FDA PUBLIC WORKSHOP

DEVELOPING ANTIFUNGAL DRUGS FOR THE TREATMENT OF COCCIDIOIDOMYCOSIS (VALLEY FEVER) INFECTION

_____

DATE: Wednesday, August 5, 2020

TIME: 5:30 p.m.

LOCATION: Virtual Silver Springs, MD 20903

REPORTED BY: Janel Folsom, Notary Public

APPEARANCES:

JOHN FARLEY

DAVID STEVENS

ERIN ZEITUNI

LISA SHUBITZ

ROB PURDIE

KLAUS ROMERO

GRAY HEPPNER

ELIZABETH O'SHAUGHNESSY

JOHN GALGIANI

ANTONINO CATANZARO

Job No. CS3856656

Page 2

ROYCE JOHNSON
JOHN REX
ED GARVEY
DAVID ANGULO
GARETH LEWIS
DAVID LARWOOD
NEIL AMPEL
SUMATI NAMBIAR

Page 3

P R O C E E D I N G S

JOHN FARLEY: -- from the Office of Infectious Diseases at the FDA. I just want to do a quick sound check and make sure that my audio is okay. Judy, could you confirm audio?

JUDY: It's fine, John. We can hear you. Thank you.

JOHN FARLEY: Excellent, excellent. Good morning, everyone, and welcome to our workshop this morning. This is our -- I want to thank everyone, particularly the speakers and panelists who've worked hard to prepare presentations to facilitate an excellent discussion today.

This is our second virtual workshop. We had our first one yesterday. It was in the middle of a tropical storm hitting Washington and actually went rather well. There's been lots of preparation to see that this workshop goes smoothly.

We're using a platform that some of you may not be familiar with, so I just want to open with just a few tips for the day and things that I learned the hard way yesterday. So, first of all, of course,

Page 4

we ask all of our speakers and discussants to speak as clearly as you can, and also stick to the time so that we can stay on agenda.

For the speakers and panelists, you will a phone icon in the upper bar on the left. It's green. You'll see that before your session or panel discussion, and at that point you can click on the phone icon and have the meeting call you and you'll be able to speak and be heard.

Note that -- and particularly for the audience -- when people are unmuting their phone to speak, there's a bit of a delay in the system so it takes a few seconds longer than you expect.

If you're not a speaker or panelist for this particular session, you'll be in listening mode like the audience, using your computer speaker and you can control that using the speaker icon.

If anyone happens to get cut off due to an internet issue, just close Adobe and then use the link to go ahead and rejoin the meeting and that should go well.

I note that speaker slides, transcripts

Page 5

and recordings will be available on the meeting webpage in the next few days.

So, the purpose of our workshop today is to hold scientific discussions to better understand the current state of coccidioidomycosis and focus on potential strategies to facilitate the development of drugs that can safely and effectively be used to treat cocci.

Now, cocci presents both challenges and opportunities due to the spectrum of disease and the need for products to address patient needs throughout this spectrum. For antifungal drugs we all recognize that there are both scientific and financial challenges, but we will make progress when we work together -- government scientists, academic researchers, healthcare providers, patients and drug developers. Let's frankly discuss those challenges and get ideas on the table for moving forward.

So, I'm looking forward to a really good discussion today. And it's my pleasure to introduce our co-chairs for Session 1, Susan Hoover from Stanford Health, and Lanling Zou from NIH. I'll

Page 6

turn the microphone over to them at this point for our first session. Thanks very much and welcome.

SUSAN HOOVER: Good morning. I'm Susan Hoover, as John said, at Stanford Health. And my co-moderator Lanling Zou is in the Bacterial and Mycology Branch of DMID at NIH. This first slide depicts all the speakers -- ourselves, the moderators, and all the speakers of Session 1.

Our first speaker is David Stevens. Dr. Stevens is Professor of Medicine at Stanford University Medical School and President of the California Institute for Medical Research, San Jose, and PI of its Infectious Disease Research Laboratory.

DR. DAVID STEVENS: Okay, these are the topics I was asked to cover. I hope everybody can hear me. I assume they can, and we'll get started.

This microbe has a very interesting life cycle, which I don't have time to get into, but there are two points on this slide that you need to be aware of: One is that there's a completely different morphological forum cycling in the body -- that's the right half of this slide. And the left half is what

Page 7

goes on in the soil. And the second thing you need to know from this slide is that it's the soil that's important for the epidemiology of this organism because it is arthroconidia growing on hyphae in the soil that releases the spores that infect you.

This slide shows the distribution of the disease. It's a new world disease. And since this slide was made, there have been some new areas discovered in Brazil, Guatemala and Colombia, but notably in the U.S., sites of endemicity have been discovered in both Oregon and Washington. And with global warming, the range of cocci in the soil is expected to increase.

This is a more close up picture of the area in the U.S. and Mexico. In the Lower Sonoran Life Zone is what the blue describes here. This is a dry region with hot summers and mild winners and alkaline soil, sparse floras and typically at a low altitude.

So, this is a typical picture of where you might find coccidioid is in the Lower Sonoran Life Zone. This is not the exclusive life zone in which

Page 8

this microbe can be found, but it's the predominant one.

And this gets into the epidemiology of this organism. The prisons in California -- state prisons have been built in a chain along the central valley. There's a number of reasons for that and one is the cost of land. But as a consequence of putting prisons in these places where cocci is found in the soil, there have been outbreaks amongst prisoners and guards to the point where a federal judge has actually made a ruling about who can be put into these prisons, depending on their risk factors.

So, as far as we understand it now, there are two species, immitis and posadasii, and as far as we know, the clinical disease caused by the two different species is identical.

This slide talks about the epidemiology. It's a fairly recent take. It takes you up to 2018, and I think it's obvious that cocci is on the rise. And there's a number of reasons for that but two of them are -- one is increasing urbanization in the endemic areas, and another relates to the

Page 9

annual rainfall cycles that occur.

So, we estimate that there are about 20 million people who are at risk of this infection. This would include residents, people who spend their winter escaping northern climates, other tourists, other travelers, and the military bases that are in the endemic areas. And the best guess we have about the number of infections per year is 200,000 per year. And this is a very underreported disease. And we estimate that illness, frank illness occurs in about a third of people who are exposed, which would amount to about 67,000 infections, patent infections per year. And we'll talk a little bit more about that distribution.

So, this is how -- a principal way the organism is spread in large numbers of people being infected at the same time, and this is a dust storm, which is fairly typical in some of the endemic regions. Phoenix, for example, or Kern County in California. And the dust storm, which kicks up clouds of dust, also kicks up clouds of arthroconidia, and they're about to descend on the homes of these people

Page 10

who have moved into the endemic area and never had an experience before with cocci.

Another way that the disease can spread is through cataclysmic climate events. This picture was taken during the earthquake in Northridge, California, and you can see how much dust was kicked up during this episode. And as a consequence there were large numbers of cases in the area of the earthquake -- cases of cocci, secondary to people breathing in the dust that had been disturbed.

One of the things we might look forward to in the future is a plan -- actually, construction has started -- for a high-speed bullet train in California to connect up the San Francisco and Los Angeles areas going through the Central Valley. And you can imagine the consequences for the workers who will be working on this bullet train.

The picture at the left is not actually workers on the bullet train; these are archaeology students and they tend to dig in Indian middens, and when they do, a lot of dust is thrown up into the air and there have been many outbreaks of archaeology

Page 11

students following one of these digs where they were perturbing the dust.

The right side is also not related to the bullet train. That's a picture taken on Interstate 5, which runs down the central valley. You can see a dust storm approaching, and you can imagine what the consequences would be for the people driving on I5 at that time, especially if they have their windows down.

Another way that the disease can spread is by fomites traveling from non-endemic -- traveling to non-endemic regions from endemic regions. This shows three of the culprits that have been implicated in that kind of spreading. And another source of infection is laboratory accidents. A typical story would be something occurring in a non-endemic region where a clinical microbiology lab person would open a plate because there's an interesting looking fungus on the petri dish, and in the course of that, manage to infect not only themselves but everybody else in the laboratory.

And this picture I put in to remind me

Page 12

that the consequences of coccidioidal infection not only to man but also to his domestic animals. This is a patient I consulted on. This is Belle, and Belle has disseminated cocci. And this adds to the economic consequences of this infection. And Lisa can talk more about this.

So, in the humans who have the symptomatic infections that we talked about, the impact is like this: The average number of days that patients feel ill is over 200, and the average number of days that they miss work or school is longer than a month. And this Congressperson has estimated that the costs to California over a decade amount to about $2 billion.

Another problem with the epidemiology is that doctors in the endemic areas are undereducated about cocci. And various studies have indicated a range but slightly more than 50 percent of doctors test community-acquired pneumonia in the endemic areas for cocci. And in Arizona, about a third of the community-acquired pneumonia is cocci. And about more than half the patients with cocci have received

Page 13

antibacterials for their condition prior to diagnosis. Antibacterials, obviously, wouldn't help. And they've had three visits to the doctors before the diagnosis is successfully made.

So, the picture, as we understand it -- we talked about estimated 200,000 infections a year, so multiple everything on the slide by about 200. But about -- for every thousand infections, we estimate that 600 of them are asymptomatic. These people would experience a skin test conversion but not necessarily any symptoms. And 400 of them will be symptomatic. We'll talk about that in just a moment.

And from these cases, there will be 50 pulmonary residuals, which means that there will be radiographic abnormalities that people will walk around with for the rest of their life as a souvenir of the coccidioidal experience.

And then, lastly, from the symptomatic cases, there are five disseminated cases and it's really these five cases, where the disease spreads outside the chest, that occupy the major efforts and attention of the medical professionals dealing with

Page 14

these five per thousand who have disseminated disease.
This shows two of the pulmonary residuals that are seen. On the left is a stable cavity, and on the right a nodule. And if you radiograph probably 100 people at random in Bakersfield, you would find a number of them walking around with these x-ray abnormalities, not at that time causing them any clinical difficulties.
And the 40 percent of the patients who have the respiratory illness can range from anything that appears to be like flu up to community-acquired pneumonia, and then there's a range within community-acquired pneumonia. It can be a walking-type pneumonia all the way to an acute respiratory distress syndrome. There are some skin eruptions that accompany this respiratory illness and the onset is generally 1-3 weeks after they inhale arthroconidia.
And the big question at this time is whether treatment would affect these primary infections; either make the symptoms less or shorten the duration, maybe even prevent dissemination. That's an unknown -- an important unknown question at

Page 15

this time.
This is a radiograph of a primary pulmonary infection due to cocci. There is nothing specific about this in the differential diagnosis of other causes of community-acquired pneumonia. And this is two of the types of skin rashes that may occur during the primary infection. What these patients experience -- fatigue, fever, chills, etc., cough, sputum production, all these symptoms, again, are not specific for primary cocci infection but can be seen in other kinds of community-acquired pneumonia, and there's a differential diagnosis issue because of the non-specificity of these signs and symptoms.
So, once -- if the infection doesn't resolve with the durations I talked about earlier, there's one of two bad ways that things can go: One is the infection, instead of resolving in the lung, can go on to produce a chronic pulmonary condition. And the other, as mentioned, is to disseminate outside the lung.
This is a picture of what can happen if the patients develop a chronic pulmonary form of the

Page 16

disease, and what happens is there are successive waves of cavities, modules, fibrosis and progressive destruction and loss of function lung tissue as the disease progresses.
The other bad way things can go is to disseminate from the chest. And we recognize that there are certain risk factors that predispose to this. It more commonly happens in males than females, it happens at a very high degree in people who are immune compromised -- and we're going to talk about that in some detail -- patients with congenital immunodeficiencies are at risk of disseminating once they have a primary infection.
The combination of pregnancy, particularly in the second and third trimesters, seems to be a bad combination with cocci with an increased risk of dissemination and a bad course once it disseminates. And there's a certain racial predisposition to risk of dissemination. People of Filipino ancestry are at the highest risk, then African Americans, native Americans, Hispanics, other Asians. All of those appear to be at greater risk

Page 17

than do whites of disseminating the disease.
And what happens when it disseminates, it's caused by hematogenous spread from the lung, and a few months after the primary infection it will either be manifest in the skin, it can go to bone or joints or other sites. And the worst possibility is the meningeal form of the disease. And, furthermore, in all these sites there's a tendency to relapse either after a successful resolution of a focal site, it will come back, or even after successful therapy, the natural history of this disease involves cycles of relapse, recrudescence, and then, hopefully, remission again once they are retreated.
This shows examples of the cutaneous form of the disease. The patient on the right has multiple granulomas of the skin, the patient on the left has a soft tissue abscess with an ulcer draining puss. And this unfortunate gentleman is showing you in his bone scan that he has multiple sites of skeletal involvement. You can see he's got multiple sites in his skull, both shoulders, a couple of ribs, there's some sites in his vertebrae, in the pelvis, in

Page 18

his -- one of his ankles. And all of these are destructive lesions due to cocci.

Another bad place that dissemination can go to is the eye. And particularly if the retinal involvement is near the macula, the patient can lose vision, which may be permanent. And the lymphatic system is another site of dissemination of disease. (Oops, I've lost my...okay, sorry.)

As I mentioned, meningitis is the worst complication. And there are, we estimate, about 200-500 new cases of meningitis a year. This disease had a natural history. Before the treatment was available, we understood that the disease was fatal within two years without treatment. So, a worst prognosis than untreated lung cancer. And even with the onset of treatment, there are many stroke events that are associated with progression of the disease, hydrocephalus can occur and compression of the spinal cord.

Another manifestation of central nervous system disease is a space-occupying lesion in the brain and this is in the differential diagnosis of

Page 19

brain abscess. And this patient is showing a cerebellar brain abscess due to cocci.

We appreciated early on that there was a special course that occurred in immunocompromised patients, and in this particular series, about half of the patients had disseminated disease. And you'll remember, I talked about in healthy persons, a dissemination rate of 5 in 1,000. So, this is 100 times the rate in non-compromised persons. And the risk of reactivation appeared to occur in persons who were receiving immunosuppression for some medical condition or experiencing a disease which in itself was immunosuppressive, such as, for example, Hodgkin's Disease.

And it also teaches you that viable cocci organisms must be living in you after an initial infection. Even if you've successfully resolved it on your own or needed treatment and the treatment was successful, the bug is with you -- and won't bother you, but if something immunosuppressive happens to you, you are at risk once again.

So, what's the consequence of that in

Page 20

2020? With a massive increase in transplantation as a treatment modality for a number of conditions and a massive use of immunosuppressives for a number of conditions, this has become a huge problem in endemic areas. And Janis could speak to this in more detail.

Another group that's at risk with having a bad course of cocci are the HIV-infected persons. And the disease in the HIV infected is about 20 times more common in endemic areas than non-compromised persons. And a low CD4 risk factor appears to be the major risk factor for the development of progressive disease. And the cases appear to be mixtures of new infections or reactivation of old disease.

I'm not going to really talk about treatment. I understood John was going to talk about this some more but I think that's changed a little bit with the latest iteration of the program. But I just want to mention one approach to treatment because I need to have it understood what I'm going to talk about next, which is trying to come to evaluations of the course using trial endpoints.

Page 21

Our approach has been to treat disseminated patients -- I'm not talking about meningeal patients who require special treatment -- but treat patients with oral azoles for a minimum of a year or six months after the disease becomes inactive, whichever of those two is longer. And use amphotericin preparations if the lesions are in critical locations or if the patient is worsening rapidly because amphotericin is more rapidly acting than azoles. And the surgeons have a role to play in some of the manifestations of the disease, particularly in bone and in soft tissue.

So, scoring systems have been developed for therapeutic trials and have proven useful, and there's experience that goes along with them. The patients were initially scored according to their culture-confirmed sites of disease, their serologic titer, and the extent of lesions. And the sum of the points pretreatment was their baseline score. A successful response was considered a reduction of the baseline score by 50 percent or more within a set period of time.

Page 22

And because cocci tends to improve relatively slowly, scoring was done at three-month intervals. And far from ideal, the scoring system does allow physicians to estimate a total body burden of disease and follow that index in the course of treatment. So, this is an example of a scoring system that's been used. There are points assigned to symptoms, to physical exam, to the height of the serologic titer, to culture positivity.

And the last point that I was asked to address, to finish up, was -- is productive collaboration in clinical trials with Latin American centers possible? And my personal perspective on this is a very resounding yes. I show here some of the studies that it's been my privilege to collaborate, in addition to my preclinical collaborations with Latina American investigations -- these are clinical studies that address clinical questions in collaborative trials. And, in my opinion, it's been the direct individual connections between people that are the key to success in these kinds of efforts.

And as far as potential collaborating

Page 23

sites, my opinion would be the best bet would be Mexico, based on the number of cases that they have there, the proximity to the United States, past history of success in collaborative ventures with Mexican investigators and clinicians, and because of the existing ties already to American investigators. And Rafael and Luis can address this to a greater extent.

So, with that, I'll conclude, and I'd be happy to take any questions. And thank you for your attention.

SUSAN HOOVER: Thank you, Dr. Stevens. And thanks again to John Farley, who's gotten us off to a good start time-wise.

Our next speaker discussing current developments at NIAID is Erin Zeituni. Dr. Zeituni has been a Preclinical Services Program Manager in the Bacteriology and Mycology Branch at NIAID since 2016.

DR. ERIN ZEITUNI: Thank you, Susan. Can I do a quick sound check?

SUSAN HOOVER: We hear you.

DR. ERIN ZEITUNI: Perfect. I'd like

Page 24

to thank the organizers for giving me the opportunity to tell you a bit about NIH's development efforts and support mechanisms for valley fever. Some of this talk will be familiar to folks who attended yesterday's workshop, but here I'll be diving more deeply into NIH's support for the single indication. Throughout the talk I'll be encouraging folks to reach out to us. So, upfront I just want to let you know that my email is my first name, dot, my last name @NIH.gov. I have no disclosures.

