeituni. Sumati is from our group at FDA and heads the Division of Anti-Infectives, and Erin is from NIH and very involved with support for antifungal drug development. So, we'll ask them to start Session 1 at this point. Thanks very much.

DR. SUMATI NAMBIAR: Yeah, thank you, John. I hope everybody can hear me okay. Good morning and I would like to add my welcome and thank

Page 7

you all for joining us for today's workshop. We look forward to a productive meeting and hope that today's discussions will set the stage for future conversations as we continue to work together as a community to advance the field of antifungal drug development.

As John said, Dr. Zeituni from NIAID and I will co-moderate the first session on the background of clinical and preclinical concentrations. I'll start with the first talk -- I'll cover regulated considerations from an FDA perspective. And then I'll also present on behalf of colleagues from PMDA, our Japanese regulators, who unfortunately couldn't join us for the workshop. So, with that, if I can have my slides up? Thank you.

Over the last few years we've seen some increased interest in antifungal drug development. In addition to the standard indications as in Candidiasis and invasive aspergillosis, there's also interest in developing antifungal drugs for the less common molds, and also for an unmet need population, which is variously defined either by the presence of refractory

Page 8

disease, resistance to existing therapies or intolerance to currently available treatments.

This is certainly very encouraging, but at the same time we do recognize that there are scientific and practical challenges that need to be addressed. We hope that in today's workshop we will be able to identify some solutions to the issues at hand, and also identify some key areas that we'll need for the discussion.

As John has mentioned, you know, we also recognize that there are several economic challenges that face the field of anti-infectious drug development at large, which includes both anti-bacterials and antifungals. Unfortunately, it's not a topic that we can address or cover in today's workshop.

It's really important to keep in mind that general principles for antifungal drug development are similar in many aspects to those for antibacterial drug development. And over the last decade and maybe decade and a half, we've made significant progress with antibacterial drug

Page 9

development and have clearly defined in scientifically sound approaches that are feasible for many clinical conditions that clinicians see.

This was not an easy task. It was achieved by engagement with stakeholders. Some of you on the call participated in those discussions. We also engaged in public-private partnerships and exercised some regulated flexibility, all supported by good scientific evidence.

There are many important lessons that we've learned from completed programs. Unfortunately, many of them also from field programs, which is not what we like to see but I think very important to keep in mind that they teach us many important lessons. We recognize the importance of those selections, the body site of infection, and the role animal models of infection play, particularly in streamlined development programs that are designed to attract unmet medical need.

Presently, there's more work to be done. There is ongoing work in defining or using novel endpoints. There's also discussion around

Page 10

designing trials for difficult to study indications and also how to develop drugs for special populations, including children. All of these certainly have relevance to antifungal drug development as well.

And just to make sure that we're all on the same page, at the very high level, you know, we have two regulatory pathways. The traditional approval pathway is generally based on an endpoint that measures how a patient feels, functions or survives. An accelerated approval is based on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality. It's important to keep in mind that even for products approved under the activated approval pathway, the statutory standards for effectiveness as in traditional approval should still be met.

So, the statutory standard for effectiveness is substantially evident consisting of adequate and well-controlled investigations. For antifungal drugs, at least one adequate and well-

Page 11

controlled trial should be conducted per indication. The supportive evidence from this single trial can come from nonclinical studies, in vitro studies, or from another indication.

I also wanted to note that for products with orphan designation -- I hope everybody can still hear me. So, for products with orphan designation, which many antifungal drugs do get designated as orphan drug product, the statutory standard still needs to be met. So, effectiveness needs to be demonstrated in adequate and well-controlled (sound drops).

Recent trials for aspergillosis, candidemia/invasive candidiasis that have been submitted to support an indication have used a non-inferiority trial design. And for these conditions there's a large treatment effect, and a justification of the NI margin is possible.

Commonly used endpoints in antifungal trials have included all-cause mortality or clinical success at a fixed time point, which has varied from six to twelve weeks. And I just wanted to point out

Page 12

that during the course of our discussion today, when we discuss alternate endpoints, I think we should keep in mind that endpoints that are selected for clinical trial should be well-defined and reliable.

The clinical endpoint should be one that measures an effect on how a patient feels, functions or survives. If it's a surrogate marker -- surrogate endpoint, it's usually a marker such as a laboratory measurement or a radiographic change that's likely to predict clinical benefit but is not in itself a measure of clinical benefit.

So, today we'll also have a lot of discussion about the role of diagnostics and how they can help us with enrolling patients in clinical trials. And we have allowed things for candidemia/candidiasis trials, use of non-culture-based tests for enrollment for aspergillosis drugs. We've allowed the use of galactomannan test for patient identification and defining patient populations.

In general, diagnostic tests do not have to be FDA cleared or FDA approved if they're

Page 13

being used for enrichment purposes, and qualification of an endpoint is also not a prerequisite for use in clinical trials.

The size of the safety database I think certainly will depend a lot upon the clinical conditions being studied and the attributes of the drug. I think it's important to keep in mind that based on signals from nonclinical studies, the trial will have to have appropriate safeguards such as monitoring and enrollment of the appropriate trial population.

We do recognize that particularly for unmet need programs and safety database would be small. We highly recommend that at the proposed dose and duration, we get safety data on at least 300 patients. There might be a requirement for additional data if a safety signal has been identified. Also, there might be a need to collect additional safety data post-marketing, either through post-marketing requirements or enhanced pharmacovigilance.

So, here are some paths moving forward, and a lot of this we hope will come up during our

Page 14

discussion today. We may not have solutions to all of these but it'll hopefully be some food for thought as we continue to work together.

How can we design data packages that are feasible and provide interpretable data, particularly for the more difficult to study fungal infections? And how best do we leverage data from nonclinical studies to support these small data packages? What is the role of external controls, particularly for certain types of fungal infections?

We're hoping there'll be some discussion around how we develop oral stepdown therapies, particularly when the product is not available as an intravenous and an oral combination. And also talk about developing products for the pediatric population, including neonatal infections.

There are two other topics that I've sort of grayed out, not because they're not important but not within the scope of today's workshop: Developing inhaled antifungal therapies and developing therapies for prophlyaxis of invasive fungal infections. These are topics that we hope to bring to

Page 15

a future public meeting.

I just want to switch gears and talk about some incentives and also about the LPAD approval pathway. I think many of you are familiar with the Qualified Infectious Disease Product designation that's given to antibacterial and antifungal human drugs that are intended to treat serious or life-threatening infections.

In addition to five years of -- additional five years of marketing exclusivity and a priority review for the first application, these products are also eligible for fast-track designation. And so far we've granted QIDP designation to over 200 antibacterial/antifungal products and 26 of these designated products have been approved.

I understand there's some interest in the community of the tropical disease priority review voucher and its applications for antifungal drug development. So, applications that have been developed for the prevention of treatment of a disease which is on the tropical disease list may be eligible for a tropical disease priority review voucher if they

Page 16

meet certain criterion.

I'm not going to read through all of them. I've given you the reference. We have a guidance, and then there's also certain criteria that are included under the Food & Drug Administration Reauthorization Act of 2017. And if a PRV is issued that can be used to obtain priority review designation for a subsequent application, that by itself will not have qualified for priority review.

So, in addition to the existing list, Section 524 of the FDA allows us to add by order "any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations." We have an open docket to which interested parties can submit additional diseases with supporting materials and we review them on an ongoing basis. As many of you are aware, cryptococcal meningitis was added to the list of eligible disease I think a couple years ago, and more recently, we made the decision to not designate coccidioidomycosis.

The LPAD pathway, the Limited

Page 17

Population Pathway for Antibacterial and Antifungal Drugs, became available under the 21st century cures, and it's based on the benefit-risk assessment that more flexibility takes into account the severity or prevalence of the infection. And I understand that this will come up for discussion and is included in a couple of the other presentations that we will hear today.

So, there are three requirements for a drug to qualify under the LPAD pathway. First is that it should be intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs. And, very importantly, it does not change our standards for approval.

So, the standards for approval under 505 or under 351 still need to be met. That does mean to have substantial evidence of effectiveness. And the written request has to be submitted from the sponsor that the product be approved as an LPAD drug. There are certain conditions for approval with regard to labeling and promotional materials.

Now, so far we've approved two products

Page 18

under the LPAD pathway: Arikayce, or amikacin, for the treatment of non-tuberculosis mycobacterial infections, and Pretomanid, as part of a combination regimen for the treatment of certain populations -- patients with tuberculosis.

The approved population for each of these products is limited. It's very defined and specific. Treatment effect was demonstrated in at least one adequate and well-controlled trial for each product.

We considered the benefit-risk profile of each of these products to be acceptable in the indicated limited population of patients who have few or no treatment options, and limitations of the data are reflected in product labeling.

And this is just the highlights section of the prescribing information for these two products. And as required under law, the sentences that are highlighted were included in labeling to convey the limitations of the data.

So, before I conclude, I will just touch upon pediatrics. Under the Pediatric Research

Page 19

Equity Act, pediatric studies are required unless requirement is waived, deferred or not applicable. And although antifungal products with orphan designation are exempt from these requirements, we encourage sponsors to consider developing products for children. I think we all recognize that safe and effective therapies are needed for this population. And in most instances, it is possible to extrapolate efficacy from adults to pediatrics. And we're also willing to consider issuing a pediatric written request if there is interest. Sorry, there's an issue with formatting on the slide.

I also wanted to point out that we recently issued a guidance on anti-infective drug development for pediatric population, and the principle outlined in the guidance are applicable to both antibacterial and antifungal drugs.

So, in summary, I've provided a high-level overview of the key considerations for antifungal drug development and reviewed some incentives and pathways that are relevant to antifungal drug development.

Page 20

As I stated early on, we at the agency recognize the unmet need and also the practical challenges in developing these products. It is very important that all of us work together to find feasible and scientifically sound solutions to address patient needs.

And there are many important lessons learned from antibacterial drug development that are relevant to and can certainly guide further discussions on antifungal drug development. So, with that, I thank you for your attention and will now present on behalf of our colleagues in PMDA. So, maybe I can get those slides for that, please? Great. Thanks.

I'm just going to go through these slides that the center has by PMDA and Shohko Sekine, who's in the Office of New Drug at PMDA, has written up these slides on the regulatory considerations for antifungal drug development, perspective from Japan.

So, they note that there are no guidelines currently for development of antifungal drugs issued by regulatory authorities in Japan. The

Page 21

development of antifungal agents is not very active currently. In the last five years, they have approved four products: Two of them were for the treatment of nail ringworm, one was for the treatment of oral candida infection, and the other product had both a prophylaxis and a treatment indication.

Provided as an example of the most recently approved product in Japan, and that is Naxafil or Posaconazole, both as a tablet and intravenous formulation. The indications include prophylaxis of deep mycosis in hematopoietic stem cell transplant recipients or patients with hematologic malignancy, and also for the treatment indication that includes the following mycoses: Fusariosis, mucormycosis, coccidiodomycosis, chromoblastomycosis and mycetoma.

The data package included clinical trial results from outside Japan and these data had been submitted to EMA and FDA. In addition, there was data available from a trial conducted in Japanese patients. The sponsor's position was that the foreign data could be utilized for evaluation of efficacy in

Page 22

Japanese patients because there were no differences in the susceptibility of the clinical isolate between Japan and foreign countries; the medical environment, treatment algorithm and pharmacokinetic profile between Japanese and non-Japanese was not different.

So, this is a summary of the Japanese clinical study that was conducted to support the approval to the active controlled open-label trial in patients with systemic and deep mycosis. The primary efficacy endpoint for invasive aspergillosis and mucormycosis was a composite of clinical symptoms and radiographic assessment and mycology assessed at day 42, and the chronic pulmonary aspergillosis of clinical symptoms and radiographic assessments made at day 84.

And they also noted that the study in Japanese patients is a recommendation and as of now, is not a requirement for programs moving forward.

So, with that, I would invite our next presenter, Dr. Botgros, rather than infectious disease specialist, working as a scientific officer for the Office of Biological Health Threats and Vaccines

Page 23

Strategy at the European Medicines Agency. So, Radu, thank you.

DR. RADU BOTGROS: Thank you very much, Sumati. Can you hear me well? Can you hear me?

DR. SUMATI NAMBIAR: Yes, yes.

DR. RADU BOTGROS: Very good. Thank you very much and thanks to the FDA for inviting me to this public workshop. My presentation will try to provide you with some important EU Regulatory considerations for developing antifungal medicines.

As most of you know, the EMA has a guidance document on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease. And this guidance has been finalized ten years ago, back in 2010, and is still in force. It reflects the recommendations and categorizations of disease of the European Organization for Research and Treatment of Cancer and the Mycosis Study Group of the NIAID and is a revised version of a 2003 document.

And I must say that these guidances have been put together as a response to scientific

Page 24

advisor requests that were made to the EMA by sponsors that were seeking approval based on nonrandomized studies with or without external or historical controls, often in difficult to treat patients.

I would now like to present a few important considerations that the EMA guideline is making which I believe are relevant for the discussion today. And one important aspect is related to the selection of the dose regimen and the use of the PK/PD in the process. And I think it's important to point out that the guideline mentions the fact that the dose selection should be based on nonclinical data, human PK data and exploration of the PK/PD relationship.

It's important also to mention that the EMA has a dedicated PK/PD guidance document that also applies when developing an antifungal. So, I think it's good to keep that in mind, and at the same time, you know, to acknowledge that the experience with PK/PD of antifungals is accumulating and has accumulated during the last decade.

It's important to mention a few recommendations that the guideline on antifungal is

Page 25

making for developers aiming at developing drugs for treating invasive fungal infections produced by either aspergillus or candida.

The recommendation is to conduct a prospective randomized active controlled trial in patients confirmed to have proven or probable invasive fungal disease. The preference is to allow a single comparator in the study or at least to restrict choices of the comparator if choosing a single one is not an option.

I should also mention the fact that the CHMP, which is the EMA main scientific committee in charge of approval of medicines, has accepted single pivotal trials for these indications.

Determination of eligibility and outcome should ideally be made by an independent adjudication committee that is blinded to treatment assignment. And I think it's important to mention the fact that fungaemia should be persistent after removal of catheters and that all primary -- possible primary foci are investigated. And the patients that have persistent fungaemia and/or established primary foci

Page 26

can be counted in the primary analysis.

The primary endpoint of the randomized controlled trials that is preferred in EU is the global clinical response at test-of-cure. The non-inferiority margin that has been accepted is 10 percent and is actually derived from mortality in data sets of proven, provable and probable cases. It is actually what has been accepted so far, despite there is awareness of the fact that the relevance for the study populations may be questioned by some.

It is important to note also that the predefined primary efficacy endpoint of all-cause mortality at day 42 or day 84 has also been accepted, provided that the global clinical response rates are supportive.

When it comes to the treatment of rare invasive fungal disease, the guideline recommends that at least one randomized clinical trial in invasive fungal disease due to candida or aspergillus should be conducted before or in parallel with a rare fungal pathogen study. The dose used in the rare fungal pathogen studies should be justified using the

Page 27

efficacy results versus candida and/or aspergillus plus PK/PD analysis using patient PK data.

I think it should be bore in mind that this recommendation is made in response to previous proposals of nonrandomized studies in patients with various rare fungal infections, some with historical controls, and which essentially were requesting approval based on data generated from such studies, plus-minus PK/PD to support adequacy of the dose.

It's important to highlight that for now, the guideline does not foresee the possibility of approving an antifungal for treatment of rare invasive fungal infections based on a positive candida or aspergillus RCT plus PK/PD. So, there is a need to have a study in rare invasive fungal infections that one should be ideally randomized possibly using unbalanced randomization, and it should compare the candidate medicines with licensed medicines or best available treatment. And in case nothing is approved or considered adequate superiority of the test regimens versus best available treatment should be demonstrated. Separate studies by fungal types are

Page 28

also the preference here.

A few words on the treatment of refractory IFD. Here it is important, I think, to note that clinical studies in these patients should only be conducted after having shown satisfactory efficacy results in one or more specific types of IFD.

The enrolled patients should have proven IFD that persisted or progressed despite previous antifungal therapy. The only exception being invasive aspergillosis, where also probable cases can be enrolled. The primary objective of such a study may need to be discussed depending on whether it is or it is not possible to use an active control.

The prophylaxis part is, of course, not part of this workshop but I just wanted to mention very briefly that here the expectation is that prophylaxis studies are conducted only after showing satisfactory clinical efficacy in a treatment of IFD. And the fact that it is expected to conduct a randomized trial with an adequate comparator and to compare rates for proven or probably IFD during treatment and for a defined period after cessation of

Page 29

prophylaxis.

The non-inferiority margin and power of such a study need to be discussed in advance and potential improved indication will likely reflect a generation of evidence for specific fungal types.

Before I finish, since the workshop discusses development of antifungals for unmet medical needs, I wanted also to say a few words about how this concept is described in the EU regulations and about the use of the term in different regulatory settings. And I think it's important to mention that there are regulatory tools in place addressing products which cover recognized unmet medical needs in Europe.

The first one is, of course, the conditional marketing authorization, which is a tool that can be employed for products where the benefit-risk balance is such that the immediate availability outweighs the limitations of less comprehensive data than normally required. And I won't -- I mean, you see on screen the definition of unmet medical need as presented in one of the regulations that we have. And so I think this is one of the tools that can be used

Page 30

for such products.

And apart from that, there is a possibility -- the other regulatory option that we have for medicines addressing an unmet medical need is the accelerated assessment. Here it's important to mention that these need to be requested by the sponsors and should be accompanied by a justification by the applicant where typically the applicant will argue to support that medicine addresses to a significant extent unmet medical need for maintaining and improving the health of the community.

And this concept of unmet medical need is actually considered also in other regulatory areas, notably in the framework of granting orphan designation or in the context of the PRIME program, the priority medicines applications, or in agreeing with the pediatric investigational plans.

So, just to summarize, I think it's good to keep in mind that we have an antifungal guidance in force in the EU; the fact that we had rather few applications for new approvals for antifungal agents, a bit more but also not too many

Page 31

for CHMP scientific advice, both for treatment and prevention of invasive fungal infections. The CHMP has been flexible on the primary endpoint for invasive aspergillosis, as I mentioned before, and I think it's worth consulting the guidance of antifungals when developing medicine targeting rare pathogens, in particular the recommendations on first establishing efficacy in candida and aspergillus and use those data to support the results obtained from small RCTs in target rare pathogens with support from PK/PD for the dose regimen. Of course, prophylaxis should be considered and investigated after treatment. And, last but not least, we have the regulatory tools available for products addressing an unmet medical need.

With that, I thank you very much. Back to you, Sumati and Erin. Thank you.

DR. SUMATI NAMBIAR: Thank you so much, Radu. Our next speaker is Dr. Zeituni from the Preclinical Services Program at the Bacteriology and Mycology Branch at NIAID. Erin's going to talk about the preclinical services for antifungal product

Page 32

development at the NIH. Erin, I'll turn it over to you. Thanks.

DR. ERIN ZEITUNI: Thank you, Sumati. Just checking that my sound is working?

DR. JOHN FARLEY: Yes, loud and clear.

DR. ERIN ZEITUNI: Thank you. I'd like to thank the organizers for giving me the opportunity to tell you all a bit about NIH's preclinical services for antifungal development. And throughout this talk I will be encouraging folks to reach out to my group. So, up front, I'd like to let you know that my email is my first name, dot, my last name @NIH.gov. And I have no disclosures.

Because it's all oriented, the mission of the National Institute of Allergy and Infectious Diseases, or NIAID, is to lead research to understand, treat and prevent infectious, immunologic and allergic diseases.

Within NIAID, the Division of Microbiology and Infectious Diseases, or DMID, has a broad mandate supporting research for over 300 pathogens. Essentially, everything except for HIV,

Page 33

which has its own division.

Our support for antifungal product development spans this full product development arrow shown on the slide, from early basic research through to clinical research. The support comes in a variety of mechanisms designed to inform and de-risk product development. Folks in the audience will be most familiar with NIAID's grant and contract mechanisms, which are the main drivers of NIAID's support for product development effort.

However, we recognize that the path to produce approval is long and can be difficult. And, unfortunately, promising products can be lost across the so-called Valley of Death due to lapses in funding or access to resources. To help stem these losses, DMID has developed free services and resources for the research and development communities to access. Those include our resources for researchers, the Preclinical Services Program, which will be a main focus of my presentation today, and clinical support.

In the interest of time, I will only briefly touch on NIAID's resources for researchers,

Page 34

which provide free reagents and services to investigators. These successful programs include the Structural Genomic Centers, which characterize three-dimension atomic structures of proteins playing important biological roles in human pathogens, including for eukaryotic pathogens, which will be of particular interest to this audience, and also BEI resources, which provide reagents to researchers such as well-characterized fungal and bacterial isolates, plasmas and more. More information about these and other programs can be found on our website.

NIAID's Preclinical Services are a suite of contracts designed to support anti-infective product development. These free gap-filling services are intended to lower the risk and help advance promising discoveries along the product development pathway.

Our mission is to keep product moving forward rather than have them stalled due to intermittent gaps in funding or access to resources. Innovators from academia, nonprofit organizations, industry and governments are eligible to apply for

Page 35

these free services. Both domestic and foreign institutions may apply, and applicants to do not need to have NIH funding.

Because Preclinical Services are intended to quickly fill discrete gaps in product development programs and keep them moving forward, there's a simplified request process allowing access year round.

Focusing in on antifungals, I manage a suite of in vitro and in vivo efficacy services that provide supportive data to antifungal drug development programs. To give a flavor of the scale of our services, since 2015, our contractors at the University of Texas Health Sciences Center in San Antonio have performed antifungal MIT testing for over 120 compounds for more than 50 different institutions.

On the right side of this slide you will see the fungal species against which we currently offer MIC testing. Our MIC testing services inform multiple stages of antifungal development. For example, early product developers might utilize our in vitro testing services to confirm antifungal activity

Page 36

in a certified lab or to explore their drug spectrum of activity if they themselves don't have access to multiple representative species of yeasts, molds, dimorphs or rare fungi.

More advanced product developers utilize our in vitro services to expand our MIC data sets and explore activity against species outside their critical path and target indication.

In vivo efficacy models are also available for antifungal product developers. Since 2015, our contracts at the University of Texas Health Science Center in San Antonio and at the University of Cincinnati have provided in vivo efficacy studies to over 25 institutions developing antifungal drugs. This table lists the various models that we offer by species and route of inoculation. Most of our models include two arms: A fungal burden arm to assess the impact of treatment on fungal burdens and tissues of interest, and a survival arm to assess the impact of treatment on mortality, both with drug on board and during a washout period after therapy ends.

Most commonly product developers use

Page 37

our in vivo efficacy services for three reasons: The first is to access proof of concept studies to support a grant application or resubmission; the second is to test efficacy against additional strains of a target species including alternate resistance profiles; and the third is to test their drug against additional priority pathogens that might not be the target of their critical path of the program. We offer these services to ensure that promising antifungals at a variety of development stages, both early and late, have a path forward to assess their microbiological activity.

In the table on the right, the models written in black are currently available under open task orders, while the models written in red would require a new task order to be solicited before coming back online. We rely on the product development community to drive which models we have available at any given time, based on the requests that we receive for testing.

Requests from product developers serve a bona fide need for us to solicit new task orders and

Page 38

I encourage you to reach out to us and tell us about your antifungal programs and any gaps that you might have.

In addition to responding to requests from product developers, at NIAID we also use preclinical services contracts to pivot and support product development needs for agents targeting emerging infectious diseases. For example, when Candida auris emerged as a pathogen of concern and made its way onto a CDC clinical alert in 2016, we had started planning for incorporating this pathogen into our testing cascade. We first incorporated MIC testing against clinical isolates of Candida auris into our task orders and workflow and later updated our panels to include the CDC, FDA, AR isolate bank when that panel was published online.

We then solicited a task order to develop and validate a Candida auris infection model. In this model, ICR mice are treated with five fluorouracil to induce neutropenia and are inoculated via the lateral tail vein with a clinical isolate of Candida auris that is resistant to fluconazole and

Page 39

sensitive to caspofungin. In the model, two study arms, a fungal burden arm and a survival arm are used to assess the impact of fluconazole and caspofungin treatments on these outcomes in comparison to untreated controlled.

The results of these model development efforts were reproducible and the protocol was proven transferrable by a subcontracting group led by Scott Filler and Ashraf Ibrahim at UCLA Harbor. With a validated model available, we have since solicited multiple task orders and tested Candida antifungals from eight institutions and counting, resulting in three publications. This approach is just one example of how we strive to develop and provide gap-filling services to support antifungals across various stages of development.

In addition to efficacy assessments, NIAID's suite of preclinical services also includes chemistry and manufacturing, including GMP manufacturing, toxicology and pharmacokinetics, rapid ADMET and pharmacokinetics screening services, and product development planning and assistance with IND

Page 40

documentation.

There are many opportunities for you to engage with us about your antifungal programs, and I want to encourage you again to contact us and start a discussion about support mechanisms that we offer, from grants on through to preclinical services. We would be very happy to hear from you.

And before closing, I'd like to briefly mention one more area of free services for product developers which are our clinical trial units, such as our Phase 1 units. These contract provide Phase 1 trials at no cost to the requester. NIAID sponsors the trial and holds the IND. Michovia's VT-1598 is a novel antifungal compound with activity against toxicity species and through our Phase 1 clinical trial unit, VT-1598's single ascending dose study is examining the safety of its administration to 48 healthy adults aged 18-45 years.

And in conclusion, I hope that this presentation was helpful to provide a clear picture of the various mechanisms that NIAID is leveraging to support antifungal product development. Again, I

Page 41

would encourage you to reach out to us. My email is located at the top of the slide. And I'd also like to acknowledge the team effort that it takes to manage the portfolios and mechanisms that were described in this presentation.

Listed are members of the branch who support antifungal therapeutic, diagnostic and vaccine effort. Please reach out to me if you have any questions, and I hope to hear from you soon. Thank you. With that, I would like to give the rest of my time back and get us a little bit closer to on time. Thank you.

DR. SUMATI NAMBIAR: Thank you so much, Erin. So, our next speaker for this session is Dr. Walsh, the Professor of Medicine, Pediatrics and Microbiology at Cornell and an attending physician, New York Presbyterian Hospital. So, Dr. Walsh will talk to us about the animal models of fungal infection. So, Dr. Walsh, I'll turn it over to you.

DR. THOMAS WALSH: Yes, good morning. Are you able to hear me?

DR. SUMATI NAMBIAR: Yes, we can.

Page 42

Thank you.
DR. THOMAS WALSH: Very good. Very good. Well, first, I'd like to thank you so much for the opportunity and the invitation to speak on this very critical area of animal models of fungal infection. They indeed do service our critical systems in development of new antifungal agents.
By way of disclosures, my staff and I have collaborated extensively with multiple industrial partners as critical elements of our advancing translational science from bench to bedside.
By way of background, animal model systems are a critical component of the process in discovery and development of new antifungal agents for treatment and prevention of invasive fungal diseases. Models of invasive fungal diseases in murine, rat, guinea pigs and rabbits have been developed and studied for development of new and previous systemic antifungal agents.
We will review today the conceptual, scientific and regulatory framework for utilizing these models, cite specific examples of their

Page 43

application and discuss their predictability for clinical trials. I just heard a beep. Are you still able to hear me?
DR. JOHN FARLEY: Yeah.
DR. THOMAS WALSH: All right, good. Thank you. Our objectives this morning, therefore, are to review the role of laboratory animal model systems and development of new antifungal agents to assess the predictability of these models for predicting outcome in clinical trials and to identify unmet needs and new directions particularly for biomarkers in preclinical and clinical studies.
So, what is the role for animal models of invasive fungal diseases? First of all, clearly in development of new antifungal agents, one commonly sees particularly in industry or in drug discovery laboratories screening of murine models. They're relatively simple, straightforward with minimal outcome parameters. The next step then will be to explore farther the PK/PD parameters in murine systems, and I'll exemplify those in some of our discussion.

Page 44

And then to move into larger animal model systems, rats, guinea pigs and rabbits, and I will exemplify those as well. Clearly, one needs complementary systems in order to be able to de-risk and to identify potential new compounds -- one needs a complementarity of the different model systems. Many animal models, of course, are also studied in pathogenesis and host defenses, which we will not address today.
What are the characteristics that are noteworthy for predictive in vivo models for invasive fungal diseases? They should reflect the host response relevant to the fungus. This is actually absolutely paramount, for the host response plays a critical role in outcome, both in the animal model systems as well as in our patients. They should have quantifiable outcome variables. At minimal, survival, human endpoints, residual fungal burden that we measure by culture and/or PCR, and a range of biomarkers including antigen and antibody but also other, for example, inflammatory biomarkers, and then, of course, the classical histology.

Page 45

What are some of the more widely used or studied invasive fungal diseases? Certainly Candida dominates in the field of laboratory animal studies. Commonly we use a neutropenic thigh model but also there are models of disseminated Candidiasis to take us a step farther that can mirror acute, subacute, chronic and CVC, central venous catheter biofilm studies, hematogenous Candida meningoencephalitis, the diseases of cutaneous candidiasis, oropharyngeal and esophageal candidiasis, cutaneous and vulvovaginal candidiasis.
For Aspergillosis, certainly there are the models of invasive pulmonary aspergillosis, which we see in murine, guinea pig and rabbit systems, and CNS disease, more challenging. But the laboratory, for example, of Dr. Stevens has done considerable work in CNS aspergillosis. In mucorales, we see pulmonary mucormycosis and models of disseminated disease.
Although we will not address, in any greater detail, the endemic mycoses and Cryptococcus models, those models certainly are stalwarts of being able to have a firmer foundation before going into

Page 46

clinical trials. Emerging and very relevant to the new compounds under investigation now are hyaline and Dematiaceous molds and models including murine and rabbit model systems of fusariosis, scedosporiosis, some of the dematiaceous molds including in our system, for example, the rabbit model exserohilum rostratum CNS infection as an example of CNS phaeohyphomycosis.

So, if we were to then explore farther now the application and use of these models, we can look to, for example, to the murine neutropenic thigh model for further understanding of the PK/PD properties. The model system has its origins originally in bacterial PK/PD studies and provides early guidance toward developing of dosing and PK/PD parameters. It identifies dosage parameters for further exploration, particularly in more advanced models representing different patterns of infection and different host groups.

One of the key components of PK/PD modeling is that of fractionized dosing studies, which then allow one to be able to model the system and to

Page 47

be able to identify, as depicted here, the appropriate parameter be it AUC:MIC ratio, peak plasma concentration or time above MIC.

Mucocutaneous Candidiasis is a common ubiquitous series of infections, particularly oropharyngeal and esophageal Candidiasis. Earlier in HIV/AIDS, but now we continue to see this in a wide variety of immune deficiencies. Depicted to the left, there's a model for fluconazole-resistant esophageal candidiasis showing the time course of resistance versus susceptible and a striking difference in response as well as histology. And the predictive capability in echinocandin, in this case, Anidulafugin, showing a dose response relationship, which was highly predictive of the clinical outcome of that echniocandin as well as others in clinical trials of esophageal Candidiasis.