To get us 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, including the coccidioidi species, which, as Dr. Stevens just demonstrated to us, are the causative agents of valley fever.

To give an idea of the scope of NIAID's

Page 25

funding for valley fever, in 2019, $10 million of NIAID's budget went to support for coccidioidomycosis research and development. Those funds were spread across the product development area that is shown on this slide, which spans basically research through to clinical research on the path to regulatory approval.

Today, I will be diving into the valley fever specific portfolios of the various mechanisms that NIAID leverages to support and de-risk product development for valley fever. Taking a look at the blue arrows at the bottom of the screen, folks in the audience will be most familiar with NIAID's grants and contracts mechanism, which are the main drivers of NIAID's support for product development effort. However, we do recognize that the path to product approval is long and can be difficult. And so DMID has developed free services and resources for the research and development communities to access. Those include the Preclinical Services Program and the clinical trial units, both of which I will highlight today.

In the interest of time, I have

Page 26

restricted this talk to a discussion of product development efforts, so I feel it's important to mention that there is also a small but mighty portfolio of basic researchers tackling the task of improving our knowledge of the basic biology of coccidioides, its response to hosts and the host response to infection. We applaud their efforts in this challenging arena and we encourage folks to continue bringing their exciting ideas forward in grant application.

Shown on this slide, DMID supports a robust grant portfolio of drugs and diagnostics targeting valley fever. The drug developers highlighted here have received a mixture of grant funding and preclinical services over the years to help support their antifungal development programs for valley fever.

Some utilize grants, such as Amplyx Pharmaceuticals' Fosmanogepix Program, while others utilize a mix of grants and preclinical services such as Mycovia's VT-1598 program and Valley Fever Solutions' Nikkomycin Program. And still others

Page 27

utilize preclinical services alone such as F2G's olorofim program. We'll be hearing from representatives from several of these companies later during the workshop.

NIAID program staff can also release program announcements or SBIR contract topics to encourage applications in research areas of special interest. We continue to emphasize valley fever research and development in recent initiatives. Through these mechanisms, this year NIAID funded several investigator-initiated grants and SBIR contracts supporting diagnostic programs targeting endemic fungal pathogens, including the coccidioides species.

Coccidioidomycosis vaccine development efforts have a long history of NIAID grant support over the years, however, this field remains quite challenging. Two NIAID-funded vaccine programs of note are the live attenuated vaccine out of the University of Arizona and the recombinant chimeric polypeptide antigen vaccine out of the University of Texas, San Antonio.

Page 28

Dr. Galgiani's live attenuated vaccine uses a strain rendered avirulent by the deletion of the CPS1 gene, an essential gene for serial propagation in C. posadasii. Dr. Galgiani is working with an industrial partner, Anivive Lifesciences, to develop the vaccine further. The recombinant chimeric polypeptide antigen vaccine developed by Dr. Wang contains the most immunogenic fragments of four previously identified coccidioides antigens as well as multiple human T-cell epitopes, and it's formulated with a glucan-chitin particle as an undulant delivery vehicle. This vaccine is in the proof of concept stage.

To help us better understand the challenges and gaps that are facing the endemic vaccine research community, NIAID organized a workshop in 2019 to engage this research community in a discussion of vaccine strategies for endemic fungal pathogens. Over the course of one and a half days, over 100 people dove into the science of the latest discoveries in this field and strove to identify actionable steps to advance fungal vaccines.

Page 29

Exciting outcomes of the workshop included expanding the field of investigators and initiated new collaborations. Additionally, the workshop confirmed the scientific gaps and challenges that needed attention, so as identifying new antigens, understanding correlates of protection and meaningful biomarkers, strengthening preclinical and clinical testing, and overcoming manufacturing hurdles including (inaudible) optimization as well as regulatory challenges.

Our program staff was poised to move forward incorporating what we had learned in the workshop, and program officers were able to leverage the positive outcomes of the workshop to develop a targeted FY22 initiative that was recently approved by DMID's counsel, moving it forward as a potential funding opportunity.

The coccidioidomycosis collaborative research centers will aim to establish highly collaborative multidisciplinary research teams to conduct translational and clinical research for improved diagnosis, treatment and prevention of valley

Page 30

fever. The goal is for these multidisciplinary centers to leverage unique resources and patient populations from endemic regions to advance the field. We are looking forward to seeing the valley fever research community continue to expand and advance in the coming years.

Switching gears away from the investigator-initiated grants and contracts, I'd like to introduce you all to NIAID's Preclinical Services, which are a suite of contracts designed to support anti-infective product development. These free gap-filling services are intended to lower the risk and advance promising discoveries along the product development pathway.

Our mission is to keep products moving forward, rather than have them stall due to intermittent gaps in funding or access to resources. these free services are available to innovators from academia, nonprofit organizations, industry and government, both domestic and foreign institutions may apply, and applicants do not need to have NIH funding.

Because this support mechanism is

Page 31

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 on valley fever, I manage a suite of in vitro and in vivo efficacy studies -- services that provide supportive data to antifungal drug development programs, including those targeting coccidioidomycosis. Because coccidioides require BSL3 facilities, accessing efficacy evaluations can be a rate limiting step, and we find that it frequently is not on the radar of early development programs developing broad spectrum antifungals. We offer these services to ensure that promising antifungals have pass (inaudible) to assess their activity.

To give a flavor of our scale of our services since 2015, our contractors at the University of Texas Health Science Center in San Antonio have performed MIC testing against coccidioides for 25 compounds from 18 institutions, and they have evaluated in vivo efficacy for five institutions and two valley fever infection models that are illustrated

Page 32

here.

Through preclinical services, we offer both a central nervous system infection model and a pulmonary infection model for valley fever. In the CNS model, the infecting inoculum is delivered intracranially to ICR mice who are then treated two days later for durations of either seven days to assess the impact of treatment on the fungal burden of select tissues, or treated for 14 days followed by a 14 or 28-day off therapy monitoring period to observe the impact on survival.

The pulmonary model has several key differences. The infecting inoculum is delivered to the lungs of ICR mice and treatment is started five days later. The fungal burden assessment runs largely the same from that point onward, whereas the survival arm of the study has a shorter treatment duration than the CNS model but with a similar off-therapy monitoring period. A drug's characteristics will help determine which model to pursue.

In addition to efficacy assessment, NIAID's preclinical services also offer a suite of

Page 33

preclinical studies to support antifungal drug and vaccine programs at multiple stages of development. These services include chemistry and manufacturing, including GMP manufacturing, toxicology and pharmacokinetics, rapid ADMET and pharmacokinetics screening, product development planning and assistance with IND documentation, vaccine testing, and vaccine and biologic manufacturing services.

So, if we're thinking back to the in vivo efficacy models for valley fever that I mentioned on the previous slide, when investigators are preparing to test their products in this rather tough model under BSL3 conditions, they need to have access to a robust preliminary data package to support that study. This includes sufficient compound for key study arms with 7-14 days of dosing, MIC testing against the strains used in the models, and understanding of the pharmacokinetics and distribution of their drugs in the blood, brain and/or lungs to help them select their doses, and the knowledge that their drugs is tolerated in ICR mice for the plan dosing schedule and duration.

Page 34

So, for those of you in the audience who are already making this checklist in your head, please know that although our preclinical services are intended to be gap filling, we do understand that there can be more than one gap in a program. I encourage you to reach out to us and tell us about your antifungal programs and your gap. And I'd like to state that once again for emphasis. Please do reach out to us.

F2G has kindly given me permission to describe our interactions has an illustrative example of NIAID's... Oops, where are we? There we go. As NIAID's interaction with drug developers. Starting in the box on the left, in an introductory call between NIAID and F2G, we described our in vivo efficacy services in general to the F2G team and mentioned that we had a single study slot available in our coccidioides in vivo testing task order. At that time, F2G had shown in silico and in vitro that their advanced agent, Olorofim, had activity against coccidioides, and we went on to verify that through an expanded MIC panel against C. immitis and C.

Page 35

posadasii at our contracting site at the University of Texas Health Sciences Center in San Antonio.

With that confirmation, we embarked on the in vivo assessment of Olorofim in the CNS infection model where significant protection and fungal burden reduction was observed in that model compared to untreated controls. Results of the efficacy model were published and as we will hear later today, F2G is exploring clinical use of Olorofim for coccidioidomycosis. This is a powerful example of the potential impact of a simple conversation. If you have a promising antifungal agent, please do contact us and we will be happy to hear from you.

Additional free services include our clinical trial units, such as our Phase 1 units. These contracts provide Phase 1 trials at no cost to the requester. NIAID sponsors the trial and holds the IND. Mycovia's VT-1598 is a novel antifungal compound with activity against coccidioides species. Through our Phase 1 clinical trial units, VT-1598's single ascending dose is examining the safety of its administration to 48 healthy adults aged 18-45 years.

Page 36

The primary objectives of this study are to determine the safety of single ascending oral doses of VT-1598 in healthy adult subjects in a fasted state and to determine the safety of a single oral dose of VT-1598 in healthy adult subjects in a fed state.

In addition to the Phase 1 clinical trial units, NIAID's Infectious Disease Clinical Research Consortium, previously the Vaccine Treatments and Evaluation Unit, have also been leveraged to support clinical studies in valley fever. An observational study of up to a thousand individuals aged greater than or equal to 14 years has the objective of assessing the prevalence of primary pulmonary coccidioidomycosis or PPC in subjects with community-acquired pneumonia or CAP in coccidioidomycosis endemic areas.

Step one of the study is to examine the prevalence of PPC among individuals presenting with CAP within 28 days of symptom onset. Step two of the study is to follow individuals diagnosed with PPC for up to 24 months to establish the clinical course,

Page 37

identify predictors of the clinical course and evaluate the response to prescribed antifungal therapy versus no antifungal therapy. This observational study is enrolling and we're looking forward to producing perfective data on the prevalence of PPC in CAP and the management of early PPC at the earliest point of treatment.

I hope that this presentation has helped provide a clear picture of the various mechanisms that NIAID is leveraging to support product development targeting valley fever. Management of the portfolios and mechanisms described in this presentation are a team effort and I'd like to acknowledge the members of the Bacterioloogy and Mycology branch who helped with the valley fever effort. They are all listed here on the slide. My email is provided at the top of the slide. Please reach out to me if you have any questions. I hope to hear from you. Thank you.

SUSAN HOOVER: Thank you, Dr. Zeituni. Our last talk before our morning break is Dr. Lisa Shubitz talking about animal models of

Page 38

coccidioidomycosis. Dr. Shubitz is a research scientist at the Valley Fever Center for Excellence, has been working on cocci since 1996.

DR. LISA SHUBITZ: Good morning. And I was asked -- first of all, I'm very honored to be a part of this workshop today and asked to -- have been asked to speak to you. And this is going to be a bit redundant with the last talk, unfortunately. This is what I was asked to talk about, but it's not going to be extensively -- it's not going to go extensively past what Erin already gave you.

So, I'm going to talk a little bit about animal models of coccidioidomycosis -- as soon as I figure out how to move the slides. All right. So, it's already been spoken about that cocci is a biosafety level 3 pathogen, in that in order to do animal work with coccidioids you have to have animal biosafety level 3 facilities. And in addition, you either need to have support of a biosafety level 3 micology laboratory also that can produce your organisms or you need to have a relationship with someone who can ship them to you.

Page 39

So, the pathogen is a significant aerosol risk to personnel, which is why you have to be working with this animal bio safety level 3. It's not really transmissible from one animal to another but you could give it to yourself or the other workers in your laboratory while you're infecting your animals. Consequently, this requires that all of your personnel be properly trained at biosafety level 3 and at handling animals at biosafety level 3, and it requires that you have at least a class II biosafety cabinet with some extra PPE such as N-95 for protection from aerosols, or you could have a class III biosafety cabinet for intranasal infections. And intranasal infections carry the greatest risk of infecting workers, but there are small aerosols that can be created even just squirting things out of needles.

The guidelines for setting up an animal biosafety level 3 laboratory are published in the Biosafety in Microbiological and Biomedical Laboratories, which is a CDC publication. And they used to mail it to you but now it's actually just available on their website as a PDF and you can go

Page 40

look at it.

And in the lower right-hand corner is a photograph of a class III biosafety cabinet. We've actually had one in place at our institution since 1998 and it has two workstations in it which makes the work more efficient for packing cages and animal transport. But this is -- I don't think everyone has a class III cabinet in order to be able to do this work, and it can be done other ways, but it's a nice safety feature.

So, mice are mostly what is used. They constitute the vast majority of the animals that are used in research and preclinical efficacy studies of antifungal drug candidates for coccidioides. The advantages of mice is that there are very well-established cocci infection models in mice that have been used for over 70 years -- the literature goes back into the 1950s.

They're small and easy to handle in statistically significant number at animal biosafety level 3, and that is indeed a factor. It's very easy to put a small cage of mice into a class III biosafety

Page 41

cabinet or a class II biosafety cabinet. It becomes a little bit more challenging when you're using larger animals. You can also involve statistically significant numbers of the animals because they're little.

There are a wide variety of strains for drug studies. Outbred mice or the ITR mouse, which is an inbred swift that Erin was talking about, are relatively inexpensive and they're used very commonly for drug studies. But if you're interested in effects of drug in the face of infections that may be more challenging due to underlying conditions in a human being, there are a lot of genetically engineered mice available now that mimic metabolic or immunologic system defects in mice that you can purchase to use.

The drawbacks of mice are that the pharmacokinetics of the drugs in mice may differ significantly from what's seen in humans, and that means that you actually need to perform -- or you may need to perform some PK in mice to understand how to use them as a model.

The other drawback is that coccidioides

Page 42

progresses pretty rapidly in mice, whereas even an immuno-deficient human, you know, may have the disease for two or three weeks before they even show up in your office because they're sick. In two or three weeks, the laboratory infected mouse is typically dead.

So, I'm going to talk a little bit about routes of administration, which Erin described some of already. But the pulmonary route of administration is the most common. This is the way the infection gets into the human host naturally, and it makes sense to put it into the lungs. This also carries the greatest aerosol risk.

So, it can be administered intranasally by insufflation of a saline suspension -- with the opportunity in a saline suspension using a pipette, which is very simple. And it's not 100 percent. You're giving this to an anesthetized animal. I think I actually have a little picture here. No, I don't. It's on another slide. Use a pipette, let them inhale it through their nose while they're anesthetized. But some of it goes down the esophagus instead of the

Page 43

airways. Much of it may be tracked in the upper airways, the nasal passages, the upper bronchi. But some of it definitely gets delivered to the lower airways where it sets up infection. And this is an affective and common way to infect mice.

So, you can give it intratracheally. There are methods of doing this. I think they're a little bit more challenging, at least in a class III cabinet, which is what I have, where you anesthetize the animals or you could deliver this with a pipette to the trachea and bypass the nasal passages. It can be done surgically, but I don't think anyone's doing that in mice.

They could be exposed by aerosol in chambers, but this carries very high risk of aerosol infection and I don't actually know anyone who's doing it. But if you're more interested in nebulized spores with well-distributed infections that go deep into the lungs, this might be something to consider. For a model for a drug, I'm not sure this is really worth pursuing.

Other methods are intravenous

Page 44

infection, which provides a rapid widespread model of dissemination very early on that doesn't go through the lungs to get to a disseminated state, and it's a little bit technically challenging. Intraperitoneal gives you dissemination but Lung Fungal Burden is a common readout because it typically goes to the lungs really easily. There is an intrathecal model for CNS infection in mice. It is technically challenging, but it is published. And then intracerebral infection with (inaudible) also produces a CNS infection.

So, here's a picture of the mouse being infected. So, 50-100 spores of a common virulent laboratory strain in 30-50 microliters of isotonic saline is being administered to this anesthetized animal. This is in the class III cabinet. Just using a pipette and applying this drop (inaudible) to the nares and waiting for the animal to inhale the suspension until the suspension's been completely administered. We did this under Ketamine-Xylazine anesthesia, which produces a nice smooth anesthesia that lasts long enough to perform this in the equipment that I have. I think other people do

Page 45

this with some kind of inhaled anesthetic, but I find that the Ketamine-Xylazine works pretty well because it lasts a little bit longer.

And in talking about this pulmonary model, it takes four days, four to five days to reach the first generation of spread of this infection, from the time they inhale arthroconidia until the first round of endospores are released to form new spherules, which increase your infection by, approximately one-hundredfold, requires 96 hours.

So, if you look in the literature, some studies utilizing mice, treatment had begun at 48 hours after pulmonary infection, which gets your drug onboard by the time this first round of spherules rupture. But we typically start to treat this infection at 120 hours, which is day five, and this gives time for the infection to become established. And while we can't really mimic what happens in the real world using a mouse model, which is that people do not show up for treatment until they're ill, it is more similar to a human seeking medical care because you're not treating just this developing first round

Page 46

of spherules and endospores -- you've actually got establishment of the infection in the animal.

In untreated mice, in 2-3 weeks, they're moribund. So, between 14 and usually 23-25 days, your mice have died if they're not being treated. And it's important to know your model to prevent cage deaths. And mice with cocci -- I guess sick mice, in general, are kind of generically this way -- but they get thin and they can lose weight very quickly. They develop a hunched posture and ruffled fur, though how ruffled it looks is dependent upon the mouse strain that you're using. They become tachypneic if you observe them just sitting in the cage with their little noses down in the shavings. And they get weak. If you pick them up, they feel weak. They don't feel like a normal mouse. And they're dehydrated based on skin turgor. If you pinch the skin on the back of their neck, it doesn't return to its normal position.

When you estimate that the mice won't survive another 24 hours, we euthanize them. We don't wait for them to die in the cage. For one thing, the

Page 47

main thing we assess in these animals is fungal burdens, and I prefer not to have to just pick up dead mice out of the cage and cut the lungs out of them.