There are numerous models of vulvovaginal Candidiasis and that has become an important area, particularly ever increasingly, and these unfortunate patients who suffer from refractory VVC and for whom there is a dearth of available

Page 48

systemic agents and strategies.

We then see with the advent of Candida auris, new models emerging of cutaneous Candidiasis. One in particular in the guinea pig, by Dr. Ghannoum and his colleagues, demonstrating the efficacy of reflects of ibrexafungerp. This is particularly important in launching into clinical trials for prevention or decolonization, as the skin serves as a distinctive source for harboring the organism, in a sense, and a source for transmission into the environment.

If we look at different patterns of Candidiasis, there are acute, subacute and chronic that can be readily modeled both in the murine models but also in our rabbit model system. Typically the acute representing hemodynamically unstable patients, which is typically rapidly fatal, associated with high inoculant and a distinct series of clinical features.

Subacute is much more commonly used in both murine and rabbit systems where one can have candidemia with deep tissue infection but are hemodynamically stable. And chronic reflects the host

Page 49

patterns of hepatosplenic candidiasis. These systems plus central venous catheter biofilm treatment studies have been the bulwark supporting the indications of ampho B lipid formulations, voriconazole, caspofungin, micafungin and anidulafungin for indications in this disease.

One of the challenging features, however, remains in children, particularly children, hematogenous Candida meningoencephalitis. And then more commonly, although not exclusively, Candida endophthalmitis in adults.

So, we do see endophthalmitis in our pediatric population as well. That prompted us to move to a distinctive model of experimental model of experimental hematogenous meningoencephalitis where we were able to show with a series of imaging, both in vitro and in vivo studies, the capacity for being able to identify disruption of blood brain barrier by gadolinium scanning.

And then leading to the hypothesis, we were able to bring in echinocandins into a pediatric population that's highly vulnerable to HCME that we

Page 50

would need to know that we could use in echinocandins safely and effectively both in the brain and the eye. And to that end, knowing whether one's compound will be effective in adults as well in treating endophthalmitis rather than later seeing breakthroughs of this infection also becomes important.

So, to that end, in our laboratory in collaboration with Dr. Hope, when he worked in our laboratory with Drs. Petraitis and Petraitiene at the forefront of this work as well, we demonstrated very nicely dose-effect response relationship of more than 99 percent being able to achieve at 12 milligram per kilogram in the rabbit model system and being able to project the AUC.

Given that the kinetics for many of the compounds that we use are very nicely reflected between the rabbits and pediatric patients, we were able to bring these findings into clinical trial, those animal studies, laying the foundation predictively that we were able to enter ultimately through a series of dose escalation cohort studies in the infant and pediatric population a randomized trial

Page 51

of echinocandid versus deoxycholate amphotericin B with no breakthrough endophthalmitis and with no evidence of breakthrough of CNS candidiasis.

If we switch our attention from Candida models to that now of pulmonary aspergillosis, I'll begin initially with the rabbit model -- the persistently neutropenic rabbit model of invasive aspergillosis, which has been a highly predictive system in identifying new antifungal agents for treatment and prevention of this frequently lethal infection.

The animal system has a central silastic venous catheter for atraumatic venous access, Ara-C for profound persistent neutropenia, further modulation with cyclosporine methylpresdnisolone. That alone can also be used to develop a model which we've employed for chronic pulmonary aspergillosis, a very distinctive and tenacious problem encountered ever-increasingly. And then providing intensive supportive care in the profound persistent neutropenia host, similar to that with what we would encounter in our oncology population.

Page 52

So, with that, one has direct endotracheal inoculation, colonization of the tracheobronchial tree. And as immune suppression progresses, colonization to nodular and segmental pneumonia, and then initiation of therapy based upon CT-scan findings. These findings, we believe, very closely mimic and recapitulation the development of invasive pulmonary aspergillosis in our neutropenic and profoundly immunocompromised hosts going out 12-14 days therapy. And even to the extent of radiologically demonstrating halo signs and characteristic nodular infiltrates as I've seen in our patient population.

So, what has been the impact of the markers that we see? Since the initial development of this model, we've been able to identify dosages, drug disposition, safety, tolerability, efficacy for all of the compounds seen here, laying the clinical foundation for the clinical trials, and predictively identifying outcome, both alone and subsequently, as I'll show you, in combination therapy, in a very robust, very predictive manner over the course of

Page 53

time.

If we look at the initial studies of AmBisome, liposomal amphotericin B applied milligram per kilogram per day compared with high dosage of deoxycholate, the AmBisome was found to be more effective and safer, increasing survival, reducing the number of viable organisms, decreasing tissue injury, preventing nephrotoxicity and also showing decreased galactomannan as a therapeutic marker.

If we then look to the AmBiLoad clinical trial, those results accurately predicted the outcome that is compared to 10 milligram per kilogram per day, 3 milligram per kilogram was comparable in achieving a favorable survival rate of 72 percent, and an overall response rate of 50 percent. If we take those data from our original comparative studies, we're then in collaboration with Dr. Hope -- we were able to identify a PK/PD model that found near maximum antifungal activity using, for example, galactomannan as well as the other markers at 3-5 milligram per kilogram per day; and found further that with all formulations that we were also able to induce a dose-

Page 54

dependent reduction of lung injury and circulating fungal biomarkers.

And the final model demonstrated that a clinical dosage of liposomal amphotericin B of 3 milligram per kilogram was predicted to cause complete suppression of galactomannan in the majority of patients, which also correlated well with clinical and experimental outcome -- once again, the robustness of the system and the predictive capacity of this particular model.

Also reflected in this was that of further studies of Posaconazole at 2, 6 and 20 milligram per kilogram -- this is out of intra -- and deoxycholate amphotericin B, where using the parameters of survival, pulmonary influx for lung weights and pulmonary lesion score, we were able to demonstrate that at the two higher doses, Posaconazole was superior to that of Itraconazole, also correlating well with biomarkers of galactomannan, galactomannan antigenemia, as well as correlating with CT-scanning volumetric outcome.

Despite both Itra and Posa having

Page 55

similar -- virtually superimposable plasma concentrations at the 2, 6 and 20, the data has clearly indicated the superiority of posaconazole in this setting, suggesting that MIC may play a critical role where the MIC was significantly lower for posaconazole than that of Itra.

These findings were predictive of the externally controlled trial where we were able to find that there were significantly greater responses in the Salvage study for posaconazole compared to externally controlled recipients. 42 percent of posaconazole recipients versus 26 percent for our control recipients.

We further found that if one evaluated survival with Kaplan-Meier analysis, that there was also similar response. Further to the PK/PD of this, we also found parallel to the rabbit model system, 1,250 micrograms per ml predicted favorable outcome compared to the lower concentrations.

And, finally, our prophylactic studies also, in the system, predicted and laid the foundation for the definitive study of posaconazole versus FLU or

Page 56

ITRA as being superior and lifesaving in prevention of life-threatening invasive aspergillosis and other mycosis.

To that point, with emerging resistance in other pathogens, we further explored in combination antifungal therapy where we were able to demonstrate in this similar model system improvement across all of the biomarkers using, again, CT-scanning as well as galactomannan with the combination therapy, in this case voriconazole plus anidulafungin with striking correlation.

With the in vitro studies, in this case, bliss analysis where the curve itself, the three-dimensional curve going positive indicates significant response.

And so, with that, moving forward into the randomized trial voriconazole plus anidulafungin versus vori alone, although the original analysis primary endpoint was not fulfilled at 0.087, one post talk analysis of six-week mortality did demonstrate in the early patients and those with galactomannan positivity a significant improvement in survival.

Page 57

If we change our focus away from the rabbit model system, we go now to a PK/PD approach where here we see dose fractionation being performed in the laboratory of Dr. Andes, Dr. Zhao, et al, where efficacy was assessed by quantitative PCR. But not many regressions using the Hill equation demonstrating a 24-hour AUC/MIC ratio that predicted the best PK/PD.

And with a stasis and one-hour q endpoint of 48 and approximately 89 mg/kg as dosages achieving status in one long chill. And then with Dr. Patterson's and Vederhold's model, for example in ASP 9726, a survival rate that demonstrates a dose response relationship and parameters that also reveal a correlation with clinical response.

Finally, we see in pulmonary mucormyocosis, a very nice correlation with clearance in increased uptake in the -- by lipid formulations by the laboratory of Dr. Pontionus and in the laboratory of Dr. Ashraf Ibrahim, liposomal amphotericin B showing a favorable dose response relationship all the way to 7.5 milligram per kilogram in their murine model of disseminated mucormycosis.

Page 58

Notably, this model was also critical in assessing the efficacy of isavuconazole, which was relatively comparable to that of liposomal amphotericin B being given at 15 milligram per kilogram per day.

If we move from the traditional models of mice, rats, guinea pigs and rabbits and look toward zebrafish, this is increasingly being used, albeit not for therapeutics but for pathogenesis and host defense and may be a useful and less costly screening tool of antifungal drug discovery.

And, finally in non-vertebrae animal model systems, we see the role, for example of ganella and we also see that of potentially dorsophila as viable tools for, again, screening in early stages of antifungal drug development.

As we look to the future, we're looking toward implementation of biomarkers from preclinical data into clinical endpoint response criteria; development of new models of emerging pathogens; and systematic integration of data from several models in predicting outcome.

Page 59

We conclude that the decision to move from laboratory to clinical trials should be predicated upon a portfolio of complementary and mutually validating preclinical animal model systems with meticulous preclinical investigation of candidate antifungal agents in a robust series of predictive model systems that will optimize study design, de-risk clinical trials and ensure tangible benefit to our patients.

I want to acknowledge the tremendous effort and collaborations that we've had, particularly noting Drs. Petraitis and Petraitiene, outstanding clinical research collaboration and collaborations that span three decades, including that of Dr. Roilides and Dr. Groll, and Dr. Hope, and Dr. Perlin. And our efforts could not be made without extensive collaborations and support through the many agencies and foundations that I've listed here as well as through our industrial partners, who have spearheaded so much of the work in developing these important antifungal compounds. Thank you very much.

DR. SUMATI NAMBIAR: Thank you very much, Dr. Walsh. That was a lot of information in a very short period of time so I'm hoping that we can discuss some of the ideas during the panel discussion.

Our next session is on clinical pharmacology consideration for antifungal drug development. We have two speakers, Dr. Jason Moore, the first speaker, who's a clinical pharmacology reviewer in the Division of Infectious Disease Pharmacology at the FDA. And Dr. Hope is the second speaker, and Dr. Hope is the Dame Sally Davies Chair of AMR Research at the University of Liverpool in the U.K. So, Jason, I'll hand it over to you. Thank you.

DR. JASON MOORE: Thank you very much, Sumati. Can you all hear me okay?

DR. SUMATI NAMBIAR: Yes, thank you.

DR. JASON MOORE: Thank you very much. As Sumati mentioned, I'll be discussing critical pharmacology considerations for antifungal drug development from a regulatory perspective.

As a disclaimer, note that the opinions contained in this presentation are my own. The objectives of this talk are to establish a framework

Page 61

for further discussion as it applies to clinical pharmacology. To do so, I will discuss at a high level clinical pharmacology considerations that are relevant for antifungals and perhaps have some specific unique aspects relative to other therapeutic areas. These will be along the lines of animal models, formulation development, exposure response and drug-drug interaction.

The first consideration pertains to animal model utility. So, not to reiterate too much about animal models after that last great talk, but animal models, as we've seen, do have utility in antifungal drug development to demonstrate proof of concept and to identify those regimens. However, challengers believe in the use of animal models to establish clinical effectiveness. Part of this is due to the appropriate selection of an animal model, one that adequately reflects human critical disease.

As an example, we can turn to micafungin. Micafungin was originally approved in 2005 in adults for candidiasis and later in pediatric patients of four months of age and older. However,

Page 62

there was difficulty establishing the effectiveness for micafungin in pediatric patients younger than four months. In part, this is due to the fact that pediatric patients younger than four months of age can't have meningoencephalitis.

Thus, the assumption that the exposure that would affected in the older pediatric patients and adults would be -- would also be effective in pediatric patients under four months, would not be valid. And, thus, we needed more data in order to be able to identify a dose regimen, first of all, in this patient population.

And that's where the rabbit model of hematogenous Candida meningoencephalitis, the one that Dr. Walsh mentioned in the previous talk, came in. It was used to identify the dose regimen for further clinical study.

However, even with the clinical study, robust clinical data in the pediatric patients younger than four months of age were difficult to obtain.

Thus, this model was used again to support the labeling information, as you can see in

Page 63

the graphic below. Essentially it indicated that seeing that antifungal activity was shown in the model and it included the corresponding human dose regimens that were predicted to note comparable exposure to the rabbit.

Note that this information was included in section 8.4 using special population pediatric use and not section 1, indications and usage, or section 2, dosage and administration.

This decision was made in part because the rabbit ACME model was originally designed to identify the dose with the anticipation of confirmation from a clinical trial in patients.

Additionally, upon review of the individual animal data, we were able to identify a range of dose measurements that were associated with antifungal activity but we could not pinpoint a specific dose regimen linked to clinical effectiveness.

The next consideration regards formulation development. Generally speaking, it's beneficial to have both intravenous and oral

Page 64

formulations available. As we've been discussing, there are a wide range of fungal infection severity from the more ambulatory patients to the patients perhaps that cannot tolerate oral medication.

Additionally, within the context of critically ill patients, it's good to be able to perform stepdown therapy starting with an intravenous agent when they cannot tolerate the oral medication and perhaps switching them to an oral formulation of the same agent as their condition improves.

With that in mind, there have been concerns with the available antifungal formulations. Echinocandins, for instance, are only available intravenously. While the (inaudible) antifungals may have both oral and intravenous formulations, there occasionally have been concerns with the oral formulations in light of variable exposure and absorption. So it should be a consideration during development for a candidate antifungal agent.

The next consideration regards the analysis of exposure-response. It is important to evaluate exposure-response relationships to support

Page 65

efficacy and safety in clinical trials. They can help to inform dose regimen selection, such as if one identified in Phase 2 is used to further optimize the dose before going into Phase 2 trials. They may also indicate the need for therapeutic drug monitoring.

As we see many antifungal agents do include exposure-response data in the labeling, there's an example shown there -- and therapeutic drug monitoring itself is not mentioned in labeling often. However, it is used clinically especially for azole antifungals. And I've lifted an example here from the 2016 IDC guidelines for aspergillosis that does recommend therapeutic drug monitoring for select azole antifungals.

The fourth consideration regards drug-drug interactions. As we've seen, several antifungals have significant drug-drug interaction liability. The azole antifungals in particular are substrates and inhibitors which have to do with their mechanism of antifungal action.

Voriconazole and itraconazole in particular have 30 plus listed drug-drug interaction

Page 66

in labeling. This is a concern because many of the patients who will be treated with this agents for invasive fungal infections have severe comorbidities that necessitate treatment by many concomitant medications that may also have drug-drug interaction liability.

For instance, in the transplant recipients, they are often treated with the agents that are also CYP 3a4 substrates, so having liability through that pathway, and also need to be maintained within a certain concentration window to optimize efficacy and safety.

Additionally, patients with HIV may also be on agents with DDI potential with these agents, such as the protease inhibitors. Thus, it is important to evaluate the drug-drug interaction potential for a candidate antifungal, both in vitro and in vivo, as applicable.

For these last three considerations we can use Posaconazole as an example. It was originally approved as an oral suspension in 2006 and later as a delayed-release tablet and an IV solution. The

Page 67

original suspension had a few concerns related to pharmacokinetics including variable absorption leading to variable exposure. The later approval of the tablet and the solution appeared to increase its clinical utility and allow it to be used in more situations.

In terms of drug-drug interactions, like many of the azoles, it can interact with CYP 3a4 substrates inducers and inhibitors. Additionally, the (inaudible) formulation can interact with drugs affecting gastrointestinal motility or pH.

In terms of the exposure-response relationship, it was assessed specifically for the oral suspension. It was noted that there was an increase in prophylactic efficacy with increases in average concentration. This information was then communicated in labeling. This revealed an opportunity to optimize prophlyaxis despite variable absorption potentially using therapeutic drug monitoring -- which, again, while not in the labeling explicitly, is often used clinically and referenced in the guidelines.

Page 68

With all that in mind, I've highlighted four specific areas for antifungals that relate to clinical pharmacology, but there are other important clinical pharmacology studies that will need to be done during a clinical development cycle, albeit perhaps with not specific considerations for antifungals. Still, these will often inform many of the other studies or areas that we've been discussing.

For instance, the in vitro CYP metabolism and transporter studies will help to inform what in vitro and in vivo drug-drug interactions studies need to be done, the food effects, bioequivalence/bioavailability studies will be very important during formulation and development. The mass balance study will help to inform the design of the hepatic impairment and renal impairment studies, which, again, will be important based on the severely ill population that many of these agents will be used in.

With all that in mind, clinical pharmacology drug development for antifungals on its face is similar to other disease states for the most

Page 69

part. There are simply several areas that may require special consideration relative to other therapeutic areas in the arenas of animal models, formulations, exposure response and drug-drug interaction characterization.

I would like to thank and acknowledge contributions from my colleagues in the Division of Infectious Disease Pharmacology and the Division of Anti-Infectives. Thank you all very much, and I will turn it back over to Sumati.

DR. SUMATI NAMBIAR: Thank you so much, Jason. William, can we start with your slides? Thank you.

DR. WILLIAM HOPE: Good morning, everybody. Sumati, can you hear me?

DR. SUMATI NAMBIAR: Yes, we can. Thanks, William.

DR. WILLIAM HOPE: So, thank you for the invitation to speak from the chilly north of the United Kingdom, in more ways than one.

So, this talk addresses the key steps and ideas to ensure patients receive the right regimen

Page 70

of a novel agent the first time. So, it's going to build on concepts that you've heard throughout the morning. And there are two key areas for discussion this morning.

So, the first would be the identification of an initial regimen, so that's a selection of the candidate dose and schedule of a new drug, and that's largely obtained from preclinical models and PK/PD bridging techniques that we're going to discuss in the next 10-15 minutes.

And then, of course, a regimen is chosen to ensure that it remains fit for purpose as the compound transitions from healthy volunteers to patients or other special populations, as it makes its way from laboratories in Phase 1 units into real world settings.

So, in terms of the historical context, the lethal diseases, as for invasive fungal infections and other infections, it's not reasonable to design clinical studies that delineate the entire dose-exposure-response relationship. And so, nonclinical PK/PD studies and other preclinical studies have to

Page 71

fulfill this purpose.

Also, it's worth remembering that many invasive fungal diseases are rare and difficult to enroll into clinical studies, and clinical trials are often simply infeasible. And that older antifungal agents, those which we routinely used, were developed -- what may now be considered relatively crudely. So, plasma concentrations that exceed MIC 90 for the proposed dosing interval. And voriconazole and caspofungin were developed in this way -- and Mike Hodges is on the call and would have plenty of experience with this and I'd be interested in his views about that.

So, what are the key ideas and challenges for identifying candida regimens for patients? And that's for a new antifungal drug or a new indication for a licensed compound. So, the first is that we do have -- and this was alluded to by Dr. Botgros -- we do have robust pharmacodynamics models that are available to delineate initial PK and PD relationships.

These provide early information on the

Page 72

plan for dosing schedule, and these models are being reviewed extensively by Dr. Walsh and candida models were used extensively by (inaudible) in the early 2000s.

Aspergillus models were not available until the early 2000s and then largely developed with NIH funding. And the endpoint was the problem there, with PCR galactomannan and survival used by different investigators. And then Cryptococcus models in mice really making meningoencephalitis also extensively used by drug developers.

So, generally, these models are robust and I will just site John Perfect in saying that they have never really let us down actually, and they may -- they enable a clear indication of the relevant pharmacodynamics and therapeutic potential of a new agent.

So, this is something of a revelation to me in my thinking recently that came after a recent FDA workshop. And the models that we have can also serve as adjunctive evidence of clinical efficacy. But this is on a different part of the spectrum to PK

Page 73

and PD.

So, there was this very interesting debate that emerged at the last FDA meeting on the 5th of March of this year on animal models to support antibacterial development. And it's this idea of separating relatively well-controlled and early models designed to establish PK/PD relationships versus models that might be more faithful mimics of human disease.

Now, John Rex summarized this very nicely, and I've given the web link, on the 8th of March of this year. And the rabbit models that you've heard about from Dr. Walsh I think in many ways have fulfilled this role. So, the model of invasive pulmonary aspergillosis, the number of different rabbit models, the candidate regimens; the CNS candida model, and the Cryptococcus model in the rabbit developed by John Perfect all really fulfilled this role in that they generally have clinically relevant background immunosuppression, they have comparable pathogenesis to humans, they have clinically relevant readouts, and that they're severe in that they usually

Page 74

are universally lethal.

And so the use of these models to mimic human disease -- I guess this example's come up on a number of talks -- but I think that this is a useful way of thinking about the contribution of preclinical models to dose identification.

So, this is the first call from me to this community. That is, nonclinical data is being used as adjunctive evidence of clinical efficacy. So, Dr. Moore just told us about the labeling of micafungin or the animal model for the micafungin label. And then some thought needs to be given to the QA issues that are involved.

So, secure data repositories may need to be considered by this community. They're extraordinarily extensive, I have to say. I will point out the GLP are not generally used -- is not generally used by academic laboratories. That would put all of us out of business. But as per the bacterial world, standardization of models may need to be further considered.

So, point number 4, that there's a

Page 75

general problem that we have of defining study endpoints, and this needs more debate. And by this I mean what is the fungal equivalent of stasis? You heard Dr. Walsh use this term. Or a 1 or 2 log drop that's used extensively and is part of the antibacterial drug development lexicon.

But this is really important because this is where clinical regimens are defined. And so this is where, generally, people will want to put an endpoint. But putting an endpoint where there's near maximal activity in the model that we have will generally take a drug beyond its safety margin.

And then there's this other idea that's being developed -- and we all do this even if we don't do it explicitly or benchmarking -- so how license compounds perform in our models. At least matching this benchmark endpoint is a way that new compounds can be developed in the context of what's our existing knowledge.

So, as we transition to the clinic, I want to make a few more points. The first steps, of course, are pretty standard, and you've heard of those

Page 76

from Dr. Moore. The bridge is pretty straightforward. So first-in-human PK providing insight as to whether exposures required for efficacy are achievable in humans. The data that's acquired can be modeled using population techniques, and simulation can be used to come up with the adequacy of proposed regimens.

And the failure at this very early stage to achieve drug targets that may be desired or deemed to be clinically relevant can trigger the requirements for more PK studies. And Tom Walsh showed you this example of (inaudible). This is exactly what happened in the neonatal program where further clinical PK studies were required to demonstrate linearity and safety of higher dosages.

This is an important point. Getting estimates of variability is key. It's not really the main or median that matters, it's rather the variability -- that's the key.

So PK variability is generally higher in patients. The coefficient variation for clearance and therefore drug exposure AUC may double as you move from healthy volunteers to patients or generally

Page 77

double. It's possible just with early relatively sanitized Phase 1 data to artificially inflate variance in simulators.

So, you take the volunteer data, you inflate the variance, and this stresses the candidate regimen in terms of its performance. And by some sort of prediction as the heterogeneity of patients in terms of their PK and more variable PK, and the implications for achieving desired drug exposure targets.

There's, of course, progressive learning and understanding that happens as programs advance, and so the effect of food, and renal impairment, and hepatic impairment, and other idiosyncrasies may be important and relevant. And also important to consider -- the PK sub-study in an early cohort of patients. Now, I see that this has already come up in a chat for later this afternoon -- as it may be relevant to make sure that the desired exposure to maintaining patients, and it may be important to co-model those data with volunteer data.

This is another important point.

Page 78

Number 6, planning for PK and PD sub-studies in Phase 2 and 3. The importance for this community that completes the bench-to-bedside loop -- so we can understand how lab animal models, how particularly they are unless they're based in some sort of reality. But here are the issues, and many on this call will hate me, but PK is generally a poor quality that is obtained in real world and requires co-modeling with richer data to provide tractable estimates of drug exposure.

It's important to also realize that uninformative PK or just bad PK data results in imprecise estimates of drug exposure or even bias. And the other problem with these studies is that the pharmacodynamics endpoints may be problematic. So, galactomannan is being used in invadable aspergillosis. The later decline of fungal burden has been moved extensively in Phase 2 and 3 in cryptococcal meningitis. It's a primary endpoint in many Phase 2 studies. And all-cause mortality and clinical response are relatively crude and noisy endpoints because they're confounded by disease and

Page 79

toxicity. So it can be difficult to make linkages.

But here's the important point. That a PK/PD sub-study really ensures patients are on top of the dose-response relationship. So, you should see, if everything has gone properly, all the patients up here. So, if you do see the (sound drops) response relationship, something has gone badly wrong generally, so the dose is not right or the regimen is not right. Either that or the drug is very variable and patients have inadvertently slipped down with the dose exposure response relationship. This would've happened -- it's typical of well-designed clinical development programs where you put everybody up, having adequate drug exposure.

And I'll make this point and it'll make someone on the call shudder, I know. But all information -- this is an important point -- all information related to dose-exposure-response relationship can be used for therapeutic drug monitoring and in control. This is sort of embedded in some of our thinking with therapeutic drug monitoring for the triazoles, but routine control

Page 80

using very precise techniques is also possible that need further work. But from a regulatory perspective and an infrastructure perspective, who's going to pay for it perspective, and demonstrating clinical benefit, as defined by the FDA also remains challenging.

So, in conclusion, the models that we have, the approaches and pathways for antifungal drugs are progressively more mature. I have noticed some differences between FDA and EMA in terms of the way in which data from preclinical models especially is weighted, and some consistency in debate about this would be helpful, I think.

And this is the last point and this is the second infrastructure that requests were made to this community. It's not the primary responsibility of the FDA or the EMA. It significantly concerns me that there does not appear to be a new generation of investigators interested in antifungal therapeutics, and that is a shame and also a significant threat to all of us in the world. So, I will stop there, Sumati, thank you.

Page 81

DR. SUMATI NAMBIAR: Thank you so much, William. So, that brings us to the end of Session 1. Erin, if there are no comments from you, I think what we can do is take a break. We are running a few minutes late, so maybe we can reconvene at, I think, 11. 5:07 might be hard. So, let's all reconvene at 11 and, hopefully, we will try to make up some lost time as the day progresses. Erin, would that be okay with you? Maybe you have it muted. So, let's reconvene at 11 and we'll start with Session 2. So, thank you to all the presenters in this morning's session and we'll talk to you soon. Thank you.

(Break)

DR. LAURA KOVANDA: Thank you, everyone. I'd like to welcome everyone to Session 2, the Current State of Mold Infections and Antifungal Drug Development Consideration. I am Laura Kovanda from Astellas Pharma Global Development, and I'm here with my co-chair, Yuliya Yaskinskaya, who is the Clinical Team Lead in the Division of Anti-Infectives at the FDA. We're going to go through a series of discussions. We'll start with Kieren Marr, who is the

Page 82

Professor of Medicine, Vice Chair of Medicine for Innovation in Healthcare Implementation, and the Director of Transplant and Oncology Infectious Diseases at Johns Hopkins.

Her talk today will be on the current state on invasive fungal infections, available therapies and unmet needs. Dr. Marr?

DR. KIEREN MARR: Hi, good morning, can you hear me?

DR. LAURA KOVANDA: Yes. Yes, we can.

DR. KIEREN MARR: Great. I'll say at the onset, thank you for the invitation to speak. I also want to apologize for hopefully what will not be a problem in that I'm sitting in a very -- pretty severe storm and have lost electricity and Internet connection several times this morning. So, let's see if we can get through this and I will try and go without slides on my phone if I need to.

I've been asked to speak of the current state of invasive fungal infections, and specifically unmet needs from a more clinical perspective. My disclosures are listed publicly on the Internet, I

Page 83

believe. And this slide shows the antifungal agents that we have available for treatment of Candida and mold infections and the timeline in which they were approved for use. There's a number of lessons learned, which is a relativity paucity of agents of few classes, and enhanced activity after 2000 but not very much after 2010. As this illustrates some of the drugs that we currently have available but not in study.

When we consider unmet needs, I wanted to frame this talk from a clinical perspective because this is the context in which it's not just the drug and above issue. We have the host involved, and this is a very real issue for treatment of infections as well as prevention, although I'll focus most of the talk on treatment.

Certainly the organism antimicrobial resistance is a problem in conferring an inadequate antifungal spectrum for a number of agents. We have very resistant molds that are fortunately less common but the outcomes are very poor. We also have failure of these drugs because of acquired drug resistance,

Page 84

and we have a unique unmet need, which is to support early treatment indications when we're not certain on the diagnosis. And I'm going to spend some time outlining this because it is a real clinical problem and I think an unmet need that hasn't had enough attention.

We have many PK/PD limitations that have been discussed to some degree. These include limitations in formulations, infeasible dosing frequency, unpredictable absorption and metabolism and poor target exposure. And certainly we have widespread and unacceptable safety features associated with toxicities, as well as in the clinical context, very important drug interactions. And, finally, we have context-specific needs or the situation where special populations really define the unmet need.

The first focus on spectrum of activity and the problem of antifungal drug resistance, I think it's very important to outline the importance of very resistant molds or refractory infections. This figure on the right is a table that I pulled from a recent review. And I like it because it basically

Page 85

demonstrates in broad strokes categorical issues both with the drugs according to the infection, and these are non-aspergillus or less frequent molds that cause disease.

And the important lesson here is that there are species such as Fusarium species, Scedosporium, Lomentospora species that have many more problems with drug resistance across classes and specific drugs. Importantly also, what you see in this table is that there's no one agent that can reliably cover all of the organisms that may be causing infection. And this is especially important in the clinical context when we don't know what is the cause of disease. And it's becoming more and more important that we can treat these infections early in the immunosuppressed host.

Mucorales -- I'm sorry for the typo here -- can be considered really, in my opinion, a refractory infection. We certainly have a problem with the lack of activity with voriconazole when voriconazole can be a primary choice for lesions in the lungs that look like aspergillosis. But these

Page 86

organisms also suffer in outcomes because they are relatively refractory even when the best polyene-based therapies are applied. And the unmet needs in these situations can actually potentially be illustrated by the need, for instance, for not only new agents but combination therapies, potentially.

There are innately resistant Aspergillus species. And that includes classically polyene resistance and aspergillus terreus. But I want to highlight, for instance, the infections caused by the Aspergillis ustus group of organisms in which we have variable or high MICs to multiple different drugs and poor outcomes, such as a larger study that was recently published demonstrated greater than 50 percent mortality at six months. These are very, very difficult infections to deal with.

We also have unusual sibling species or what has been called cryptic species. An example is Aspergillus lentulus. These are organisms that are being increasingly studied because they're being increasingly found in multiple parts of the world. They have high MICs to azoles that appear to be 51a

Page 87

mediated but also have high MICs to polyenes and echinocandins with very poor clinical responses. In fact, these were first identified as breakthrough isolates in azole prophylaxis studies. And so these MICs appear to be truly clinically important.

And, again, I'm going back to the issue that these are difficult to diagnose and study with low frequency of disease and very poor outcomes. And inevitably, when we have people with documented infections caused by organisms such as Aspergillus ustus, they're really pretty far advanced.

Of course, we also have problems, increasing emerging problems with azole-resistant Aspergillus fumigatus. This is associated with acquired resistance associated with multiple mutations in the cyp51A gene. They occur at episodic frequency in different environments, predominantly associated with azole use in the agricultural setting, first reported in the Netherlands. But when you review the literature now, they're actually identified in many different nations all over Europe, South American, Japan, India, Taiwan, Africa, Australia and more

Page 88

recently in the United States. I think that you can safely conclude that this is a problem that has emerged and is now of potentially global concern. And that we probably don't understand the overall importance of azole resistance currently because not many clinical centers are actually measuring azole resistance as a matter of routine, and this can be certainly associated with failure of disease in biomarker defined settings in which the organism is not recovered.

This also illustrates again what I'm talking about when we put the problem in context. That failure is contact-specific. In fact, the discovery and the unmet need of azole resistance, either as an acquired trait or as an innate phenotype emerges after therapy is applied. And so we currently have large populations of people in which the overall goal is to either prevent or to treat early. And, historically, we've referred to the early treatment category as empirical therapy, previously defined by fever. We've gotten much better at that and currently our early treatment strategies can better be

Page 89

categorized as syndromic or radiographic evidence of disease or even biomarker-guided therapy. And we do have unmet needs in identifying the best clinical trial pathway for approval of these patients that have disease that has not been microbially defined.

This is an example of what I'm talking about. These are people that have early pulmonary lesions, either with our without biomarker positivity. Some of our biomarkers that can be used have very good sensitivity but clearly poor specificity. But in this context, we are forced to choose a first line therapy for -- with activity against molds.

Optimally, we would have a drug that has activity without causing undue harm as an early therapy, and that would have a very broad spectrum of activity. I think this early treatment category is really truly a current unmet need.

I'll turn to unmet needs in PK/PD limitations. I think we all agree that we have abundant holes in all mold-active agents. Poleyens and echinocandins lack enteral formulations, which cause problems with regards to our overall strategy,

Page 90

especially stepdown and administering drugs in people who have long-term needs. And that is especially important in the context of mold infections.

Azoles suffer from unpredictable absorption and metabolism. And we have poor target exposure. Some of the biggest problems that are becoming apparent are getting drug into the airway, especially into the epithelial lining fluid or the lung lining fluid in the upper and lower parts of the airwaves. This is critical for airway disease and treatment in certain special populations, such as lung transplant patients and people with chronic lung disease for various different reasons.

And this is the setting in which people are turning to more inhalational exposure to address the balance between airway delivery and avoidance of systemic toxicities. We won't spend a lot of time on inhalational drug delivery during this day, but it's certainly something to consider with regards to the unmet needs of systemically delivered drugs as well.

And this is the reminder to discuss the problems that we currently have with safety. There

Page 91

has been actually a learned helplessness that we've been taught in the youth and the development of antifungal drugs as we've accepted toxicities in almost every organ system, especially liver toxicities with azoles and renal toxicities with polyenes.

I'll just note that it's very, very apparent that cumulative exposure to toxicities in multiple organ systems lead directly to poor outcomes in complex and vulnerable people, especially in the oncology setting, in the ICU setting, and in transplant recipients.

And there is a growing problem with regards to drug interactions that define an increasing group of people that have unmet needs. Historically, we've considered problems with giving azole drugs in the anti-rejection -- or in the setting in which anti-rejection drugs are being administered after a stem cell transplant or a solid organ transplant, but this problem has grown with the introduction, especially with antibodies and biologics that can be metabolized by the cytochrome p450 system in which azole drugs are relatively or absolutely contraindicated. And there's

Page 92

an expanding list of agents that complicate our ability to give azole drugs, both for prevention and for therapy, early therapy and definitive therapy.

And I'll just say at the onset that this problem is not just solved by not giving the anti-mold drug; the problem is defined by going on and off of these drugs in settings where these anti-cancer agents can be variably metabolized or even stopped and started during regimens that require long-term therapy in a maintenance setting in order to establish effective anti-leukemia or anti-lymph activity. And I've listed some of these here.

Historically, and the one that we've appreciated the most would be for treatment of people with ALL that are receiving Vincristine-based remission induction chemotherapies. But there are many more drugs that have emerged and are increasingly used in the last several years. This includes the treatment of acute myelogenous leukemia with use of FLT-3 inhibitors, such as midostaurin, BCL-2 inhibitors, specifically venetoclax for IDH1 or 2 inhibitors listed here. This also includes people

Page 93

with chronic lymphocytic leukemia or those that are receiving targeted B cell therapies such as ibrutinib, venetoclax and idelalisib. These are settings in which we have many more difficulties in administering drugs that interfere with cytochrome 450 metabolism. And there are many other disorders in which these drugs are being explored or are increasingly used. That is, for CLL, Waldenstroms macroglobulinemia, other lymphomas, severe chronic graft vs. host disease, or relapsed/refractory lymphoma.

So, in my opinion, there is an increasing number of special populations that are defined by the optimal therapies in which they should be receiving for treatment of their oncologic underlying disease.

And there are other context-specific needs or special populations that we need to consider as unmet needs. Currently, I think, perhaps one of the most well-established is the lung transplant recipient. This is a setting in which both candida and mold infections are relatively common, especially the candida infections early because they develop

Page 94

anastomotic and pleural space infections and relatively later, with mold infections.

Recent studies have shown that the prevalence is not small -- 19 out of 100 surgeries was estimated from a review that was recently published from Duke. We have a problem with airway clearance, and it's because of this that there's a risk for invasive disease as well as tracheobronchial manifestations. And so that increases the weight of importance of delivering the drug straight into the airway itself.

And I'll just add that this isn't just a problem with infections, because the activity, the established infection, and potentially even colonization can exacerbate and increase the risk for longer term graft rejection. Because of this problem that was recognized many years ago, the community has turned to inhalational delivery for the most part during the early period of time when the patient is within the medical center. But the regimens used are variable. They include conventional deoxycholate, Amphotericin B, as well as lipid formulations ABLC,

Page 95

liposomal Amphotericin. There are centers that deploy early echinocandin therapy, especially during this early peritransplant period to also avoid the candida systemic problems, for instance, in the plural space. And there are centers that provide routinely prolonged azole-based preventative therapy. The problems here are exacerbations and toxicities, and the rate of early discontinuation is unacceptably high.

Other special populations that are growing in importance include people with chronic airway disease, necrotizing aspergillosis, and the constellation of manifestations therein. But also the growing indication of antifungal therapy in people with cystic fibrosis. Increasingly the CF setting is appreciating that antifungal administration for what was historically considered benign colonization may have a therapeutic effect at decrease CF exacerbations, much like the classic scenario of treating gram negative organisms such as pseudomonas with inhaled tobramycin. So, I think this may be, for instance, an emerging unmet need that has attracted attention by the Cystic Fibrosis Foundation.

Page 96

Now, I was asked to also focus on the post-viral aspergillosis condition that has been increasingly outlined with the unfortunate emergence of SARS-CoV-2. And in order to do that, I'm going back as a reminder that influenza-associated aspergillosis has been studied especially in Europe, in Canada, as well as in Asia but not necessarily in the United States. And for the past five years, some very good cohort studies have estimated the incidence of aspergillosis subsequent to severe influenza infection to be ranging from 7-31 percent.

The CDC has sponsored a study, a survey study that documents that it's poorly recognized in the U.S. and largely leading to diagnostic bias. But this certainly is an entity that requires more attention to bring down the mortality associated with severe influenza infections.

And, unfortunately, we also now have witnessed the, what I think is a documented emergence of a secondary complication of COVID involving aspergillis in the airway as a cause of airway disease and invasive disease that has been coined COVID-

Page 97

associated pulmonary aspergillosis or CAPA. This emerged from many smaller case reports and case series, first in Europe. I'll point you to, I think, what is the definitive evidence of this as an important clinical entity from a reasonably large prospective study in Italy that is in a prepub form in clinical infectious disease currently.

They used biomarkers and cultures on BAL or other tracheal aspirate fluids to document essentially 28 patients that are on mechanical ventilation after COVID-documented disease have this entity. They also applied multivariable modeling to identify the significance and it is a predictor of death, and there's some indication that therapy can lead to potentially better outcomes.

And so this is something that is an emerging unfortunate unmet need, I think, both in the preventative context as well as for documented treatment.

I like this slide that was given to me by Cidara in that it illustrates that there are a number of different manifestations that are

Page 98

potentially of clinical importance here that include not only invasive disease where there's hyphal growth and invasive pneumonia, but this can involve the airways, exacerbating inflammatory conditions and causing an overt tracheobronchitis in which the organism may be very difficult to eradicate, and in which some of the complications can include, for instance, post-obstructive bacterial pneumonia.

This slide is very quick. I think that we should consider beyond the molds, although it's not a topic for today -- cryptococcus histo and coccidiodomycosis are certainly important unmet needs.

So, I'll summarize here. We do have good drugs but they have a limited spectrum of toxicities and drug interactions. We have broad needs for rare molds that have innate resistance, acquired resistance, and we need to have a drug that we can reliably use for earlier treatment. We have special populations that include lung transplant, people with chronic lung disease and post-viral syndromes. Thank you very much.

DR. LAURA KOVANDA: Thank you, Dr.

Page 99

Marr. We'll go right into the next session, or next talk, which is from myself, Laura Kovanda. I'd like to thank the organizers from the FDA for asking me to come today and talk about my experiences with antifungal development.

To begin, I'll start with the orphan designation that's available when a disease affects less than 200,000 persons per year in the U.S. This is important to today's discussion, as most systemic fungal infections qualify for this designation.

The benefits include not only 7-year market exclusivity but other benefits such as tax credits and waivers for user fees. But this comes with some challenges for orphan drug development, namely, a small number of eligible patients and lack of acceptable comparators, to name a few.

Which brings me to Cresemba. The clinical development program was initiated by our partner Basilea in 2002, and the Phase 3 program commenced in 2007. In 2010, Astellas (sound drops) license, development rights and assumed sponsorship of the Phase 3 study ongoing. Qualified infectious

Page 100

disease status as well as orphan drug status was granted by the FDA for both evasive aspergillosis and mucormycosis, and later invasive candidiasis, which was not included in the initial submission.

Over the 13 years leading to the market authorization in 2015 in adults, the program included 44 clinical trials, which enrolled more than 2,100 subjects, nearly 1,700 of whom received Cresemba. Importantly, just over 100 -- or, sorry -- 1,100 subjects were in the Phase 1 studies alone. 403 subjects were in the two Phase 3 trials for invasive aspergillosis and mucormycosis but were in the NDA package in 2014.

To put this into perspective with regards to the resources needed to invest in this program, the Phase 1 program alone cost nearly $30 million. The Phase 3 invasive aspergillosis and mucormycosis studies combined cost over $100 million. These finances do not include the development cost for Basilea prior to licensure or the cost of the licensure itself and the preclinical development, including new toxicology, in vitro, in vivo, and

Page 101

manufacturing. As a reminder, Rescemba, isavuconazonium sulfate is a water-soluble prodrug. The active moiety, isavuconazole, is a broad-spectrum triazole antifungal. My finger's going...

Important points which have already been discussed, these infections occur in severely immunocompromised patients which have high comorbidities. The rare infections, aspergillosis occurring in, approximately, 12,000 cases per year and 500 cases per year of mucormycosis. They're difficult to diagnose and treat.

The development path for invasive aspergillosis was clear as the standard of care for comparison was established with Voriconazole. However, for mucormycosis the approach had to be different. Treatment paradigms include a multimodal approach including treatment of the underlying disease, immediate antifungal therapy and surgical debridement. Not treating mucormycosis is associated with nearly 100 percent mortality, and delay in therapy is almost as bad as no treatment.

So, can an active controlled study be

Page 102

conducted in this extremely rare condition? What comparator is available for study? No randomized controlled trials have been conducted for mucormycosis. The only available approved therapy in the U.S. at the time was amphoterici B deoxycholate. And it is only in IV formulation, has high toxicity, and lipid formulations are typically the standard of care, but not approved for mucormycosis.

We conducted two Phase 3 studies to support the initial registration. The SECRE study in Invasive Aspergillosis and the VITAL study which included multiple rare invasive fungal infections but focused on the inclusion of mucormycosis.

To put the study results for mucormycosis into context, we performed a matched case-control analysis using an invasive fungal disease database called FungiScope out of the University of Cologne. The matching criteria included severe disease, hematologic malignancy and therapeutic debridement. Matching was conducted independently and blinded to outcomes. Up to three controls per Cresemba case were included. All caused mortality was

Page 103

analyzed as the endpoint.

In the VITAL Astellas trial, 46 mucormycosis cases were included in which 21 had primary therapy. The results showed better efficacy relative to untreated historical controls and similar efficacy relative to Amphotericin B from the literature as well as the matched controls.

This approach is supported by 24 CFR 314.126, which states that "Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include diseases with high and predictable mortality."

Now, let's take a quick look at the invasive candidiasis trial for Cresemba. This study compared IV Cresemba to IV Caspofungin with the option to switch to oral therapy after Day 11 in both arms. The study included 450 subjects. The active trial, as we called it, had significant enrollment challenges. It took over 5 and a half years to complete enrollment. If we dissect this a little bit, we see

Page 104

that the monthly enrollment never exceeded 20 patients per month. And with 30 countries open to enrollment through the trial, only 25 countries enrolled at least one patient. 80 percent of enrollment occurred in eight countries. With 158 sites open to enrollment, 70 percent enrolled at least one patient. That's great but we had 43 percent of these enroll two patients or less. Spreading sites across multiple countries globally is a huge cost driver for clinical trials and a major resource burden to manage such a large clinical trial footprint.

We tried many mitigation tactics, such as closed nonperforming sites. We also decreased our sample size by just 100 after reviewing, in a blinded manner, the actual evaluability rate, which was revealed to be 10 percent higher than the original study design function. In the end, the final evaluability rate and power were just over 90 percent.

This was a tremendous effort, however, in the end, the trial did not meet its primary endpoint. Which is another key point when designing non-inferiority trials. Study design and endpoints

Page 105

are driven by the comparator chosen. To justify the non-inferiority margin, you need a frame of reference. Both the comparator regimen and the placebo for historical untreated population.

For the active trial, the original study design was caspofungin followed by voriconazole with the primary endpoint assessment at two weeks after the end of therapy. This regimen had never been tested in clinical trials.

So, in order to anchor on the historical registration trial for caspofungin, we modified the study design and used the available historical data. Unfortunately, the endpoint of end of therapy -- IV therapy favors the echinocandin.

My last point brings me to the post-approval stage. Once a drug gets approved, everybody asks, what's next? Are you ready to study the next super rare fungal infection? After a large development program and three Phase 3 clinical trials with one that did not meet its primary endpoint, there are careful considerations of the next set of studies. First and foremost are the post-approval commitments

Page 106

that are required by the FDA. I show here the three defined for Cresemba in the U.S. The cost for these run in excess of $10 million.

Our other priority is pediatrics. Orphan drug status waives the requirement for pediatric development, however, we at Astellas with our partner recognized the significant unmet need in invasive aspergillosis and mucormycosis in pediatrics. Our pediatric program is ongoing but it can run in excess of $20 million, which our current program is.

Finally, the typical life cycle of a post-approval rate is shown here. The first five years approval life cycle is establishing product and conducting post-approval commitment, including pediatric studies. For Cresemba this also included finishing the invasive candidiasis program at a cost of more than $80 million.

It's typically not until the fourth or fifth year where the separation from the margin occurs in order to look for areas of reinvestment and depends on the market condition. The activities you look for are areas of high unmet need as well as areas of data

Page 107

gaps. But you need to consider the financials. The new activity has to either increase the life cycle prior to the loss of exclusivity, increase the margin enough, or at least cover the cost of the investment.

For invasive and fungal infection studies where the typical costs are, approximately, $125,000 per patient, and where the durations are 3-5 years on average, this is challenging. And similar to the antibacterial world where the net present value calculations are nearly always negative.

So, to conclude, the Cresemba development program is not likely to be replicated as is. Each Phase 3 study costs in excess of $125,000 per patient; it requires a global footprint and the study durations are long. Alternative options to randomized clinical trials are available for orphan diseases, but generally accompany larger efficacy and safety trials with another invasive fungal disease.

The high cost of antifungal drug development from discovery to the initial marketing authorization, post-approval commitments, pediatric development topped with the cost of product upkeep

Page 108

such as commercial manufacturing and product education, etc., are not a sustainable business scenario today and weigh heavily on decisions to reinvest post-approval.

Emphasizing the need to continue to introduce new push and pull incentives to continue investment in new antifungals to address the significant unmet needs of patients. Thank you.

We'll go now to our next speaker, John Rex, who is the current CDMO of F2G, Ltd., which is an antifungal biotech, with more than 30 years of development focused on antimicrobial agents. Dr. Rex?

DR. JOHN REX: Thank you, Laura. And am I clear?

DR. LAURA KOVANDA: Yeah.

DR. JOHN REX: Wonderful. Thanks. And thanks to the FDA for organizing. This has been a great workshop so far. I'm really enjoying the content.

So, I wanted to talk at length about push and pull incentives for antimicrobials, but I'm going to focus on something much more specific to

Page 109

getting an antifungal developed. And before I can get to the point I want to make today, I need to give you a little background on the drug that we currently have in Phase 2. It's called Olorofim. It's a novel mechanism candidate antifungal drug that inhibits pyrimidine biosynthesis.

It has broad microbiologic activity but it's limited to the ascomycete mold fungi, which means it covers Aspergillus, Lomentospora, Scedosporium geserium, and all of the dimorphic molds -- histo, lesto, coxi. But it does not cover candida, it does not cover crypto, and does not cover mucola.

Dosed by mouth in a 30-milligram tablet, it has breakthrough therapy designation based on its preliminary clinical evidence showing substantial effects. And it's now in an open label Phase 2 study of patients with invasive fungal molds and limited treatment options.

The key idea here that I want to point out is that endpoints, as was already noted, are a tricky thing, and I want to point to a specific problem with endpoints, which is that we have to date

Page 110

mostly used endpoints at 42 and 84 days, and all-cause mortality has been a strong tool that we've liked because it's so clear. And it does seem to work pretty well for acute pulmonary aspergillosis. But it's also a blunt tool and get entangled with underlying disease and it -- because patients are dying of leukemias and other things along the way. And it also doesn't work at all for infections that progress more inexorably and slowly.

The alternative that we heard about was the EORTC-MSG defined overall global response endpoint, which has three elements: Clinical, radiological and mycological. And logically, success requires improvement on all three sub-elements, and failure, likewise, is going the wrong way.

But there is an intermediate space that you see 20-40 percent of the time in which something's better, something's worse. And this leads to a categorization of stable. And a particular way this occurs is just somebody will be clinical better but the radiology has not yet improved. And when you get scored as stable, stable is lumped with failure. So,

Page 111

stable is a failure on the overall clinical response and that has a really big impact.

And for pulmonary IFDs it does work but extrapulmonary IFDs can be very slow and even pulmonary IFDs can be very slow. And I was going to say that stable is very definitely the prelude to success. It enables -- staying alive is the way you get this done.

So, let's -- coming back to the trial that we're running, we learned this in running our current open label Phase 2 study. To get into the study you have to have a proven invasive fungal infection. Most of our patients are highly immunosuppressed and they all come to us with limited treatment options. That's why they come into the studies because they're in trouble -- they've tried pretty much everything else and it's not working for them. Some of them come to us with months of prior therapy.

We advise a main phase duration of 84 days, which is adequate for many patients, but extended dosing is provided for complex infections.

Page 112

If you look at the dosing graph to the right, you'll see there's a block of patients, loosely a third, that declare that they're done at day 84. But there's a pretty good sized group that go on for very extended period. And that X-axis does run out to 500 days.

And this group that goes on long stable at day 84 has been a common finding and a prelude to ultimate success at the end of therapy. So, let me show you a case that highlights this.

This is one of the cases that was part of our breakthrough therapy designation request. And it's that of a 49-year old healthy woman who had breast augmentation surgery. She develops a Lomentospora prolificans infection of the breast implant. Lomentospora is resistant, as we heard earlier to all of the antifungals and her infection spreads through the adjacent cartilage, sternum, 4th, 5th and 6th ribs. She tries everything, serially and in combination along with debridement and along with hyperbaric oxygen. The infection remained uncontrolled. And if you look at the picture on the lower left, nine days before she came into our study -

Page 113

- when they were bringing her, they had fungal colonies growing in the base of the wound.

Olorofim monotherapy began in November 2018 and 84 days later, she looked better, her wound was improving and she was a failure because her radiology had not yet improved. Clinically she was responding but she was an EORTC global response of failure at day 90.

She goes on to take 322 days of Olorofim. Day 140, nice granulation tissue at the base of the wound. Day 243, closed up. She's now been off-drug for ten months, and as far as we can tell, it's a cure of her infection. Next slide. I have the button.

So, here are my conclusions. Day 42 all-cause mortality, a useful tool but it has limitations. EORTC-MSG defines an overall response endpoint but, you know, it works okay at day 42 and 84 for many pulmonary disease but it does not work well for extrapulmonary infections and sometimes lung infections and anything that takes a long time for the radiology to improve.

Page 114

And my argument is that it is important that stable be defined as success. Language matters. You could argue that it comes out in the wash just to define stable as failure. But this is not consistent with clinical practice, and the word failure when you're reading quickly, it failed. So, 20-40 percent of the patients in recent studies that had a structure kind of like our program have failed at day 84. No, they haven't failed. They were stable and they were on their way to getting better.

So, the scoring of failure sends the wrong message to clinicians and payers, and some of these people had very significant improvements in their quality of life. If you go back to -- I'm not going to go back to the slide, but if you look at the footnote of the slide, we shared another case -- the case I showed you was shared in Egment, or it was shared in the Egment abstract, but there's another case in the Egment abstract book. Same fungus. A lady with leukemia who got many, many months of good quality of life, control for osteomyelitis with Olorofim.

Page 115

So, and that quality of life measure, I think, is an important bit that we need to think about. So, the label of stable just is not right anymore, and we developed these endpoints some years ago before we understood some of the consequences of managing more difficult and invasive fungal infections, and it's something I'd like us to reconsider. Thank you very much.

DR. LAURA KOVANDA: Thank you, Dr. Rex. Our next speaker is Matthew Schueler. He has a patient perspective. Mr. Schueler is Founder of the Henry Schueler Foundation, which raises money to support its mission to fund critical research into rare subtypes of pediatric leukemia and fungal infections like mucormycosis. Mr. Mueller -- Schueler?

MATTHEW SCHUELER: Thank you. Can you hear me okay?

DR. LAURA KOVANDA: Yeah.

MATTHEW SCHUELER: Wonderful. Thank you for having me. And I have been listening to some of the presentations. I'm going to give you a very different perspective, that from the patient. My son, unfortunately, being a statistic of the unmet needs that exist with the treatment of fungal disease. I'm going to share with you a reflection that I prepared and participated in part at the FDA hearings on Cresemba back in February -- excuse me, January of 2015.

Page 116

"The silence of the evening is broken only by the sound of my footsteps on the sidewalk. The sky is fading into night, illuminated in our neighborhood by the house and porchlights which turn on. Houselights now ablaze as dinner approaches. I see the homes I know to be filled with families, moms or dads busy in the kitchen, brothers and sisters laughing in the living room, bickering over the TV channel or lost on their phone.

"I imagine my own children in the family room -- Henry, Anna and Joe, waiting to eat together as a family. I see myself arriving home. The workday is a bit shorter as summer winds down. I imagine my arrival punctuated only by the over-affectionate greeting that I get from our dog, a warm

Page 117

greeting from my wife Susan, and a greeting shouted to my children in the living room. An unenthusiastic but normal response in return acknowledging my presence.

"We sit down to eat as a family in the relaxed and sometimes careless fashion that families do, never imagining that we would not be together, taken for granted the warmth and joy of each other's company. Individuals all, yet bound together by sibling and parental ties, conscious of our closeness despite the occasional rudeness that occurs at a dinner table.

"And then it returns. That sickly reminder that all is not the way I still imagined. That one of us is absent. My oldest on removed from life by nature. Cruel and unforgiving. His legacy left for us to shape and keep alive. The lights still burn for families intact removed from our reality. For them, the dinner table still awaits. Into the evening darkness I walk.

"Although we are now almost 13 years removed from Hank's death, his loss is felt deeply every day. No matter what I have done or will do in

Page 118

my life, my greatest accomplishment and blessing is and was to be a father to my three children, Henry, Anna and Joe. Like any parent, you want to protect your children from harm, teaching them the right things to do, encouraging them to think before acting recklessly. Cancer and its many complications, including fungal infections, follow their own rules despite a parent's best efforts.

"My oldest son Hank, as he was known, received a diagnosis of acute lymphoblastic leukemia, ALL, the most common of childhood leukemias, in early November of 2006. He was 13-1/2 years old. However, his ALL was a very rare subtype known as hypodiploid ALL, which occurs very rarely, only 1-2 percent of all ALL, and in 2006 had a very low survival rate, 20-30 percent with chemotherapy alone.

"Because of this prognosis, the unanimous medical recommendation from several medical academic institutions for Hank was that he undergo a bone marrow transplantation immediately after his initial heavy course of chemo at what is now known as Lurie Children's Hospital in Chicago. Neither his

Page 119

younger sister Anna or his youngest brother Joe were matches for him. He ultimately received marrow from an anonymous 27-year old donor from Germany and began the transplantation regimen on his 14th birthday, the 9th of March, 2007 at Children's Hospital of Wisconsin.

"He did quite well. He even returned to graduate with his 8th grade class at St. Mary of the Woods Grade School on the northwest side of Chicago, and in May to his spot as the captain for his traveling baseball team. He was far from healed but he was back in the game.

"Hank had a great summer and was doing well medically. Unfortunately, over Labor Day, after he had just begun high school, he relapsed. His odds of long-term survival decreased to 10 percent. He underwent additional chemotherapy which wiped out his new immune system, and he eventually contracted a rare and deadly invasive fungal infection known as mucormycosis at the end of September.

"The doctors told us that the infection present in his lungs and sinuses would likely kill him

Page 120

in a week to ten days. He underwent six surgical sinus debridements in seven days and was given all the antifungals available to him, including amphotericin B, which wreaked havoc on his kidneys, and posaconazole, the newest antifungal hope in this small medicine chest of antifungal therapies. And it wreaked havoc on his already weakened body by the intense chemotherapy he had received to stave off the raging return of his leukemia.

"Yet, he refused to quit, despite overwhelming odds against survival. By a minor miracle hasted by the absence of chemo for a few weeks while he fought against this new infection, his new immune system began to fight back and he began to show signs of recovery from the fungal infection. By the end of October, although still weak, he came back to his family and neighborhood in Chicago and the giant trees on his street bearing orange ribbons welcoming him home.

"After receiving another bone marrow transfusion the day after Thanksgiving, 2007 back at Children's Hospital of Wisconsin, the fungal infection

Page 121

returned and reemerged. He had undergone the hyperbaric treatment, he had undergone the amphotericin, he had undergone the posaconazole. The infection now spread through his sinuses into his orbital areas. It slowly took his eyesight. He was placed on a ventilator to breathe to overcome the respiratory effects of a disease which attacked his lungs -- lungs which had never failed him on an athletic field or a program or wherever a game was being played.

"Hank suffered a massive cerebral hemorrhage and died on the 14th of December, 2007. More than 2,000 people came to his wake. More than 1,000 family, friends and neighbors attended his funeral. We had to place dark sunglasses on him in the casket to cover the black rings of disease around his eyes. He loved his then 12-year old sister and 8-year old brother, who loved him as their big brother and protector and whom he loved with all his heart. He left his parents with a broken heart that will never heal.

"Hank was the last kid you would expect

Page 122

to get sick. Though bright in school and multi-sport talent, he was not the best student nor the best athlete in any one sport. Yet, he was an undisputed leader on the field, on the baseball diamond and in our neighborhood. Like so many childhood heroes that we've all been witness to, he withstood the devastating treatment of his outpatient chemo and the barbaric regimen of a bone marrow transplantation without complaint. He accepted what happened and began preparing for the rest of his life.

"Because of his death, many of our close friends including several of his former coaches approached us about forming a foundation in his honor to remember him and perhaps provide some hope for other similarly afflicted. Hank had told my wife Susan after he experienced the relapse that he just wanted to grow up and find out why this happened to him so he could prevent it from happening to other kids. Out of this pledge, we formed the Henry Schueler 41 and 9 foundation.

"We've sponsored targeted research at St. Jude's Children Hospital on hypodiploid leukemia

Page 123

through the work of Dr. Charles Mulligan and the Mulligan Lab, which has drastically enhanced the knowledge of the origins of hypodiploid and altered the treatment regimens for those who are diagnosed with it. The foundation has also proudly sponsored the first United States based international conference on mucromycosis chaired by Dr. Thomas Walsh, who spoke earlier, who proudly serves as the Henry Schueler Scholar on mucromycosis.

"His first conference took place in Chicago in January of 2010. Out of this inspired conference came the research that formed the basis for the most comprehensive medical supplement on mucromycosis published as a supplement to the Journal of Infectious Diseases in February of 2012. And just last September -- excuse me, just last November, we sponsored and hosted the second such international conference here in Chicago, where we learned of the advances that science and medicine have made in their fight against fungal disease and learned alarmingly of the greater prevalence of fungal disease throughout the world, and perhaps even more alarmingly, about the

Page 124

true lack of progress in fighting fungal diseases.

"Hank never quit a game early and he never quit fighting his disease. The family and friends who comprise our foundation helped instill that attitude in him when he was on the playing field and we remain determined to carry that fight forward in his absence.

"We live and, yes, Hank lives to carry the fight forward in his honor for future children and adults who are also destined to face this nemesis, the nemesis of cancer and fungal infections. Through our work we assembled some of the foremost experts in the world who voluntarily came to Hank's hometown to brainstorm on the best medical approach to a fungal infection that cruelly and silently attached him like it does other patients, when they are most vulnerable, and then it took his life.

"December 14th is the day he died. Nothing will ever change that. It is also the day that inspired the seeds of a gift of life for others. Yet, despite our best efforts and the work of so many researchers and physicians who have supported our

Page 125

cause, we cannot do it alone. The work of this committee and the many, many contributors today at this meeting are a vital need to all those persons facing known and emerging fungal pathogens without the knowledge and medicines to fight back. More education, more research and funding is needed. New drugs are needed. Nothing was more devastating in Hank's inspired fight against his leukemia than for him to contract a deadly fungal infection. And nothing was more helpless to have such few options to fight that infection.

"Hank did not die from the rare leukemia he had; he died from a fungal infection that cannot only attack immunocompromised patients but also organ transplant patients, diabetic patients and traumatically injured persons, including soldiers and citizens injured in battle or by natural catastrophe. Fungal diseases can attack a body and cause massive disfigurement, infection and devastation. No person should ever experience such an end of life. No parent or family member should have to witness the ravages of such a disease.

Page 126

"Isoconazole, known as Cresemba, approved by the FDA, made by Astellas -- approved by the FDA was the first antifungal medicine that offers an important option for treatment of some fungal diseases such as aspergillis and mucor. Hank had only one proven medicine, amphotericin B, which was developed over 50 years ago to fight fungal infection. That simply cannot be the best this country can produce.