With intravenous infections, these are something that I have not performed, so this is based on literature. But doses of, approximately, 50 spores intravenously produces deaths after day 12, according to Clemons. And in published studies using intravenous infections, treatment is indeed usually instituted within 48 hours post infection. If there's more updated information on that, I don't actually have it.

Intraperitoneal infection is something that carries a little bit less aerosol risk than an intranasal infection. It usually requires more arthroconidia to initiate the infection by this route but it's very reliable. It is technically easy to perform at biosafety level 3 compared to an intranasal infection. The animals do not have to be anesthetized. And this can be easily accomplished in a class II cabinet without probably a lot of other protective -- other protective gear.

Page 48

It is a 2-3 week infection model, which is similar to the intranasal and intravenous, and what you see in these is granulomas of the cranial mesentery, spleen and liver with dissemination to the lungs. It's very prominent in a miliary pattern.

The intracerebral and intrathecal administration routes produce meningitis models. And the intrathecal is put into the mouse in the (inaudible) thoracic upper lumbar area. The intracerebral goes directly into the brain but both models actually produce meningitis and a meningomyeltis, so it goes up and down the spinal cord. You find the organisms in the cord and in the brain regardless of which method that you use.

Clinical signs occur in these mice in 6-8 days post infection and your deaths usually start by day eight. The clinical signs are paresis, paralysis, ataxia, circling, head tilt, seizures and obtundation. And within my experience, these animals need to be evaluated twice a day for animal welfare purposes. Because once the clinical signs begin, the animals may progress very rapidly and they'll be dead

Page 49

in 24 hours.

With this model you generally institute treatment within 48 hours because of how rapidly this progresses. And the assessment is either fungal burden or survival. And I recommend assessing lungs and spleens, not just your brain and spinal cord because this very easily goes to both of those places.

So, in terms of assessing mouse models after treatment, survival is one thing that can be assessed. You treat them for a given period of time and then stop your treatment and see if they die.

Organ fungal burdens at a specified time after stopping treatment are probably the more common assessment, and organ fungal burdens may be your primary measure. There is the question of eradication versus reduction in colony-forming units. Many of the antifungal candidates we have do not eradicate the infection, so often you're looking for excellent reduction in fungal burden compared to your controls.

We quantitate colony-forming units or CFU by tenfold serial dilutions of homogenized

Page 50

tissues, which are usually limited to the lung and spleen. If you're doing CNS models, you're maybe doing spinal cord and brain as well. And you can also qualitatively assess dissemination by incubating whole organs on plates, which is a reasonable approach if you've got some experience with your models and you gave an intranasal infection and you expect control, and you're not that interested in whether there are three organisms in the spleen or ten, but you just want to know if it's there at all. Body weight is a really good measure and indicator of progression of infection, even before your other clinical signs become visible.

The rabbit can be a very reliable model of coccidioidal meningitis and arteritis that is more similar to the disease in humans than what we can produce in mice. The infection is performed cisternally and the size of the animal allows some serial cisternal sampling of CSF, so you can get some intermediate measures in a rabbit that you cannot in mice.

The post-mortem analysis would include

Page 51

histopathology, you can do fungal burden of the spinal cord and the brain, you can evaluate cerebral spinal fluid, and this has been reported to be a good model for humans.

Some of the drawbacks of this is you need to understand the PK of your drug in this species, which may not be a routine part of what you're producing. And there's an increased cost of animals, the labor to handle them and take care of them, and the cost of housing them. So, you end up with fewer animals and you might end up with less robust statistics. Your facilities need to be able to manage the larger animal models at animal biosafety level 3.

I include this slide on nonhuman primates because they're possible, though I don't see that most people would be interested in using them. But they could be used experimentally but it would be extremely expensive, and there are other reasons not to. I would recommend an intratracheal infection with arthroconidial suspension that's been administered using a nebulizer after having worked out this dog

Page 52

nebulization model that produced very good infection.

It seems that most drugs at this stage would probably be implemented in some kind of a human trial and not ever go through a nonhuman primate. But if you have a product that you really think you'd like to put into a primate, there could be some opportunities to treat naturally infected nonhuman primates that are in primate centers within endemic areas.

From some small amount of personal experience, there can be some challenges with administering drugs daily to nonhuman primates and also monitoring because the animals require anesthesia in most cases.

I'm going to talk only briefly about naturally infected dogs because I think they're a rather interesting preclinical assessment model for drug efficacy. In southern Arizona, where I work, we have a very high caseload and it's actually really not difficult to enroll cases. And we worked with a company with one of the VT drugs in doing a clinical assessment of their drug in naturally infected dogs.

Page 53

And unlike nonhuman primates, they usually do not require anesthesia to monitor.

And it is possible to assess improvement in pulmonary disease within 30-60 days of treatment using radiography, serology and serum chemistries and CBCs. These are really easy to collect on client-owned dogs. And the owners are actually extremely grateful for the opportunity to get a potential treatment for their animal, and they're really dedicated. We get very low dropout rates in dog studies -- just dog studies, in general.

The drawbacks to this, of course, are cost, the time it takes to perform this because you do have to enroll animals and it's, you know, similar to enrolling in human clinical trials -- they come in spurts and fits. And you may not end up with statistically significant numbers that would help drive your development, and you could end up with primarily descriptive data from such a study, but maybe it would be valuable to you.

The potential advantages of this model are that it does involve naturally occurring disease

Page 54

in a model that's already sick, in a species that has a rate and range of disease that's pretty similar to humans. And the dog is a common PK and toxicology species, so you may know exactly what you need to give them in terms of dose. And oral administration to dogs is actually pretty easy.

So, in summary, the mouse model is the workhorse of the preclinical testing of antifungal drug candidates because they're small, the models are really well-developed and these studies are very cost effective.

If you need a more advanced meningitis/arteritis model, the rabbit can be an option for you. The drawbacks being that you need some technical expertise, it will cost more, and you may have to have extra facilities to do this. And then there are some larger animal models, both naturally infected and laboratory-induced that exist that you would need to weigh the benefits of doing that for your drug.

Thank you very much for your time. I really appreciated the opportunity to speak to you.

Page 55

LANLING ZOU: Hello? Everybody can hear me?

SUSAN HOOVER: Yes.

LANLING ZOU: Oh, okay. Hi. This is Lanling Zou. I'm the co-moderator. I just want to thank everybody, all the speakers this morning for their excellent presentations. They're very comprehensive and informative. I think it's time for a short break. Please rejoin us at 12:20 for the next talk. All right, see you then.

(Break)

LANLING ZOU: Welcome back. It is my pleasure to introduce our next speaker, Mr. Rob Purdie. He's currently the Patient and Program Development Coordinator at the Valley Fever Institute. He's going to speak about patient oriented clinical trial design. Bob, please take it away.

ROB PURDIE: Thank you. Can everybody hear me okay?

SUSAN HOOVER: Yeah. Yes.

ROB PURDIE: Oh, great. Thank you. Good morning. I'd like to thank the Food & Drug Administration for hosing this workshop and allowing me to be a part of it. It's a privilege to be able to speak on behalf of the Valley Fever patient community. Let me get my slides going. There it goes.

So, I will be sharing some of my personal experience as a patient, as well as knowledge I have gained through countless interactions with other patients to provide a perspective on the difficulty many patients face in fighting valley fever. I will also share some of the work being done at the Valley Fever Institute to support patients using a 360-degree care model, and the opportunity and importance of patients in efforts to develop, test and validate new drugs.

So, I could easily spend 15 minutes just sharing my valley fever journey, and for the sake of time, I'll share the aspects that are relevant to today's topic. My story is very similar to the experience many patients have with disseminated cocci. My valley fever story began with a headache on January 1st of 2012. I was diagnosed with a sinus infection, and after two trips to the urgent care and two

Page 57

unnecessary rounds of antibiotics, I saw an ENT specialist who confirmed I did not have a sinus infection.

My next diagnosis was cluster headaches, and eventually I developed other symptoms including double vision, which brought me to the Emergency Department at Kern Medical in Bakersfield, which is now home to the Valley Fever Institute, and I was admitted to the hospital on February 5th, where the doctors told me I had cocci meningitis. The nearly six weeks it took to be diagnosed with cocci seemed like a long time, and for many illnesses that would be a long time, but I've talked to countless patients who spent months seeking a diagnosis for their valley fever, so I feel I was extremely lucky to be diagnosed in six weeks.

For most people, valley fever is an inconvenient lingering flu-like illness with extreme fatigue. Disseminated coccidioidomycosis is a devastating life sentence. And if you're lucky, you're able to have a functional life. One of my personal goals as part of public education efforts is

Page 58

to better communicate the difference in disease severity and the impact that cocci can have.

I was started on 1000 milligrams of Fluconazole and discharged from my hospital on February 18th of 2012. I was readmitted to the hospital on February 19th with bilateral plural effusions and I remained there until I was discharged on March 5th. When I was discharged in March, I'd lost 70 pounds and three months of my life and my headache was still there.

By mid-May, my headache was almost gone, I had no energy, no appetite and I was constantly thirsty. I also had the cracked lips common with patients on high-dose Fluconazole. I felt like I was living life with a water bottle in one hand and ChapStick in the other.

In October of 2012, I was readmitted to Kern Medical because I clinically failed Fluconazole, which means that my doctors failed to see an improvement in my clinical endpoints after six months of use, even though my drug levels were in the therapeutic range. I was discharged three days later

Page 59

and started on 600 milligrams of Intraconazole. I clinically failed Intraconazole as well, and on January 15th of 2013, I was started on 450 milligrams of Voriconazole. By summer of 2013, I clinically failed Voriconazole as monotherapy and IT Amphotericin B was recommended to be added to my treatment. I began my IT Ampho treatments on December 3rd of 2013.

So, not all failures are the same. Some failures are due to the side effects of the drug, and my Ampho treatments continued twice a week until June of 2014. On June 18th of 2014, after my treatment, I had lower body numbness and trouble walking. At my next treatment, my dose was cut in half, but I had the same problem.

My treatments were moved to once a week at the lower dose and the side effects were still present but manageable. My health improved and treatments eventually moved to once a month. The Voriconazole combination therapy was effective in controlling my disease, but it came at a cost. As soon as I started taking the Voriconazole, I took precautions to protect my skin from the sun but even

Page 60

with those precautions I was diagnosed with squamous cell carcinoma.

After my second diagnosis, I failed Voriconazole due to the skin cancer, and I was started on Posaconazole. Even though I'm no longer on the Voriconazole, I still have to limit my time outdoors. Summers at the beach or spending the day by the pool are all very popular activities in Bakersfield but I'm not able to participate due to my skin cancer. I still require quarterly follow-ups with a dermatologist and I've had four more squamous cell carcinomas removed, one of which required reconstructive surgery on my ear.

The side effects I experienced with Posaconazole, while not as medically concerning, do have an impact on my life. I experience frequent nosebleeds but they're usually very minor, and profuse sweating, which makes me self-conscious and has caused quite a bit if concern at some of the events I've attended. And even with my improved quality of life, the impact of the medications are just beneath the surface.

Page 61

The impact on the quality of life form side effects can influence patient adherence to treatment. Patients with non-complicated disease who experience severe side effects may discontinue treatment, and patients with severe disease may not adhere to care well. I've spoken to several otherwise intelligence patients who discontinued their treatment just because the side effects had a greater impact on their quality of life than their disease.

The azoles used to treat valley fever are used off label and at higher doses than they were approved for. Because of this, patients experienced more extreme side effects. When a patient goes to Dr. Google to find out information about how they're feeling, many of the side effects that they say they're experiencing are listed as reasons to stop taking the drug and talk to their doctor.

Patients and their families need more than awareness information about valley fever. Knowing the likely side effects of the drugs and the importance of continuing treatment can affect whether a patient follows treatment guidelines.

Page 62

Before a patient is treated with Amphotericin, they are given a cocktail of medications to control the side effects of the drug. When I'm given IT Ampho, I become almost instantly nauseated and I can actually feel my body react as the drug spreads and I become violently ill. Luckily, I have one bad day every ten weeks. Some patients need the drug two or more times a week. For those patients, there are no good days. These patients may skip treatments due to the side effects of the drug and many of these patients experience other difficulties due to the severity of their disease.

The burden of valley fever can be broken down into direct and indirect costs. The direct cost of the disease can be calculated pretty easily and estimating some indirect cost such as lost earnings are a little bit more difficult. But how do you calculate the emotional cost of deteriorating relationships with your family and friends, or the result of the isolation and depression which are, unfortunately, too common. Eight years later, I'm still battling with these things.

Page 63

The impact of cocci on quality of life is just as important to patients as the CF titer is to most physicians. For many of these patients, the quality of their lives have been reduced to a point where they're unable to survive independently, and many are dependent on government assistance of some type. There have been multiple times over the course of my illness that my family relied on assistance programs, and my family is still recovering from the finance destruction of chronic illness now.

So, the Valley Fever Institute at Kern medical was established in 2015, and part of our mission is to share the knowledge accumulated by our doctors in diagnosing and treating valley fever. More than 1,500 patients are treated by the Valley Fever Institute each year, many of us with severe forms of the disease.

Our coffee clinic sees over 200 patients a month, administers approximately 90 IV infusions of Amphotericin and 40 intrathecal inspections. Importantly, the Valley Fever Institute is moving beyond clinical treatment of patients to

Page 64

begin to address the socioeconomic impact of cocci. With the opening of the new Valley Fever Institute, we're able to advance our goal of moving to a 360-degree care model for our patients. We're adding social and support services in addition to clinical care.

We are a teaching, treatment and research facility and our mission is to improve patient care, promote education and awareness, and conduct research to benefit our community, and our research team is growing. It includes six physicians, a clinical pharmacist, a research nurse, many research assistants, and we're adding an infectious disease fellow in 2021.

At the Valley Fever Institute we have the largest population of valley fever patients and many have consented to contact for future research. In addition to providing a research source, our patients have provided our doctors with experience in treating severe cocci that they're able to share through CME and other educational events. In addition, our experts share their experience with

Page 65

unique and difficult cases through published case studies in academic journals and infectious disease conferences.

The patient program coordinator role, which I occupy, was established to address the difficulties faced by our patient population, provide education and awareness of valley fever to the public as well as provide information and resources to patients.

Cocci is a disease that has a disproportionate impact on the poor and marginalized members of our community. As a patient, I have a unique understanding of our other patients, which enhances the institute's ability to understand the patient perspective.

I still vividly remember my first appointment at a cocci clinic. Speaking with other valley fever patients in the waiting room, I realized that in spite of everything my family had been through and we were still facing, we were very lucky. Speaking to patients, especially ones recently diagnosed with disseminated disease, being able to

Page 66

offer hope and encouragement is the most rewarding thing I've ever done.

Working with the valley fever community and those fighting valley fever has given me a new purpose and energy and I've had a new opportunity to work with the doctors at the Valley Fever Institute who I credit with saving my life.

Patients are concerned first about how they feel, and a distant second about how the disease is improving. If you ask a patient how they feel, I don't know any one of them that's going to tell you that their CF titer hurt too bad to go to work, or they missed class today because their white blood cell count was elevated. The impact of the disease and its treatment on the lives of patients cannot be fully assessed by calculating hospitalization costs or reviewing patient records.

The use of patient-reported outcome measures provides an opportunity to record and evaluate the patient's self-assessed health or quality of life. The loss of quality of life here is substantial for patients who suffer from the most

Page 67

severe cases. There's been a disconnect between the clinical aspects of treating valley fever and the quality of life experience by patients that's beginning to narrow.

As a valley fever patient, I've been able to communicate with patients in a different way than a researcher or clinician would. My interaction with our patients as well as valley fever patients nationwide provide insights that benefit the patients as well as our doctors and provides a foundation for improved treatment and research.

The patient population at the Valley Fever institute is a resource that can be used for research into health-related quality of life. Current research at the Valley Fever Institute utilizes several different scoring systems to evaluate patient-reported outcomes for our research. And I'm very excited to say that along with our Psychiatry Department, our doctors are conducting research into correlations between cocci and depression, and we're hoping to expand on these efforts in future research projects.

Page 68

For patients newly diagnosed with cocci, treatment will be different from any illness they have ever had before. Patients who are used to a course of antibiotics or some over-the-counter medications for common infections are surprised to learn that even for uncomplicated disease, 3-6 months of medication or more is required.

The expectation that recovering from cocci will be like recovering from flu is quickly destroyed. However, we have the same treatment goals and expectations for cocci as any other illness. We want medications to resolve the disease and remove any impact of it from our lives. Patients are very concerned about the cost of medication. The out-of-pocket cost is the only cost that matters to us because that's what determines if we can afford it. For some drugs we must get special approval from our insurance companies, which is not always easy or approved.

Patients may also require the use of patient assistant programs to get the medication they need, and the more complicated and restrictive these

Page 69

programs are, the less likely that the patients who are the most at risk are going to be able to qualify without a support network -- either family, friends, advocates or navigators. And in order to benefit from new drugs, they must be available through insurance or other programs. So, documenting improved patient outcomes benefits patients, doctors and drug developers.

Manageable and minimal side effects are an important part of ensuring a good treatment outcome. The limited drugs available to treat cocci can have side effects that are as bad as the symptoms of the disease. Patients want to resume our normal lives. We want to go back to work or school and we want to spend time with our family and friends again.

Many validated patient-reported outcome surveys are available for evaluating the impact of cocci. When evaluating which survey will be best for your research project, there are some important considerations. First, patients want to be heard and many are eager to participate in our research. I've had patients from Northern California ask about

Page 70

driving all the way down to Bakersfield to take part in our research.

We have a high participation rate among our patients who have been asked to join our research studies. There are some important factors of our patient population that must be accounted for when considering which surveys to use. First, the population in endemic areas is heavily Hispanic and any survey must be available in the dialects of Spanish that are spoken in Mexico and Central America. And in California, a variety of other languages including Tagalog and Punjab are helpful to have available as well.

Low literacy rates among English and Spanish speakers are prevalent in the areas endemic for cocci. Materials that use simple language and limit the number of questions are necessary to ensure that surveys are accurate and completed.

What matters to research using materials for health-related quality of life and what matters to us as patients completing them are the same: how a patient feels, how a patient functions

Page 71

and the survival of the patient.

Thank you for your time, and I'm happy to share more information about my journey and experience as well as the experience and stories from some of our other patients that we have begun collecting. Again, thank you for your time.

SUSAN HOOVER: Thank you, Rob. We now have a period for formal public comments. There have been two requests received to give comments. This is a 15-minute interval, so these speakers will have about seven minutes each. Our first speaker is Klaus Romero of the Critical Path Institute. Dr. Romero is the chief scientific officer at the Critical Path Institute.

DR. KLAUS ROMERO: Thanks, everybody. Just a quick sound check that you can hear me?

SUSAN HOOVER: Yes.

DR. KLAUS ROMERO: That's fine. So, yeah, thanks for the opportunity. I'm actually very honored to follow Rob in his presentation to talk about real world data in how we can use and leverage real world data to optimize the design of clinical

Page 72

trials for drug candidates, both new drug candidates but also candidates for repurposing to treat valley fever.

So, I'm going to start by giving quite a bit of credit to both the agency and NCATS from NIH for the development of the CURE ID smartphone application. If you have not downloaded it, I strongly suggest that you do. It's a great application that allows clinicians to report their real-world experience with using both on-label and off-label drugs to treat infectious diseases. And, of course, valley fever, we posit that to definitely benefit from the clinicians from the trenches treating the patients, reporting their experience in a way that is not intrusive, in a matter that is easy to comply with, and without concerns for protected health information being disclosed through the application.

The specific application that we foresee for valley fever through the CURE ID program and the CURE ID app is to be able to capture that real world data of the experience of the clinicians treating the patients with their results for the

Page 73

different drugs that are used and the different experiences that are unique to each patient, as Rob indicated his very informative presentation.

And the intention is to be able to catalogue that real-world data to be able to then generate actionable hypotheses and identify signals that can be used to optimize the design of clinical trials for valley fever drug candidates.

But in addition, things don't just stop with leveraging the real world data to inform clinical trial design -- the intention is to also be able to have that information readily available for researchers to also facilitate the advancement of the real world evidence generation based on those real world data that are captured through the application.

So, around the CURE ID app, the Critical Path Institute has launched, funded by the FDA, the CURE Drug Repurposing Collaboratory or CDRC. And Marco Schito, who's on the phone with us today, acts as the Executive Director for this effort. The mission of the CURE ID -- of the CURE Drug Repurposing Collaboratory revolving around the CURE ID app is to

Page 74

essentially become that central global hub for real world data to be integrated and to leverage the real world data to generate real world evidence than can be then leveraged to inform and optimize the design of clinical trials to test different drug candidates against a myriad of disease, as I'll explain in a minute, but of course we definitely see -- and the Critical Path Institute being based in Arizona, we recognize the impact of valley fever, and we definitely recognize the opportunities that are ahead with the collaborator to impact drug development in valley fever.

So, this is a snapshot of how the collaborator is structured. So, we have the advisory committee made up of C-Path, FDA and NIH or NCATS representative. And then we have a different set of working groups that are focused on infectious diseases on one hand and certain oncology indications on the other hand. And you can see that we're running a pilot project with the disease of the hour, COVID-19, but we're very interested in setting up and formalizing the working group for valley fever. And

Page 75

being in Tucson, of course, we're in the stages of setting up the collaboration with the U of A, John Galgiani and colleagues.

And then we have the other working groups that are going to be dealing with the data analytics. That's more the world of the Quantitative Medicine Program at C-Path. And then, of course, a regulatory science workgroup that is going to interact with the regulators to, again, organize the real-world data into real world evidence that becomes actionable to optimize a whole process for medical product development against valley fever.

And another important aspect that is not captioned on the slide but an aspect that we incorporate in every single one of our collaborative efforts at C-Path is the patient representation. So, Rob, we would love to follow up with you after today to discuss options for collaboration.

And so, with that, I'll stop and -- I did it pretty much on time, so, yeah, that was that. Thanks again for the opportunity and we look forward to hearing from you if you are interested in

Page 76

participating in the collaboratory. And at a minimum, give CURE ID a check because it's really worthwhile as a resource for clinicians in the trenches. So, yeah, with that, I'll stop. Thank you so much.

SUSAN HOOVER: Thank you, Dr. Romero. And our final public commenter is Dr. Gray Heppner. Dr. Heppner is the Chief Medical Officer of Crozet BioPharma, and I'm hoping he will correct my pronunciation.

DR. GRAY HEPPNER: Thank you. Can you hear me?

SUSAN HOOVER: Yes.

DR. GRAY HEPPNER: Good. First of all, thank you so much for allowing me to touch on the related topic of vaccine development for coccidioidomycosis. A vaccine is needed, it's feasible and it's cost-effective -- but where is it? There is a strong imperative for a stronger public-private vaccine partnership to bring forth a much needed public health measure.

Who needs a vaccine? I think we've heard today from the very moving patient testimony,

Page 77

from epidemiology reports and from clinicians that a vaccine is needed. This disease is devastating, it's unavoidable and it's difficult to treat. And like so many problems in life, prevention is worth more than a cure.

Who needs it? It's people who live across the Americas, North America, Central America, South America. It affects the most disadvantaged people among us as well as people who don't think of themselves as disadvantaged. But a vaccine is clearly needed for these high-risk groups, older adults, very young, military personnel on training maneuvers, immunocompromised, working transplant patients, certain ethnic groups -- African-Americans, prisoners and people whose occupations do not allow them to escape the exposure to this essentially unpreventable exposure and disease.

I think it's worth bearing in mind some very simple observations about coccidioidomycosis. First of all, a valley fever vaccine is feasible. And why do we say that? Well, firstly, human infection is protective against subsequent infection of disease,

Page 78

demonstrating that almost all people's immune systems are able to mount an effective immune response after exposure.

A live attenuated spore-based vaccine has been developed. We heard about this earlier as a collaboration between Anivive, the University of Arizona, and other parties. The vaccine has already been proven safe and protective in mice and dogs against the human pathogen, and it's encouraging that a public-private venture is underway.

I would be remiss not to note the importance of public sector support, particularly DMID NIH support, which we heard about earlier, to facilitate the important basic science, immunology, proof of concept in preclinical models and toxicology. It's my point of contention that the same vaccine is likely to be safe and effective for humans that will require substantial additional work. This is a clinical grade manufacturing known as GMP, and careful clinical development to demonstrate actual efficacy.

So, like so many infectious disease problems that affect mankind, we know that vaccines

Page 79

are feasible, they've often times been demonstrated in preclinical models against human pathogens and yet they don't exist. The late Adel Mahmoud at Princeton as well as Stanley Plotkin and other advanced leaders in vaccinology made the observation that there are numerous infectious diseases that regularly claim untold numbers of lives around the world; that there are few vaccine candidates for combatting these ailments. The reasons are not new. The pharmaceutical industry may deem the markets not sufficiently profitable to recover investments, and government has not provided sufficient incentives.

So, what I'm referring to now is what we in vaccine development called the valley of death - the developmental valley of death, which is almost as foreboding as the valley fever itself. Looking from left to right, I think this is a well-circulated diagram outlining the basic fundamentals of vaccine development. It's important to both academics, and NIH funds the basic research, but after this, the translation into clinical development and eventual life insurance so that the countermeasures can be

Page 80

utilized are sadly lacking.

Incentives are needed for industry to invest in a vaccine to protect people at risk of these and other unpreventable diseases. People may ask why does cocci lag behind? Well, it doesn't seem to affect enough people to merit financial interest form pharma. CEPI, the Coalition for Epidemic Preparedness & Innovation, has addressed these gaps for diseases which affect larger groups of people. But here, we today are gathered to talk about why and what needs to be done to solve the valley fever problem. It does disproportionately affect poor and marginalized populations. The potential direct market has not catalyzed commercial vaccine efforts.

I'd like to mention and bring to your awareness today the Priority Review Voucher. This device, which is authorized by the FDA, would enable vaccine developers to develop vaccines because it would incentivize the development. It would provide a pull mechanism to reduce risk for vaccine developers who are on the margins or on the fences about investing the initial effort to bring something

Page 81

forward from proof of concept through GMP manufacture, phase 1, phase 2, phase 3 and licensure.

Recently, a group of academics together with support from certain Congressmen have asked the FDA to approve a Priority Review Voucher to incentivize the vaccine development for valley fever. This was not accepted and an appeal is underway. But I bring it to your attention today, and I thank you for this time, as a needed incentive to help develop a vaccine which would be of great benefit to people across the Americas. Thank you again for this opportunity to speak today.

SUSAN HOOVER: Thank you, Dr. Heppner. There will be a lunch period now, and please be back by 1:35 p.m., that's Eastern Time, for the start of session two.

(Lunch Break)

COURT REPORTER: It's 1:35 p.m.

DR. JOHN GALGIANI: Great. Hi. This is John Galgiani. I'm one of the session moderators for Session 2. Janis Blair is the co-moderator. Unfortunately, Janis is called away to cross-cover

Page 82

another physician at her medical center and she assures me that she'll get here just as soon as she can, but that's the reason you've got me alone for a little while here.

I am going to introduce the first speaker, who is Elizabeth O'Shaughnessy. Dr. O'Shaughnessy is a clinical reviewer in the Division of Anti-Infectives at the SEA. Dr. O'Shaughnessy?

DR. ELIZABETH O'SHAUGHNESSY: Thank you, Dr. Galgiani. Good afternoon, everyone. During the next 20 minutes I would like to cover regulatory and clinical trial design considerations which are applicable to the drug development for cocci. And this will be a high-level talk, and there is some overlap between this presentation and the FDA presentation yesterday, so participants who are attending both workshops may hear some of the same information.

So, by way of background, the FDA has recently seen renewed interest in drug development for cocci and, therefore, this is an opportune time to discuss this topic and for us to better understand the

Page 83

challenges involved. The general principles for antifungal drug development are similar in many aspects to those for antibacterial drug development, however, there are particular challenges with antifungal trials. For example, patient recruitment and, of course, financial challenges. So, this talk will include an overview of the regulatory approval pathways, available incentives, the general content of an NDA package, and clinical trial design considerations.

So, as you all know, there are two FDA-approved drugs for the treatment of cocci, Ketoconazole and Amphotericin B deoxycholate. And the current standard of care includes Fluconazole, itraconazole, or Amphotericin B in more disease. And other treatment options include azoles such as voriconazole or posaconazole.

So, at this time, we have no approved new drug application for cocci for decades but there is hope. Examples of investigational drugs studied in phase 1 human studies and in animal models of cocci, include VT-1598, Nikkomycin Z, Olorofim, and

Page 84

Foxmanogepix. And property available information on these drugs is available in the reference slide.

So, regulatory pathways for approval include traditional approval, which is generally based on a clinical endpoint measuring how a patient feels, functions, or survives. An accelerated approval is based on surrogate endpoint that is reasonably likely to predict clinical benefits or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality.

So, the limited population pathway or LPAD is for drugs that are intended to treat a serious or life-threatening infection in a limited population of patients with unmet medical needs. Examples of recent approvals in this LPAD pathway include Pretomanid as part of a regimen for the treatment of extensively drug-resistant tuberculosis or intolerant or nonresponsive multidrug-resistant tuberculosis; and then Arikayce for the treatment of pulmonary nontuberculous microbacterial infection.

Just to go into a little bit more detail about accelerated approval -- accelerated

Page 85

approval is appropriate for drugs and candidate to treat serious condition and generally provides a meaningful advantage over available therapies and demonstrates an effect ton a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit. It is important to note that the trials meet the same statutory standards for safety and effectiveness as traditional approval.

And this pathway has been primarily used in settings where the disease course is long, and an extended period of time would be required to measure the intended clinical benefit of the drug. So, it has less of a role in acute infectious diseases. And for drugs granted accelerated approval, post-market confirmatory trials have been required to verify the anticipated clinical benefit.

Now I'm going to switch to available incentives. And many of you are familiar with the Qualified Infectious Disease Product designation. Drugs being developed for treatment of cocci may be eligible for QIDP designation and it can be requested

Page 86

at any time before submission of an NDA. QIDP provides for an additional five years of marketing exclusivity for certain drugs and for a priority review for the first application for QIDP. And the priority review timeline is six months, as compared to ten months for standard review. And drugs that have QIDP designation are also eligible for fast track designation. And many of the drugs that currently have QIDP also have fast track.

So, fast track designation can be requested if the drug is intended, whether alone or in combination, for the treatment of a serious or life-threatening disease and it demonstrates the potential to address unmet medical needs for such a disease or condition.

And the information available to support designation will depend on the stage of the drug development. So, the supportive evidence could include activity in a nonclinical model, a mechanistic rationale, pharmacologic data, or available clinical data.

So, just some key points on fast track

Page 87

designation -- it allows for frequent interactions between the review team, including pre-IND meetings, end-of-phase 1 meetings, end-of-phase 2 meetings, etc. It also allows for submission and review of portions of the application known as a rolling review. And just to note that the designation may be rescinded if it no longer meets the qualifying criteria.

Then, finally, we have the breakthrough designation. For breakthrough therapy designation, the clinical evidence must show that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints. There is intensive guidance from the FDA on the drug development program beginning as early as phase 1. It could be eligible for priority review if supported by the clinical data at the time of the NDA submission, and the drug receives all the benefits of fast-track designation.

The remainder of the presentation will focus on the content of a new NDA application data package and on aspects of clinical trial design. So, when seeking an indication for cocci, at least one

Page 88

adequately controlled clinical trial is required with supportive evidence from nonclinical and in vitro studies are an indication. And for those with orphan designation, the statutory standard first needs to be met, which is effectiveness demonstrated in an adequate and well-controlled investigation.

So, supportive evidence from nonclinical studies include information on the activity of the drug, antifungal drug in vitro and in animal models of disease. And we just heard a very informative talk on the various animal models of cocci from Dr. Shubitz. Some considerations for the design of animal model studies are listed below. For example, information like the route of drug administration, the timing of the initiation of treatment and outcome measures such as survival and changes in fungal burden and target orients.

As we know, PK-PD assessments in animal models provide valuable information for design of clinical trials. The division does not have a preferred animal model of cocci to assess antifungal activity or for PK-PD assessments. Considerations

Page 89

should be given to the target infection sites when selecting an animal infection model. And PK-PD assessments from an animal infection model have the potential to aid in selecting a dosing regimen for clinical trials, characterize and compare the drug's activity from clinically relevant exposure at the target infection site, and provide supportive evidence for the drug's activity.

These are some high-level points on clinical trial designs. For non-inferiority trial designs, one must be able to provide a data-driven justification for the non-inferiority margin. A drug or regimen recognized as a current standard of care is acceptable as an active comparator and recent trials for invasive fungal disease have used the NI trial design.

A superiority trial design could include a placebo where it's feasible and ethical, an active control or an external control for single-arm studies, for example, with contemporaneous matched controls.

Moving on to clinical endpoints. So

Page 90

that we're all on the same page -- so, a clinical endpoint directly measures a therapeutic effect of a drug, an effect on how the patient feels, functions, or survives. Clinical endpoints for cocci will depend on the spectrum of clinical presentation or on patterns of disease, localized versus disseminated disease, for example, and characteristics of the patient population.

A cocci scoring system has been used in published cocci trials. One could consider a patient reported outcome measure, as mentioned in an earlier talk. And if a biomarker of disease is proposed, for example, a serological marker or cocci DNA, it should be reasonably likely to predict clinical benefit.

To define a PRO, a PRO is a measurement based on a report that comes directly form the patient about the status of the patient's health condition without interpretation of the patient's response by a clinician or anyone else. And PROs can be useful for clinical outcome assessments for chronic infections. And we look forward (inaudible) to the discussion and appropriate endpoints for cocci trials. This is a

Page 91

very important aspect.

What's the role of diagnostics? It's important that the diagnostic test adequately detects the disease of interest. This is especially important in non-inferiority trials to ensure that the population studied has the disease of interest. For example, we've used the Galactomannan test in invasive-aspergillosis trials for patient identification and definition of patient populations.

And, in general, diagnostic tests do not have to be FDA-cleared or FDA-approved for use in a clinical trial if being used for enrichment purposes. If the diagnostic test is not FDA-cleared, the information supporting the intended context of use should be provided. And qualification of a diagnostic as an endpoint is not a prerequisite for use in clinical trials. And as you know, the CDER Biomarker Qualification Program helps develop biomarkers as drug development tools.

So, the final word on safety -- obviously, safety of study participants is paramount. So, based on safety signals from nonclinical studies,

Page 92

appropriate safeguards need to be included in clinical trials. A safety database at the proposed dose and duration is likely to be small in cocci trials; therefore, additional safety data may be needed if there is a significant safety signal. Additional safety data may be requested through a post-market study or enhanced pharmacovigilance post-approval.

In summary, the presentation provided a high-level review of some key considerations for drug development for cocci, which include regulatory pathways and incentives relevant to antifungal drug development. And I just covered at a high level some trial design aspects, endpoints, diagnostics and safety considerations.

As always, we encourage sponsors to engage in early discussion and continue dialogue with the Division of Anti-Infectives, and particularly when planning novel approaches to clinical trial design. There are some references, and just before I finish, I'd like to acknowledge the contribution of Dr. Joe Shane, clinical pharmacology, and Dr. Bala in microbiology for their input, and thank you all for

Page 93

your attention. Thank you.

DR. JOHN GALGIANI: Okay, thank you, Dr. O'Shaughnessy, for the first presentation. I am the second presenter today. I'm, as I said, John Galgiani. I've been at the University of Arizona faculty since 1978, and for pretty much all of that time I've been interested in studying coccidioidomycosis, and in 1996 founded the Valley Fever Center for Excellence at the University of Arizona.