"After more than 50 years of only one medicine for mucormycosis and now Cresemba, we still need new antifungal agents to treat this and other fungal infections and save the lives of future children and adults. Henry wanted to find out why this happened to him so he could prevent it from happening to other kids. I hope and pray the work of this committee will bring this medical and scientific community closer to fulfilling Hank's living wish."

Thank you for allowing me to participate.

DR. LAURA KOVANDA: Thank you, Mr. Schueler, that was -- always heartbreaking to hear,

Page 127

and thank you for bringing us this very important patient perspective.

So, in the interest of time, we're going to move quickly to the next presentation and skip the break. Our next presenter is Dr. Peter Pappas. He's going to present the design and conduct of clinical trials for newer antifungal agents. Dr. Pappas is Professor of Medicine, Infectious Diseases Department and a scientist in the Cancer and AIDS Centers at the University of Alabama at Birmingham. Dr. Pappas?

DR. PETER PAPPAS: Thank you, Laura. And thank you, the organizers, for asking me to spend a few minutes talking about really what I see as some of the challenges. Others have spoken to some of the obstacles and the challenges, and subsequent speakers will field this as well. So, I'm going to kind of spend the next 10 or 12 minutes talking about some of the things that I see as obstacles towards the conduct of clinical trials. I'm making certain I can advance this. Let's see... Okay, there we go.

My disclosures. There we are. Okay,

Page 128

my disclosures are listed here. And then I want to just talk in broad terms about the challenges to all antifungal clinical trials. And I would say, you know, a couple of obvious things, that with the exception of invasive candidiasis throughout the world and then cryptococcosis in lower income countries, these are relatively rare infections and enrollment by its nature tends to be very slow. And so numbers are a big deal and we've talked about that already.

Delaying diagnosis is also an obstacle. And as Kieren and others have spoken to, it really calls for the need for, you know, rapid, sensitive and specific nonculture-based diagnostics. This seems to be a huge limiting factor. And in the setting of cryptococcosis and certainly aspergillosis, we've largely gotten around the need to culture -- have culture positivity to include a patient into a study. But it's certainly a major challenge for many of the other fungal infections as well.

And determination of anti-fungal resistance, which is a growing problem. It's been spoken to already. But it's slow. And susceptibility

Page 129

breakpoints -- what really determines resistance is not clearly established for each organism.

And so when one puts all this together, traditional, randomized, controlled, double-blind clinical trials are problematic and they really are only applicable, in my view, to candidiasis, aspergillosis and cryptococcosis. And if one adds to that -- let's say we want to study aspergillosis -- I'm sorry, Candida auris, as an example, well, then we've really upped -- we've raised the bar even more because we really don't have a quick way of identifying and enrolling those patients. So, we have to come up with different strategies.

Now, for invasive candidiasis, antifungal resistance is now widely recognized as an emerging problem. It's especially a challenge for Candida glabrata among the more common organisms. And taken as a whole, the antifungal resistance in Candida constitutes, you know, maybe 5-25 percent. It varies considerably, depending on the prevalence of glabrata and auris, and if there are epidemic strains in a particular institution. But if one were to choose to

Page 130

study antifungal resistant Candida organisms, you're really biting off quite a challenge.

Now, coupled with that, some of the recent observations. If we look at the most recent trials of invasive candidiasis, I think it best -- and we don't have these numbers exactly but our estimates are based on our own experience are about one in ten patients qualify. Even though they have a positive culture there are going to be other things that disqualify these patients and the most common ones are listed here.

Too much prior therapy, the patient is too sick, contraindicated drugs, especially in the cases of azole therapy, and then concomitant illness -- preexisting liver or kidney disease or both. Another obstacle is, you know -- well, one of the endpoints has been global response, which includes clinical, mycologic and being able to survive.

These clinical endpoints I think are a particular sticking point and I'm going to suggest that maybe we should reconsider this. The clinical endpoints are soft. They include fever and/or

Page 131

localized symptoms, and they are a requirement for enrollment into a Phase 3 trial -- not so much a Phase 2 trial. But these are soft in the sense that fever and localized symptoms, etc., can be caused from a multitude of other disorders and not just an invasive Candida infection. And so the reliance on these or the requirement of these for enrollment into a trial become, I think, again, just another obstacle, whereas the mycologic and survival endpoints are pretty hard.

We don't yet know how to incorporate for Candida these non-culture based assays. We can use them for screening, we can potentially use them to enroll patients, but then ultimately, at least for Candida, we're left with basing our decision as to how an individual responded based on the result of the culture and its clearance.

And so while we have several tools potentially to help us identify candidemia or invasive candidiasis early, it's not clear how to use those once the patient is enrolled and, again, without a positive culture most trials are left with a patient that's essentially unevaluable.

Page 132

Laura's already talked about this. This study was published, and I will simply just underscore the fact that this is a disappointment because it took five and a half years to complete this trial, it went through a lot of fits and starts, and the study failed for a lot of different reasons. And Laura showed this slide in graphic form earlier. But we didn't meet the non-inferiority margin. And so Isavuconozole is not an approved agent for treatment of invasive candidiasis.

Now, there are a lot of reasons for failure of this trial, but one of them was that the arm that is caspofungin followed by voriconazole had never been studied. And there were many, many challenges to investigators in putting a patient on this trial.

In the recent trial, the rezafungin trial, which is a Phase 2 study, looks at long-acting echinocandin rezafungin given once weekly. And in this Phase 2 trial with a randomized controlled trial, double-blinded, etc., individuals could be treated with either rezafungin once weekly or caspofungin

Page 133

followed by fluconazole. A little bit more traditional perhaps, and there's a lot of leeway in the choice of when to transition to the azole when that's appropriate. This trial went a little bit smoother. It's recently been accepted for publication in CID and all the details are going to be provided there.

And I would argue that at least with the rezafungin trial, that the main obstacle to enrollment in that study really has to do with the unique characteristic of rezafungin, and that s to do with once weekly dosing and how comfortable clinicians are or subjects, for that matter, being potentially randomized to a drug that's only given once a week. Even though there is sufficient pharmacokinetic data, etc., to show that it makes plenty of sense, it is enough of a departure that I think it presents a bit of an obstacle. But certainly a sound agent. And as this is studied, the Phase 3 trial comparing rezafungin to caspo versus flu, which is ongoing, I think is enrolling slowly in part because of this perceived obstacle.

Page 134

Now, what about focusing on resistant candida species? Again in the absence of rapid diagnostic that can identify these, you really, I think, are left with having to develop strategies that enrich a population for potentially MDR or drug-resistant candida. And, you know, such as an SICU/MICU or even stem cell transplants where everyone was receiving fluconazole, prior exposure to antifungals, breakthrough infections or recent epidemiologic factors, which could include as a consideration Candida auris.

But those are the strategies we're left with. We can't a priori enroll only patients with any fungal-resistant strains at this point in time given the limits of our technology. And so in designing a study like this, one has to really define a population that is enriched for a greater risk of having an antifungal resistant strain. I think that's our reality at this point. And so, for instance, a study that would target Candida auris or Candida glabrata is going to have to include some of these considerations that are listed here.

Page 135

Let's see if we can get to the next slide. Okay, we are, I think for the first time, looking at an observational trial of candidemia and echinicandin failure. This is a study that Ostrosky-Zeichner is honchoing and it's an observation retrospective trial. We're going to capture 120 patients that have been seen in the U.S. This study is now really being rolled out at this moment. And I think it'll give us a very good look at the isolates. Sort of why individuals fail echinocandins in this retrospective, but we do have the isolates and we do have -- or will have the historical data on these patients and treatment data. So, it should be a very good and, hopefully, current look at some important questions as to potential resistant strains.

Ibrexafungerp. This is a compound that has also expansive challenges. Most of you know this agent. It's an oral glucan-synthase inhibitor. A Phase 2 trial was completed. It was an MSG study, MSG10. And this trial, despite the fact that the drug has very good in vitro activity and seems to be well-absorbed, well enough absorbed, for sure it struggled

Page 136

to enroll. And with a target enrollment of 90, we were able to enroll about 27 patients over the course of 18 months. And the problem here was, again, either patients or -- I'm sorry, subjects or investigators' reluctance to step down to an oral therapy, particularly after patients are beginning to feel better.

Now, the FURI study, which has been its follow, follow study, or follow-on study, which is sort of a salvage trial, seems to have done much better in that it's able to target patients who have drug-resistant Candida isolate or failing or intolerant to conventional therapy. But in a standards Phase 2 type of trial which had limited -- which required limited exposure to echinocandin, for instance, there just seemed to be a resistance to transitioning to an oral agent, especially after patients were beginning to feel better clinically. And so it represents an ongoing challenge, even for a compound which looks really quite good against -- in an oral formulation against a host of Candida isolates.

Page 137

This is a compound, Fosmangepix, which -- APX study or APX compound, just completed a Phase 2 study, enrolled 22 patients. This really focused on Candida glabrata, another azole-resistant Candida species. But, again, even enrolling 22 patients, approximately 10 sites, took about a year and a half to complete this. Success looks very good but there were obstacles to this, again, because the focus was trying to enrich, encapture patients who had more or potentially resistant agents including Candida glabrata.

Now, basically, if Candida -- candidemia is a challenge, invasive aspergillosis is also a major challenge. It has about a tenth of the frequency of invasive candidiasis. Most cases nowadays are diagnosed with serologic rather than culture-based results or histologic results. There are obvious challenges that I think have been touched on earlier. And I won't go into this in great detail. But again, I think the biggest challenge and one of the things that has really saved invasive aspergillosis is the development of sensitive,

Page 138

reasonably specific non-culture based tests, including galactomannan and PCR especially.

And so this, plus the definitions, which have been accepted as reasonable ways to accept a patient have really allowed this disease to be studied. Otherwise, I think we would really be having a major challenge in trying to enroll patients into trials like this.

The traditional approaches. I'll just give you some timelines. Voriconazole and posaconazole monotherapy just got completed. It's in its seventh year when it got completed. Kieren and the group actually enrolled, almost in record time, four years to complete a study which enrolled almost 400 patients. And this is a combination study. There was a lot of enthusiasm for doing this. And then the isavuconazole voriconazole study, also about four years. But remember, what made these studies possible was the fact that we were allowed to use surrogate markers in order to enroll these patients.

Upcoming studies. I'll just mention these. Amplyx, Scynexis potentially, F2G is well on

Page 139

its way toward developing a Phase 3 study comparing it to a lipid formulation of invasive aspergillosis. And they're likely to take the traditional approach, requiring the large sample size as well.

Now, the exception to this, I think -- and I'm going to kind of end with this -- is the combination studies or studies for cryptococcal meningitis. And what really separates these studies from others has been, I think in a word, a surrogate endpoint, and that's the availability of this mycologic endpoint, the CSF EFA, Early Fungicital Activity. This really has allowed us to use a tool to -- that's correlated with clinical improvement, survival as an outcome measure that allows one to easily assess patients based on serial CSF cultures as to whether patients are a success or not using really a laboratory measure.

But in doing so, it has really changed the way these studies can be done. And this allowed a number of these trials to be done mostly in the developing world. None of them have been conducted primarily in the U.S. But this is a great example of

Page 140

how using a surrogate endpoint has really revolutionized the ability to do these studies, going on endpoints that are not based purely on mortality or clinical response.

I think the need for better diagnostics is really, really clear her. And if we are going to move forward with better design, more efficient, more rapid and meaningful assays we just have to move to markers that are not so culture based. And I think that if we use the example of what we've seen with cryptococcal meningitis and especially invasive aspergillosis, I think we see a way towards the future. What's lagging behind, of course, is the technology. And the validation -- even if we have the technology -- the validation of some of these markers, the T2, the PCR, etc., that really would make for a more rapid and efficient enrollment into these trials.

And I think, you know, it's obvious that the future standard model for randomized control trials targeting antifungal-resistant organisms really doesn't work all that well, especially for the less common infections. And I think that enriching these

Page 141

trials so that we target high-risk populations together with rapid molecular diagnostics really becomes essential if we're going to move into a new phase.

Finally, I just want to say something about the global population. We have -- certainly in our antifungal trials, those would be -- we've gone through the MSG, we've had really limited penetrance into international sites. We have used them but with a great deal of care. And I think that what we have learned over time is that many of these international sites are terrific. Many of them are highly motivated, do phenomenal work, but I think those opportunities are available but it does take screening, familiarity with the sites, some education. But there is enormous potential out in the global community.

And with that, I will stop. And thank you for your attention.

DR. LAURA KOVANDA: Thank you, Dr. Pappas. We'll now go right through to the next presentation, which is the statistical considerations.

Page 142

We have two speakers for this. We'll start with Dr. Dixon. Cheryl Dixon is a statistical reviewer at the FDA Center for Drug Evaluation and Research in the Office of Translational Sciences. Dr. Dixon?

DR. CHERYL DIXON: Hi, yes, good morning. Are you able to hear me? Hello?

DR. JOHN FARLEY: Yes, we can hear you.

DR. CHERYL DIXON: Okay, thank you. Well, I guess it's actually good afternoon now. And as was stated, I am a statistical reviewer from the Division of Biometrics IV that provides statistical support to the Division of Anti-Infectives. Today I want to discuss some general aspects of clinical trial designs in currently used endpoints for antifungal drug development along with some issues that have recently been considered.

When it comes to the design of the clinical trial, our preference is still a randomized controlled trial, whenever possible. These trials can be designed with a non-inferiority or a superiority design. In order to interpret the results of a non-inferiority trial we need to have a data-driven

Page 143

justification of the non-inferiority margin. The date needed will be a conservative estimate of the treatment effect of the active control on the same endpoint used for the clinical trial. In this way, we can be assured that the new drug is effective by showing the new drug is within this margin to the active control. External or historical controls may also be considered when a randomized control trial cannot be conducted.

For the typical invasive aspergillosis and candidemia/invasive candidiasis trials, we have justified non-inferiority margins for an endpoint of all-cause mortality that allows us to conduct interpretable non-inferiority trials. Although an endpoint based on a global or overall response has been used in past trials, historical data is typically not available for new treatment to allow for a data-driven justification of a non-inferiority margin based on this endpoint without making many additional assumptions. Therefore, all-cause mortality is the preferred primary endpoint when a non-inferiority trial is proposed.

Page 144

For invasive aspergillosis, the preferred non-inferiority margin is 10 percent when voriconazole is the control and six-week all-cause mortality is the primary endpoint. For candidemia and invasive candidiasis, the preferred non-inferiority margin is 10 percent when the control is a regimen of an echinocandin with a possible switch to an oral azole and 30-day all-cause mortality is the primary endpoint.

Since there is a fairly wide effective treatment compared to no treatment for these indications, we have been willing to accept wider non-inferiority margins than those just mentioned to consider granting a limited use indication if a product has the potential to address an unmet medical need. However, to get a labeled indication without a limited use statement, a trial with a preferred non-inferiority margin will be needed.

Although we have justified those margins, we need to keep in mind that they are trial-specific in that they depend on factors including the trial design, the control used and the patient

Page 145

population being studied. There are some challenging situations where the currently justified margins may not be sufficient to interpret non-inferiority without further considerations.

The first situation considers a new antifungal that is available only as an oral formulation. It will be studied for the treatment of candidemia and invasive candidiasis as an oral stepdown from an IV echinocandin. As I previously mentioned, the non-inferiority margin we have justified is based on a regimen containing an echinocandin followed by an oral azole. So, the interpretation of non-inferiority with such a control would be in the setting of the regimen containing the ecinocandin and the new oral antifungal, and not necessarily an assessment of the efficacy of the new oral antifungal itself.

So, in order to assess the effect of the new oral antifungal and interpret non-inferiority, we will need to differentiate for the regimen the treatment effect of the IV antifungal therapy from that of the oral stepdown therapy. So, it will be

Page 146

necessary to determine whether there is data that is available that will allow us to make this assessment.

The second situation is a study where the population to be studied is proposed to be one with limited treatment options due to an azole not being the treatment choice. This possibly includes patients who might be refractory to a current antifungal treatment. The non-inferiority margins we have justified are based on the mutually treated subjects. However, the treatment effect of refractory subjects may not be the same as initially treated subjects. It is possible that such subjects might have a higher mortality rate, even with treatment, which could lead to a smaller treatment effect when it's compared to new treatment; or they might have a lower six-week mortality, so that they've already survived long enough to be refractory to treatment. Thus, this will need to be considered in the interpretation of non-inferiority in the margin used.

Of course, in any situation a superiority trial can be proposed. Although most likely a placebo control would be considered unethical

Page 147

in the list of indications that we are considering today, and unless the new drug is a groundbreaker, superiority to an active control may not be achievable. However, a special case of a superiority design would be an add-on trial where the new antifungal is given in combination with another antifungal and is compared to the other antifungal alone.

In some situations it may be difficult to design a randomized control trial, such as with the rare molds in Candida auris where most of the currently proposed trials are single-arm, uncontrolled trials. Therefore, an external control is needed for interpreting the results of the uncontrolled trials. The interpretation of this uncontrolled trials can also be strengthened by the conduct of an adequate well-controlled trial in the more common molds or yeasts.

Some issues that need to be considered when proposing the use of an external control are the availability of patient level data, the similarity to the study population, noting that controls shouldn't

Page 148

be found based on autopsy data, ensuring that assessments are made at comparable time points in the disease process, and the matching process of the external controls to study subjects that may be applied. Additionally, pathogen-specific external controls are recommended when multiple molds are being studied under a single protocol.

I've just briefly touched on some of the issues regarding the use of external controls, but Aaron Dane will further discuss external controls in his presentation.

My next couple of slides you've already seen this morning but I have a few additional points to make. As mentioned, commonly used endpoints in antifungal trials have been all-cause mortality or a global overall response endpoint, both assessed at a fixed time point from randomization.

Whatever endpoint is used, the endpoint selected should be well-defined and reliable. Clinical endpoints are most relevant as they directly measure the therapeutic effect of a drug on how a patient feels, functions or survives. Additional

Page 149

types of endpoints include surrogate endpoints, which is a marker such as a laboratory measurement, radiographic image, physical sign or other measure that is likely to predict clinical benefit but is not itself a measure of clinical benefit. These types of endpoints will need more discussion with the agency regarding their relevance and impact on the type of approval.

Diagnostics play a large part in the antifungal setting and are frequently used in clinical trials for enrichment purposes. It is important that the tests adequately detect the disease of interest, and this is especially important in non-inferiority trials where we need to ensure that the population studied has the disease of interest.

For candidemia and invasive candidiasis trials we have allowed the use of nonculture-based tests for enrollment. However, an accompanying positive culture taken during the screening period is still needed to be included in the primary analysis population.

For invasive aspergillosis trials we

Page 150

have used the galactomannan test for patient identification as well as inclusion into the primary analysis population. It is acknowledged that there is growing interest in the field to also use these types of diagnostics as endpoints. For example, a decline in galactomannan levels for assessing response to treatment.

While qualification of an endpoint is not a prerequisite for use in the clinical trials, it will be necessary to understand the relevance of the endpoint for predicting clinical benefit and interpreting the effect of treatment before it would be considered for use as a primary endpoint.

I will conclude my presentation with a couple final comments on the global or overall response endpoint. As I previously mentioned, a global overall response endpoint is not recommended as a primary endpoint for non-inferiority trials due to the inability to provide a data-driven justified non-inferiority margin in most cases. However, it is still recommended to be assessed as a secondary endpoint in non-inferiority trials.

Page 151

We currently consider treatment success a complete or partial response in order to assess the effect of the new antifungal. However, we understand that for some, a stable response is considered a positive outcome since it allows the patient to be suitable for continued treatment of their underlying disease.

We have indicated our willingness to look at additional analyses based on a dichotomy of complete, partial, stable response versus progression or death for assessing a global overall response endpoint. And that the best way to describe the results of treatment response in any future labeling would be determined upon review of the final data.

With that, I thank you for your attention and I now turn the presentation back over.

DR. LAURA KOVANDA: Thank you, Dr. Dixon. We'll now go to Aaron Dane. Aaron Dane is a Director of DaneStat, is a statistician with over 20 years of experience working in clinical development in the pharmaceutical industry. Dr. Dane?

DR. AARON DANE: Can you hear me okay?

Page 152

DR. JOHN FARLEY: Yeah.

DR. AARON DANE: Oh, great. Thank you. So, hello, everyone. So, as was mentioned, I'm a statistical consultant for the pharmaceutical and biotechnology industry, and I'm going to talk through some of the clinical trial design considerations for antifungal development, particularly focused on areas of rarer molds and more difficult to find patient populations. So, the two areas I'm going to talk about today, one is the use of external controls to supplement clinical trial data and when is it this an appropriate approach? And also the key points to consider when that's undertaken. And also the idea of looking at alternative statistical criteria in a study of rare molds.

So, first of all, I'll go through the external controls in limited populations. So, the first key issue here is when using external controls with a small patient number, is how we do that. So, it may only be possible to recruit 50-100 patients with rare molds in a reasonable time period. So, the choice is between a very small randomized trial or a

Page 153

single-arm trial.

And when this is undertaken, a small randomized trial gives randomization, so it may give -- you know, remove any bias from treatment allocation. But the problem is the heterogeneity may make it difficult to compare treatments because the background disease may be different in the two treatment groups, which doesn't happen in a large randomized study.

Alternatively, in a non-randomized study, this would mean comparing with the externally generated data, so there are still issues to consider in terms of whether it's reasonable to make that comparison, and that's what I'll come on to in later slides.

It's also key to say that when patients have no treatment options, a single-arm study may be the only option, so in that case, we do need to think about how we would put any results into context.

So, it's worth saying in all of this that randomization is generally preferable. But if there is no clear standard of care or there is a robust external dataset, it might be that the external

Page 154

data provide more reliable information than a very small randomized study.

So, what are the key aspects of using external controls -- is their robustness and their comparability to the randomized data or the clinical trial data. So, contemporary and matched controls are most useful because you'd expect them to be more similar in terms of disease setting and standard of care to the clinical trial that was being conducted. One question -- how contemporary does that control have to be? And this would be something that would be specific to the disease in question or the fungus in question as to how quickly standard of care is changed and how far back you could go.

Additionally, considerations would be data validity -- so, can we verify the data that's been used from that external control? And also a very important aspect is the potential for bias or lack of comparability to the randomized trial. So, there are a number of features that would have to be considered and document.

So, some of these have been mentioned

Page 155

already, which are: Are the patient population and treatment of patients similar? Were the data collected under similar conditions? Are the regions of the study similar? Are the endpoints defined in the same way? And are there differences in the reporting of cases or the identification of patients of the external subgroup? And also another quick question could be is matching possible or necessary and could that help any comparisons be more robust?

One of the key elements I've mentioned there is the patient population and patient care. So, some of the things I've just touched on. So, are patients identified in the same way? So, are all available patients with the disease in question included in the external cohort or is this a selected subset? So, this could be important if that external cohort only includes more severely ill patients, and that was why they made their way into that external group -- because that means they could look more severe and that could bias any comparison with the clinical trial data.

And, similarly, are the external

Page 156

controls and trial patients identified at the same point in the disease course? So, here it could be that maybe the external cohort are identified in a more acute phase of the disease, where if this clinical trial identifies patients after that, then that wouldn't be a meaningful comparison. So, again, that would be necessary to consider that and be clear about the groups who were comparable.

Other components are is the patient prognosis similar? So, this could be are the risk factors consistent between the external cohort and the clinical trial? Or even are the risk factors consistent across sites and countries within the external cohort?

And also is there a consistent approach to the management of patients in the external cohort? So, again, this could be even within a country or between countries. Is a standard dose and duration of treatment used and is that appropriate? And is the standard of care for each country or site used sufficient to allow for comparison with the clinical trial?

Page 157

So, assuming that all of those features have been considered and it is reasonable to use an external control, there are two possible ways that could be done.

Now, the first one could be to actually use that external control data alongside a single-arm trial. And the aim here -- so, this is an example that was mentioned by Laura earlier, which is -- this was isuvaconazole and the FungiScope registry. And the idea here is the top row is actually the survival rates for the new agent.

So, what that shows is that the survival rate is pretty good, it's 60 percent. And then there's some uncertainty of the confidence interval there. And then a registry such as FungiScope could be used to provide some matched control and show that for a patient who receives an effective therapy, that they show a similar survival rate.

If possible, in that registry, it may also be possible to show a matched group who weren't treated and show that there was a big difference and

Page 158

the survival rate was much lower.

And, similarly the unmatched survival rates from the literature and from a registry would also provide additional information on treated and untreated patients or patients with inappropriate therapy, again, to show that there's a big benefit and that treated patients tend to see a similar survival rate in those groups.

So, the alternative approach, which may require more patients, is using external data alongside a randomized trial. So, an approach here that's possible is a Bayesian-augmented control design.

So, as an example, a traditional design may require 700 patients, so that could be 350 per arm. An augmented control design would recruit less patients than that but in a 2:1 ratio with more patients receiving the new agents. And then that data would be supplemented with data from an external clinical trial which use the same comparator. So, that information would then be used together in the analysis.

Page 159

And provided the control group response rate in the clinical trial is similar to that external clinical trial, the external control rate, this would allow similar Type 1 error and power with fewer patients. So, Kurt Viele has outlined this possible approach and the exact details are case-dependent, but this does have the potential for more efficient trials or being able to actually produce some outputs and results in a more feasible way.

The main risk here is that the true control arm is different from the external data. And dependent upon the direction of that, it could lead to reduced power in the analysis or it could lead to an increase in Type 1 error or an increase in incorrectly approving a new product. So, those two things are important and would have to be considered, and that would be part of a detailed consideration of that eternal data in that previous clinical trial, whether it was reasonable to use that alongside the clinical trial data.

Okay, so that, hopefully, gives us an idea of some of the points to consider and a potential

Page 160

way that external data could be used when it's not possible to recruit large numbers of patients into a clinical trial. And the other approach is an alternative statistical criteria for an area such as rare molds.

So, this was an approach that I developed in collaboration with Professor Nigel Stallard at Warwick University in the U.K., and also Paul Newell and John Rex have been very helpful in finessing this as we've been working through it.

So, this was a talk I gave at the FDA-Pew Workshop in November last year, and this is an abbreviated version of the talk, which -- because the issues still apply here with the rare molds, and a possible approach that could be used.

So, the key aspects we talked with this are that (sound drops) clinical trials has some key areas. So, what we're most interested in is that we want to be confident when we run a trial that we can show an effective treatment works. But we also want to be confident that we're not going to approve ineffective treatments.

Page 161

And the question is can we look at the traditional statistical criteria differently for rare molds? So, these patients are very hard to find for clinical trials. And, really, the idea is that it's better to provide a framework for evidence of effect in these rare molds rather than having no data at all, which may well happen if there is no clear path forward in terms of how these trials are going to be interpreted.

And what we've done with is looked to draw on the ideas used in the orphan drug area. And as I've just mentioned, the idea is that even with the smaller studies we need a framework for decision making so it's clear what study would be classed as successful before that study's undertaken.

So, the aim here is to propose a framework for decision making and sample size where feasibility is very challenging. And just to clarify that this is not an interim analysis where you look at the data after a small number of patients have been recruited and decide whether to continue. This is about the total design and the total size of that

Page 162

study.
I also mentioned this talk focuses on traditional frequentist statistics, but this idea -- we also consider this in a Bayesian framework, but the principles are the same which is why we're focused on the frequentist approach.
So, firstly, when we were looking at this, one of the key areas we were considering was large versus small trials with rare pathogens. So, clearly a larger trial leads to higher power and more certainty, but the issue is -- in some of these settings, a very large trial is not feasible to do. So, if we're unable to run the study at all, then it deprives patients of this new therapy if no one can see a way forward.
But, equally, a trial that's too small may be more feasible but it could lead to a large chance of making the wrong decision and, again, that's something that we want to avoid. And because of that, the common theme through all this is how to work with a smaller dataset and actually balance those two issues. So, how can we make sure we've got a good

Page 163

enough chance of bringing through effective treatments without increasing the chance of a wrong decision?
So, what are we aiming for when we do this? So, really, in any trial, if a test is worth the control, ever patient randomized to test with in the study risks a worse outcome. Then they key component is if the test is approved, it's probably perpetuated. And this is why we want to minimize the chances of incorrect approval or the Type 1 error.
On the other side, if the test is better than control, then ever patient randomized to control risks a worse outcome in a study. But if a test isn't approved, the problem is perpetuated in this case. So, this is why within this small dataset we want to keep the power high to make sure we pull through effective treatments.
And, finally, if the test and control are similar, we would still want to make those additional therapies available because there may be a number of reasons why the existing therapies are not good enough and are not going to continue to be effective. So here, again, we'd want to keep the

Page 164

power high.
The key component here is when we run the trial, we don't know which of these situations is true, so we have to understand the Type 1 error and power for a range of scenarios and arrange of sample sizes.
So, just to recap, so this idea of finding a sweet spot, which might be a reasonable sample size that's feasible but also manages the risks appropriate is we need to find a sample size where we have a good chance of success when a treatment's effective, a low chance of approval when it's ineffective, and a reasonable chance of success when it's similar. And another component we can consider, which I'll touch on later, is the expected number of patients benefitting after the trial is maximized.
So, the following plot summarizes this information. And what this is showing -- so, this is an example which is showing the chances of demonstrating non-inferiority if you were using an 80 percent confidence interval and a 20 percent non-inferiority margin. So, the 20 percent NI margin is

Page 165

used -- has commonly been used in areas of unmet need. And the 80 percent confidence interval is a departure from the usual 95 percent confidence used.
The left hand plot shows that when the test agent is performing better than the control, the power would be high for a positive effect so that we'd have a good chance of bringing forward that treatment. The middle plot is showing what happens when the outcome is similar for test and control. And what it shows is the power is reasonable when you get to about 50-60 patients per arm. I don't know if you can see on this plot, but what it's showing is that the power gets to about 80 percent at that point. So, you'd have a reasonable chance of success for a similar outcome.
And the right hand plot shows that when it's less effective, so the test is worse than the control in this case, there would be a 10 percent chance of incorrectly concluding non-inferiority. So, this is still a reasonably low chance but the reason this is highlighted here is because that's a greater chance than you'd have traditionally with a 95 percent

Page 166

confidence interval where that would be 2.5 percent. And this is where there would be a balance between the unmet need, what was required in terms of new agents, and whether this would be a reasonable risk.

So, in addition to this -- so, why use the different statistical criteria? So, in addition to the power and the risk of incorrect approval I've mentioned, there's another consideration which is if the patients -- what they may receive after the study. So, in a trial where one treatment is less effective, many patients will receive this suboptimal therapy. So, as is true with any clinical trial, 50 percent would receive suboptimal therapy with a 1:1 randomization. But in a limited population, this could be a large proportion of the patient population as a whole that are included in the trial. And as a result, that may be that there's a relatively large portion of the population that are receiving an ineffective medication, which is why you might want to make a decision earlier in that case.