I'm also, in terms of disclosures, the chairman of the board and a significant stockholder of Valley Fever Solutions, which we'll touch on in terms of the development of Nikkomycin Z, or the attempts to develop Nikkomycin Z. It was the spinoff that we created for that purpose to help move this drug along.

So, the points that Dave Stevens and others made this morning about the impact of valley fever I think are very, very relevant. I'm not going to try to reiterate any of those. But I would like to make a comparison, which I find especially useful, between the impact of valley fever compared to the

Page 94

impact of polio in terms of rates per 100,000 people. And you can see that the average number of reported cases prior to their being a vaccine for polio was about the same per 100,000 people for polio as it is for coccidioides. And a parallel with polio occurred at about the same frequency as disseminated disease.

There's a small problem or difference between these two diseases in that polio is worldwide and cocci is down to a very constrained part of the world in those highly endemic regions.

So, like polio, I think of coccidioides as a biohazard, albeit for a small endemic population and the people who live there and the visitors. But in the same way it is a biohazard for Americans and for others in the Western Hemisphere. And where it's endemic, I think we've seen the evidence that this illness is anything but trivial. The impact -- overall economic impact that I am starting to use is about $1.5 billion annually, and that's based in part on Leslie Wilson's publication for costs of cocci to California, and we replicated that model for Arizona, and the two combined us just under $1.5 billion.

Page 95

Hers, Leslie's was for 2017, ours was 2019 for reference years. And I think the public health benefit clearly justifies the idea of trying to develop better therapies and, in fact, vaccines.

However -- and this is the point that I'll -- the lesson that I will try to emphasize in my presentation -- the business model for developing valley fever drugs and vaccines compete very poorly against other investment opportunities. And that's the theme that I'm going to try to develop here.

So, Nikkomycin Z has been around for a long time. These cartoons show you the resemblance of the drug, Nikkomycin Z, to the substrate for titin synthase and, in fact, Nikkomycin Z is a competitive inhibitor of titin synthases.

Here are a large list of fungi and their MICs, and the one I want to point to is the one on the top, which is -- sorry about that -- which should be looped around coccidioides, which is by far the lowest, .0625, compared to the other MICs in vitro.

Rich Hector in the 1980s published in

Page 96

1990 the experience of using Nikkomycin therapeutically in mice. And in his study he had eight mice that received no drug and eight mice who received Nikkomycin. And the eight animals, very similar to what Lisa Shubitz was showing -- they had fungal growth with 2 times 10 to 6 (inaudible) units per lung in the mice that got placebo, but in the Nikkomycin, seven had sterile lungs and one had a single colony grown. So, there was a very dramatic difference with the therapeutic effect of Nikkomycin Z that Richard found.

And if this were to hold up in human trials, this would completely reverse the strategy. And later, we'll be talking about therapeutic strategies. But basically the strategy is to wait until people develop complications and then aggressively treat them. If we had a cure for this disease, we would reverse that and try to diagnose as early as possible all infections and cure it before the complications developed.

So, the timeline as I said, this drug's been around for quite a while. It was discovered by

Page 97

Bayer in the 1970s. Rich Hector, the data that I showed you was done in the 1980s. In the 1990s, Shaman Pharmaceuticals initiated the development program for Nikkomycin Z, but then went out of business and that really slowed down progress, when the company goes out of business. And it sat for five years until the information and actually part of the GMP-made drug that Shaman had done was transferred to the University of Arizona, and we at the university started to try to move this drug forward and we made significant progress.

In 2006, we got orphan drug designation, which, as you heard, gives you seven years of exclusivity. We also initiated, because the IND had been inactivated, we reactivated it and formed Valley Fever Solutions to help us with development. In 2014, we obtained a QIDP designation which adds an additional five years to exclusivity, which for this drug, being as old as it is, creates much of what we depend on for protection for development.

And in 2015, we conducted a Phase 1, two-week multidose study in 32 subjects and in 2019,

Page 98

we had a pre-Phase 2 Type C meeting with the FDA. It was to be face-to-face in Washington, but there was a snowstorm, so from our hotel room we did it by telephone, but it was a very productive meeting, as those are.

And then we are continuing to improve manufacturing processes and David Larwood has been spearheading that, one of the speakers later in the afternoon. So this is some data just to show you the relationship, what we know about pharmacokinetics, shown here is the human data from 250 q.12 up to 750 q.8 in oral dosing. This is a couple of data points for mice on milligrams per kilogram on the X axis and dotted throughout here are dog levels that Lisa Shubitz did in a Phase 2 trial in therapeutics in client-owned dogs.

And shown here as the ED 50 and ED 80, are the effective AUCs in mice, and you can see that clearly the absorption is sufficiently good that you have good reason to think that if you went to a clinical trial with any of these doses, it would be done well and it would be certainly within the range

Page 99

you might expect to see therapeutic results.

Here is, over the last 15 years, the support we've gotten to do what I just summarized for you, and you can see numerous funding items from the NIH over the last 15 years. We've also had orphan drug grant money from the FDA and we've had philanthropic support from the JT Tai and Company Foundation and also the Valley Fever of the Americas Foundation, a foundation in Bakersfield.

Noticeably absent from this list is any private investment, and that's kind of the point that I'm going to try to make. This slide is not well formatted for you, but shows you the Phase 1, which goes up and Phase 2 that continues to go up and on the right hand, in log scale, is cost of drug development and as I think you know, even without this being appropriately formatted, that the costs just continue to go up.

Here we are at the beginning and this timeframe going through Phase 2 and on to, hopefully, approval at the FDA is where the real money is needed for the final push. And so just to summarize, then,

Page 100

my comments, therapy is clearly an unmet need. I use $1.5 billion, but it's certainly, without quibbling, that kind of a public health problem. The drug has a novel mechanism of action. Its pharmacologic profile is excellent and at this point, we see no evidence as yet of any untoward reactions to the drug.

The experimental data in the mice suggest it might be curative and the real issue is that development is simply limited by finances. And I think the take-home message is that the business models for new Valley Fever therapies compete very poorly against other investment opportunities. Future paths forward likely will require a government response to the public health need. I mean, this is a public health problem and it is easy for me to see how you might think that the -- it would be appropriate for a federal support to help with this.

So where could that support come from? Well, the FDA, we've heard some of the options they have. I'm going to focus on the Tropical Medicine Priority Review Voucher Program which just recently, they decided at -- to determine that the request for

Page 101

coccidioidomycosis to be a part of this program should be declined because it is -- has a potential significant market for a vaccine.

I was quite surprised at that determination and without going into that in any detail here, I think we are hoping and others may be hoping to put together a response to explain why we think they should reconsider that. Also, we've seen from the presentation from NIH now the SAnds is being supported by NIH in the past and I think Neil Ampel will likely touch on the Mycosis Study Group, maybe Tony Catanzaro as well, about clinical trials we've done in the past with NIH Contract Support.

That could certainly be resurrected, but I think it would take a lot and I think we would get a lot of benefit, in fact, from that kind of support. And then finally, I think since I see this as a biohazard that BARDA could easily be thought of as appropriate to consider support for this. Even though it's not a worldwide problem, it does impact greatly Americans who live in or travel to these endemic regions.

Page 102

So those are generally the comments I had. I think that was my last slide and I thank you very much for your attention and I see we're doing very well on time and so I think with that, let me introduce our third speaker, my good friend, Tony Catanzaro.

Dr. Catanzaro is a professor of medicine at University of California San Diego who's been working in the field of chronic pulmonary infections including cocci, focusing on therapeutics and diagnostics. Tony.

DR. ANTONINO CATANZARO: Thank you very much, John, and thank you to the organizers for inviting me. Can you hear me okay? Is sound coming through okay?

DR. JOHN GALGIANI: Yes.

DR. ANTONINO CATANZARO: Okay, good. So yeah, thank you very much again for this invitation and to provide a kind of -- almost a 50-year overview of studies that I've participated in with a variety of colleagues and we had a really good start, as you point out, John, with the cocci study group when I was

Page 103

kind of lost at a California Thoracic Society meeting with nowhere to go and Hans Einstein invited me to go to the cocci study group meeting, which was an ongoing organization at that time and over the years, has developed quite nicely from a casual kind of sharing of common interests into a very organized, scientific organization for the presentation of data and for the support of, at least emotional and scientific support, for studies of various kinds.

And I'm happy to say that the cocci study group had a big part in my development and Neil is going to go on and talk about future developments as was pointed out.

But one of the things that I learned very early on is that the immune response to cocci was very, very important and back in '72, it was recognized that if you had -- if you didn't respond by a skin test 1 to 10 coccidioidin, your chances of having a very poor outcome and actually dying were quite substantial.

And based on that, I undertook a number of studies of the cell mediated immune response, kind

Page 104

of translating it from delayed type hypersensitivity, cell mediated immunity and demonstrated a lot of T cell dysfunction, both in lymphocyte transformation and migration inhibition factor and other in vitro studies of cell mediated immunity, and recognized the similarly to the model that is shown here that Ward Bullock presented for leprosy where delayed type hypersensitivity was inversely coordinated with the clinical disease, so when the disease was localized with leprosy, there's a good delayed type hypersensitivity response, went it disseminates and these become more severe, delayed hypersensitivity is markedly impaired.

And that's very much the situation that we saw with cocci and it's kind of made me think I was aware of some studies that Sherwood Lawrence had done in 1955 with transfer factor, which is a set of proteins, soluble proteins derived from peripheral blood that have the capacity to transfer delayed type hypersensitivity as well as cell mediated immunity from people who didn't have to people who had it -- to people who had cell mediated immunity to people who

Page 105

didn't have it.

And I wondered if this could help the response in patients with coccidioidomycosis, and so initiated with a whole bunch of colleagues, and I think this is an important point to emphasize that each study on coccidioidomycosis require a collaborative group. There's no one center that really sees enough patients to do a meaningful study and you've got to bring people together.

At that time, amphotericin was the drug of choice, in fact, that only drug available and so patients were having a tough time and so we decided to continue the amphotericin but simply add transfer factor. And we thought we had a really nice response with 30 patients out of 49 having a favorable response, but obviously without any controls, it was hard to know what that really meant.

And so we put together a plan to do a double blind study, but NIH declined to fund it and so we established the Cocci Cooperative Treatment Group, a small group of unfunded trials, and we used the same model where patients were treated with amphotericin

Page 106

and transfer factor was added, but we did a double blind. The transfer factor from coccoid in positive donors, transfer factor from cocci negative donors, and normal saline as a control. And unfortunately, we were unable to see any different in the three groups, whether by skin testing, by cell mediated immune responses, or by clinical results.

So it was a complete failure. Luckily, right around that time, there were a number of drugs becoming available and we launched a series of studies over the 40-some years which I'm going to review very, very briefly today, starting with ketoconazole, and studying patients with chronic pulmonary coccidioidomycosis, and looking also at patients with disseminated coccidioidomycosis, and I think that this really started to bring home the fact that chronic coccidioidomycosis is a very complex clinical manifestation.

So in those days, the standard of practice was not to treat people for cocci unless they had symptoms or disease for six weeks or longer. That meant we had chronic disease. But once you got to

Page 107

chronic disease, they went on for literally years and just having a clinical response or, say, serologic response was simply not enough.

You can see here that the responses were not that good for pulmonary disease and were a little better for disseminated disease, particularly for synovitis, and for abscesses, but when you get to osteo and abscesses, fistula, the persistence of lesions was a really major problem with ketoconazole.

So at that point, we started to look around and saw the mycosis study group had a scoring system and we thought that would really be a good idea to try to put that into effect and David Stevens started to talk about that and we had a clinical score based on clinical criteria, on radiographic criteria -- - obviously, this was focused more on pulmonary disease -- and the serologic response.

And with that kind of a tool, we're able to see for infiltrative disease we see right at the beginning of disease, showing the scores across that most patients had rather high scores, and then at the end of treatment, they had low scores.

Page 108

So it really worked well in infiltrative pulmonary disease and in soft tissue disease, but we started to see weakness appear with disseminated disease and with cavitary disease that the responses were significantly less good when we broadened the look from just the presence or absence of cocci in the sputum to a broader mycosis study group analysis.

We moved on to fluconazole, and initially started with low doses of 50 to 100 milligrams in 14 patients and found that they were definitely responsive, but relapses happened very, very quickly and in very high numbers, so 50 to 100 milligrams is clearly not enough fluconazole.

This was backed up by in vitro studies with serum concentrations of fluconazole at 50 and 100 milligram dosages and then with the good news that it went on into CSF and so that opened up the possibility of looking at meningeal disease and so we had a one-armed study looking at 50 cases of cocci meningitis treated with fluconazole and we had very nice responses.

Page 109

And I might say that there were no withdrawals due to side effects, and at that time, we thought that fluconazole had little or no side effects, to this was pointed out by the patient centered group, the side effects really were significant, they just did some -- were overlooked in those initial studies, and also were really relatively low doses of 400 milligrams.

Moving on, we started a very nice study with the mycosis study group involving chronic pulmonary and non-meningeal disease and we had -- where patients were started at 200 milligrams and non-responders were moved up to 400 milligrams, and we see here the slope down very nicely over a period of time and then with the double blind study, which everybody talked about, where we looked at fluconazole 400 milligrams versus itraconazole 200 milligrams in patients in patients who had progressive, non-pulmonary -- excuse me, nonmeningeal cocci.

We used the mycosis study group scoring system at four, eight, and 12 months and we saw that at eight months, 63 percent responded to fluconazole;

Page 110

63 percent responded to itraconazole, so they were pretty equivalent. For skeletal disease, there was quite a difference with 57 percent responding to fluconazole and 76 percent responding to itra, but he P value wasn't really high enough and the big bad news was that relapse rates were significant with 28 percent following fluconazole and 18 percent following itraconazole.

So this is the good, the bad, and the ugly of fluconazole treatment that response rates were pretty good, but relapse rates were rather significant when drug was stopped.

We went on to look at nonmeningeal disease with posaconazole which was the first drug that gave us any indication that there might be a fungicidal drug. All the drugs up to this point are fungistatic, but posaconazole had in vitro evidence to suggest it was fungicidal, so we launched a study and enrolled 20 patients.

Unfortunately, the study was stopped at 173 days before the pharmaceutical company observed toxicity in animals that they felt was simply

Page 111

unacceptable with the development of tumors in animals and so they stopped the study, but we looked at the results and we found that four had cultures at the onset -- at the end of treatment, four had converted to negative. Nine had a satisfactory response and side effects were quite limited, so posaconazole looked really nice in this very brief study of only six months of treatment.

So in summary, cocci is a very complicated infection where simply eradicating the fungus is just the beginning of the response to treatment. There's a lot of tissue damage, particularly in the lungs with chronic pulmonary disease and that tissue damage opens the way to secondary infections so that patients can get rid of cocci and still be highly symptomatic and be quite sick; and conversely, patients can be quite asymptomatic, even with positive cultures, so it was really complicate and requires an assessment to be multidimensional.

And again, that multidimensional aspect we need to look at side effects in a very detailed way

Page 112

and the impact on the quality of life, both the disease and the treatment are very significant and were not at all recognized in these early studies but has really come to bear fruit in recent analysis as was pointed out very nicely by the patient centered presentation we heard earlier.

So we evaluate a series of increasingly effective antifungals and maybe we're going to get to fungicidal drugs, but starting with the fungistatic drugs, there's often relapses following initial treatment.

So I want to acknowledge the pioneers who participated in the cocci study group when I first started up, and the continued activity of the cocci study group, its evolution from sharing tales to a really scientific group which is embarking on a new frontier and I want to acknowledge the many, many people who have shared my interest and enthusiasm and point out that all the publications that I referred to have been with collaborated -- hasn't been a single pub that I've done with single authorship, not one.

And I want to thank the sponsors, both

Page 113

NIH and CDC and pharmaceutical houses. A lot of the studies that were presented were funded in part by NIH and in part by pharmaceutical houses and I obviously have to point out the patients who've been incredibly tolerant in looking for new diseases, new treatments, despite the fact that both the disease and the treatment have great side effects. Thank you very much for your attention.

DR. JOHN GALGIANI: Tony, thank you very much for your presentation. Our next speaker is Dr. Royce Johnson. Dr. Johnson is an infectious disease specialist with many years of experience in multicentered, large and small clinical trials and serves as medical director of Valley Fever Institute at Kern Medical Center. Royce.

DR. ROYCE JOHNSON: Thank you, John, and thank you to the organizers. It's my pleasure to be able to share some thoughts that come on the tail of many of the things that have been said today. Wait a minute. This is -- I'm having trouble advancing the slide. It's not working. Let me try the computer. No. Where's the arrow? Okay.