So, the size of the trial and how that relates to this expected number of patients beyond the

Page 167

trial who might benefit is something that you can look at, and we can look at that graphically. All of that is beyond the scope of this talk, but really the key message here is that a much larger study does not always provide the best outcomes in a limited population because of this feature that actually there may be fewer patients left to receive therapy beyond the clinical trial. So, what that means is that it may be more of a balance to work out which is the best size of study to conduct.

So, in terms of considering alternative statistical criteria -- so, really, this is a framework to display tradeoffs when only a small trial is possible. So, the questions are what's reasonable in terms of false positive and false negative rates? And as a community, deciding how to trade these risks when it's impossible to run a large trial. And the idea being to be able to run a trial which has got some statistical criteria and we can agree on what they are, rather than maybe the potential of having no trial at all.

And really the idea that data on 100

Page 168

patients with rare molds can be informative, but we need clear criteria so that they can be agreed and it's clear what's required of the trial. And then it will be a case of how to maximize our chances of approving a more effective drug with, for example, 100 patients. But also limiting the risk of approving a less effective new drug.

So, the summary here is that considerations of power, chances of incorrect approval, and the estimated number of patients that may benefit during and after the trial will be important and could be used to agree to success criteria for trials of rare molds.

So, just to finish, my final slide is just a summary -- studies of rare molds are incredibly challenging to recruit, and it's not possible to design studies in a traditional way with traditional statistical criteria. And two of the possible approaches could be to use external controls to help provide robust evidence, but the external rates need to be robust and comparable to a clinical trial. So, that's critical with any of this. And also a large

Page 169

treatment effect will be helpful if we're comparing with untreated controls and been given the difference in the data source. And also alternative statistical criteria can be useful for rare molds when there's a high unmet need and could make it feasible to actually conduct a randomized study. Thank you.

DR. LAURA KOVANDA: Thank you, Dr. Dane. Let's go right to our last talk for this session. Dr. Aspasia Katragkou is currently a fellow in the Transplantation-Oncology Infectious Disease Program at Weill Cornell, and she'll provide an overview of pediatric antifungal development consideration. Aspasia? Are you... There you are. Okay.

DR. ASPASIA KATRAGKOU: Hello?

DR. LAURA KOVANDA: Yes, we can hear you.

DR. ASPASIA KATRAGKOU: Hi. I'm Aspasia Katragkou. Good afternoon from New York. I would like first to thank the organizers for extending me the invitation to talk about pediatric antifungal drug development. I have no disclosures. Can you see

Page 170

the slides that I'm changing? Because I'm using my phone.

So, this is the outline of my talk. I'm going to talk briefly about the epidemiology of invasive fungal infections in children, about the use of antifungal drugs in pediatrics. I'm going to talk briefly about antifungal agent clinical trials in kids, the pipeline of antifungal agents in kids, and also I'm going to discuss about the challenges in pediatric drug development and what can be done.

So, Candida species are the leading cause of invasive fungal infections in children. In children, typically there is a predominance of non-albican species in pediatrics (inaudible)... There are some emerging reports of Candida auris in children. Mostly they come from South American Asia. The risk factors seem to be common for all kinds of species -- like prematurity, surgery and malignancy. And the mortality range is depending on the study from 10-30 percent, which seems to be substantially lower compared to adult mortality. The interesting thing is that the incidence of candidemia neonates in infants

Page 171

seems to be declining after 2009, while it remains stable after 2012.

Regarding mold infection, aspergillosis seems to be the most common with fumigatus and flavus being the most prevalent species. The risk factors here are hematological malignancies, sold organ transplantation and primary immunodeficiencies. The mortality is around 18 percent. And species of the Mucorales family are more rarely mentioned in children, and the risk factors here are hematological malignancies, other malignancies, stem cell transplantation (sound drops) --

DR. LAURA KOVANDA: Aspasia, I think we're having trouble hearing you. If you could move closer to the mic, please.

DR. ASPASIA KATRAGKOU: Can you hear me now? Hello?

DR. LAURA KOVANDA: That's better. That's better.

DR. ASPASIA KATRAGKOU: So, the mortality regarding the Mucorales family is higher, like 33 percent.

Page 172

So, the use of antifungal agents in pediatrics -- there are not many data regarding this topic. Overall, there seems to be an increased antifungal use over time as we have seen with respective cohort studies and isolated studies from Children's Hospital.

What is true is it seems to be suboptimal use dosing of antifungal agents in children. In a point prevalence study that has been done in 2012 from the ARPEC study groups in 226 centers around the world, they found that the most common indication for antifungal use was prophylaxis followed by empirical treatment for febrile neutropenia. The most frequently prescribed agents were fluconazole and deoxycholate amphotericin B. And the most interest finding is that almost half the percent of the cases were receiving suboptimal therapeutic doses. Something which indicates their clinical trial designs were not very well regarding the PK/PD data in neonates and in children.

What's been going on with the antifungal agent trials in children, data from the

Page 173

United States show overall that the clinical trials in children are ten times less compared to adults. In a recent search in the clinicaltrials.gov website, I found that the clinical trials in fungal infection in adults are three times more compared to children. And also from a relatively recent registry from October 2007 to 2017, from the 17,500 pediatric clinical trials, less than 1 percent of them involved pediatric clinical trials. And from these trials, 80 percent involved antibacterials and only 19 percent antifungals and just 1 percent both of them. And from these trials, only 10 percent of antifungal trials included neonates.

And as you can see to the right of this slide, to the graph, these are the results from an online survey done between August and September 2015 where pediatricians replied what are the barriers in order to implement trials in children. The most reason causes were difficulty in obtaining research funds, and training research staff, or raising the required number of patients. And from the ethical and regulatory perspective, they were having difficulties

Page 174

preparing all the required regulatory documents, addressing IRB questions, and obtaining patient concern.

So, to the next slide, which is taken from an article from the New England Journal of Medicine, children are not little adults. It sounds like a cliché nowadays, but indeed, there are many developmental changes that influence drug disposition in infants, children and adolescents.

So, in all of these panels, for example, in Panel A it shows how the activity of many cytochromes in the liver changes over time. In panel B it shows how the body disposition changes over time. Panel C, how the structure and the function of the GI tract changes. Lower, we can see how the tubular secretion and the glomerular filtration rate changes. And at the end we saw how the perfusion and hydration diminishes from infancy to childhood.

So, children and adults have also differences in the infections they acquire. For example, the Candida CNS infection is more prevalent in the small babies, less than three-months of age.

Page 175

The mortality of candidemia is less in children versus adults. Also, invasive aspergillosis has different imaging findings in children compared to adults. And the tinea capitis in children appear -- seems to be specific for the children as compared to adults.

Also, there are differences in the hosts that affect these infections. And in children, the neonates seem to be more susceptible, children with primary immunodeficiencies or they have different rates of comorbidities than children.

So, this is a very busy slide which wants to say that (sound drops) --

DR. LAURA KOVANDA: We're having trouble hearing you again.

DR. ASPASIA KATRAGKOU: Can you hear me now? Can you hear me?

DR. LAURA KOVANDA: Yes, that's better.

DR. ASPASIA KATRAGKOU: So, the relationship between adult and pediatric doses can be linear or nonlinear and this doesn't seem to be drug class specific dependent.

So, for example, for amphotericin, for

Page 176

all the formulations of amphotericin, the relationship between adult and pediatric doses seems to be linear. This is not the case for azoles where Voriconazole seems to be linear but nonlinear for the rest of the azoles. And the next slide shows the echinocandins, where there is linear also only for anidulafungin but it's nonlinear for caspofungin or micafungin.

So, I'm moving to the next slide. So there are specific considerations regarding the antifungal agents in children. Historically, pediatric drug dosing has been extrapolated from adults by use of a linear modeling, namely dividing the adult dose by an average adult weight like 70 kilograms automatically, or more rarely, dividing by the body surface area divided by 1.73 square meters.

Nowadays, the antifungal treatment in children has been advanced and studies until now have shown us first that the antifungal pharmacokinetics and doses differ --

DR. LAURA KOVANDA: Aspasia, I think we lost you again. Can you speak closer to the mic?

DR. ASPASIA KATRAGKOU: Hello? Hello?

Page 177

Hello? Can you hear me? Can you hear me? Hello? Hello?

WOMAN 1: We can hear you, Aspasia.

DR. ASPASIA KATRAGKOU: So, the conclusions regarding antifungal agent use in children until now is that antifungal pharmacokinetics and dosing differs dramatically between children and adults. Second --

DR. LAURA KOVANDA: Aspasia, I think your connection is going in and out.

DR. ASPASIA KATRAGKOU: I think it's my Internet connection. It's not probably good because of the storm probably. So, second then in their individual pharmacokinetics viability increases with increasing developmental aids. And third, antifungal drug exposure targets -- varies between young children, children and adults. All these findings are really important because of how --

DR. LAURA KOVANDA: Aspasia, I think we're going to have to make an adjustment. I don't know if others cannot hear as well.

DR. ASPASIA KATRAGKOU: Can I call you

Page 178

back? Hello?
DR. LAURA KOVANDA: Should we stop here and maybe --
WOMAN 1: It looks like some people can't hear her.
DR. LAURA KOVANDA: Yeah. I think either we have to make an adjustment or maybe we take a break now and maybe we can come back to it after lunch. Or how should we proceed? I'm not sure if it's going to get better right now.
WOMAN 1: I think we probably will need to disconnect for lunch.
DR. LAURA KOVANDA: Yeah. Why don't we go ahead and take a 30-minute lunch break? I'm sorry, Aspasia, I think we're having trouble with your connection, maybe because of the storm. So, go ahead and take a 30-minute break. It is one (sound drops) on the East (sound drops) so, let's come back in 30 minutes.
(Break)
DR. LUIS OSTROSKY-ZEICHNER: This is Luis Ostrosky from Houston, and we're going to start

Page 179

the afternoon session, Session 3: Current State of Candida auris and Antifungal Drug Development Considerations. The session is going to be chaired by Dr. Helen Boucher and myself, and it is my pleasure to introduce as first speaker, Dr. Tom Chiller.
Dr. Chiller's the Division Chief for Mycotic Diseases Branch at the CDC and he is going to be talking to us and giving us an overview of Candida auris and emerging resistant candida. Tom.
DR. TOM CHILLER: Thanks, Luis, and great to be with everybody. Look forward to giving a very short overview of Candida auris and sort of where we are. I know many of you, if not all of you, know about this organism and we've all been hearing about it for the last several years, so I'd like to focus more on some of the updated information, at least, that we have and then touch on briefly, unfortunately, other emerging resistant candida what we're starting to worry about.
I don't have any disclosures. I think many of you saw recently, we put Candida auris on the urgent threats list from the CDC report on

Page 180

antimicrobial resistance. This is obviously important for this kind of thing that we're talking about today, drug development, as well as other issues that help prioritize these organisms in our scope when we're looking to develop both diagnostics, drugs, and measures to control, treat, and contain them.
I always like to put this slide in there because, really, for all of us, this has been a paradigm shift, this new species for candida infections. We really have a yeast acting just like a bacteria. Resistance is the norm with this organism. It thrives on skin. It contaminates surfaces, patient rooms, and it spreads, now we know, readily in healthcare and even non-healthcare settings; although, most of the documented spread is in healthcare settings.
Here's a current look at where we are with cases around the U.S. You can see that the major cases still remain in the three states of Illinois, New York, New Jersey. We are seeing more cases in both Florida and California, and you can see here that there have been new states that have reported one case

Page 181

in the recent past.
This gives you a look at our numbers. You can see here we're up to over 1,200 clinical cases and about twice as many cases that we call screening cases, where we have gone and looked for, essentially, colonization in healthcare facilities or in long-term care facilities. We also have some COVID-related challenges with this particular organism. We know that decreased screening has been going on and so there are actually less observations as to how much is spreading with facilities.
We have been doing screening, certainly, in hotspots and that, as you can imagine, has decreased dramatically. There's also been reporting delays and so I think those are just common for many of the things that are happening right now in the -- during this COVID pandemic, unfortunately.
The other thing that we're concerned about is some of the changes in patient movement patterns and these changes have to do with sick patients going in from long-term care facilities and moving into ICUs and back out. Of course, the

Page 182

vulnerable in this population are the exact patients in these long-term care that we've been worried about, MDROs, multidrug resistant organisms in general, but Candida auris specifically.

So there's been some concern about that, and then of course, widespread -- even more widespread empiric anti, certainly bacterial use, less so antifungal use, and you can see here from these two graphs that all the colonization levels are down, but we've seen some interesting sharp increases in C. auris when there is culturing done in some of these long-term care facilities, and that's what the graph on the right.

So what about the epidemiology of this organism that's been now around for a number of years? You know, we have seen some outbreaks happening in previously well-contained areas of the country like in Southern California and the Mid-Atlantic. We also have seen several cases reported to us without links to any known cases or healthcare abroad, and so understanding how those cases developed or arrived.

And then we're seeing -- and we always

Page 183

have, but it hasn't been the main source of transmission in acute care hospitals, but we're certainly seeing more of that now as well as just regular skilled nursing facilities, not just the skilled nursing facilities with ventilator care, which has really been the crux of this outbreak occurring in those ventilated patients.

Most common specimen sources of the clinical cases that we've detected to date continue to remain about half in blood, but we see a lot, up to a third in urine, which of course are often not identified, as we know, and then less so in wound and in sputum. And then, of course, long-term colonization has been one of the issues we've been battling with and trying to understand, and you can see here from -- this is from data, I think, out of Chicago that was presented last year at SHEA, and just gives you a snapshot of some of the different things we're dealing with.

You can see some patients, by the blue diamond, are negative upon screening culture, and they remain negative throughout the duration of their stay

Page 184

in this long-term facility, despite the fact that their bed -- not bedmates, but their roommates are positive. And so there's some interesting dynamics going on here where you can have a positive roommate and yet you remain negative that entire time.

So we're still trying to understand that transmission. This also, obviously, points out that some people can be positive and stay positive for hundreds of days or they can go positive, negative, and back to being positive still not understanding whether that's a reinfection or simply they just remain colonized. We think it's more of the latter that they remain colonized, and obviously colonization testing is not a perfect sensitive way to document, as we know they can -- that the Candida auris can be found in multiple different body sites.

So talking briefly about resistance, here's a look at somewhere around 1,600 isolates that we've tested: 80 percent resistant to azoles, about a third to the polyenes, and low numbers, which is good, resistant to echinocandins. You can see about a third are multidrug resistant, in other words, two or more

Page 185

drugs, and we have found pan resistance in two different states, but thankfully, this is still exceedingly rare in this country.

There are, however, major difference by clades. You know that Candida auris has principally four but now five different clades that have been identified, and this, you can look at some of this resistance that can vary geographically, depending on where the clade is and this is looking at azole resistance. You can see South Asian clades have almost all got azole resistance. The African clade, again, has very high levels; whereas, the South American clade, which is found principally in Illinois, has very low levels of azole resistance.

In contrast, you can look at amphotericin B resistance. Again, South Asian around a third, the African much lower, and the South American clade even lower amount, and then finally looking at this sort of with a round-about way of all three classes of drugs, you can see here that the different regions and therefore different clades have different levels of resistance, where echinocandin

Page 186

resistance, again thankfully, remains relatively rare in most of these isolates to date.

We have reported, as you all know, on pan-resistant C auris for completely unrelated cases reported with resistance to all three classes: three from New York, one from Maryland. None had international travel or healthcare. All of these were mechanically ventilated and had been in long-term care and all cases initially had Candida auris cultures sensitive to echinocandins but developed resistance while being on echinocandin treatment, which of course, is concerning.

Switching back, then, out of Candida auris and into a couple new areas in candida. First, an old area, Candida glabrata, as we know, still making up a large number of our candidemia patients in this country we've got now 12 years of ongoing surveillance in 10 sites with over 2,500 isolates and you can see there that the resistance to fluconazole remains relatively stable. The three-plus echinocandin resistance has climbed over time.

You can see among those isolates

Page 187

resistance to flu, around 10 percent are also resistant to echinocandin, so suggesting that these are sort of multidrug clusters, and you can see among the echinocandin resistance, again, 25 percent resistant to flu. So clearly, those that develop resistance are more likely to be multidrug resistant.

Some of the familiar candida species, again, that we've seen, Candida parapsilosis, we're seeing resistance approach around 10 percent in the U.S. Certainly, this is higher in some other countries, so it's one thing we've been wondering about is how our parapsilosis will develop resistance over time. Guilliermondii species complex, we've seen some very high fluconazole MICs in our surveillance.

And then finally, some new species that we're sort of watching and potentially concerned about. These species are maybe for lack of a better word, cousins or closely potentially related to Candida auris in some way, and in fact, Candida haemulonii, the first species where we do see fluconazole resistance, was often mistaken with some of the older ways to detect species in microlabs as

Page 188

Candida haemulonii, not Candida auris.

But there is truly Candida haemulonii, as well, out there, as well as duobushaemulonii, where we've seen some fluconazole resistance and high amphotericin B resistance and Candida kefyr, where we've seen a few very high fluconazole MICs. And if you look here at sort of the Candida haemulonii species complex, you look at whole genome sequencing, and I know this is very small, but suffice it to say, these are separate species from Candida auris, although close, and we've seen now transmission of haemulonii and duobushaemulonii in Panama in hospitals there and we're -- are wondering now as whether this sort of transmission is going to be akin to the kind of healthcare transmission we're seeing with Candida auris.

And again, concerning, because again, these are relatively resistant organisms. And finally, duobushaemulonii. We have recently been in touch with colleagues in Puerto Rico where you can see, based on the whole genome sequencing here, we have a very tight cluster of 12 isolates from 11

Page 189

patients, 10 isolates actually from one facility.

These were collected over about a year-and-a-half from both blood and abscess specimens, and again, this is a very resistant, at least azole resistant organism and we're wondering again is this a newer emerging species that is also going to be transmitted in those healthcare settings, and that's concerning to us.

Finally, a few resources for you to see about resistance and Candida auris on our web page, and I will end there and just thank all the collaborators that we work with on a daily basis, especially our state and local health departments and clinical, academic, and international partners as well as NIH and the rest of the folks at CDC. So thanks for your time.

DR. HELEN BOUCHER: All right, I'm going to jump in. This is Helen Boucher from Tufts. Good afternoon, everybody. I think my mike was unmuted, Dr. Ostrosky. It's my pleasure to introduce Dr. Baoying Liu from the NIAID, who's going to speak to us about funding opportunities on clinical research

Page 190

at the NIH. Thanks very much.
DR. BAOYING LIU: Can anybody hear me? Hear me okay? Okay.
DR. HELEN BOUCHER: Hear you well.
DR. BAOYING LIU: Thank you very much for the opportunity to present. For today's talk, first I will provide some highlights from the NIAID Candida auris workshop. Which took place back in January. And then I will focus on our funding opportunity on clinical research.
Understanding the biology, antifungal resistance, and the clinical implications of Candida auris workshop was held at NIAID conference Center on Fishers Lane of Rockville from January 28th through 29th, 2020. NIAID sponsored this workshop. My colleague, Dona Love, who is a busy mycology program officer, along with NIH intramural investigators, Julia Segre, Mihalis Lionakis, and the CDC comptroller, Brendan Jackson and myself were on the organizing committee to put together the workshop agenda.
And through the link on this slide, you

Page 191

can assess the workbook agenda and most speakers' presentation of the workshop.
Objectives of this workshop is to bring together a diverse group of stakeholders including representatives from academia, industry, and the government agencies to determine what is known about this organism, what are the most serious knowledge gaps, and discuss how to best leverage resources to combat this unique fungal pathogen.
The picture on the right is our Fishers Lane NIAID building. We are extremely lucky to have this meeting in person just before the pandemic. Our registration was maxed out with over 100 attending in person and over 100 remote attendees.
This workshop has covered very ambitious agenda. It includes five scientific sessions, which are the first five bullet points here and the three breakout sessions in this one-and-a-half day.
We covered topics from basic biology, resistant mechanism, immunology, epidemiology, decolonization, diagnosis, efficacy and therapeutics

Page 192

in the pipeline. Clinicians also shared their academic experience in managing Candida auris infection in the United States, United Kingdom, and South Africa. We united a total of 24 speakers including international speakers.
Our next slide, I'm trying to capture the major takeaways from the breakout sessions. This is very high-level summarization. I could only pick several topics to share. One of the topics that consistently came up is the access to clinical isolates, especially isolates with sequence data. During the workshop, attendees also discussed about how much patient metadata we can get without compromising patients' privacy.
After the workshop, based on the feedback from participants at the workshop, five new isolates were added to the AR isolate bank and are now available to the research community, so the link I provided here is the CDC/FDA AR Isolate Bank. Right now, multiple isolates from each clade are available in the collection.
A second topic to share is about

Page 193

decolonization, for example, questions like how to start a decolonization in the real-world setting. What are the facts to focus on? What is the goal of decolonization in the context of persistent colonization?
The third topic I wanted to share is about special considerations for resource limited settings. For example, we need to first understand transmission dynamics in this setting, so those patient populations are different and often without surveillance systems in place.
And lastly, we discussed about clinical studies. Currently, there's no treatment (inaudible) and there are very limited data to detail disease progression, treatment, and the treatment outcome. For example, a clinician shared a disconnect between blood culture clearance and the patient outcome.
In other words, so some patients after antifungals were given, blood culture were clear but patient still died. So the question is, what's the treatment that could impact outcome? Is it due to the comorbidity? Maybe not.

Page 194

So again, it comes to the same topics that we discussed today, how to design a clinical trial. This one-and-a-half-day workshop allowed the community to work together to define the current status of Candida auris with research and identify that to allow development to move forward.

With the speaker's permission, slides have been made available on the website I provided here, I will repeat, you can access the workbook agenda and the speak -- most speakers' presentation through this workshop. So that's that.

For the second part of my talk, I will focus on our funding opportunities. NIAID supports basic (inaudible) and clinical research targeting Candida auris. Approximately 50 percent of NIAID's mycology portfolio have this candida species. Many of them are incorporating Candida auris studies into their research. Because this FDA workshop has a clinical team to, today I'm going to focus on our support on clinical research.

First, these investigator-initiated clinical trials, which include standard R01, R21, and

Page 195

the U01 surveillance mechanisms. All these three mechanism are clinical trial required. R21 and R01 grant mechanism do not need to include NIAID staff and are designed for non-high-risk clinical trial.

For the high-risk clinical trial, NIAID utilize the U01 mechanism. When I talk about high risk, high risk refers to an unlicensed product or for licensed product for an unapproved indication. NIAID also supports clinical trial planning; it's called R34. This mechanism is to support timely development of all materials required for future clinical trial, for example, to establish a team and to develop clinical protocol.

I want to point out here, funding of R34 doesn't guarantee all implied funding of subsequent U01. Budgets are limited to $150,000 direct costs for up to one year.

So NIAID also supports small business to conduct clinical trials. We call this mechanism U44. U44 is a very attractive mechanism for small business to conduct clinical trials, so I will briefly introduce U44 at the next slide.

Page 196

Lastly, NIAID also have contract mechanism to help conduct Phase I clinical trial. I may already have mentioned that in morning. This contract mechanism is a clinical service, just like the preclinical services you heard this morning. NIAID is holding the IND and then they sponsor the clinical trial. Of course, it will be the collaborators or partners so use that interest applied entirely.

So this slide, I'm trying to provide two examples for the current grant opportunities. For U01, like I mentioned early, it support high risk clinical trials. In addition, if your request equal to or more than $500,000 direct cost per year for any year of proposed trial, then a prior consultation with NIAID staff is needed.

The purpose of prior consultation is to take into account program priority, visibility, safety, and the cost. It's not scientific review and will not replace peer review process. If you request less than $500,000 direct cost per year, you don't need to go through this prior consultation process.

Page 197

Your application will go right to the review.

For U44, like I mentioned, is a small business, Phase 2 clinical trial implementation grant, just like SBIR small business Phase 2 grant, you can request up to $1 million total cost per year for up to three years with waiver topics. You need to adequately justify why such a budget is required. You can apply a Fast Track Phase 2 if you have a prior Phase 1 or Phase 2B if you don't have a prior Phase 2.

Here, I want to emphasize for the implementation grant that new one and U44, in your grant application package, you need to include all elements that are necessary to conduct a clinical trial. For example, you need to already have a clinical protocol. You also need to have clinical monitoring plan, data management plan, and they must be used.

Finally, for updates on funding opportunities, please consider to subscribe to NIAID Funding News, so I have provided links here. I also suggest you to look for NIAID council-cleared concepts. It shows upcoming potential opportunities.

Page 198

These initiatives are something we want to support and we care deeply.

Again, these are the resources that are available for the community. Please consider to apply. We would like to see more clinical research applications coming in. Please do not hesitate to email me. I would like to help you to navigate this process. With that, I conclude my presentation. Thank you very much.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much, Dr. Liu. We're going to move on with the agenda. The next block is a block where we're going to discuss lessons learned from antifungals for high unmet medical needs, so it's going to be a rapid fire with three speakers. We're going to start off Dr. Michael Hodges, who's currently the Chief Medical Officer at Amplyx. Mike.

DR. MICHAEL HODGES: Thanks. Good afternoon everybody. Many thanks for inviting me to speak at what is a timely workshop. I've previously been involved with the development of fluconazole, voriconazole, and anidulafungin, and now fosmanogepix.

Page 199

My presentation will focus on two important points highlighted in the FDA's earlier presentation, namely the unmet medical need and practical challenges developing antifungal drugs. Now, the talk is applicable to both the unmet needs in Candida auris, for example -- and also the rare molds. My disclosure information is below, and as Luis said, I'm a full-time equivalent and a Chief Medical Officer at Amplyx Pharmaceuticals.

We have fosmanogepix in the clinic and it has a broad-spectrum activity against yeast, molds, and dimorphic fungi. Fosmanogepix has the drug characteristics that have potential to address many of the unmet needs I'm about to tell you, for example, wide tissue distribution to the brain and deep into the gut. Its two formulations, IV and oral, high bioavailability, and no signs of the renal hepatic toxicity that are the Achilles heel of some of the standard of care therapies.

On the righthand side of this slide are the Phase 2 trials that we are currently enrolling and setting up.

Page 200

Invasive fungal infections are associated with high mortality, despite the treatment and when looking at randomized control trials for invasive candidiasis, day 30 mortality is between 10 and 18 percent. Invasive aspergillosis, the six-week mortality is 20 percent. When you look at the real-world picture, it is actually much higher. Invasive aspergillosis recent review showed 38 to 85 percent mortality and for Candida auris, 30 to 72 percent mortality.

The cause of this residual mortality is due, in part of course, to the underlying severity disease, but also the poor diagnostics that we have leading to a delay in treatment, and also the limited choice of antifungals. As we've heard previously, there are only three drug classes available: the polyenes, the azoles, and candins.

Consequently, we need new antifungal drugs pretty urgently.

If you go to the next slide, we heard from Tom in recognition of the increase in drug resistance, and the negative impact on public health,

Page 201

the CDC has included three serious fungal infections on the CDC Threat List: azole-resistant Aspergillus fumigatus, drug-resistant candida species, and more recently, Candida auris which is typically drug resistant.

The fluco resistant candida is also recognized on the WHO Priority List. Coming right up to date with the SARS-2 pandemic, we see that patients with viral pneumonia are at high risk for secondary infections, including invasive aspergillosis, and that's now coined coronavirus-associated pulmonary aspergillosis. This has an extremely high mortality, just like with the post-influenza pulmonary aspergillosis.

Now more than ever, we need new antifungal drugs. We need antifungal drugs that have better drug characteristics to address both the unmet -- sorry, to address the antimicrobial resistance, but I want to really point out that equally important to antimicrobial resistance, are what terms the drug deficiencies, for example, the toxicities, the drug interaction, the lack of available formulation, and

Page 202

the lack of suitable exposure in some tissue compartments.

Also as FDA have pointed out, we won't solve the problem of the unmet without better diagnostic tests and we really need to take a one-health approach to tackle this public health crisis.

We've heard from the FDA earlier that the antifungal and antibiotic development share similar aspects of drug development and we would agree with this, but we also think that there are unique challenges and I would like to point these out. Antifungal clinical trials have always been difficult to recruit, and they probably are getting harder to recruit patients. We are, in essence, an orphan drug population and this will require a global search for the eligible patients.

Clinical trials in invasive fungal infections are extremely complex, take a long time to conduct, and can cost upwards of $100,000 to $200,000 per patient, and I think this was confirmed in an earlier talk by Laura Kovanda.

The Phase 3 randomized controlled

Page 203

trials in invasive candidiasis have historically required numbers of around 300 to 600 patients; however, recruitment per site is extremely low. These trials have taken many years to conduct and require many sites to be open in the chance that a site will recruit a patient. In reality, many of these sites will not recruit any patients and they will likely screen hundreds of patients but will not enroll. This is both expensive and inefficient.

More recently, these trials have been conducted in patients with limited or no treatment options, for good reason; however, it will just increase the scarcity of these patient who might be eligible for the trials, and these practical challenges, along with the scientific and economic challenges, discourages sponsors and investors to develop antifungal drugs.

On the next two slides, I provide some examples of the randomized control trials that have been conducted. The trial that I'm most familiar with is the VORI vs AmB/FLUCO trial, and we had 101 sites, my colleagues and I at Pfizer, and 50 percent did not

Page 204

recruit any patients and it required much more resources to manage and monitor these sites than other trials that were being conducted at the same time. This study took four-and-a-half years to enroll, and I think the example presented by Laura Kovanda would be as with fluconazole trial which required twice as many patients, took eight years to conduct.

Again, the trial I'm most familiar with is the Herbrecht study, the VORI vs. AmB, and this, again, was a high resource intensive trial taking three years to conduct.

So in summary, we think that invasive fungal infection drug development would benefit from a new paradigm for demonstrating the statutory requirements of substantial evidence, similar to other orphan rare -- drugs to treat life threatening diseases.

Clinical trials, as I've said, have historically been difficult to conduct and I think it's going to become harder and this trend will continue. Drugs to treat life threatening rare orphan diseases have been approved based on small datasets

Page 205

that support the substantial evidence of effectiveness required for approval of all drugs.

Recently, and FDA are to be congratulated for this, they have issued the LPAD pathway guidance document for drugs intended to treat serious or life-threatening infections in a limited population, and this would permit the risk-benefit assessment to be flexible to consider the severity, the rarity, and the prevalence. However, LPAD pathway does not alter the overall FDA approval standards.

Two drugs, as listed, have been approved through the LPAD pathway; however, it is unclear how far this flexibility might extend in the approval of new antifungal drugs that address high unmet medical need of invasive fungal infections.

And I'll pause there and pass over to my colleague, David.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much, Dr. Hodges, and it is a pleasure to introduce Dr. David Angulo, who's the chief medical officer at Scynexis.

DR. DAVID ANGULO: Candida auris.

Page 206

Thank you, Dr. Ostrosky. I'm going to focusing my talk in the development considerations for Candida auris specifically, and as a disclosure, I'm a full-time employee of Scynexis.

As an outline of what we are doing and as an example for what we are -- we care very deeply about these -- participating in this particular workshop that I think I can praise the agency for organizing and thank you for inviting us. We are developing the ibrexafungerp, which is a novel glucan synthase inhibitor that has a different structure from the enchinocandins, which are the only glucan synthase inhibitors approved today. This different structure allows for oral bioavailability which is, we know, a limitation of the echinocandins at this point, that they're only available intravenously.