Page 114

DR. JOHN GALGIANI: Royce --
DR. ROYCE JOHNSON: So this is my only disclosure. I'm having trouble still with slide advance.
DR. JOHN GALGIANI: Royce, below the slide there's a left and a right arrow on your --
DR. ROYCE JOHNSON: I saw those and I was clicking on it, but it didn't want to move. Okay. So we skipped a slide. Can we go back? Yes. So I want to -- there's been several mentions about the MSG scoring system and the second part of my talk, I'm going to talk about this extensively, and I think it has been very important in the history of coccidioidal investigations. This was spearheaded by Bill Dismukes. I had the honor of knowing him and all four of the other authors, two of whom, I think -- one of whom, I'm sure, is here today with us electronically and that's Dave Stevens, but also Jack Bennett was one of the authors along with Dick Graybill and Stat Jack Remington. Those five, I knew them all. Some more, some less.
This, my data comes on the tail of

Page 115

David and John's and I actually -- the 150,000 number I have up there was from a David Stevens article. I do have some sources that think that the number of actual infections per year could be as high as 350,000. David quoted 200,000. The fact of the matter is, I don't think we know, but I'm guessing that most of the estimates are actually on the low side.
We all agreed based on C.E. Smith, that 60 percent of the infections are asymptomatic, 40 percent are symptomatic. About 10 percent are diagnosed and these are largely pulmonary and slightly different number than David; 1 percent disseminated which at the low end would be 1,500 infections a year. About half of these are meningitis and about half are not meningitis, meaning any other place in the human body can be infected with this fungus.
There's some problem with advancing the slide.
WOMAN 1: If you say next slide, we can advance for you on our end. Just let me know if this is the correct slide you should be on and we'll go

Page 116

from there.
DR. ROYCE JOHNSON: Go back one. Let me just see where I was. Yeah, next slide, please. I'll just do that because I'm having trouble getting it to advance.
coccidioidomycosis is a very complicated host-parasite relationship and Tony touched on that with his early transfer factor studies and studying the immunology of this disease and its immunogenetics is a key, I think, to going forward with disease understanding, but not our subject for today. Severe disease is failure of host defense, in my mind. Most of the time, I think that being more significant than differences in coccidioides pathogenesis or virulence. So the solution to this is newer and better antifungals, the main talk today, also immunomodulators and, of course, the holy grail being a vaccine that's effective. Next slide, please.
The original MSG score was aimed at all fungal infections, not specific for cocci; although, there was specific reference to cocci and its chronicity and difficulty. It was generic. Since

Page 117

1980, obviously, we've learned a bit about this disease, perhaps not as much as I would have hoped, and the original MSG did not deal with the variety of nonmeningeal sites that occur. So I'll come back to this a bit later in the talk. Next slide, please.
So we looked at all the studies where the MSG score had been used in cocci, many of which have been shown to us by Dr. Catanzaro. We also looked specifically at the search engines. We looked at the data from the FDA in their 2017 draft publication about multiple endpoints in clinical trials, which I'll come back to. In fact, first we're going to talk about clinical trials and the things we need to accomplish and second, we'll talk about revisions we've made to the MSG 2020 score that we think would make it a better tool for conducting trials. Next slide, please.
So in getting a drug approval, you have to show two things. In the olden days, it was only number one, safety. But then came along the idea that you actually had to show drugs worked before you could sell them, and the concept is substantial efficacy.

Page 118

Next slide, please.

So I'm not going to spend any time on this, but the FDA, I think in particular wants to be sure that you conduct a trial that is not a chance win, meaning that the odds that the result occurred has to be something like less than 1 in 40. Then you have to have clinical importance, as in preventing death, but preventing mortality and other benefits are more difficult to prove but equally worthy. Next slide.

I'm not going to go into this. Again, all of us are aware of this, that have ever done any kind of science, so the statistics of showing efficacy. Next slide, please.

So endpoints have to be designated prospectively. Although I would -- of interest, I looked at remdesivir study recently and after the trial had started -- of course there was something of an urgency, wasn't it -- they actually changed some of their points during the course of the trial, but this is considered to be tacky unless you're dealing with an emergency. I'm not making any particular negative

Page 119

comment about that trial, but at any rate, the endpoints need to be of three types: primary, which should be single or few; secondary; and exploratory. Next slide, please.

So we have to control prospectively, most of the time at least, endpoints. So if it's specific point in time and I think this could be a bone of contention in terms of cocci studies in particular. You'll notice that the MSG 2020 study or the MSG 20 study that was ITRA versus FLU that had a significant relapse rate was a one-year study. That's actually one of the longest studies that's been done in cocci.

So the time to success in this fungus is longer and picking that time is, I think, critical to showing efficacy, albeit, if we had new fungicidal drugs, conceivably that time point could be moved back. Exploratory studies would have to be done, I think, to try and demonstrate that. You have to also define the population that you want to study and for the most part, our interest has been in studying people with disseminated disease, that very small part

Page 120

of the population.

The SAnds-PCC study is really the only major large study that is now ongoing and many of us are participating in that has tried to look at primary disease. Then also at the beginning of the trial, not later, you have to have an analytic program. Next slide, please.

And that -- to show treatment effect, you have to have a point time estimate. Obviously, you have to have a P value, and to determine the significance, you have to have a confidence interval. Next slide.

So cocci, as has been discussed at least somewhat, is a very complicated illness, in the sense that it's actually not an illness. It is a whole series of illnesses that are caused by the same fungus. It is going to be very difficult to not have multiple different outcomes in a cocci trial because of the nature of the disease.

But the FDA in its wisdom has actually guidance in that document that I referenced earlier for having composite endpoints and you can have more

Page 121

than one clinical outcome, but all the outcomes need to be affected by the treatment and they need to be reasonably similar clinical importance. That last part is a bit of a stretch, but I think we can make those. Next slide, please.

So multicomponent endpoints, within patient, two or more components. Observation of the specific components in that patient. You have to come up with a single overall rating determined by specific rules, hence the score system. The next words, ordered categorical or continuous numeric scales are deemed appropriate. I think this means that you can use ordinal or numeric data, either one. Next slide, please.

So the MSG done in 1980 was about improving clinical relevance. Some parameters that are used in that score system are actually not easy to reproduce. I think many of us have had the experience of having our forehead temperature checked as we come in to work and found out that on a cold day, our temperature could be 93.5.

So despite the fact that Santorius was

Page 122

measuring clinical temperatures in 1592, and this became a common measurement in the 19th century, we've eliminated it from the score system. I know this is anathema to infectious disease doctors who basically view themselves as general practitioners for people that have a fever, but we removed it.

Headache, again there were scores in the meningitis sections of the MSG score for severity of headache. We have great trouble thinking that we would get reproducible data from a variety of patients in a variety of sites on monitors like that. So we have made significant changes to the score system. Next slide, please.

So we looked for relevant clinical manifestations of disease and variables that were easily reproducible, especially across centers. Next slide, please.

So we retained pulmonary and nonmeningeal as one score system, although I would point out that, in fact, unlike the original MSG which concentrated on chronic pulmonary disease, we didn't include it. I think chronic pulmonary disease and

Page 123

drug studies don't mix nicely, so we're really talking about acute or really severe pulmonary disease and the score system as reconceived by our group.

Meningeal disease remains a separate score system, although conceivably, they could be combined if a study called for that. Severity is based on clinical parameters, laboratory and radiologic data. Next slide, please.

So this is one of several slides that I'm not going to go through, in fact, which is the MSG 2020 score system. NMD means nonmeningeal disease, so it's divided into meningeal and nonmeningeal, so this first set of slides is the nonmeningeal piece of the score system as revised. So we have general things on this slide -- next slide, please -- including the skin test, you might notice.

The pulmonary section was revised a lot because we decided to look at severe pulmonary disease rather than chronic pulmonary disease, so we've divided it into people with modest respiratory failure, the next line being people that have the minimal requirement for ARDS. The next series of

Page 124

sections involve specific organ systems that are involved in the disease. The first one is skin, which is by and large the mildest disease. Next slide, please.

And then we went on to subcutaneous, joint, and bone, all common site. Next slide.

Intraabdominal, not a very common site, but we do see it. Lymph node disease, as was demonstrated in a slide of one of the previous speakers. Then we left another slot for other sites of dissemination, so that included the retina, which we had a nice picture of earlier, or the epididymis -- both begin with I -- E, I mean. Next slide, please.

Then we retained the complement fixation titers. We endeavored to shrink it. Some of my colleagues balked at the -- how much we shrank it. There is a question about this creating too much weight on the complement fixation titer, but unsaid by anybody at this meeting, the complement fixation titer is both diagnostic and prognostic if it's performed in the right laboratories, and for diagnosis and prognosis in studies, there has to be tight control of

Page 125

where the laboratories are done, otherwise these are of no benefit for diagnosis or prognosis, either one.

We also gave scores for diagnostic criteria, but we decreased the weight on these as they're not easily available for all patients. Next slide, please.

So to -- we also changed the categorization of scores in terms of percent reduction. As was pointed out earlier in the original score system for nonmeningeal disease, you had to have a 50 percent score reduction to be called a success. We adopted this terminology from the oncology literature and so we have responders, partial responders, non-responders, and progressors. This may be contentious, but this is what we're thinking that we might so. Next slide, please.

This is the meningitis section. We reordered the wording for level of consciousness to modern Plum and Posner definitions. We also include a section which we have liberally borrowed from our cryptococcal colleagues on intracranial pressure, an absolutely key thing to take care of in cocci

Page 126

meningitis. We have some advances in neuroradiology that I won't go into. Next slide, please.

We retained spinal fluid, as I call it, the currency of cocci meningitis because you clearly can have patients that feel wonderful on treatment but have a spinal fluid that still looks terrible. Actually, this has been a bone of contention between John and myself for the last, how long, John? Twenty-five years? Next slide, please.

So we retained the greater than 40 percent requirement to be called a success in meningitis, but we did again add this oncology looking partial responder, non-responder, and progressor idea to the score system analysis. Next slide, please.

One second. I lost my picture. Rob of our group gave a very nice talk about patient suffering with this disease, which I noted when -- every early in my career in cocci going back a lot of years of people that suffered personal, financial, and of course mortal results from the disease.

So at the suggestion of Jack Bennett, we think that we should add to any analysis in any

Page 127

study we do an analysis of patients' perception of their illness and the results of their treatment and so the vehicles for that, the SF 12 version 2 is being used along with the PROMIS and the SAnds-PCC, so we have some familiarity with that.

Jack actually suggested the SF-36 which some of my patients have objected to that when we've tried it because of its length, and then in talking with John Rex, the EQ-5D-5L he thinks is a beneficial way to gauge outcome in trials. Perhaps on its own merits only. I think it don't quite agree with him yet, but who knows. Next slide, please.

So in conclusion, we've endeavored to develop a more complete and objective system of evaluations and parameters that are clinically available and reproducible and hopefully could meet FDA guidance in an appropriate endpoint -- composite endpoint. Next slide, please.

And from Bill Dismukes and his co-authors, two of whom I think are present, "We hope the spirit of these remarks will spark lively discussions as well as constructive criticism, challenge, and

Page 128

controversy... if indeed such healthy discussion, argument, and dialog ensues, then we will have satisfactorily accomplished our goal."

And again, I want to thank my collaborators at the Valley Fever Institute, Jack Bennett for looking at some of our thoughts before this talk, and John Rex, as well. And thank all of you for your attention.

DR. JOHN GALGIANI: Thank you very much Royce. That's very good and I'm delighted to say we've done wonderfully on our time. We're now here for a break and I think we'll just reconvene at the time schedule which is 2:55, so we'll have a little more than 15 minutes to get started. I think we should stay at time so the people that were planning to be on this agenda by the announced schedule will find us there at the time we're supposed to be after the break. So 2:55.

(Break)

DR. JOHN GALGIANI: John, are you with us?

DR. JOHN REX: I am.

Page 129

DR. JOHN GALGIANI: The floor is yours.

DR. JOHN REX: Okay, I just managed to -- come on, computer. Here we go. There's a button on my keyboard that locks up my screen and I bumped it. So anyway, so John Rex here from F2G and many thanks to the organizers. It's actually been a very interesting conversation. It's good to get the community together.

There are five industry speakers. We have loosely coordinated, but it's really mainly so that we would each come up with somewhat different topics. There'll be some repetition and -- but our theme was pick something out of what we have learned and try to tell that story. And so here's the story from F2G's perspective.

So understand the point I want to make, you need to know a little bit about the compound we have in Phase 2. It's called olorofim. It's a novel mechanism antifungal that inhibits pyrimidine biosynthesis. Its broad activity against the ascomycete mold fungi, so aspergillosis, Lomentospora, Scedosporium, all those things, but also histo,

Page 130

blastospora, cocci, all the endemics.

And it has a very potent activity. It appears to be fungicidal. It does not, however, work for candida, crypto or (inaudible) because the inside target is completely different, just is never going to work.

Dosed as a 30-milligram tablet, it has FDA Breakthrough Therapy Designation based on its preliminary clinical data and its now in the middle of a Phage 2 open level study, patient with mold invasive fungal disease where the patients have limited treatment options. Now, the point that I want to make is that because of some data I'm going to show you on the next couple of slides, we got interested in the question of how could you design a randomized trial in cocci, and this led us to the theme with endpoints.

We've already had some discussion about that today and I think we'll discuss it more during the Q&A. The endpoints that I'm most familiar with for antifungals are, they'll some out of the classic invasive molds trials. So 42-day all-cause mortality is a reasonable endpoint for acute pulmonary invasive

Page 131

aspergillosis.

It does get entangled with underlying disease a little bit, because patients who get this infection also are -- have underlying syndromes that put them at risk for dying for other reasons, and it doesn't work at all for infections that progress inexorably but slowly and that's going to be the case with cocci.

EORTC-MSG built over time to an overall clinical response endpoint that was described in 2008 and it is built from clinical, radiological, and mycological responses and overall success logically requires improvement on all three of these sub-elements; whereas failure is likewise obvious, but the category of stable, sort of an in between state, is -- exists and is categorized as a failure.

And you can be a failure, for example, by feeling better, but your radiology hasn't yet improved. Same radiology but you feel better. That can lead you to being a stable failure. And you know, like the 423-day all-cause mortality, this system works okay for the relative acute pulmonary invasive

Page 132

fungal disease, especially IA. But it -- this turns out not to work very well for cocci and the theme I'm going to bring up here is that we need something else because symptoms improve way before radiology and mycology and the idea of a PRO is definitely going to come up.

So here's a little bit from our dataset. IN this study, as of about 10 days ago, we had enrolled seven patients with symptomatic cocci. They fall into David Stevens' category earlier of active, progressive disease: lung, brain, bones, skin. They had all had significant prior therapy, months, in some cases years, with existing agents but they all, at the time they were enrolled, had active disease. They had problems that were not being solved by what they were receiving. At this point, they have been on the study for -- add about 10 to these numbers, but basically a few weeks to over a year.

All of them have noted clinical improvement within one to four weeks of initiating olorofim. Major improvements in activities of daily living and functional mobility. However, their

Page 133

radiology and their mycology changes at a snail's pace and a case is instructive.

So this is a patient that we presented or tried to present at ECCMID this year. You can find the abstract in the ECCMID abstract book. A 45-year-old male with diabetes who had mild CN -- clearly pulmonary and CNS disease. The CNS disease wasn't a big deal. It was his lung disease that was really problematic. Progressive dyspnea, weakness, fatigue, fevers.

He even had needed supplemental oxygen. He was staying home using a walker and really suffering and he got a little bit of everything over time. You can see this list of drugs. It was not making him better. He kept coming back to the ER because he couldn't breathe.

We enrolled him on the study in May of last year.

DR. JOHN GALGIANI: John, are you still there? I don't hear Dr. Rex.

DR. JOHN REX: I'm back. The call got dropped. Sorry. Can you hear me?

Page 134

DR. JOHN GALGIANI: Good, and John, unless you have some other arrangement with the others, you're going to need to wrap this up in the next minute or so.

DR. JOHN REX: Okay. Well, I am about to be done. So this guy steadily improved but at day 85 he was -- clinically he was better, but he was, as an overall response, he was a stable failure. I can tell you he's gone on. He would actually now be an EORTC partial response based on improvements of radiology.

If not EORTC-MSG, then what? I would just say that we've explored the idea of EQ-5D-5L which uses a point score of 1 to 5 across five dimensions of how do I feel and you code it numerically and we'll still need to say that he did not fill this out prospectively. We weren't smart enough at the time to have this in place. We have it in place now, but qualitatively, what he did with his improvement is similar to what we see in the other patients, too.

So in summary, we have a clinical

Page 135

response approach based on the EORTC-MSG but it's actually too slow. The clinical improvement is -- gets way out ahead of radiology and serology and that actually leads to stable disease for a long, long time that gets categorized as failure.

Further, disseminated cocci is quite diverse. It's -- there's no real one set of symptoms that's going to match everybody, as was -- been discussed, and so a suggestion from our date is that something really simple like EQ-5D-5L and maybe the NIH PROMIS score could be used is not clear cocci-specific elements are going to be all that helpful because of the varied disease syndromes. Thank you.

DR. JOHN GALGIANI: Thank you, John. Glad to have you with us. Our next speaker is Ed Garvey. Dr. Garvey is a consultant for Mycovia Pharmaceuticals. Ed. No, that's not Ed's presentation. That's half an hour from now. Ed, do you have any slides?

DR. ED GARVEY: I do. I do, John.

DR. JOHN GALGIANI: Okay. AV, we need -- to have slides for Dr. Garvey?

Page 136

WOMAN 1: I'm sorry. Let's just take a two-minute break. They should be loaded and --

DR. ED GARVEY: I could do this without the slides. I could do it very quickly. It's a very simple presentation, if that helps.

DR. JOHN GALGIANI: What say you, AV?

WOMAN 1: Are you there?

DR. ED GARVEY: Hello?

WOMAN 1: Yes, go ahead and please proceed. I apologize.

DR. ED GARVEY: No problem, no problem. So thanks to the FDA for organizing this and for inviting Mycovia. Quickly, who is Mycovia? Mycovia is really the continuation of Viamet Pharmaceuticals and we have focused on developing the next generation fungal CYP51 inhibitors by rationally designing an increase in potency and selectivity.

By definition, maximizing the therapeutic index to be able to achieve greater clinical efficacy with little or no side effects. We have two compounds that are in development, 1161 is our lead compound that is now in three Phage 3 studies

Page 137

to be finished this year.

The subject of this talk will be 1598, and the -- really, there's two messages I want to give. One is our experience to date with developing 1598, and that is the fact that we've done it by and large through external funding. So that's the message I want to give and it's similar to what John gave earlier that there are a number of different avenues that you can explore and we've taken advantage of these, a lot of them through NIAID and we've had R21/R33 grant through NIAID. We've had numerous contract services through NIAID and we also had a large DOD grant that really covered a lot of our GLP safety studies, so by and large, we were able to get 1598 through the IND with external funding.

We hope to also do a lot of the clinical development. As Erin mentioned earlier, 1598 is poised to start its SAD study through DMID. They are actually performing -- conducting that study and we've proactively looked at a number of opportunities to do the MAD study and to do Phase 2 and 3, again, through external funding. We've taken a large

Page 138

advantage of all the incentives that are available through the FDA and we've, of course, used external KOLs in terms of shaping our clinical design. So that's the path in terms of 1598.

The message I want to give as far as the future, is that we are continuing to use external funding to progress 1598 and as John mentioned in his talk, you're almost forced to do that because of the lack of support that is seen either through large pharma in terms of partnering or in terms of funding opportunities through other avenues.

So and the other part of the puzzle that we're grappling with is not only funding but how to actually do the Phase 3 study in cocci, because of all the points that have been raised both yesterday and also today in terms of endpoints and disease definition and numbers of patients, et cetera, et cetera.

So therefore, our current development path for 1598 is to focus on crypto -- cryptococcal meningitis. We feel like there are a number of external funding agencies that could provide funding

Page 139

for those studies and the medical need for crypto is so huge it's hard to ignore and in addition to that, the importance of having very robust networks that have been built by folks like Tom Harrison and Jeremy Day make that a doable approach, we feel, and that in parallel to that, we hope to possibly explore cocci by a grant, possibly a U01 grant opportunity and to use a design that has been talked quite a bit about in a Phase 2 type POC study.

The only other thing I want to mention is a couple thoughts that have -- were raised yesterday to increase the enrollment numbers would one consider expanding to all endemics, histo and blasto, or would that complicate matters too much, and I think the consensus yesterday was that it wouldn't, that the increased enrollment would outweigh those disadvantages.

And then the other idea is to really focus on crypto as our additional robust clinical trial design and approval in establishing a robust safety database and then possibly is there an avenue to get approval for cocci through a smaller study,

Page 140

like I just described.

So those are the key messages I want to basically repeat that have been said over the last couple days and I'll turn it back to John.

DR. JOHN GALGIANI: Thanks so much, Ed, for your presentation. Our next speaker is David Angulo. Dr. Angulo is chief medical officer at Scynexis. Dr. Angulo, are you with us?

DR. DAVID ANGULO: Thank you. Thank you very much, John, for the introduction and thank you for the invitation to participate in this workshop. So I see that aren't really my presentation, which is -- should also be there, but let me just briefly introduce you why we're interested about -- why we have an interest about this topic.

We are developing ibrexafungerp. This is an oral glucan synthase inhibitor. It's structurally distinct from the other glucan synthase inhibitors that are right now out there like the echinocandins and as such, it has oral bioavailability and it has activity as suspected for the glucan synthase inhibitors for candida, aspergillus,

Page 141

pneumocystis, and also for coccidioides and the other endemic microbes as well.

Interesting, we have some very high tissue distribution, so typically the concentrations that we achieve in the tissues are very, very high -- higher than they will normally see, let's say, with the other glucan synthase inhibitors, and we are conducting -- we have conducted a series and we are conducting a series of different clinical trials in different indications. We have completed our Phase 3 programming in vulvovaginal candidiasis. We are ongoing with our studies in recurrent VVC, invasive aspergillosis, and Candida auris infections. And for the interest of this particular talk, we do have a new study that is ongoing for refractory invasive fungal disease. That is for a serious -- several infectious diseases, fungal infectious disease that are included in this program, in this protocol and coccidioidomycosis is one of them.

So interestingly here, when looking at the guidelines regarding what's right now recommended for treatments, it's interesting to see that only one

Page 142

of the products and actually -- well, not any longer because amphotericin B deoxycholate is not recommended -- that amphotericin B is the only one that actually has something in their label that really8 speaks about the indications of coccidioidomycosis.

Fluconazole, itraconazole, and all the products that we had been hearing about often used for this particular -- for this particular disease as the standard of care, they simply don't have the indication in the label and we wonder what may be the reason for that.

And there is also interesting statement in the idea saying 2016 guidelines for the treatment of cocci that no clinical studies exist to guide the optimal dose or duration of fluconazole or other antifungal therapies for persons with primary pulmonary coccidioidomycosis.

So that is definitely a gap there in the research in this particular condition and let's see what the -- why the gap may be. I think that we have heard what are the challenges, but trying to really focus on some of the areas that we consider may

Page 143

be responsible for this gap and what could be opportunities to fill those.

So the studies in coccidioidomycosis will be already -- are complex and the reality, they don't happen quite often. And the number of cases that we do have for this disease we need -- let's say here, I'm just using CDC numbers, around 150,000 cases a year. I can go, as we heard in previous presentations, it could be substantially underreported.

And they reported about 15,000 cases in 2018. So those are the cases that are likely to get treated, the ones that get diagnosis and likely to get treated. And so I think that the most recent study that I saw in clinical trial that got treatment study for cocci was this one that was attempted by NIAID. It lasted from 2015 to 2018. They were trying to enroll patients with pulmonary -- with pneumonia, community acquired pneumonia and tried to see if early treatment with fluconazole could have a benefit in dose, particular endemic area.

The number of sites was quite good,

Page 144

nine sites in Arizona and California. If you look at the sites, very reputable sites, however the study was terminated because of lack of feasibility. So message here is conducting clinical trials in cocci are not that simple. It's complex.

Then treatment duration is long and what that means, one of the implications of a long treatment duration, at the bottom of the slide you see an example here of a study that was fully presented previously, the itraconazole versus fluconazole study, to really the assessment of efficacy, the most relevant assessment of efficacy occurred after eight months and 12 months of therapy. So these are long studies and what that requires is that you need to have the numbers to do the study's long-term toxicology. You need to have multiple efficacy assessments and long-term treatment relations, which really increases the drop-off rates and the overall cost of the study and requires significant amount of clinical trial supplies, just to get there.

And there are also market implications. So let's say that about 12,000 to 15,000 people is

Page 145

treated in a year. So what do we think that is going to be the percentage of that market share for the new agent? It probably depends on the difference in attributes with these particular new agent may have, it have -- I don't know, I have the percent cure rate and certainly within three months of therapy probably can take a very substantial amount of market share.

However, if you could rest on that, it's very likely that currently available treatment options that are genetic would likely to continue to be used in a substantial proportion of these patients. So really, the market share that you're going to get out of these 12,000 cases a year is going to be a smaller than the whole and then after you're able to get approval, what is the market access that you're going to get and what market access means.

It's actually the use of your product because it is actually being reimbursed. So all these institutions that are responsible for determining what is get -- what gets reimbursed and what doesn't get reimbursed, they really want you to show that either you're superior to the current standard of care that

Page 146

is very inexpensive, fluconazole generic, in order to be able to allow for reimbursement of your drug, or they will put your product on as second line therapy that a patient needs to fail first the inexpensive standard of care options before getting into the treatment of this particular patient being approved.

So that even reduces ever more what is your opportunities to really sell the product once it is out in the market.

So I don't think that it's a mystery here why there are so few runners in this race. So clinical trials are complex, long, and not so easy to enroll. There are not too many people. The cost and time of development for traditional Phase 2 and Phase 3 randomized controlled trials versus the standard of care is significant. The market opportunity is limited and it's unlikely to grow significantly in the upcoming years, let's say.

Difficult to predict what the market access is going to be before having your Phase 3 data. So how the -- one's to decide if this is going to be reimbursed or not are going to -- how the decisions

Page 147

are going to be made before having the Phase 3 data is very difficult to figure out.

The return on investment will likely take a long time and so these are clear conclusions. These are difficult to fund development programs via traditional investors. I think that's the key reason why there are few runners in this race. What helps --

DR. JOHN GALGIANI: Dr. Angulo, we do need to sort of wrap it up pretty quickly here.

DR. DAVID ANGULO: This is the last slide.

DR. JOHN GALGIANI: Okay.

DR. DAVID ANGULO: Non-dilutive funding to support Phase 2 and Phase 3 and then active coccidioidomycosis clinical trial networks in order to facilitate the (inaudible) start of these trials, reevaluation of the endpoints which is happening in please to hear in the past presentations. And a streamlined regulatory path. The idea of yesterday of really combining several conditions to really try to get a study much more robustly and easy to enroll.

And for sure, we need to ensure

Page 148

commercial sustainability of a product once it is in the market. Thank you. Thanks for the opportunity.

DR. JOHN GALGIANI: And thank you very much. Our next speaker is Gareth Lewis. Dr. Lewis is vice president of specialty brands at Mayne Pharma, which includes responsibility for their antifungal commercial on-market performance and development pipeline. Dr. Lewis. Are you there, Dr. Lewis?

DR. GARETH LEWIS: Yes, thanks, John. I was just coming off mute there. Yeah, thanks very much. Appreciate the opportunity to participate and speak, so I think -- if you could move to the next slide. I'm going to actually have very similar thoughts to those that David outlined a second ago, so we're very much of the same mind in terms of the challenges ahead.

Before that, let me just put into perspective, Mayne's interest in participation in this area. We have reformulated itraconazole oral products which was -- obtained FDA approval about a year-and-a-half ago, so yes, as with the other itraconazole labels we're not indicated for cocci, but certainly

Page 149

see an opportunity for its utility in this population.

So in recent times, we've been working closely with the MSG ERC to conduct an endemic mycoses clinical trial which is now close to completing enrollment, so that's given us some direct experience of enrolling and conducting a clinical study in this patient population at the moment and it's a study that's ongoing. It was targeted in a cohort for approximately 20 proxy patients between California and Arizona and other participating sites and this has created some challenges, really, just because of the analyses of infections and also year to year variation in patient numbers.

So it is difficult to enroll and apart from the number of infections which are -- we talked about all day as being quite low, we often find that patients will -- just will be triaged and assessed by community physicians and won't always get referred on to academic centers for evaluation and so yes, while there might be patient numbers out there in the community, those presenting and coming to trial sites where many of the audience here today are leading

Page 150

research at these hospitals, they don't always come through and therefore by the time they get to these hospitals, they're not always valuable for including in the trial.

Our inclusion criteria were acute naïve infections, so not disseminated to these or not chronic, ongoing, challenging disease, so certainly if you are seeking a trial where you are studying related disease patients there's going to be even fewer of those in circulation.

So yeah, certainly we are seeing that it's very challenging to enroll and recruitment here is -- can be years instead of months. A second point is -- I'll be fairly brief on this. There's been a lot of expert discussion on this already today. Certainly the considerations of what constitutes clinical benefit is very important.

Yes, there are hard clinical endpoints, but then as the speakers before me just now have been talking about, PROs, quality of life, symptom management, disease burden, all these points are really important to consider, especially as we then

Page 151

try to translate to what is the true socioeconomic impact of disease and then as we have new therapies that can benefit this disease, it's important that we can demonstrate the improvement on such outcomes as we can then get to a cost-benefit analysis of new drugs as well as the clinical endpoints.

So really, that then takes us to the commercial barriers which are very, very similar to, as David ran through, something -- we agree entirely. There are very few patient numbers. There are very few patients are treated, and then as with our existing low-cost alternative treatments, albeit off label out there, the likelihood of product uptake is fairly low.

So whilst this is an orphan disease indication, the dynamics are very removed from some of the rare oncology indications where drugs have a significant premium or high value per patient. That's not going to be the case here. So and thirdly, the challenge of insurance coverage and patient access restrictions as were mentioned a minute ago are very relevant.

Page 152

So it's essential that we can generate clinical data that really show an advantage and a strong place and position for the new products that are coming through and obtaining FDA approval so that we can then have the strongest possible position to take to the insurers to enable affordable patient access.

So all in all, yeah, we see the same challenges as my colleagues before me in terms of the investment considerations. There is a small revenue potential here, given the patient population and market pricing. The cost barrier to develop is large with long, complex trials and then there's the significant execution risk with long trials, difficult enrollment, the many other external factors that needs to be taken to account before you can get to approval.

So all in all, yeah, to many pharmaceutical companies that just really can't make this investment consideration stack up to the challenge because here we clearly see this as a disease state that has many unmet medical needs and is worthy of solid investment.

Page 153

Those are my points. Thanks for your attention and I'll pass the baton.

DR. JOHN GALGIANI: Thank you, Gareth, very much. And our last speaker for this segment is David Larwood. Mr. Larwood is CEO and president of Valley Fever Solution. David, the floor is yours.

DAVID LARWOOD: Thank you, John. Thank you everybody. Thank you to the NIH for this support and to the FDA for sponsoring this excellent meeting. Dr. Galgiani spoke earlier about the history of nikkomycin Z and some of its attributes. A word about -- first a couple of slides. This is the hyphae form of the disease. This is a serial form of the disease which many of you are familiar with.

I became a peripheral observer of the cocci community as an infant when my father, Tom, did a residency in Bakersfield under Chief Hans Einstein after a bout of paralytic polio for my father and myself, the family returned to Bakersfield as Dr. Einstein was instrumentally involved in the amphotericin trials for cocci, they became clinical partners for decades.

Page 154

Cocci, of course, expresses in these horrible lesions so that's not -- oh these aren't presenting well at all. Oh, heck. Those are nasty picture of horrible diseases, so I'll just go on to the next slide.

The structure of the molecule resembles a substrate per chitin synthesis as John mentioned in his slides. The novel mechanism is fungicidal in many instances, and in fact, it's so effective in impacting chitin that it's used as a probe to study the mechanisms of action, particularly in Canada. It's been used a lot in Canada.

It's demonstrated to be fungicidal in mice and we have some interesting and recent results we're anxious to publish fairly soon. I look forward to telling you about them. So early publication by Richard Hector which john mentioned, was the studies in -- I don't see, do I have a pointer? Doesn't matter. Sorry, studies in mice.

So pulmonary infection, relatively low dose gave a very high level of protection. In meningococcal, meningocerebral version of the

Page 155

challenge 50 milligrams per kilogram gave a moderate protection, but not really enough. Subsequent studies have been very interesting. That'll be the subject of a couple upcoming publications which we're excited to share.

Looking at -- Dr. Shubitz earlier mentioned a couple of studies in natural (inaudible) in dogs. This is one of them. The results were very promising and although the population was very small, a third of population reached near resolution in just a two-month study. Dr. Johnson mentioned that it would be interesting if a drug was fungicidal -- I'm sorry, I skipped over that.

One of the aspects of nikkomycin that's been recognized for a long time, in the meningococcal study, I don't have a good pointer here. Can I make the pointer work? I can make the pointer work. So in the azole treatment, it's protected during therapy and then falls off sharply after therapy. That is consistent with many, many observations and -- what's it doing now? Okay.

Sorry. The slide's doing -- my

Page 156

screen's doing funny things to me. Anyway, so -- sorry. The protective element of the azoles wears off as soon as therapy stops; whereas in cocci is persistent, so it's been judged to be fungistatic for quite some time. Hopefully, the pointer goes away. We'll make that go away. Okay.

Talking about this slide, just -- I'll touch more of my background. In my medicinal chemistry PhD program at UCSF, I co-invented my second commercial drug pegylated liposomes. About a year later, members of our small group invented the first amphotericin B liposomes. Continuing with the story, trial strategy.

This has been discussed really a lot. I don't have a lot to add. All the considerations that people have talked about are very important for it to be working in these things. One of the important characteristics for any drug that's being developed is supply limitations. Can you manufacture the quantities that you're going to need? There are many points where people can trip up.

In preparing for an article I did

Page 157

recent -- looked at recent reviews and I thought this chart from Rauseo and there was another interesting one from (inaudible) at Davis that listed a chart of drugs in development against a variety of fungi and you'll see nikkomycin is listed in the column. They didn't pick up the fact that in Canada, there's been a lot of work done in Canada, but that's okay.

You'll see the VT applied the VT series and the olorofim series. Others that have been discussed are also in this chart, but the point here is that if you're looking for a rare disease like the endemic fungi, only what, roughly half of these candidates even are expected to touch the endemic fungi, so this just illustrates that it's difficult to do development in this area and that's going to be hard for people who are -- the business evaluation.

Several of the components that we look at, nikkomycin is active against chitin which is very involved with cell walls. So depending on what organism you're looking at, the cell wall structures could be quite different, and that has some relation to which drugs are effective against which fungi and

Page 158

why they're not effective against all of them.
This illustrated how chitin is one of the core layers protecting the membrane and interfaced as it's tightly interlinked with the various beta glucans, so some of the most effective therapies. Nikkomycin is very effective as a monotherapy against endemic fungi, but it's effective against other fungi including aspergillosis when mixed with the anti -- with the chitin in the beta glucan inhibitors, the echinocandins.
You see quite a number of organ -- of drugs here being used to impact the cell wall structure. So this is considerations. I live for silicon -- I spent a decade as a VP at two startups in Silicon Valley including five years there as general counsel of a public company, buying and selling companies which informs my discussion a bit later.
I became a full-fledged member of the cocci community in 2007 when I joined John at Valley Fever Solutions. For good measure, I finished a double MBA in 2009. Dr. Galgiani has submitted the business models for cocci drugs compete poorly in the

Page 159

business world. We've talked much of the challenges of trials, choosing endpoints and much more. For many investors, even the life sciences, there are alternative investments that simply seem more attractive. Our last two speakers, Dr. Lewis and Dr. Angulo point out the commercial difficulties and Dr. Rex is very well aware of the challenges of bring any drug forward.
So the team. Who's involved in this thing? The technology. What's the answer, the solution, the target? Who interesting is the market? You could have a fabulous drug for a fabulous associated disease, that just isn't -- that isn't going to sell much product and competition by others and the time to when you can get there are important considerations.
Fortunately for us in this space, the anti-infectives tend to do fairly well in trials, go from Phase 1 to Phase 2 to Phase 3 and through the NDA we scored generally high in the success rate, so that's helpful. Rare diseases tend to do a little better than average drugs, so that's also helpful.