It also results in a different interaction with glucan synthase that has shown to lower the impact of common FKS mutations that can show resistance to echinocandins. The in vitro and the in vivo activity of the compound includes all kind of relevant species of candida, including Candida auris,

Page 207

aspergillus, pneumocystis, and coccidioides. And in particularly interesting attributes of ibrexafungerp is the extensive volume of distribution which allows to achieve high concentrations in most patients.

The clinical development with the oral formulation has in progress in several fungal diseases. We have completed two Phase 3 studies in vulvovaginal candidiasis, one study in invasive candidiasis, and we have ongoing studies in patients with the recurrent vulvovaginal candidiasis, invasive aspergillosis, refractory invasive fungal diseases, and infections to Candida auris.

Now focusing on, really, the challenges of really one of the aspects that are very relevant for Candida auris development, developing new drugs for the treatment of Candida auris infections is challenging. And I hope to be able to highlight some of these challenges that would allow the conversation to move forward towards addressing those challenges, joining as a scientific, regulatory, and industry community.

Let's start by highlighting some of the

Page 208

regulatory background that may apply to the development of new drugs for candida. The typical development program for invasive candidiasis included a single, randomized controlled trial, Phase 3, and to demonstrate noninferiority against the standard of care.

This model has been successful for the development of several antifungal agents to date, but we've just heard from previous speakers that these are very challenging studies to conduct, long and expensive. The LPAD pathway may provide a framework for alternative approaches. Based on the scope of the LPAD, I think that we could all agree that Candida auris infections could be subject to an LPAD consideration.

They are certainly severe, at least most of them, with low prevalence, very few treatment alternatives. They are life threatening and additional treatments are definitely an unmet medical need. The LPAD allows for a more streamlined clinical development program while keeping in mind that substantial evidence of effectiveness must be

Page 209

provided, but allows the acceptance of a greater uncertainty, based on a risk-benefit assessment.

I think this provides us an opportunity for the whole community to work together, identifying physical ways to provide substantial evidence of effectiveness for this infection, considering the current unmet needs and limited treatment options.

The typical development program for invasive candidiasis includes a Phase 2 study, typically, followed by a Phase 3 study randomized control, power to demonstrate noninferiority to standard of care.

And I'm just going to take here as an example the most recent development program implemented for invasive candidiasis which is still ongoing. They estimated a sample size needed for the Phase 3 about 220 patients, which is lower to what is typically needed in a Phase 3 program and with the need to demonstrate noninferiority of the standard of care and they estimated it will take about two years to enroll these number of subject in 64 hospitals worldwide.

Page 210

Any one of us involved in conducting large multicenter clinical trials would recognize this is a very substantial task. So if it takes about two years to enroll 220 subject in 64 centers, for a condition that has a U.S. incidence of about 25 cases a year in the United States and the overall development program here will take about four to five years with a cost easily north of $60 million.

This particular development path is difficult to be fully applied for very rare organisms like Candida auris.

Development. Some of the enrollment challenges for development, specifically challenges for Candida auris is that enrolling patients with Candida auris in clinical trials is difficult. There are a limited number of patients. We're talking about here an incidence of about 500 cases a year in the U.S., and many are heavily treated before they even are identified for potential participation in a clinical trial.

They have a high mortality. They are difficult to enroll. You need to identify multiple

Page 211

centers in multiple countries in order to really try to get a sufficient number of cases. In this particular case, makes those trials very expensive and long, and then you need to chase the hotspots because those hospitals that were initially identified as potentially good sources for these type of patients into your clinical trials few months on the road, they may not be as good alternative as they look at the beginning.

They -- you need to be really chasing countries. You need to be chasing hospitals that really may have that incidence. Clinical evidence from a statistically powered randomized controlled trial in patients with Candida auris will be, obviously, unlikely feasible. So alternative approaches are needed to generate the substantial evidence of effectiveness, and a well-balanced definition of substantial, in light of the unmet medical need, will facilitate and accelerate the availability of new therapies.

There are multiple elements that contribute to the evaluation of the effectiveness of a

Page 212

drug against these multidrug resistant pathogens, and this is the opportunity to discuss what is the weight of the contribution that each of these elements can provide to the overall conclusion, considering that a large clinical dataset may not be feasible, at least not in a reasonable timeframe. Here, new antifungal agents that -- sorry. The new antifungal agents will typically have available a robust set of clinical data showing interactivity and efficacy in animal models, and also typically we will have PK/PD analysis showing or justifying the selected doses.

So there is here the opportunity to discuss how much weight these particular clinical assessments can contribute to the evidence of effectiveness, and this is something that altogether community, scientific community, regulators, and industry should be involved with. We should also have sufficient -- obviously, sufficient safety data for intended doses and duration.

However, the most challenging part is the demonstration of efficacy in the clinical setting and following only traditional approaches, may limit

Page 213

the ability of new therapeutics in the future, so we should be open to discuss how to implement alternative and more feasible approaches that will still provide substantial evidence of effectiveness we need with the acceptance of a greater uncertainty based on the risk-benefit assessment.

Here's some of the options. There's really four opening for discussion. Probably the most common option is a randomized controlled trial in all invasive candidiasis, all the species, that is enriched with candidiasis patients. I think that nobody would argue that this is invisible alternative or this is an alternative that has been following the path; however, it does take about four to five years to get new products through these paths and certainly it's multiple millions of dollars.

There should be other alternatives. For instance, a randomized controlled trial in other candida or other fungal diseases plus or supplemented with a small study in Candida auris patients. This could be there are no randomized comparables to system that controls external controls or it could be, as it

Page 214

has been suggested in the past, a randomized controlled trial but it will not be necessarily powered, so discussion of what is the pros and cons of these alternatives, I think, is warranted.

There are other alternatives, multiple studies, a smaller in different fungal diseases that are particular relevant to the condition that we're talking here. It could be esophageal candidiasis. Could be other type of candida infection that really together all put the weight of evidence that this particular product does give activity or the product that is being in question has activity against candida infections.

So the development opportunities. We need to identify efficient development paths for new therapeutics for these challenging infection that are well defined, streamlined, feasible within a reasonable timeframe, and obviously endorsed by regulatory authorities, scientific community, and executable within the industry framework.

They should be supported by funding and funding in this case needs to come from different

Page 215

sources. We know that most of us in the industry, we rely upon not necessarily from grants. We rely upon really investors from investment community and they need to really see an opportunity for return of investment for these type of conditions; otherwise, the funding would not come.

We also are very appreciative of funding from other -- several institutions, et cetera; however, it needs to be a roundup approach that really enable these particular programs to keep moving forward.

Alternative development approaches seems justified bases on the unmet need, the limited number of cases, the high mortality, the high rate of multidrug resistance that we're seeing with these particular pathogen, the transmission potential and the potential public health impact. We need to understand how to really address the fact of permanent colonization that we saw in some of Dr. Chiller's slides and how this impact public health and how we can impact that as well.

And we all have advanced the

Page 216

nonclinical models to really be able to better predict or at least better estimate what is the treatment effect of a particular drug. I think that we should take advantage of those models as well to really help us moving these development programs forward.

So with this, that is -- I end my presentation here, really trying to highlight some of the areas that we consider. We can all work together to really have better definitions of substantial evidence of effectiveness, particularly for these particular condition that will allow us to find a clear and physical development path for new therapeutics. Thank you.

DR. LUIS OSTROSKY-ZEICHNER: Thank you, Dr. Angulo. And to finish this rapid-fire session, it's my pleasure to introduce Dr. Taylor Sandison who's the Chief Medical Officer at Cidara.

DR. TAYLOR SANDISON: Thank you, Luis and appreciate the opportunity to talk, so thanks to the organizers. I'd just start off by saying that David and Michael and I talked and kind of organized our talks so we didn't overlap, so there are some

Page 217

things -- what they have said already, I fully agree with and I think my job here is just to real -- paint a little bit of the lessons learned from our individual trials and then maybe summarize some of the key points of our consolidated talks.

So just to kind of paint the picture where I'm coming from, this is rezafungin. It's a novel echinocandin that's once weekly dosing with prolonged PK and the studies that we've conducted, we've done a number of Phase 1s, but I think the ones we'll be most interested in will be, we have a completed Phage 2 study which had -- numbered 207 patients which yielded 183 mITT patients.

And then we have an ongoing Phase 3 trial similar to that Phase 2 in the treatment of candidemia and invasive candidiasis, and an ongoing Phase 3 trial in prophylaxis of invasive fungal disease in the allogeneic blood and marrow transplant population. And then the proposed indications would be for the treatment of candidemia and invasive candidiasis as well as prophylaxis.

So our goals are aligned in that we're

Page 218

trying to enable approval of safe and effective antifungal drugs to improve the options, to improve patient outcomes, but we have a number of challenges and one is the changing environment. I think we've seen over the past few years how Candida auris has changed a little bit how we're looking at fungi and alerted us to the needs for new antifungal options.

And of course, even the epidemic with COVID most recently kind of highlights the unexpected nature of these future challenges, and then just the need to expand our antifungal armamentarium so that either new mechanisms of actions or improvements in toxicity or drug-drug interactions, all these things are available for doctors to enable them to improve outcomes for these patients.

We've already heard from Dr. Kovanda and Pappas and Hodges and Angulo about the enrollment challenges, so I'm not going to dwell on that except to say that we did experience that in our Phase 2 STRIVE study as well with the enrollment below what we expected it to be from past pivotal studies and I think just to give you a frame for that Phase 2, it

Page 219

took us for the 183 mITT subjects, we had about 60 sites and it took us almost three years.

So that kind of gives you an idea of how difficult it can be, and those challenges are multiplied even before COVID came along. There's always issues with decreasing amounts of candida from sites, and then COVID, of course, has increased the complexity and challenges: fewer sites available for clinical research, increased risk of missed visits due to COVID, threatening the study visits for these immunosuppressed patients that are really at risk of getting COVID. We can see why they wouldn't want to come back to the clinic or hospital.

So I'm just going to touch on that briefly, but the true magnitude and duration of this impact is still really to be determined, whether it needs to be addressed in terms of our experience for antifungal drug development.

The other thing I wanted to discuss briefly was exclusion criteria. So the largest reasons in our STRIVE study in the Phase 2 study for failures were prescreen failures, I should say, were

Page 220

due to 96 hours from randomization for the candida cultures and greater than 48 hours of prior antifungal therapy. As it's already well documented and physicians on the call realize, really, you got to control the source and early, directed, appropriate antifungal therapy is the way you decrease mortality.

So most sites don't wait to find out and so, you know, with these slow-growing cultures, often greater than two days, antifungal therapy already on board. Another high impact reason for exclusion was the lack of abnormal vital signs, so fever, hypothermia, hypotension, tachycardia, tachypnea, things that are attributable to invasive candidiasis. This was determined to be imperative by the FDA as it's felt to reflect how a patient feels, functions, and survives.

However, I think many of the doctors also understand that means immunosuppressed populations, who are the ones who are at risk of invasive candidiasis, often don't develop the same types of signs of infection that other patients would ordinarily or they would ordinarily, if they weren't

Page 221

in the situation with either some sort of immunosuppressive disease or drug.

So where does this lead us? I think we talked about some of the development options in both Michael's slide and David's slides and -- but I think there are still a number of unanswered questions. I think Dr. Kovanda brought up a good one, which is, have we reached the point where large scale Phase 3 studies for antifungal agents are no longer feasible?

We have a lot of things to consider. We brought up the fact that the negative MPD associated with these new antifungal agents, in part because of these large randomized global trials leads to decreased interest from big pharma and from investors and things like this.

There's also the added issue of you get studies that go on for three, four, five or more years, you start risking confounding and kind of undermining your trial with the risk of that confounding due to improvements in diagnostics and treatments and standard of care between the beginning of a trial and the end of trial, so that supportive

Page 222

therapy may lead to differences in outcomes.
More patients may be surviving later in the trial as compared to the beginning, and if you have any kind of imbalance in the randomization from one to the next, that could potentially confound your study as well. So there are a number of things to consider about this, in addition to whether it's feasible from a business standpoint, but also from a scientific standpoint, does it really make sense.
And then under substantial evidence, David talked about this a little bit, but given the recent advances in PK/PD target attainment, can we put more emphasis on that in lieu of a Phase 3 clinical trial powered for inferential statistics, depending on the unmet needs and sort of other categories and things that are part of the assessment of what's required?
I think in the past, Dr. Nambiar has brought up a number of places where PK/PD looked good and then the clinical trial, they didn't look so good. So I think you can't just get rid of the clinical trials completely, but maybe some balance between

Page 223

those needs to be assessed and certainly there's been a lot of progress made over the past 10 years in that kind of targeted payment assessment.
And then given the described challenges, how can we define -- I mean, this seems a bit like a moving target. We don't really know what to aim for in terms of what's substantial evidence of effectiveness. And is that even considered for, like, the full kind of candidemia, invasive candidiasis stud or whether it's a single species development program, like for Candida auris alone or even for a salvage therapy study where considerations have to be made for -- not just for patients that fail but why did they fail.
Did they fail for -- because of poor source control or is it really resistance and things like this, so trying to get definitions and some kind of pathway assigned would be extremely helpful in helping to allay some of the concerns and challenges.
And then finally, should we consider some leniency in some of the key exclusion criteria, if only to prevent or in -- sorry, increase patient

Page 224

experience with these candida drugs? It may take, for instance, if you take out some of these, like the 48 hours or the 96-hour limits for empiric therapy for drug culture -- I'm sorry, candida culture, could you include more patients, then you get more experience and see how the drug works and, of course, there is some concern, obviously, that they get too much of a drug or the candida's been there for too long and maybe it's more of a subacute infection, but there are some things that can be done in terms of stratification and analyses that could also help assess that in a analysis way, rather than just taking them out from the beginning.
And then the other option I discussed before is also this idea of including abnormal signs of infection, where -- in a patient where if you have candida growing from a blood culture or another normally sterile site, there's not really a way to say that they're not truly infected and the fact that they don't mount a systemic response with abnormal signs could be because of the steroids they're on or because of their underlying leukemia or something along these

Page 225

lines that really limits our ability to test these drugs in the patients that really need them.
So those are just kind a brief summary and a few ideas of what we've seen at Cidara and what we've discussed amongst ourselves from the industry perspective, and so I appreciate the attention and the invitation, and I'll pass it back to the moderators. Thank you.
DR. HELEN BOUCHER: Thank you so much. Those were great talks and lots of food for thought for our discussion. For the last speaker of this session, I'm privileged to introduce Dr. Luis Ostrosky-Zeichner from the University of Texas where he is the Vice Chair of Medicine for Healthcare Quality, the Director of the Laboratory for Mycology Research, and professor in the Division of Infectious Diseases. Welcome, Luis.
DR. LUIS OSTROSKY-ZEICHNER: Thank you very much, and for the next few minutes, we're going to be discussing some clinical trial design considerations for Candida auris specifically. These are my disclosures: I've been participating with most

Page 226

of the sponsors in this seminar and I've been involved in antifungal development for the past 20 years.

So we are a long way from amphotericin B research. The package insert for amphotericin B has six pages compared to the multiple, multiple pages we're seeing in package inserts right now, and it's very interesting to consider that this is the antifungal that has the widest and broadest indication for most of the mycosis we're treating currently and most of the data are based on in vitro susceptibility testing or anecdotal cases.

Since then, we've been steadily developing antifungals; 1950s was primarily the polyenes. We have griseofulvin and 5-FC in the 1960s and '70s. The '80s was the era of the first-generation azoles. We moved on to second-generation azoles and then we go in the lipid formulations, the second-generation triazoles, and the echinocandins in the 2000s. And we're in 2020 and we haven't really released a new antifungal since then.

So how do we use antifungals in candida at this point? This is the new sort of continuum of

Page 227

treatment that we've created and for the most part, we are working on the right hand of the slide, which is full-blown disease and sequelae, but where we should be working, because the evidence has shown time after time that by the time we're working with positive culture or histology or invasion, we're probably a little bit too late.

We should be working on prophylaxis, preemptive therapy that is based on markers and empirical therapy which is based on high-risk profiles in a setting where we know that our microbiology is less than perfect.

We actually have a pretty good sort of pipeline of candida clinical trials, starting with the now classic Rex in 1994, fluconazole. We pretty much use the same mold for any clinical trial trying to bring a candida drug to market, which is -- so you can see here in the slide which is a summary of the AMBIS paper, Meta-Analysis of these Clinical Trials. In general terms, we deal with candidemia, plus/minus signs and symptoms.

We have limited representation of

Page 228

invasive disease, and immunocompromised patients. We've treated patients for two weeks, usually, from the first nadir culture and we always work on an intent to treat population that receive at least one dose of the antifungal and most of that comes our clinical microbiological success at the end of therapy.

The problem is that the system no longer works in 2020 and definitely doesn't work for Candida auris for the reasons I'm going to show you coming up ahead. So this is the anatomy of a candida trial and everything starts with screening where you have a patient that needs to have signs and symptoms, may or may not have radiological findings.

This is less relevant for candida than (inaudible) infections, and you want to have some evidence of infection. Then there's a couple of days that you get to enroll the patient. At that point, you need to confirm that your microbiology was positive back then is still positive, and then we go into therapy where we monitor signs and symptoms, again, radiology to a certain extent for candida, more

Page 229

for molds. We continue to get microbiology at the end of therapy, signs and symptoms, radiology if available.

We look at microbiology outcomes and we look at crude mortality, for the most part. And then there's usually a follow-up visit where, again, we look at signs and symptoms, microbiology, radiology, mortality, and this is where we assess for relapses that has always been a concern for any candida therapy.

Common pitfalls in the scheme. Well, the first one has always been the disease definitions. And although we just released the revised update to the consensus definitions late last year, we still have a problem with candida definitions because for the most part they focus on a positive culture or possible histology and we sort of still relegated the role of beta-glucan or another biomarker which is T2 Candida as evidence for not proven but for probable disease.

Another big problem with the definitions is that we actually could not reach

Page 230

consensus for ICU settings regarding risk factors and definitions, so we elected to take out the whole ICU theater so that we could get ahead and publish the definitions and there's a group still working on ICU definitions. So a big problem, specifically, when you deal with candida and Candida auris.

The second pitfall we have is that we are dealing with a framework for assessing outcome adjudication that was published 12 years ago. We probably -- we started to work on it two years before, so we're working with definitions that are 14 years old and as I'm going to show you in the next slide, we have learned a lot over those 14 years that have not -- all of the elements that we chose for the framework are applicable or work anymore for fungal infections. So again, this is, mea culpa, we need to as a group really sit down and re-look at these outcome definitions and update them, bring them to 2020.

Among the pitfalls within the definitions, we have that we require signs and symptoms. And as all of you know that work in mycology clinical trials, signs and symptoms are not

Page 231

always present, even in the setting of proven disease. So we used to think that candida could be a contaminant. We used to think that molds could just be present in bronchiolar lavages, but not anymore.

At this point in time, we do understand that some of these organisms may be there and may not be giving signs and symptoms acutely. And we still are requiring signs and symptoms as criteria to end treatment to clinical trials, mainly because that's one of the things we follow.

However, signs and symptoms, when present, can be multifactorial given the complexity of the patients we're working with in fungal infection and the fever that the patient is having could be related to the patient's underlying disease, other interventions that we're doing to them like several chemotherapeutic agents, and these patients don't exist in a bubble. They can have other infections so this could be the trichomonas infection and not candida that's continuing to give the patient fever.

And finally, we've learned to understand that again the signs and symptoms may or

Page 232

may not correlate with overall clinical improvement with radiology or with microbiology, so when we're really heavily based on signs and symptoms, we're already working behind the eight ball.

Talking about the eight ball, microbiology. So sort of the natural history of growing, identifying, and getting susceptibilities of candida and the contemporary microbiology lab usually takes at minimum three days and at maximum or under ideal conditions five to seven days. So if we're relying on a process that is going to be taking anywhere from three to 96 hours, we're immediately behind the eight ball when we're trying to enroll patients into clinical trials within a very limited time window. So again, working with contemporary microbiology, we're automatically narrowing the enrollment window to very critical times.

So once we have a culture that is growing candida that has been identified as Candida auris, we probably have eight hours to enroll the patient in the clinical trial, given the current constraints of timing that we have been working with.

Page 233

Another problem is that blood cultures have very poor sensitivity where they do not have specificity and molecular ID is not mainstream yet throughout the world.

It is relatively well represented here in the United States, but in many of the countries where we need to be working to enroll Candida auris patients or patients with resistant candida species, molecular microbiology is not mainstream by any means, so again, a very big limitation here.

Another issue with assessing microbiology is that it's not always feasible to resample invasive sites. So for blood cultures, it's pretty straightforward. We can do as many blood cultures as we want, but for that hepatic abscess, it's a big production to go back in and get a resampling to declare the patient has been a microbiological success.

Biomarkers and serologies. I think we can all agree that beta-glucan, T2, and other biomarkers have been clearly established as an enrollment criteria for clinical trials. They give us

Page 234

sort of evidence that the patient has a fungal infection. Where we have struggled is to really nail them down as surrogate markers for success of therapy.

So despite some publications out there specifically about beta-glucan and to a more limited extent to T2, we do not have the level as yet, but we need to accept them as surrogate markers for outcomes. So this is another big problem with microbiology.

Radiology. Radiology has a very, very high sensitivity, but probably the lowest specificity of any diagnostic modality we have. So the problem we have, again, primarily with mold infections but to a certain extent with candida is that radiological findings don't necessarily correlate with clinical improvement.

So I'm showing you here a brain abscess. I'm showing you hepatosplenic candidiasis and this -- the brain abscess, of course, is something that you expect to resolve on imaging when the patient is being treated and has a success, but hepatosplenic candidiasis is a much more complicated disease to be evaluating by radiology as changes may last for months

Page 235

and months and months, when a patient is probably completely cured.

And then, we have to consider a patient's safety and think about the ethics of repeated exposures to radiation if we want to use this end point.

Finally, another end point that has been very, very controversial is mortality. This is the classic paper by Dick Wenzel that explored that attributable mortality of candidemia that really gives sort of the piece of information we needed to know that candida was not just a colonizing agent and that it had an impact on mortality and on eventual state, but again since this paper, which is a couple decades old we really haven't made much of an effort in studying attributable mortality for candida and therefore we're stuck with crude mortality, which as all of you know, the population that is likely to experience candida is a population that is likely to die from many, many, many other things, so we're stuck, again, with a very imperfect measure where candida is probably contributing only a percentage of

Page 236

the reason that people are dying.

We don't really know most of the time if people are dying because of candida or with candida at any given time. So I was always taught that you shouldn't bring up problems without bringing solutions and these are my proposed solutions to these problems that I've just mentioned.

I think we need disease definitions that are very nimble in a dynamic process. We cannot be taking 10 years to update the ER -- the CMS definitions anymore. We need to really be addressing them in a living website with live information, much like we're trying to do with some of the other guidelines that we're working on and sort of bringing this to 2020 where not everything has to be published in a print journal.

We need a new panel by experts for really talking about what are the new response outcome definition looking like. So I think we need to deemphasize signs and symptoms. We need to really put some thought on using biomarkers as surrogate endpoints. I think, again, there's some evidence that

Page 237

we can use them to a certain extent. We need to definitely deemphasize radiology in outcomes.

I can't tell you how frustrating it is, not for candida, but in some of the VRCs that I've participated in to be seeing patients with mucormycosis or other failed mycosins that are alive and well at two, three years out but they still have some imaging changes and we're calling them stable or failures because of imaging, so we really need to address radiology in a completely different way.

Again, I think we need to deemphasize crude mortality and work towards attributable mortality, and one thing that I think we need to do away with is composite endpoint. We haven't had much chance to talk about this here, but we had a few clinical trials that were amazing, sort of breakthrough trials, but by using composite endpoints, we always had kind of a scratch your head reaction after the clinical trial results came out.

So we need clear, single end points and try to avoid composite endpoints going forward. I think immediately, what I think we need to do is

Page 238

expand enrollment and prior antifungal windows, recognizing the way microbiology works currently and the forces out there that are sort of pushing empirical therapy as fast as possible because it is associated with increased mortality and I feel this is what LPAD was created for.

This is exactly the setting where we need to be working on an LPAD framework where I think we need small open label trials in high incidence areas both in the United States and EX-U.S. primarily, where we can collect a key series of 20 to 30 very, very well studied cases and compare them to contemporary controls, so I know the Fungiscope database was kind of the big example of semi-contemporary controls, but I think we can be collecting data in a contemporary fashion along with the studies so that we have sort of the data we need to have a control that is relevant to the disease state that we're studying.

Again, I think this needs to be paired up with very strong preclinical and safety data and this is a path forward, in my opinion, for Candida

Page 239

auris. Again, I just want to emphasize that the space we should be working on now is really the left hand side of the slide, where we need to start thinking not only of the traditional clinical trials that look for a patient with a positive culture and see what happens afterwards, but we need to keep pushing the envelope into prophylaxis, preemptive, and empirical therapy, even for Candida auris where this is going to be a little more difficult.

Again, at this point, this kind of information has permeated throughout the United States and worldwide, where we understand that waiting for positive culture is going to double or triple your mortality off the bat and most hospitals in the United States are really working on an empirical framework where we're starting antifungals empirically the day we're culturing the patient, and this is where we need to be going.

So next generation clinical trials, this is my forward looking statement here, have to be really grounded upon molecular microbiology and I truly believe that it's just a matter of five to 10

Page 240

years where we have whole genome sequencing in clinical laboratories, at least in the United States and other developing -- developed countries, and we are going to be working with point of care biomarkers, so again, all this lateral flow work is really going to bring enrollment and outcome monitoring to the bedside as opposed to working with reference laboratories, which is what we have to work with right now.

Again, I think we need to be doing away with traditional trials and moving into strategy trials looking at prophylaxis versus preemptive, preemptive versus empirical, empirical versus full, and all the iterations that you see there and that is really going to move the needle as opposed to just another sort of licensing clinical trial for an antifungal.

And finally, I think we are already in the era of personalized medicine and this is exactly where we need to be working on, which are uncommon pathogens, resistant pathogens, taking advantage of the tools that are coming up right now, really looking

Page 241

at pharmacogenomics and again, a little bit of forward thinking, genetic risk will really be the key to enrolling some of these patients into the more high-risk and strategy trials.

This is my last slide. I want to really invite you to read this paper that came out of the MSG annual meeting. This is our blueprint for research that was drafted a couple years ago, published this year. We are going to be postponing the next MSG meeting due to our friend COVID until next year, but this is a really good thing to take home and read and look at where the priorities for medical mycology are in the next couple years.

Again, I want to thank you for your attention and I'm going to turn it back to Helen.

DR. HELEN BOUCHER: Thanks very much, Luis. I think we are now scheduled for a break -- for a 10-minute break. So guess we should plan to be back at around 3:15 for our panel discussion. Thanks very much.

(Break)

DR. HELEN BOUCHER: Hi, it's Helen

Page 242

Boucher. We're ready to start the panel discussion. Along with Luis Ostrosky-Zeichner, I'm here to guide us through some discussion of these six questions over the next about hour-and-a-half and the way we're going to manage this is we'll go through each question and we'll direct it to one person to start and then invite everyone to join in and just ask you to use the "raise your hand" feature on the software and we'll just go through as many as we can in the order that we received the questions.

So the first question is asking us to discuss important factors to consider regarding trial populations like host factors, length and type of immunosuppression and predisposing conditions including COVID, and to address the question about heterogeneity in the trial population, whether that's a good thing or whether it raises concerns and how that should be handled.

And so we thought we might ask Dr. Thompson if he wants to kick this one off. G.R., would you like to chime in?

DR. GEORGE THOMPSON: Sorry?

Page 243

DR. HELEN BOUCHER: G.R., would you like to chime in on the first question?

DR. GEORGE THOMPSON: My connection's not very good. Can you --

DR. HELEN BOUCHER: Okay.

DR. GEORGE THOMPSON: -- repeat it?

DR. HELEN BOUCHER: How about Dr. Pappas?

DR. PETER PAPPAS: G.R., we can see you. Want to give it a shot?

DR. DAVID DENNING: This is David Denning. I'm happy to make one comment on that, if you wish.

DR. HELEN BOUCHER: Thanks, David. Go ahead. Can hear you great.

DR. DAVID DENNING: Well, when you look at the combination trial with invasive aspergillosis with voriconazole and meningitofungin, if you look at the outcomes in neutropenic patients, there was really no difference at all between the patients at all in outcome, and that includes this stem cell transplants, although there weren't very many of those, but if you

Page 244

look at the non-neutropenic patients, there's a very big difference in outcome.

But because the numbers enrolled were small, it didn't quite reach statistical significance but it was about a 30 percent difference in outcome, which wasn't something that came out of the discussion in the paper, probably because of the numbers not quite reaching statistical significance. My theory is the prophylaxis being sort of almost universal in neutropenia, we -- if we want to do invasive aspergillosis studies, we have to move away from that population, to a great extent, and that means thinking about patients who have COPD, influenza, COVID-19, other types of -- lung transplants, other non-neutropenic type of patient groups and that, I think, is going to require working across the definitions of the MSG or RTC because some of them we haven't got definitions for.

They didn't work very well and it's going to require a different way of thinking about outcome because the scans in many of these patients are abnormal with their underlying disease, let alone

Page 245

their aspergillosis. So I think there's -- I think the answer to your question, yes, there's a lot of difference in the aspergillosis area.

DR. HELEN BOUCHER: Great, thanks for that. Looks like Kieran Marr has a comment.

DR. KIEREN MARR: Hi, there. Hi, I think I can be heard now, I hope.

DR. HELEN BOUCHER: Hi, Kieren. Go ahead.

DR. KIEREN MARR: Fabulous comment by David about the combination therapy study and the heterogeneity in outcomes witnessed within that study. I'll add that I think that the issue is not that there's no heterogeneity with neutropenia. It's that if you looked very closely at the underlying disease, it's apparent that neutropenia itself is, as John Rex calls too blunt an instrument.

It's a -- it encompasses people that have outcomes that are very heterogeneous within and if we looked -- when we looked, actually, at the underlying diseases of the population, the populations that did worse within that are people that had acute

Page 246

leukemia that was relapsed. And this, to me, outlines progressive learning that we continue to experience in that there are ways to understand the outcomes within categories. Neutropenia and non-neutropenia itself are not adequate to actually -- to encompass, actually, the predicted outcomes, especially if you're looking at survival.

So I think it's really important to discuss heterogeneity. I agree with David completely and that we need to go deep within the underlying disease and other predictors of outcomes within those.

DR. HELEN BOUCHER: Great, thanks very much, Kieren, for that. Dr. Pappas.

DR. PETER PAPPAS: Hey, how are you doing?

DR. HELEN BOUCHER: Great. Nice to hear your voice.

DR. PETER PAPPAS: Good to hear you as well. Something that comes to mind that I guess could be obvious but it needs to be stated, and I think that the -- one of the areas where heterogeneity really does play a role in general, I believe, is in these

Page 247

cryptostudies and I guess the day of throwing all these patients together, HIV and non-HIV, really, I think, is over.

And within the HIV population itself, I mean, there really kind of four populations -- I mean, within the cryptopopulation itself, there are really four populations. There's the transplant; the HIV; the non-HIV, non-transplant but still compromised patients, patients with renal failure, hepatic failure, steroids, et cetera; and then the normal host.

And those are so different in terms of their responses and so forth that a trial that would throw them all together or just divide them into HIV and non-HIV, really I'm not sure that would teach us a lot. And I don't know how many ways you can stratify patients of that nature, so it seems to me that that's a group where same disease but very different populations lead -- could lead to very, very different outcomes.

DR. HELEN BOUCHER: Great. Thanks very much. Mike Hodges.

Page 248

DR. MICHAEL HODGES: Thank you. Just a couple of comments on the underlying diseases. I think Pete, in one of your papers with the late Claudio Viscoli, Jack 2009, where you looked to caspofungin for the treatment of invasive aspergillosis, you found that Karnofsky score and whether the patient was in remission for leukemia had a big impact on the outcome.

I might also throw in length of neutropenia or neutropenia recovered or ICU ventilation as well, high grade graft versus host, mismatch unrelated transplant, and even a high serum galactomannan greater than 1.5 may all be big prognostic factors. That's one point.

I want to make another point about the randomized controlled trials, the three randomized controlled trials that have been conducted for invasive aspergillosis. They tended to be in the hem/onc population, for example AML, neutropenic GM positive.

And what we're finding is the patients who are on the ICU who don't have hematological

Page 249

oncology malignancies but have viral pneumonia either the kappa or the influenza, they have a far greater mortality than the patients who have the underlying disease of hem/oncs and as people around the panel will note better than me, there are people looking to get better definitions for the coronavirus-associated pulmonary aspergillosis and there are already existing definitions called the AspICU definitions for pulmonary aspergillosis secondary to influenza.

So two points there, and I'll pause and hand it back to Helen.

DR. HELEN BOUCHER: Thanks very much, Mike. Dr. Perfect.

DR. JOHN PERFECT: Hi, thank -- okay, thank you very much. It's my pleasure today to listen to this. It's going to cost me about five hours tonight rounding on the transplant ID service, but other than that, I wanted to make a statement on heterogeneity. It is all -- they're all heterogeneous type situations and what I wanted to do is make some kind of statement which I think is probably off base, but I think it's important.

Page 250

In this day and age of computerized -- for the amount of information we get today, we should be changing the game completely. We should have centers that actually know what these patients actually do and what happens to these patients. It's unconscionable that we do a candidemia study and we have 50 -- 30 to 50 patients that can't be put in the study and we get one on the study. That's not right.

So what I would say is trying to pick the heterogeneity in this thing is, what's the solution. I think part of the solution would be is you take 10, 15 centers throughout the United States or Europe or wherever that's got these type of patients and you dive down. I know things change, but if you dive down in the type of patients that they have and understand what they are and what their outcomes are, we may not need -- and our controlled population is right there.

It's right there with us and we can reduce the number of patients we put in the studies and we could control for the heterogeneity.

DR. HELEN BOUCHER: Thanks very much,

Page 251

John. John Rex, and then we'll turn it to Dr. Ostrosky to go to the next question.

DR. JOHN REX: There we go. The little voice said the microphone is on now. Heterogeneity cuts two ways and only -- I think there are two things you want to know about a compound. You want to know, does it work, and then how best can you use it. And the question of does it work needs to be answered as cleanly as possible and I would actually argue that you want the heterogeneity because it reflects the real world, but you also want to bias it towards a greater degree of immune compromise, because that's where the signal efficacy is the sharpest. But then the question how best to use it is something that can take years to study. I know -- Pete, your comment about HIV versus non-HIV, I fully recognize, very different diseases.

What I think is probably true, that HIV, cryptococcal meningitis, is a harsher testbed for a new engine. If it works there, probably work elsewhere, but may use it a different way, so I want to just emphasize the idea that getting a drug, you

Page 252

know, goal number one has to be to make the compound get to the place where it actually stays available to us and that means initial approval with an adequate data package to get you started, and then we do the rest -- then we do the next 10 years' worth of work after that.

And so heterogeneity early on, I think, you do want to pick up some of it and I think you want to bias it towards the -- bias towards greater degrees of immune compromise.

DR. LUIS OSTROSKY-ZEICHNER: Thank you. thank you very much, Dr. Rex. We're going to move on to the second question which is, what are the settings in which external controls and other alternative trial designs need to be used to obtain adequate and interpretable data? Are there gaps in those sources for external controls and what do we need to do to address them?

And to start off the discussion, we would like to invite Dr. Patterson to chime in. Tom, are you available?

DR. THOMAS PATTERSON: Yes, I sure am.

Page 253

Thanks, Luis and Helen. I think that that's a really important area that we do need to explore. Clearly, I think, we've heard the challenges of looking at sort of our standard randomized trials and how it's really become truly almost impossible to do, so that I think we do need to look at these external controls as ways to facilitate enrollment and get results quicker so that we'll have more interest in developing drugs in the field.

I think that's been painfully clear from the discussion today, but I hope we can also move to alternative trial designs, specifically using alternative end points. I think we've seen the potential for -- in crypto, where that can happen and be very valid. I think it's been shown pretty well that those alternative measures of, like, declining counts and such have clearly not only been shown initially to be useful, but then validated by large trials which are possible, or were possible at least, in crypto and so I hope that'll happen.

I hope that'll be able to happen with other sort of markers that we can use to develop

Page 254

(sound drops).
DR. LUIS OSTROSKY-ZEICHNER: Thank you. Thank you, Tom. I see Thomas' hand up.
DR. THOMAS WALSH: Hello.
DR. LUIS OSTROSKY-ZEICHNER: Yes.
DR. THOMAS WALSH: Hi. This is Tom -- Tom Walsh. I'd like to address, and it ties in with the first question as well as the second and that is, the question of heterogeneity but also controlling for that. Granted, we've been successful with candidemia trials and those (inaudible) but unfortunately going on an extended time, but the real challenge is well before us, are the less common mold and yeast pathogens. We've heard again and again the challenges that are in those. Problems are going to be exaggerated dramatically.
If we see these as true public health risks, then clearly waiting for five, even years is just not acceptable. We have a number of registries that have been very well developed, expanding and strengthening those and using the external control strategies with even better statistical refinement

Page 255

greatly enhanced the capacity for enrolling patients robustly who have a need or the option for receiving a potentially life-saving antimicrobial agent, for example, for Lomentospora prolificans or for mucormycosis and strengthening, therefore, the external control and having the robust database can help immensely.
But aligning along with the heterogeneity, which is really also something that would need to be controlled, is the -- if we are having randomized studies, is the need for robust stratification. We're told commonly, well, you can only have two strata.
But we know painfully from the DEFEAT study in mucormycosis that if you do not stratify on the key areas of heterogeneity, it can be a disaster and can give you conclusions completely the opposite, and those conclusions are going to be -- and the need for having the proper external controls and having the proper stratification with a typical investment become all the more critical with the less common mold and yeast pathogens.

Page 256

DR. LUIS OSTROSKY-ZEICHNER: -- very much, Tom. I see Kieren has her hand up. Kieren, do you want to make a statement?
DR. KIEREN MARR: Hello, this is Kieren. Are you talking to me? I didn't have my hand up. That's old.
DR. LUIS OSTROSKY-ZEICHNER: John Perfect, you have your hand up. Would you like to make a remark?
DR. JOHN PERFECT: Well, that was an old hand, like Kieren, but I'll make a remark. Yeah, I agree completely with Tom. As I said before, my first talk was -- my first discussion was the question of external control and I think we're missing the complete boat. It's going to take time. It's going to take money. It's going to take effort. But we can extract an awful lot of information on what we already have today and put everything in the context when we study a new drug and I think to use it completely -- completely change that way, so I agree completely with Tom's statement.
I'm sorry, my hand was up for the other

Page 257

one, but same. I agree with this kind of study of external control. Very in depth of control, so we really know the patients we have. We have so many patients out there, but we're not using them adequately.
DR. LUIS OSTROSKY-ZEICHNER: We have Aaron Dane who wants to make a remark.
AARON DANE: Hi. Again, following up from Tom's comment, I think it's right that we've got some good external control data in some of the more common areas. When we go into the rarer areas, that's probably where we could derive most benefit and what it would be worth thinking about is whether we've got external control databases or whether we need to build them which are more complete.
So the idea that it should be a complete case series, for example, rather than a selected subset who -- where there's maybe more interest in reporting a case. So I think that's the important component for some of these rarer molds and these rarer areas where we might need to think about whether we've got a complete external control set or

Page 258

whether it's something we need to think about how we get to that.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much, Aaron. We have Dr. John Rex.

DR. JOHN REX: So am I -- can you hear me?

DR. LUIS OSTROSKY-ZEICHNER: Yes.

DR. JOHN REX: It's hard to know when you're on and off mute. So external controls can definitely be used here and there's an advantage, not for all of the fungal infections but for some of them in that they are relatively chronic. Acute infections do get better sometimes on their own and I'm reminded here of that paper by Fleming and Ellenberg entitled, "Why We Need Randomized Controlled Trials for Ebola."

The shorter the duration of the infection to either spontaneous resolution or any other outcome that can be influenced by supportive care, the harder it is to know what it means when you intervene in the course of an ongoing process.

On the other hand, somebody's been running along with cryptococcal meningitis for several

Page 259

months; they're not going to get better tomorrow. And when you intervene with a new agent and they -- and you bend the shape of the curve of their clinical course, it -- I know the plural anecdote is not data, but when you have diseases that are relatively chronic and that do not remit, that's just what they do in the cancer world.

This is what we do in metabolic diseases. We look at relatively small numbers of individuals with progressive inexorable processes and we say, look, they didn't get better today because of magic, so I think that we really -- I think we're underusing it, but we have to use them very selectively. Over.

DR. DAVID DENNING: Luis, can I make another point? Or Helen.

DR. HELEN BOUCHER: Sure, go ahead.

DR. DAVID DENNING: The -- I think one of the things that's tricky and I was slightly perturbed about, that is indication from the MMA that in order to take a drug through you have to have an RCT in candida or aspergillus before you could really

Page 260

study anything else, assuming that you had a mold active drug or a yeast active drug. I mean, there are clear indications for rarer infections and I think it would be really helpful for the MAA to consider somebody who had, for example, a mucormycosis only drug and how they would approach that because doing an RCT in that context would be impossible, I think. That's one comment.

And then the second, related to that, is that within a population of patients, so you might decide to set out to do an RCT in aspergillosis, but actually your drug has little merit in azole resistance or in rare species such as -- or rarer species such as terreus, which are amphotericin resistant, and you want to be able to take a subset -- preplan a subset analysis of those resistant strains with your new drug, that I don't think you'll get enough within an RCT to get that set, so therefore historically controlled parallel group or group collected alongside in other centers with a natural history of what happens in those patients, to me, would be essential to try to get that additional

Page 261

indication for not only aspergillosis but azole resistant or resistant aspergillus.

So I see multiple ways in which this might be helpful, the rare pathogens and resistant pathogens within a population as the two key areas.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much. Let's see, Karen Higgins.

DR. KAREN HIGGINS: Hi. Hi, I'm the statistical team leader working with the Division of Anti-Infectives at FDA and I agree with a lot of the discussion so far. You know, I think there are cases where externally controlled trials can be useful, but I do think we need to keep in mind, they really are weaker trials. They're not able to control for many factors.

The patients come from different sites and they're just not the gold standard as randomized controls, so as Cheryl said in her talk, having a historically controlled trial be supported by a randomized controlled trial is certainly helpful and we'd love to see that whenever possible, so we do understand there are certain circumstances where that

Page 262

would be difficult to do. I just wanted to point that out. Thank you.

DR. LUIS OSTROSKY-ZEICHNER: -- much. Let's try Dr. Bennett again.

DR. JOHN BENNETT: I had a comment about John Perfect's statement about using data from one's own institution. Looking at my institution, the problem I see is switching from one drug to another and back again, so it's hard to know what each individual drug is doing and in addition, because the data is prerecorded and each patient is different, it's fair to use the same criteria to look across sets.

So I think having external data has some value, but if you don't control for it and get the right data and there's some control over drug usage, it's very difficult to interpret the data. I noticed in the mucormycosis approval for isavuconazole, a fair number of the patients were started on the other drug first, salvage therapy if you will. When they were given isavuconazole then switched to another drug, but because an ITT, intent

Page 263

to treat analysis was used, the final outcome was recorded as if they were still on isavuconazole, but they weren't.

And I think this just indicates they probably have external data. It's not as clean as if you were trying to control it from the beginning. So that's the end of my comment. Thank you for asking.

DR. LUIS OSTROSKY-ZEICHNER: Thank you, Dr. Bennett. Dr. Nambiar.

DR. SUMATI NAMBIAR: Hi. I've been muted and unmuted repeatedly. So mine was more with stratification. I think we've heard that there are concerns with using external controls but there, in fact, might be some situations where that might be the only option. We've also heard that the need to collect the data on external control, how do we go about doing it and does anyone have suggestions on how such data can be collected in a systematic manner so that it can be available and applied in a more consistent manner. Thanks.

DR. LUIS OSTROSKY-ZEICHNER: Thank you, Dr. Nambiar. I think one of the examples of the way

Page 264

we're collecting contemporary data is the nature study that Dr. Pappas mentioned, where we're actively collecting people that failed antifungals in candida in a way that would be almost ready for a clinical trial, a way -- exactly the same way we collect data for a clinical trial.

So I think launching these types of initiatives where we're sort of intentionally collecting contemporary controls in a compliant fashion is going to get us a very long way, so that's what I would like to contribute there.

We have Dr. Botgros.

DR. RADU BOTGROS: Thank you very much. Can you hear me?

DR. LUIS OSTROSKY-ZEICHNER: Yes.

DR. RADU BOTGROS: Yeah, on the external controls, you know, what I wanted to say is of course our view is that they should never be the first choice, but we accept that for instances like rare fungi with high mortality, it might be unavoidable to have this approach. And I was thinking that maybe in view of the fact that matching the

Page 265

external control is generally difficult and difficult to interpret sometimes, whether it would not be good to have efforts focused on aiming to construct through BAFF datasets that could be accepted and used in the regulatory process. Thanks.

DR. LUIS OSTROSKY-ZEICHNER: -- very much. Back to Aaron Dane. Aaron, do you want to try to answer Dr. Nambier's...

AARON DANE: Yes, so it took me time to come off mute. So when -- yeah, in response to Dr. Nambier's question, I guess similar to the previous comment, it was -- I think one approach that could help would be if there were certain sites which were known to have a particular issue with a particular pathogen, for example, then getting complete cases with patient level data could be a way that we could do that and hear that, so that may be available already in some situations.

That could be a case where you know you've got everybody with that pathogen in question and you know you've got the level of data you need to be able to try and match them up with the clinical

Page 266

trial population appropriately and that could include prior therapies and the time on those prior therapies as important components of any comparison.

DR. LUIS OSTROSKY-ZEICHNER: Thank you, Aaron. Dr. Walsh, do you want to make a comment? Or Dr. Pappas?

DR. PETER PAPPAS: Yes. Can you hear me?

DR. THOMAS WALSH: Are you able -- yes, can you hear me? In addition to the very fine points that have been already made, may I suggest please that we appreciate that we are not working in a clinical trial vacuum. There are two areas where there -- where we could grow tremendously. One is from national -- from the National Cancer Institute efforts. There is, for example, the Experimental Therapeutics Committee for Rare Cancer. There's also the Alliance for Clinical Trials in Oncology.

There are a number of organizations that specifically focus on rare cancers without massive, randomized trials and I would just wonder whether it might be worthwhile addressing to the --

Page 267

within the FDA regulatory setting, even potentially a combined conference as well as perhaps pioneering in deficiencies where clearly there are -- there's little opportunity, especially for the metabolic diseases, to be able to do robust randomized trials to use some of the -- to adapt some of the regulatory and statistical models that they employ.

This is not the first time that we're looking at rare diseases and, in that regard, it might inform us in terms of subtleties of clinical trial design, and also rationale and president that we haven't used. That's one.

Two is jumping ahead a little bit, but there -- as proof of concept and working with rare molds, rare yeasts, multidrug resistant organisms including auris, if we are working in the context also of preclinical data, strong preclinical models, redundant, consistent PK/PD driven model systems that are also co-spaced, it provides a reasonable underpinning of proof of concept that the results that are being seen in clinical trials are not just random error.

Page 268

That good outcome, if it does correlate well with the clinical -- with one's preclinical research, provides the reassurance in that regard. For example, with you look at isavuconazole, as Dr. Bennett said, yes, there were significant limitations, obviously, in that clinical trial design. But we're talking about a deadly, life-threatening disease for which we really have no other therapeutic options other than a nephrotoxic agent, which sometimes works.

And that is the robustness of the preclinical data, and one of the reviewers at that time said, yes, I understand the limitations of the clinical dataset but "I am persuaded by the preclinical data." Our EMA colleagues do take a very robust approach and quite often a working translation, we're asking ourselves is this working.

Is this working in the dose and in the host in well-developed preclinical models to ostensibly be able to interpret limited clinical data, so I think integrating that into our decision making can help immensely.

DR. LUIS OSTROSKY-ZEICHNER: Thank you,

Page 269

Tom. Pete, you wanted to say something?

DR. PETE PAPPAS: Yeah. Yes. I've heard what everybody's said and I want to kind of go back to what John said, and I particularly -- I mean, this particularly relates to candidemia. One of the comments that I made during my presentation is really the sheer numbers of patients who are screened but don't get enrolled into candidemia studies.

In every one of our annual meetings or biennial meetings, we have always put as a priority and unfunded priority, the -- our capacity but kind of inability to capture what happens to those patients who are screened for but never enrolled into a candidemia study.

And again, the ratio is, I think on the low end, 1 to 10. On the high end, it may be 1 to 50. So for every patient that's enrolled, there are somewhere between 9 and 49 patients who are not enrolled for candidemia, for a variety of reasons that don't have to do with patient just refusing consent. The understanding -- our understanding has been that there is tremendous value in really understanding what

Page 270

happens to those patients, particularly at sites that are already participating in a clinical trial.

Understanding what Jack Bennett said, too, because there's a lot of heterogeneity in these patients in terms of coming on and off drugs and so forth, but surely we can -- well, again, we won't know until we gather data, but until we gather that data and are incentivized to do it financially and then -- and therefore given the capacity to do it, we're really missing just a huge opportunity to find out what happens in the real world and really understand what the outcomes really are in these diseases, and whether it's candidemia or other rare molds doesn't really make any difference, but capturing those patients, the data pertaining to underlying diseases, treatment, and outcome can -- the limiting factor here is not a lack of interest.

It's not heterogeneity. It's really nobody gets funded to do that, no companies and no institutions pay for that kind of information, which I think is really a treasure trove and it's something that we're -- we just have always overlooked and I

Page 271

think everybody recognizes that we're not really seeing maybe the true picture of candidemia outcomes, et cetera based on our clinical trials alone. That's all.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much, Peter. Before I turn it over to Helen, I'd like to see if Tom Chiller wants to chime in and discuss, is there any databases that the CDC that have sufficient granularity where they could be used as controls?

DR. TOM CHILLER: Yeah, thanks. Thanks, Luis, and I'm just here listening to the discussion, I think, more than anything else and learning from all you guys who are out there battling these clinical issues. I think from the CDC's standpoint, we would like to figure out, because this is -- I think as Tom Walsh and others have described, because this is a unique population, a unique bunch of diseases that are quite different, some of which are more rare than others, it just lends to us working together as a community to when things are -- when trials are conducted or tried to be conducted, we

Page 272

can't try to learn from what's happening with that data, I think just as Pete was alluding to, for example the 9 to 49 patients with candidemia that never make a trial, someone needs to be looking at that data (sound drops) et cetera.

So I think that's the role for our group and working with others, is to try to look at that. There are lots of problems with big data, as you know, and with hospital data, trying to characterize definitions, but I think we continue to try to look at that data to at least be able to inform you guys on what's out there on risk factors and on what populations might be worth studying.

And I think one of the things we've been surprised about in looking at mold surveillance, and we're only doing this in one site in Atlanta, is that the classic patients that we all describe as getting mold, these transplant patients, these patients with leukemia, et cetera, are the overwhelming minority of patients that are coming out in our surveillance study.

So it's more steroids, chronic lung

Page 273

disease, et cetera. It's -- so a lot of the studies that we do looking at these infections are done potentially in a very minor part of those who actually are getting these infections in our hospitals. I know you all know that, but it's interesting to see it play out in pretty rigorous surveillance, albeit in one site.

So, yeah, I don't have great insight into harnessing big data because of all the limitations, but what I do think we ought to be doing is working together on this and trying to squeeze as much out of any study, pre-study, et cetera that we do so that we can inform the next one.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much, Tom. Two quick more comments before I turn it over to Helen for the next question. One is from Mike Hodges.

DR. MICHAEL HODGES: Yeah, just a quick one on the external controls or historical controls. We want somewhat of an external control. Two drugs have been approved. Two antifungal drugs have been approved using external controls. One, caspofungin,

Page 274

one isavuconazole. The latter used a database called Fungiscope from University of Cologne, and that database is still up and running and still increasing patients' data into its database as we speak. So it is contemporaneous.

DR. LUIS OSTROSKY-ZEICHNER: Thank you. Thank you very much, Mike. And final comment of this question, David Angulo.

DR. DAVID ANGULO: Thank you, Dr. Ostrosky. So a provocative question here regarding what could be the right source for this external control and I do wonder, are there regulatory datasets that have been used for approvals previous drugs, a potential source of external controls.

Because if those datasets are extraordinarily comprehensive, many of them may be relatively recent and probably regulatory agencies are the ones that have in their hands the largest amount of data about issues of invasive candidiasis and outcomes, risk factors, et cetera, invasive aspergillosis, so is there any possibility to have access in some way, supporting not a specifically

Page 275

particular drug, to a particular study, but is there any way that that information that has been collected by multiple sponsors can be leveraged to facilitate the development of other antifungal agents in the future.

DR. LUIS OSTROSKY-ZEICHNER: All right --

DR. DAVID ANGULO: Thank you.

DR. LUIS OSTROSKY-ZEICHNER: -- David. I'm going to turn it back to Helen for the next question.

DR. HELEN BOUCHER: Great. Thanks very much, Luis. Great discussion, everybody. We're going to turn our attention now to children and ask about novel approaches and strategies to facilitate development of antifungal therapies for children and I thought we might ask Dr. Tom Walsh to kick off this part of the discussion.

DR. TOM WALSH: I want to first ask as to whether Aspasia is available. Aspasia Katragkou is completing her second chief residency now at Queens Hospital in New York Presbyterian Hospital System, but

Page 276

was also assigned to outpatient today, so Aspasia, are you on the line? No, hearing not. So I'm then taking Aspasia's role in trying to address this really important question. Certainly, the strategies that we have taken previously and I think the overarching effort given the population of newborns, premature infants, toddlers, children, adolescents is to provide a tangible benefit wherever, whenever possible.

That has been the overarching approach that we've taken in 14 different clinical trials, pediatric clinical trials for antifungal therapy. You have to ask, where might that be. Obviously, for defined interactions, that's as possible, but before we do so, we need as Aspasia described, a really solid foundation for the pharmacology and classic safety tolerability PK.

And we talk about heterogeneity and nowhere is it really so vitally important as to recognize the different age groups, and so there is a neonatal network that's chaired by Dr. Danny Benjamin, which has certainly been tremendously successful and that would really be the best place in which to

Page 277

characterize new antifungal agents in the newborn population.

The timing of that, though, really depends largely upon the findings in the older population, in which case, then you're looking at patients usually between two to 12 years of age and that might include a stratification, then, in the adolescent population. Historically, we've attempted to provide the benefit in pediatric oncology, particularly in a prophylactic or an empirical setting, increasingly would use prophylaxis for ease and practicality and its comparable efficacy, and so in that regard, one can envision a target population in AML, treatment for blastic leukemia, patients where there are already adult data, where we can have specific centers, we'd have our consortium. There are other consortiums as well and with that, collaborating with our industrial partners and a classic dose escalation cohort design.

Those studies can be done relatively efficiently and yield tremendous -- tremendously important data. As Aspasia indicated, there is

Page 278

considerable interpatient variability, for a number of reasons that she articulated. But with that, with proper modeling, one can usually obtain, especially based upon good preclinical data and the preexistent patient population of adult data, in part a dosage that would hit target attainment.

The next question, though, now that we know the dosage, in which populations do we aim to show some efficacy? There are different regulatory requirements and I will defer to our colleagues insofar as what those may be, depending upon the requirements of the compound, but nonetheless, we do need that experience in target populations. And with that, we really look toward the networks that have been established both in Europe and U.S., in order that we can identify patients and who might those patients be: certainly, oncology but also primary immune deficiencies, patients with cystic fibrosis, many of the medical and surgical patients who are hospitalized. These are the common conditions that we encounter in typical case series.

Ultimately, it requires an approach

Page 279

that we work way, way and against anticipation as we see new compounds beginning to be approved and not wait for the regulatory approval, but instead already contemplating which patients may benefit and which would be the likely organisms that we should target with a given compound.

DR. HELEN BOUCHER: Great, thanks very much. Laura Kovanda.

DR. LAURA KOVANDA: Can you hear me?

DR. LUIS OSTROSKY-ZEICHNER: Yes.

DR. LAURA KOVANDA: Okay.

DR. HELEN BOUCHER: Yes.

DR. LAURA KOVANDA: So thank you. I just wanted to make a couple of comments, having been through the pediatric development for a couple of different compounds now and through some challenges in this effort. I thought I would just echo one -- what Tom said with regard to the PK/PD and understanding that exposure response relationship in other populations, especially when very good evidence in either animals or in adults to bridge.

And the other is the challenges with

Page 280

regard to enrollment and if I go back to some of our experiences. Once you're able to establish the PK and you're able to do that, maybe if you're lucky to do that, in the setting of a prophylactic population, but the enrollment can go quite well as Dr. Walsh alluded to, but as we go and we need to explore as we are with CRESEMBA, in the population that really needs the drug and at a dose that we hope to recommend in the future, that is in a population that requires therapy.

So now we're talking about a very -- even more rare than in the population that -- adult population where we already did a randomized controlled trial so I thought I'd just share maybe an opportunity that we thought that we at Astellas could pilot and we're working with the International Pediatric Fungal Network just more recently to enroll in our trial and in a way that hopefully can be a little bit more innovative with smaller set of sites but allow for an expedited startup process.

It sort of requires us to be more nimble on the sponsor side and work harder to find patients, but it allows the patients' physicians to

Page 281

sort of come to us almost in a compassionate use sort of setting where you allow the physician to come to you versus already having the site set up.

We just started the pilot and we haven't had anybody knocking on our door, so to speak, yet. But we're hoping that this could eliminate the need for a large global trial where we see some of these sites to get 30 patients across the globe, and hopefully that could be an option in the future, working closely with these networks.

But I will say, at this point, it's just a pilot and it requires a lot of -- basically 96 hours from diagnosis to start of the study drug, so it's not a very long time to get the paperwork involved completed. But I thought I'd share that.

DR. HELEN BOUCHER: Great. Thanks very much, Laura. Luis, back over to you.

DR. LUIS OSTROSKY-ZEICHNER: Thanks, Helen. So question four is please discuss if consideration should be given to pooling different types of fungal infections or whether there are enough differences between the species to warrant separate

Page 282

studies. Also discuss if there are important considerations with the body site as seen with antibacterial drugs. And to kick off the discussion, we would like to invite Dr. John Rex.

DR. JOHN REX: Is -- sorry for the delay, but my microphone has now been turned on. Thanks, Luis. You know, there are -- so the answer to this is both yes and no. There are times when it is appropriate to think separately if you've got really disease patterns. You know, cryptococcus has got a really different disease pattern from aspergillus. But separating by shape and color also has its limits. I mean, is aspergillosis really different from scedosporiosis? And is that really different from fusariosis? I mean, you know, sometimes, they spread a little bit differently in the body, but at the end of the day, they are filamentous fungi and if you've got -- and it doesn't come down to just, as Paul Ambrose would say, "It's the MIC, dummy."

And interesting, if you say -- if you insist on, I want separate data for scedosporium, scopulariopsis, rasamsonia, and name two other rare

Page 283

ones, you'll never have anything for anything. I mean, it really is not -- it's not even helpful to say, gee, every fungus has to be studied by itself. There are a few that we can study reasonably well and maybe -- they may really reduce to three: candida, crypto, and aspergillus. Those are the only three that you can study in a large enough scale to fully understand them, I'm just saying, the list may stop. There may have been more chosen, but there aren't many and so the vast majority where we have -- we (inaudible) mucor, no I don't see how you can do a randomized trial there. The (inaudible) common aspergillus, you're not going to do that. And on body sites, I come back to my heterogeneity comment from earlier. I think body sites, they are different. Not going to deny that, but you need to leverage what you know about your compounds and there's actually value in collecting heterogenous patients.

Fungi don't stay put. We know aspergillus can involve pretty much any part of the body. And in actually collecting some information in which you've got somebody with osteomyelitis and

Page 284

somebody with a brain infection as well as somebody with a pulmonary infection, I think, is helpful because that's the kind of stuff that when we're taking care of patients, we have to know.

The fact that it's -- that the disease the patient presents with -- name a fungus and body site that's not in the label. I can't look at the patient and say, oh, I'm so sorry. We can't treat you because you're not in the label. We actually have to do what we can do. And I think we should be trying to collect those cases and I think the more diverse the dataset we represent in the label and in our collective publications about the data, the better off we are because the fungi are very diverse and each one of them is so rare. Over.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much. We have Dr. Shawn Lockhart from CDC wanting to make a comment.

DR. SHAWN LOCKHART: Yeah. So in actuality, we really already group them together in general groups, because I mean, we say, oh, well, we're studying candida. But candida is not actually a

Page 285

genus. Candida is huge. It's just a group of yeasts that don't have sets. It's this ginormous polyphyletic group that includes everything from saccharomyces up to Candida auris and down to these meyerozymas and these pichias and these hortaes and all these really diverse yeasts, and yet we just call them all candida because that's how they're lumped together and we treat them as, okay, this cures candida.

So in a way, we're really already doing that, but the other argument is if you have a drug that seems to work good against dematiaceous mold, how long is it going to take you to find enough dematiaceous molds, and quite a few of them react the same way, at least, in vitro to drugs and I think grouping them in those general ways is about the only way you're going to do some things.

Do we separate rhizopus and mucoid? I don't think we can do it and have a trial. It was hard enough to get 12 cases, so how are you going to get 24, if you have one rhizopus in there -- in your study and one mucor? So I think they have to be at

Page 286

least roughly grouped.
DR. LUIS OSTROSKY-ZEICHNER: Thank you very much. Any other comments on this question? We have Dr. David Denning from across --
DR. DAVID DENNING: Yeah --
DR. LUIS OSTROSKY-ZEICHNER: -- Atlantic.
DR. DAVID DENNING: Yeah, I've got one comment. I think there are a couple of situations where you would naturally group. Mycetoma is an example. There are quite a lot of fungi that cause mycetoma. They're not easy to grow and even more difficult to identify and -- but the immunological and the histopathological characteristics are fairly distinctive, so you could definitely enroll those and then you could look at -- that's happening, of course with the ravuconazole study which is ongoing, primarily in Sudan.
I think the same could be true for chromoblastomycosis, so it, like mycetoma, these are both neglected tropical diseases with the WHO, so I think that would be helpful. I -- if one was to do a

Page 287

study in mucormycosis, I think it's inevitable that they're grouped, but -- and the disease patterns, not only are the fungi different, but the patterns are different, of course, so you have primary rhinocerebral, but you also have other patterns of disease, particularly pulmonary, but also cutaneous.
So you're going to mix and match study different patterns of disease, different underlying diseases such as diabetes or leukemia or whatever, as well as different pathogens. And I could imagine a study where it wouldn't be difficult -- it wouldn't be easy to do, of CNS fungal infections which would include maybe taking out crypto, but you could have a whole load of different dematiaceous fungi, aspergillus, (inaudible) mucor, (inaudible) and so on, and they can all be grouped together and look at the outcome, because that's a difficult diagnosis to get to fast, and speed of treatment is very important, and then you try and sort out the different pathogens later.
So I can see that there are definitely some indications where I think this would be the right

Page 288

thing to do, but -- medically, but also from a strategic drug development perspective. But obviously, not everywhere.
DR. LUIS OSTROSKY-ZEICHNER: Thank you for that comment, David. We have Mike Hodges again.
DR. MICHAEL HODGES: Yeah, hi. Question for the panelists or perhaps George Thompson as well. What about grouping the endemic mycoses? And also another question, what about grouping talaromyces with cryptococcus? Thank you.
DR. GEORGE THOMPSON: Yeah, hi, this is G.R. Can you all hear me now?
DR. LUIS OSTROSKY-ZEICHNER: Yes.
DR. GEORGE THOMPSON: I do think that the endemic mycoses really are one of these pathogens that really should be grouped together for the purposes of study. There's tremendous heterogeneity in these different groups. Some are immunocompetent. Some obviously are not, and then the host immunology is vastly different between these different patients who, for example, a Filipino patient may get just severe cocci meningitis whereas other ethnicities

Page 289

handle it different immunologically.
So it may be very difficult to tease those groups apart for purposes of a trial, and we've been fairly successful grouping these together with -- MSG 15 study is ongoing, doing quite well. There's a number of others sort of in discussions for development, so I do think they really need to be put together for the purposes of these trials, given the difficulty in not doing that. And then the question about crypto and talaromyces, I think the conduct of those studies is actually fairly similar as far as the ability to look at CFUs and some of these things as surrogate markers of endpoints, but probably would defer to David or John Perfect for that as well.
DR. DAVID DENNING: Can I make one more comment on that? I think one of the challenges is that particular grouping is that most of the patients are HIV, and we now know that we need to delay ART in crypto cases, but we don't delay it in talaromycosis or histoplasmosis, so I think there might be a very technical reason for not grouping them there.
DR. JOHN PERFECT: Yeah, I agree. I --

Page 290

DR. LUIS OSTROSKY-ZEICHNER: Go ahead, John.
DR. JOHN PERFECT: Sorry. Sorry, that thing went off and on on me. Mike, I'm shocked you said, I thought talaromyces. The pathophysiology, the organism, the -- and crypto would be pretty dramatically different. Sites on infection would be different and I wouldn't put -- I'd split the talaromyces with -- closely to end endemic mycosis with HIV, but I don't think there's things go together, personally.
DR. LUIS OSTROSKY-ZEICHNER: Thank you, John. Pete Pappas.
DR. PETER PAPPAS: -- muted.
DR. LUIS OSTROSKY-ZEICHNER: We can hear you now.
DR. PETER PAPPAS: Thank you. Thank you. No, I just wanted to agree with G.R. and John. I think endemic can be studied together. I think they are rare enough but also similar enough that they can be grouped and cocci is the one that kind of stands out to me that's -- of course, they're all unique, but

Page 291

cocci does kind of stand out as being sufficiently different than -- maybe you can study it by itself, but you can -- you certainly can include paracocci sporo, even some of the newer endemic mycoses.
I'm not sure that -- I mean, the newer forms of blastomycosis that have been described, I think they're all similar enough at this point that they -- in order to study them, they sort of have to be grouped. That's all I wanted to say.
DR. LUIS OSTROSKY-ZEICHNER: Perfect. Thank you very much. I'm going to turn it back to Helen for the next question.
DR. HELEN BOUCHER: Great. Thanks very much, Luis. So we've heard some allusions to PK/PD, and now we're going to get to talk about PK/PD. So the question is, what is the role of supported preclinical animal models to provide proof of concept that an antifungal agent is active against uncommon fungal diseases, for example, scedosporium, fusarium, et cetera.
And I thought we could ask William Hope to kick this one off.

Page 292

DR. WILLIAM HOPE: Thank you, Helen. I'm not -- this is difficult, isn't it, because we don't really have the preclinical tools that we have for candida and aspergillus and cryptococcus, so I think at the end of the day, that's all the preclinical models do offer is, it is supportive and I think that our main tactics still have to be to generate deep knowledge in preclinical and early phase clinical studies in one of those three main diseases, not only because they're most important numerically, but because we have the most robust tools to start there and then if there are other -- for those rarer diseases and there are some models, but they're much less...
DR. HELEN BOUCHER: William, we lost you. Okay, we'll give William a minute to see if he can reconnect. Erin Zeituni, did you want to add any comments in this regard?
DR. ERIN ZEITUNI: Thank you, Helen. I was waiting to be taken off mute. Very excited to hear all of the comments from this panel. This has been excellent. Thank you all so much.

Page 293

I think this is a conversation that's very familiar to a conversation we're having in bacterial models for hep and bap for resistant bacteria where you have these rare patients to try to access and the possibility of having preclinical models so the supportive data to support those trials, so it's a conversation that we're continuing to have there and I'm curious to hear what the panel thinks about it in this context.
DR. HELEN BOUCHER: Great, thanks very much. William, were you able to reconnect?
DR. WILLIAM HOPE: Without problem, yes.
DR. HELEN BOUCHER: Great, go ahead.
DR. WILLIAM HOPE: I'm not -- I didn't hear the last contribution, but I don't know whether -- how much you heard. Was I -- sorry, I apologize, speaking to myself for five minutes, but well my main comment was I think that the first models of rarer molds have relatively little to offer because (sound drops) than for candida, aspergillus, and cryptococcus.

Page 294

So the majority of the preclinical dose exposure response relationships have been established in those very well-validated and characterized model systems.

DR. HELEN BOUCHER: Great, thanks very much. Luis, I'll hand it back over to you.

DR. LUIS OSTROSKY-ZEICHNER: Thanks, Helen. So question six is "Discuss how clinical trial networks can facilitate antifungal drug development and some of the barriers to establishing such networks." First, I'd like the current president of the mycosis study group to --

DR. JOHN PERFECT: Okay, Luis thanks for the opportunity to talk about the clinical trial network. Actually, the mycosis study group has done this for many, many years. I think it's still very effective at doing that. I think that one of the things I actually believe is that there needs to be a more even robust clinical trial network.

Have to realize that what we have here is evolution which no one really talks about which is dealing with the infrastructure of all this, more and

Page 295

more regulations, more and more coordination, various things.

It's very, very costly and very, very expensive for many of these systems to actually get up and by the time they get up, the study's over or you don't get any patients and stuff like that, so the networks that we do today have been kind of ma and pa operations and stuff like that, and the truth of the matter is, the amount of demands on them are so incredible today that it can't be ma and pa. They don't have the resources to be ma and pa.

So I think clinical networks are extraordinarily important, but I think coming down to one big word, which is money. Is somebody going to take the time and effort to set up clinical trials, whether it's in the United States or Europe, a series of places, because there's big places, have tremendous amount of fungal infections and we're not utilizing them very well because the infrastructure is hard to keep up.

But I think that antifungal development needs to go into that group, just as I said with

Page 296

external controls. If they had money and things, they can suck all that data out. It just takes a little bit of time, but they can see what they're system is and then bring new patients in and have a system set up to actually be pretty facile, be pretty quick on it.

So without going farther with kind of details with this type of stuff, I think that on a practical basis, I think having trial networks that are ready and robust and can do these kind of things is actually the wave of the future, just as you had cancer centers and stuff like that, you have fungal centers that have all the abilities, if they're supported with an infrastructure, that can move very, very fast on these things.

Surely, the patients are there. That's not the problem. The problem is actually funding the infrastructure and coordinating it.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much, John. We're going to go with Pete Pappas and then after him, John Rex. Pete, go ahead. Go ahead.

Page 297

DR. PETER PAPPAS: Thank you. Thank you. I like what John says, and of course, obviously, we believe in networks. I think the MSG was the first real successful clinical trials network and what you're really asking for is administrative support. That is, if the system that existed and could exist now includes one where companies can innovate, people can think, people can create new compounds.

There's a huge incentive now or a better incentive now to create these new compounds by virtue of the Gain Act and other initiatives, making it a little bit easier and more profitable to develop these, but you still need -- and I agree with John. It doesn't have to be one network. I mean, there could be multiple international networks, but as it is right now, certainly within the U.S., I mean, the MSG serves a purpose now of consulting with a number of different companies how to design this particular trial, which are the best sites historically that perform.

I mean, these are the sorts of things that could be enhanced, could be tremendously

Page 298

buttressed, and MSG could not only -- or a clinical trial network, whatever you want to call it -- could be empowered to go out and train sites more than we do instead of simply relying on the same sites, because quite honestly, one of our roles has to be the training of the next generation of clinical mycology experts.

Our group is a group that's growing older and there has not been an incredible influx into our discipline, as say, there has been, you know, hepatitis C or HIV. There need to be that kind of investment. I mean, this -- these are collective -- collectively, this is a public health issue, a major public health issue.

And there's been not a lot of investment on the part, you know, the government in terms of supporting these networks. We have done it mostly on our own and we have, to the extent that we can, gone out and tried to lasso in some of the better international sites, but certainly not all of them. And even not all of the national -- of the U.S. sites.

But, I mean, these are the types of

Page 299

things that a network can do that can facilitate the conduct of these trials, even run simultaneous trials, give the best advice that can be given to entities, including competing entities. And getting back to another point, we have just a huge, huge denominator of patients who are screened, never enrolled, and then we don't know what really happened to them.

The individual investigator pretty much has to do that on their own and there's no collective or community effort to do that because the funding is lacking. So lots of opportunities. Most of them are being missed by -- through really, lack of funding and I agree with John. I think the main issue right now is administrative support, funding, and how to capture those patients in detailed registries that otherwise escape us.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much. Very thoughtful. Dr. Rex.

DR. JOHN REX: There we go. My microphone's on. So I want to broaden this just a little bit and go back to some of the things that Laura Kovanda said. She pointed out the cost of

Page 300

developing drugs and from the moment you've got a molecule that actually is looking like it probably is a drug, you only need another $100, $150 million to get it to initial approval, and then you only need another few hundred million dollars to keep it on the market, manufacture, do the pharmacovigilance, and do all the pediatric requirements and so forth that keeps it on the market.

Those are big numbers and the theme for this whole community to pay attention to is the notion that the antibacterial enterprise has fallen flat on its face because of the economic of antibiotics. Five of the last 15 antibacterials that were approved in the United States, the companies behind them are now bankrupt.

Antifungals might have a little bit easier of a path because the unmet need is a little crisper for a period of time, but you get one or two interesting new compounds approved and all of a sudden, there will be no new antifungals because there is no reimbursement for them. And the theme that I would like everybody to start to pay attention to is

Page 301

that the lessons in the antibacterial world about the need for appropriate polling centers, and that was briefly mentioned by Laura Kovanda, and let me just decode that.

This is the idea that we pay for new antimicrobials in the same way that we pay for fire extinguishers, fire departments, and life insurance. That is, we don't get up and say, gee, I think I'll buy a fire extinguisher because my house is on fire. We actually buy on in advance of my house catching on fire and we're actually pleased to have it, even though my house doesn't catch on fire.

And antibiotics need to be paid for in very much that same way. So when you come down to this idea of funding clinical trial networks, we've looked at that exhaustively. We funded antibacterial networks through the New Drugs 4 Bad Bugs Project in the United States, the ARLG and the -- I'm sorry, the E -- ARLG in the United States.

And for a while, you can keep them going, but if they don't have things to work on, the gas runs out of the car and the car comes to a stop.

Page 302

And the way that you have stuff to work on is you've got industry able to actually bring products forward and get them appropriately reimbursed. So it's a very deep pocket with -- we've touched a few times in the cost of doing this work, the costs are serious and it's important that we as a community speak clearly and frequently to the need for appropriate reimbursement for new antibacterials and antifungals.

And I commend to you a variety of materials on this and I don't mean to be self-serving, but if you follow the -- my AMR Solutions newsletter, you'll learn about this over time. There's some great stuff in the Lancet ID recently about this and we want to pay -- look at the writings of Helen Boucher about New Drugs 4 Bad Bugs, look at the writings of Neil Clancy.

So please pay attention to this, because otherwise none of this stuff will stay active. It'll work for a little while, but then it'll run out of steam, so, over. Thank -- sorry about the rant but thank you for listening.

DR. LUIS OSTROSKY-ZEICHNER: Thank you

Page 303

very much. I'm going to turn it back to Helen. There's some questions in reserve we have.

DR. HELEN BOUCHER: Great. Thanks very much, Luis. So we thought that was difficult. Now let's talk a little bit about susceptibility testing. So the question is, how can we obtain data that can adequately support susceptibility testing, interpretive criteria for new antifungal drugs, in general? And then second, what is the role of interpretive breakpoint in developing drugs for cocci and what is the impact of that pathogen being BSL-3?

So two questions in the breakpoint category that we can put out. And let's see, if nobody raises their hand, Dr. Patterson, do you want to take a stab at that to kick us off?

DR. THOMAS PATTERSON: -- give that a -- - yeah, so I think that that's a really important question, you know, from the fungus testing there in the study that G.R. led with Nathan. They looked and showed a number of strains of coccidioides that were -- - that have higher MICs to fluconazole. It's kind of our clinical opinion that that's relevant, but it's a

Page 304

hard question.

It's not with -- such a chronic disease, it's really hard to sort that out, but I think with more agents coming along with activity against a number of these disease -- in these diseases we've talked about is really going to be important to try to sort that out, and I do think that preclinical models can help answer that question to get rid of some of the heterogeneity, of course.

With cocci, it's harder because there are not very many groups that work with cocci now because it's really hard, too. It's hard in animals and so I think those are -- make it more expensive and more difficult to do, but I think it's still a really important question. G.R. may want to comment.

DR. HELEN BOUCHER: Sure. G.R., do 3you want to comment?

DR. SHAWN LOCKHART: So going back to the first question, unfortunately the way the CLSI works, there really aren't going to be any breakpoints for most bug-drug combinations unless there's outcome data, and I see that as a real problem and one that

Page 305

UCAS seems to have moved past, at least to some degree.

But right now, as far as the CLSI is concerned, without outcome data, they are not going to establish breakpoints and so we're always going to have relatively few breakpoints and we're always going to be dependent on clinicians' intuition, so to speak, for deciding whether or not an MIC of 2 to drug X is going to be efficacious in a particular patient. So that is a handicap of the way that the system works in the U.S. right now.

As far as cocci testing, in preclinical trials, I think it's a great idea, but it's never going to go beyond that. Being a BSL-3 agent, no one's going to do cocci testing in their laboratories in their hospitals or probably not even in most reference laboratories outside the fungal testing laboratory.

DR. HELEN BOUCHER: Great, thanks. And just for the record, that was Shawn Lockhart, and now, G.R., you're up.

DR. GEORGE THOMPSON: Oh, they unmuted

Page 306

me. So I think that cocci is an example of how this investigation has gone backwards. So, you know, we had sort of salvage studies. We have one randomized trial and then we looked to try to explain the results of that ITRA versus FLU study by looking at, you know, large scale susceptibility testing almost 20 years later for all the reasons that Shawn just illustrated. You know, in vitro testing is pretty difficult. You do it in the (inaudible) form rather than the spirulina spore form, so there is some criticism with that as well.

But, you know, this week, we found -- we think the in vitro results sort of line up with what we found clinically. MIC-50 for flu was 8 compared to very low MICs for the mold activate azoles, so -- and we think that explains pretty nicely why ITRA basically beat fluconazole on the animal study.

So I do think that this is important. I agree with Shawn, we're probably not going to have outcomes data. I think that as a clinician, I think that's fine. We're forced to do that on a regular

Page 307

basis in the care of patients with other fungal infections, too. But I think that this does sort of illustrate the importance of in vitro testing, animal models, and then seeing if we sort of agree with that by just clinical acumen. I'll stop there.

DR. HELEN BOUCHER: Great, thanks so much. So Dr. Denning next and then back to Luis.

DR. DAVID DENNING: So just a quick comment about the aspergillus world where with the azoles, we now can detect resistance without growing any organism at all using either the diagnostic PCR or para-sequencing, in our lab, and I think there will be others who can do that.

I would really like to see the regulatory team address this issue of non-culture based resistance detection as opposed to depending upon culture, because I think this is a very important new area of development and something that would really accelerate the development of drugs for resistant pathogens. We have just written a -- published a paper on high volume cultures for aspergillus in respiratory samples for patients with

Page 308

allergic and chronic disease.

I suspect it will also be true for invasive disease, but it's harder to generate the data, and if you use a much hard -- larger volume, you get many more cultures and then you can do more susceptibility testing. So there's also a need, I think, for those organizations that approve laboratory methods and care about such things to adopt a much better, more sensitive systems for culture than are there.

So it's a call for better culture and it's a call for using non-culture and resistance detection as part of our regulatory approach in the future.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much, David. We have two specific questions from the audience. The first one is, "Can NIAID Preclinical Services provide access to specific antibodies?" I don't know if you want to answer that, Erin?

DR. ERIN ZEITUNI: Sure, thank you. And thank you to the individual who submitted that

Page 309

question. So it's a little bit difficult to understand exactly what they're looking for, but as far as access to antibodies, if those antibodies are found in the BIV sources, it would be something that you could have as available.

If you're looking for development of antibody program, a biotherapeutic, we do support those programs, but without additional information about exactly which specific antibody they're looking for, I would just encourage that individual to get in touch with us and we could very happily discuss it more.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much. The final question we have is, "Please elaborate on FDA EMA differences in the weighing of preclinical data." And I'd like to invite William Hope to start off the discussion there.

DR. WILLIAM HOPE: Thank you, Luis. So I -- this is slightly sensitive, isn't it? So I'll just try and keep it as general as I can. So I think -- and I'm going to talk about everything that I've witnessed. I think that in the U.S., there's been a

Page 310

lot of interest in using survival in laboratory animal models and that's both in antibacterial as well as in antifungal drug development.

And in Europe, there's an interest in using complex in vitro systems like (inaudible). So I think the way, just on reflection, that -- and as I've tried to say in my talk, there are two separate but completely complimentary systems, and that is, there's useful information from a PK/PD perspective, trying to understand how the drug is docking with its target.

And then there's the more clinically relevant, if I could use that term, model systems, the rabbit model system, for example, where survival actually may be very reasonable and clinically relevant endpoint, so I think that what people are sort of expressing, this range of model readouts, but I -- we had similar model systems and we had so many biomarkers.

I do not believe that they delayed quota in terms of one being any better than the other. They should be views as a complimentary package. But the problem, of course, these model systems are

Page 311

expensive and they are very time consuming and so if you go down one path with one agency and then get told to do a whole other experiments down another path, that may cost six or 12 or more months and a lot of money, so that -- I think there could be a degree, given that the reliance on these model systems to get them maybe better aligned as has happened in other contexts.

DR. LUIS OSTROSKY-ZEICHNER: Thank you very much for that answer, William. With three minutes to spare I'm going to turn it back to the FDA. Dr. Yasinskaya's going to do a summary and closing remarks. Thank you very much.

DR. YULIYA YASINSKAYA: Thank you very much. Good late afternoon to all of you. This was an amazing discussion, presentations, and very robust discussion today on what development consideration we have for antifungal drug development at -- for the drugs that aim to address unmet medical needs.

The major takeaway from today's presentation discussion, you know, given that we had a very ambitious agenda and very loaded questions for

Page 312

the discussion, that the most immediate unmet medical need is obviously for delayed-resistant factory molds, both that developed acquired resistance and had innate resistance to antifungal therapies.

These invasive fungal diseases are rare and have high morbidity and mortality (inaudible). We have issues of adequate antibacterial (inaudible) of activity and also potential difficulties in attaining efficacious exposure in target organs, have problems with drug-drug interaction, specifically for azoles, given their metabolism -- metabolic pathways and also organ toxicity that eventually result in poor outcomes both in clinic and on clinical trials.

Obviously, underlying diseases, immune suppression, site of invasive fungal diseases, as well as propensity to dissemination affect the management and pose therapeutic challenges.

So we also know that there are a lot of difficulties now in enrolling even in, you know, common, in these candidiasis, invasive aspergillosis studies in very efficient manner.

(Inaudible) put strains on the

Page 313

scientific community, investigators alike, and investors as well. So the existing clinical trial framework appears to be time consuming and costly, so we're looking for more efficient ways to conduct medical trials. And while such standards for approval of antifungals for common and uncommon invasive fungal diseases do not change, regulatory agencies in the U.S. and across the pond are willing to exercise flexibility in accepting smaller data packages and additional supportive both clinical and nonclinical data.

We cherish our collaborative efforts, public and private partnerships, and engagement with stakeholders along with the robust scientific research and evolving understanding of natural history of invasive fungal diseases and their response to the therapies, both in clinical and nonclinical models and these will help inform and more streamline approaches for antifungal development.

We think that alternative clinical trial design and use of biomarkers to select trial participants as well as monitor their responses to

Page 314

therapy are critical for future antifungal development for invasive fungal diseases. We know that pediatric population is a therapeutic orphan population and as the diseases -- antifungal diseases, invasive fungal disease are -- generally have orphan designation, pediatric population tends to be left out.

We commend Astellas and other companies that take it upon themselves with help of BPC as well to take upon themselves and evaluate pediatric patients with the invasive fungal diseases, both in the randomized controlled setting as well as in investigating nonclinical models and also conducting very thorough PK/PD assessment to inform dosing in pediatric patient, including neonates.

So we might consider animal models going forward to inform dosing specifically in neonatal patient population, but that would also need reach PK and safety data. We also need to consider when we're thinking about developing trials -- clinical trials for invasive fungal diseases, we need to think about emergent multidrug resistance pathogen with ability to spread extensively in healthcare

Page 315

setting and/or complicate viral infection in the many healthy ventilated hosts such as flu or COVID-19.

What we have learned today, what -- clinical models and their routine and potential notable uses is that of course we use (inaudible) proof of concept studies and also in those (inaudible) PK/PD modeling support clinical trial just like the dose and exposure of the target in clinic. We now start thinking about potentially using animal model data to supplement clinical randomized controlled trial. In that, we need to think about suing potentially multiple animal models to complement each other.

We approach both quantitative outcomes and qualitative outcome which is, you know, user biomarkers, burden reduction, humane endpoints, and so on. And the more animal data we have, specifically if we have individual animal data that the regulatory agencies can review and how it correlates with available clinical trial outcome data, that will obviously alleviate some uncertainties of what -- certainly not clinical, not a clinical trial endpoint

Page 316

might mean in this particular scenario.

And the animal model data might be very helpful also to be used in support of clinical trials for difficult to study mycosis, such as multidrug resistant fungal infections, invasive aspergillosis, and mold. Also, there was the discussion about potentially using nonclinical model for informing rate points for fungal pathogens.

With regards to clinical trials, there was a lot of discussion with regards to how to vet and develop the clinical trials to streamline them to (inaudible) more efficiency potentially enrolling patients with infections in multiple body sites at the extremes of age with different underlying comorbidities, understanding that that will bring significant heterogeneity in the outcomes.

Also there were thoughts of potentially combining and pooling across different fungal species as it relates to crude grouping, like for example MUCORALES rhizopus, as well as endemic mycosis together. And although they're potentially different -- the (inaudible) to a particular drug study, these

Page 317

data would definitely enrich the clinical concepts generated and might be helpful and formative for clinicians.

What do we? We got to multidrug resistance fungal infections, whether we need enrich patient population, that is something for us to consider going forward and designing clinical trials for invasive fungal diseases.

So additional endpoint that -- the point that had been brought up on multiple occasions during today's presentations and discussion was the use of point of care diagnostics to improve trial efficiency in both enrollment and obtaining treatment response and particular targeting high risk for fungal infections. That might be concerns in delay of treatment and also improve speed of enrollment and shortened duration of clinical trials as well.

We had discussed that stable outcome potentially to be considered to be included to figure in the success for outcome assessment in clinical trial due to length of time in changing that stable outcome into success over time. Again, because we

Page 318

want to make the trial more efficient. And a lot of discussion in regard to trial networks.

We want them to be more robust, understanding that they're very expensive and we need administrative and governmental support, to support the evolution, also, and the maintenance of the infrastructure as well as putting money and feeding the development of new clinical scientific investigators.

Going forward, we still have a lot of gaps, uncertainties, and remaining challenges in sort of honing into very straightforward path for antifungal drug development. We're not sure that the animal model for rare unmet medical need in invasive fungal disease is of high enough quality to really support regulatory actions or labeling; however, we're seeing already a lot of discussion and actually evaluation of data submitted for animal models that being included in the U.S. package inserts, and particular in Section 12.4 Microbiology, to provide some data for the clinician; although, you know, it might not necessarily result in the indication and

Page 319

specific dosing recommendation, but it will provide them with additional information that they can use in deciding what type of therapy and at what particular dosing range will be effective for their patients at hand.

We do lack randomized controlled trials in pediatric patients and neonates, understandably that we're able to slide some PK/PD data from adult and older patients and with some supplemental information from animal models, we potentially might be able to reach some certainty of the dosing regimen that -- be appropriate for this patient population.

There was a lot of discussion on external control data sources and availability. We would like to have a current matched external controls with -- where patients would be readily identified with risk factors characterized and sufficiently adjusted and matched for stages of invasive fungal disease.

We also would like to see patients level data to make -- to assure data validity for the external controls. And for noninferiority studies,

Page 320

obviously, the questions remain with regards to margin justification. We know that the margin justification ties to a particular comparator for which we have data relative to placebo and therefore there might be some uncertainties with regards to the margin and therefore that does impact the trial design going forward.

Also, there were discussions about expanding, potentially, enrollment criteria in order to simplify antifungal trials, but we need to keep in mind that extending the duration of the trial antifungal therapies might drive the trial -- noninferiority trial physically towards a noninferiority as well.

So we do expect regulatory flexibility in accepting certain smaller packages with additional support data were from -- made in nonrandomized clinical trials but also from nonclinical data. We need to define more what that flexibility actually is and what kind of uncertainty we're willing to accept for particular indications.

We understood that there's some questions about feasibility of using (inaudible)

Page 321

mortality, the fact that this endpoint is particularly noisy, whether we can start moving towards an outcome that's described by actual simple mortality, and also potentially using biomarkers, but we need to understand that in order for a biomarker to be considered to be a primary endpoint, we need to know, particularly for accelerated approval, that it's predict the clinically meaningful outcome.

As we talked about heterogeneity in outcomes related to underlying disease and risk factors, there was understanding that different groups, neutropenic versus non-neutropenic, might potentially have different outcomes and -- or HIV positive versus non-HIV patients for cryptococcosis, for example, and therefore that that needs to be thought through when the trials are designed. We heard pros and cons of having heterogenic population in the study.

And there was a point brought up about nonculture basis in testing for endemic and nonendemic fungi, whether this needs to be considered going forward. We need to see more data, how this non-

Page 322

culture-based testing is better and more sensitive relative to what we know about the cultures and that obviously will have help with regulators as well as the clinicians at the bedside.

We see multiple ways of taking this discussion, this presentation forward into designing more efficient clinical trials and the fact that we will continue engagement with the stakeholders with the industry, with the public-private partnerships, and reviewing the data presented today and the data presented during continued discussion with the agency of what type of flexibility we can exercise and how that will be supported by the scientific evidence.

Again, we're going to be looking closely at the nonclinical model data to support smaller data packages as Dr. Walsh had presented today. We are really looking for redundant, consistent animal models and that defining that PK/PD driven. We're going to be looking more closely at the novel endpoints and looking justification for those endpoints and predicting clinically relevant outcomes.

Also was interesting, fascinating,

Page 323

innovative trial designs that have been presented by Aaron Dane with data augmented controls and randomized control setting as well as smaller clinical trials in trying to find that sweet spot for a sample size and potentially using 80 percent confidence intervals with a 20 percent noninferiority margin for some of the harder to study fungal infections.

And natural history clinical studies with contemporary best available therapy or -- yeah, best available therapy will help us to enrich our external control data benchmarking. Particularly, it's most important for rare invasive fungal disease and molds and then endpoint was brought up with a patient who has been screened but actually are not able to be enrolled in the clinical trials, outcomes of these patients also will potentially inform this internal control data.

And then we discussed the pediatric data. We understand that master protocol clinical trial works are extremely helpful and the (inaudible) sampling and extrapolation from all the kids, it's helpful as well. Again, we need to do microdosing,

Page 324

obtaining very robust PK data using physiologically based PK and clinical trial simulation for study design optimization in order to achieve appropriate dose finding in this patient population.

We need to achieve consensus on design definition, outcome adjudication, using signs and symptoms versus clinical improvement as endpoints and utilizing biomarkers as endpoint in clinical trials.

So lots of work has been done in the past (inaudible) and a lot of work to be done going forward, but I think we're in that sweet spot where we can -- if we'll be probably able to change outcome for the new antifungal in the works and thank you very much.

DR. SUMATI NAMBIAR: Hi, Yuliya, can you hear me?

DR. YULIYA YASINSKAYA: Yeah.

DR. SUMATI NAMBIAR: Hi, this is Sumati. Thank you very much, Yuliya, for that excellent summary and we're coming to close this workshop and on behalf of everybody at the FDA I would really like to thank all the speakers and panelists

Page 325

for joining us and for your contributions to the discussion today.

Special thanks to Mr. Schueler for joining us and sharing his story. We want to assure you that we're all in this together and we hope to work together to find safe and effective therapies for patients. I think that clearly is our intent.

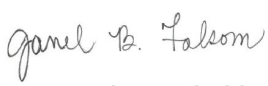
Also, many thanks to all the participants for calling in. I know it's been a long day, but certainly very fruitful and as I said at the beginning of the day, hopefully one of a series of discussions that we will have on this topic.

So I know many of you will be joining us tomorrow when we'll talk about drug treatment for cocci and I look forward to that discussion. Those of you that would not be joining us, again, many thanks for participating in today's workshop and really appreciate everybody's input. Have a good evening and back online tomorrow. Thank you.

Page 326

CERTIFICATE OF NOTARY PUBLIC

I, JANEL FOLSOM, 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.



JANEL FOLSOM
Notary Public in and for the
STATE OF MARYLAND

Page 327

CERTIFICATE OF TRANSCRIBER

I, SONYA LEDANSKI HYDE, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings 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.

SONYA LEDANSKI HYDE