Page 160

These are all plus factors for the business considerations.
We talked about development costs. This chart was interesting. When I looked at it originally, I noticed that the anti-infectives list for Phase 3 trials is running about $25 million. Yesterday, we heard stories where they could easily cost $300 million or certainly well over $100 million.
So the --
DR. JOHN GALGIANI: David --
DAVID LARWOOD: -- average --
DR. JOHN GALGIANI: You're going to need to sort of wrap it up in the next minute or so.
DAVID LARWOOD: Okay. Well, that would be good. So, with averages and such, the trials are expensive. This also can impact the drug business prices. So looking at a decision tree, the invest -- the money invested now is uncertain until you get all the way through this thing, so I just extracted this from a bio -- no, this was from ERC -- I think I got this from the NIH, the pages. The point is that if you get to success, it's wonderful but if you fall

Page 161

even a little bit short of success, it's very costly. So that's another risk factor that business people are going to look carefully at.
Projections show that the systemic antifungals that are used for Valley Fever about two-thirds, about $1.8 billion of sales. If you look at specific drugs, it's interesting to note, these are just projections that I took from a model about a year ago so they were projected at the time. One thing you notice here is there are very long tails. Ampicillin is being reformulated. It's still selling at significant numbers. Fluconazole, which is decades old, is still selling and making money, so this is another factor in the business considerations. And I thank you for your time.
DR. JOHN GALGIANI: David, thank you so much and you all have been really responsive to being in this tight timeframe. We have Janis Blair, my co-moderator with us, right, Janis? Are you with us?
DR. JANIS BLAIR: Yes. Can you hear me?
DR. JOHN GALGIANI: Why don't you take

Page 162

over?
DR. JANIS BLAIR: Okay. So the last speaker of this session will be Dr. Neil Ampel. Dr. Ampel is professor emeritus of medicine at the University of Arizona College of Medicine and my colleague as a supplemental consultant at Mayo Clinic in Arizona.
DR. NEIL AMPEL: Can you all hear me, first of all? And this isn't my --
DR. JOHN GALGIANI: Yes, Neil.
DR. NEIL AMPEL: -- slide. Yeah, so I have to get my slides up, Janis and John. Have to go to the beginning. We'll wait on that. This is somewhere, not in the beginning at all. See if we can go -- there we go. I'll get -- okay.
So I want to thank the organizers for asking me to talk. This is, I think, based on a discussion we had in the pre-meeting about how to move treatment studies for coccidioidomycosis further and so what I thought I'd do is talk -- use the past, tell us where we are, and make a suggestion for the future.
So what was the past? Well, the past

Page 163

modern age of therapeutics was the Mycoses Study Group. This was started in 1978 as a contract through NIAID. It was awarded to the University of Alabama at Birmingham under William Dismukes as it's PI and its goal was to perform multicenter collaborative clinical trials for the prevention and treatment of invasive fungal infections.
In 2005, the contract was terminated and that was effective in April 2007. And I think it's worth paying at least a little homage to Bill Dismukes who was a mentor to many of us on this call and the purpose here is not just to pay that homage, but to realize he was the brain child of the MSG and it was extremely productive in the years that it was funded.
And this is the structure. I've lost some of the brackets here, but it'll still make sense. So the way this worked was NIAID funded MSG at University of Alabama Birmingham to design and implement studies on fungal diseases and as part of that was the coccidioidomycosis subgroup, of which John Galgiani was the subgroup leader and you see the

Page 164

other major members: David Stevens, Tony Catanzaro, Royce Johnson -- who are all on this call -- Dick Graybill is not.
And the way it worked was there was industry funding that came into the particular study, but MSG provided administrative design and statistical support and I want to give a little shoutout to Gretchen Cloud because this was one of the ways MSG was so important. Gretchen was a statistician at UAB Cancer Center and she was just primary to both design of studies, implementation of studies, analysis of studies.
Without her, many of these studies would not have worked, so that's what MSG added to the coccidioidomycosis subgroup, and I think it was critical.
And this is just a short list of publications. These were ones that actually have NIAID Mycoses Study Group in the title. There are more. I think I left some David Stevens papers out, but if you just look at this short group, what you'll see is the iconic papers of antifungal therapy for

Page 165

coccidioidomycosis, including treatment of meningitis with fluconazole and including the only comparative trial of two antifungals for cocci, which I'll go over in a bit.
So that was the past. Where are we now? Well, as I said, since 2007, and actually well before that, there have been no controlled trials for coccidioidomycosis and the only comparative placebo controlled trial ever done was published in 2000 and that was the one that John was the lead author comparing itraconazole to fluconazole. We've had no other controlled trials.
Since that time, we have case reports and case series and there's a huge problem with that. Case series are, by definition, inherently biased and I certainly published them and I'm very aware of those biases and we have to work around them because that's the only trials we have right now. But they're extremely problematic.
First of all, they result in reduced strength of recommendations and we see that in the current guidelines where many things are not based on

Page 166

randomized controlled trials. They are, in fact, based on expert opinion which is problematic. For example, I worked with John for 25 years. I now work with Janis. We are all considered experts. We all each treat coccidioidomycosis a little bit differently.

So if you ask John or Janis and me, you might get a very different answer about how to manage a case, because it's based on our experience. A better example that I use because I don't want to use anything topical, I used some many years ago in HIV, the use of corticosteroids for pneumocystis. Prior to randomized controlled trials, there were many case reports. Some said, don't use steroids in pneumocystosis. Others said, use it. Other said, use it before. Others said, use it after.

When we had two randomized placebo-controlled trials funded by NIAID that showed that starting corticosteroids at the time of antimicrobial therapy for pneumocystis, led to marked reduction in mortality, it was practice changing. It changed practice, literally, the day those two papers came out

Page 167

in the New England Journal, so that's the strength of doing controlled trials and not depending on case series, which we are now.

Now, you've heard over and over, over the last few hours, why the present model that relies on industry support is not adequate for therapeutic trials in coccidioidomycosis. We've already heard pharmaceutical companies currently operate under a much stricter profit margin than they ever have in the past. Cost of developing new drugs is prohibitive and there must be a large market to support new drug development.

We've heard this all before. This is just my take. You've heard others. I just looked at invasive molds. There are about 180,000 hospitalizations for invasive molds over a 10-year period. For cocci, it's about a fifth of that. so at least five times lower. Moreover, the market for preventive therapy for invasive mold disease is huge, but it's small for cocci. So what does this lead to? Developing antifungals for the larger market and then using them because they're available for cocci without

Page 168

specific studies, and that's the place we've been in now for the last 15 to 20 years.

We've already said the cocci market is small. So it's not an attractive target to develop new antifungals and we really need something beyond industry support alone to do good clinical trials.

So what is the future? Well, first of all, what are some of the present unanswered questions? We've heard a couple of times about the SAnds study, which I call the formerly known as FLEET which is an attempt to understand how we manage primary pulmonary disease and this is one of the problems. There are two papers, one I authored with John, another that Janis did, which suggest that patients who don't get treated may do as well as patients who do get treated and that treatment may not prevent dissemination.

But again, those were case control studies and so they are inherently biased and so there have been these attempts which we've heard today to try to do a better study. That's still an open question because this FLEET SAnds study was not well

Page 169

designed.

What's the best antifungal for nonmeningeal disease? As you saw, we keep using fluconazole. Is that really the best drug or are there others? What about pulmonary versus disseminated? Even more important, management of coccidioidal meningitis. What's the best antifungal there? Again, we are often trapped to use fluconazole and only use other agents after the patients fail. So what's the best triazole? What about newer antifungals like olorofim?

What are -- what should we do there? And therapy ever be stopped? What's the role in intrathecal amphotericin B, another area where experts disagree? And what's the role of intravenous amphotericin B? So there are many questions. And finally, we need more answers on the patients on biologics and transplants.

So what should be the future? Well, many people have proposed, well what about the Coccidioidomycosis Study Group? And some people suggested -- I'm now the current president -- well,

Page 170

you guys do studies, and so I want to explore that for a bit. This is the definition of the cocci study group that is on the University of Arizona Valley Fever Center for Excellence website, and I think it's very accurate except for one area and that's research studies.

So I'll come back to that. But I want to take a more granular view of the cocci study group because I think a lot of people who aren't involved with it think it's a little more than it may be. First of all, it's a non-affiliated organization whose primary goal is to host an annual meeting dedicated to presenting new information and research on cocci. And it does that very well.

I would say in the last decade the presentations there rival any at any national or international meeting. They're very good. Moreover, we've been able to get NIAID and the mycology branch of CDC to come and interact with our members and that has been very helpful and we'd encourage FDA at our next meeting.

It currently has a board and bylaws,

Page 171

but that's a relatively recent development. It is not legally or financially organized. In fact, its money is held by (inaudible) which is the 501(c)(3) at Kern County Medical Center, so we don't hold our own money and we're not organized in any legal manner. And we have never as an entity overseen a research study.

So why should be involved in this? Because its members and its prominent members have all been involved in designing and doing studies, many of whom have been involved in the original MSG studies. So we have a tremendous amount of expertise.

So what's the proposal I'm going to make today? Well, G.R. Thompson, one of our members and I think who's on the call proposed to me about a year or two ago, how could be use the cocci study group to design some studies. And I talked to G.R. and in fact said -- went over these issues that we're really not an entity. We really have no funding, but what we had was expertise.

And the concept we came up with is perhaps we could use our membership to build a consortium and also help design the study. And G.R.

Page 172

went ahead and did that and working with Mayne, and you heard Gareth, on Suba-itraconazole and UC Davis and University of Arizona Tucson were already working on this.

We put together a consortium: UC Davis, Kern Medical Center, Mayo Clinic in Arizona, and University of Arizona Tucson, which are all entities that are extremely -- have a long history of interest in coccidioidomycosis and are essentially all referral centers for cocci. And so this served as sort of a model. Could we do this?

So that may increase the number of studies we can do with this model, but it doesn't answer all the concerns that we have about moving the field forward, getting good clinical data on therapeutics. For example, doesn't provide independent design and statistical support. It's probably not going to look at best management practices, save for primary pulmonary disease.

It may not be a good mechanism to look at newer drugs or targets, so the idea that G.R. and I are interested in and I've talked to Pete Pappas at

Page 173

MSGERG, is could we go back to the older model where MSG not has a new coccidioidomycosis subgroup, so MSG provides us, again, with that statistical and design support and administrative support that allows us to do studies that are beyond what industry would give us.

So that's all I have to say and I'll end right there.

DR. JANIS BLAIR: Thank you very much, Neil. We will -- we have scheduled right now a break and we'll be back at 4 p.m. to start the moderate panel discussion.

(Break)

DR. JANIS BLAIR: Never really can tell if everyone is back or not, but I will thank everyone in advance for their participation. We actually have a generous amount of time for this next session and there are three questions that have been posed for our consideration. I will say that for panel members who want to make a comment, it's probably going to be easiest for me to see if you show a raised hand icon and then we will call on you to speak. You can,

Page 174

instead, type something in the Q&A box and we'll try to keep that monitored as well.

So the first question that has been given for our consideration is, what are some considerations for drug development with regard to specific populations? For example, but probably not limited to, a varying array of immunocompromised patients, pregnancy, pediatric and other patient groups.

DR. JOHN GALGIANI: Janis, I see Tony has his hand up. You want to recognize him?

DR. ANTONINO CATANZARO: Yes --

DR. JANIS BLAIR: Yes. Let's start with Dr. Catanzaro, though -- oh, yes. Okay. Yes, I see him. Thank you.

DR. ANTONINO CATANZARO: Thank you very much. I want to take the privilege of being an older member to bypass the three questions you've posed and follow up to Neil's presentation which I think was excellent, and that is that we need a mechanism. When we look back, the Mycoses Study Group with a strong core that builds, disputes, and Gretchen Cloud had

Page 175

within the investigators supporting a group of knowledgeable investigators, but the point I want to make is that none of the studies they did were without the contribution of industry support.

So we have the combination of a strong core, knowledgeable investigators, and industry all working together under one goal. And I think that that model worked very well for MSG and really needs to be reinitiated in this critical time when we have not only vulnerable populations but also a number of drugs that need to be studied.

DR. JANIS BLAIR: Thank you, Tony. Does anyone want to follow up on Dr. Catanzaro's statement? George Thompson.

DR. GEORGE THOMPSON: Yeah, can you hear me okay?

DR. JANIS BLAIR: Yeah.

DR. GEORGE THOMPSON: Yeah, I would echo that. I mean the Mycoses Study Group in conjunction with the cocci study group was very successful and Tony gave a really nice overview of those studies, and then we, honestly, sort of coasted

Page 176

on those for over a decade. There's a number of new compounds in development, which we heard from today, some of which are, of course, fungicidal, a lot of promise with that with olorofim, you know, its upcoming Phase 3 trials for that compound and I think the others we heard from as well.

There's really promise and indication for those. And, you know, we've really built a nice infrastructure that Neil gave a nice overview of. Used to -- and since that, it's even expanded further for some other studies that are planned, UC San Diego is involved in that. UCLA, an enormous medical center will be involved in that as will UCSF, so I -- and we have done some nice collaborative work already which most of you have been authors on.

So I completely agree. I think that it would -- we had a successful model for a long time and that really just needs to be sort of set back up in the same fashion it was, the Mycoses Study Group. You know, Bill Dismukes did a fantastic job. Pete Pappas has done also, you know, enviable job as well and Jerry McGlynn has been their statistician there now

Page 177

for a number of hears with numerous Mycoses Study Group studies, so I think that the existing infrastructure just seems to be leveraged to move this forward in rapid fashion.

DR. JANIS BLAIR: Thank you, G.R. I think I see Dr. Johnson, Royce Johnson.

DR. ROYCE JOHNSON: Yeah. To go back, I certainly agree with what Tony and G.R. said, but to go back to the question about doing studies in immune incompetent populations if I, for formulate it, meaning pregnant individuals maybe that are on immune modulators, so forth. I think -- but Janis, you might be better to answer this question than I, that the numbers of those patients is too small to construct a meaningful study for therapy. It's conceivable that there could be prophylaxis studies.

DR. JANIS BLAIR: Yeah, I'm not sure. I think you're right on some of the populations being very, very small, probably too small to do any kind of efficacy, but I think we actually have some fairly substantial groups within immunocompromise patients in that there's a fair amount of solid organ transplant.

Page 178

Again, treatment is a thing, but also I think prophylaxis, prevention studies would also be very helpful as well.

DR. JOHN REX: Yeah. So pick up on the theme of those populations. They will be -- you won't get terribly many of them in any given -- actually, clinical trial disease, but you can do a lot with developing data to show that your PK is constant across those groups, show that you -- however you're dosing, you want to show that it works in the various populations.

You need to be ready for DDI issues. That's very standard work today on Phase 1 healthy volunteer stuff and silico modeling, you can know and be ready to study your DDI issues and actually have them well established and do your special pops work, your hepatic and renal failures well.

A lot of this just boils down to reasonably standard, preclinical safety work and just standard Phase 1 studies. And while I'm on the theme of the preclinical studies, one of the hard things in this space for everybody to be aware of is cocci will

Page 179

be treated for a long time. That means that you've actually got to do extended duration safety tox studies and those take a long time and you can't just set off a study, be a nine-month safety tox because you don't really know enough to know how to set that up.

So there is a real stumbling block for getting compounds going to achieve the, I guess, to achieve flight here. You've actually got -- there's a whole bunch of background work that is generally invisible that has to be done. Over.

DR. JANIS BLAIR: Okay, we'll call on Dr. Ampel next.

DR. NEIL AMPEL: Yeah, thank you, Janis. I'm actually going to take on question three because I think it has some relevance. This is something we discussed in the very excellent vaccine meeting we had, I think March a year ago in Rockville, and we do have serology as a biomarker, but we know it's imperfect and there's been a lot of interest in measuring cellular immunity but as I pointed out in that meeting, is it's really an unknown unknown.

Page 180

We have presumed that expression of cellular immunity, thereby skin test or cytokine release, tells us something we -- someone's protected, but we actually don't know that and again, that would be another area of study that, again, industry, pharmaceutical isn't maybe so interested in but as a general area, what are the biomarkers of protection because we actually don't have as much data on that to be confident.

DR. JANIS BLAIR: Thank you for your comment. I see a raised hand with Dr. Bennett.

DR. JOHN BENNETT: I'd like to turn to the subject of outcome, and we've already heard how difficult it is to measure outcomes in a disease that has different manifestations. But one of the things that all of them have in common is that we want our drugs to make people feel better and function better, and although Royce Johnson and John Rex have already raised this, I want to raise the possibility that we could do this with an iPhone -- a cellphone app.

That is, we could send people an email and over the long course that we're treating them, we

Page 181

could ask them to respond. Now, the challenges are if you're sick, you don't want to do anything that's longwinded and we don't want it to be complex. It needs to be in language that's appropriate, but we need that kind of outcome data and I -- there's a model for this and that is in multiple sclerosis, they developed an app that they set up by email to see how people are functioning.

Now, they don't ask them how they're feeling, but I think that's important, too, because they want to know if the person's multiple sclerosis functioning is better and I think with that kind of a model in mind, it's a challenge, but it might be a way of getting long-term outcome that is meaningful to the patients. That's the end of my comments, Janis. Thank you.

DR. JANIS BLAIR: Thank you, Dr. Bennett. Calling on Dr. Galgiani.

DR. JOHN GALGIANI: Yeah, let me make a couple of comments regarding the discussion about immunocompromised and other small groups and also John Rex's concern, a valid concern, about the length of

Page 182

these courses of treatment. We have in the past just decided to allow immunocompromised patients and pregnant patients enroll in the studies -- I could be wrong about some of them, but I think in general that was the case -- and let the investigator or the practicing clinician make the decision about that, and in addition, in early studies, and I'd really be interested to know if the FDA wants to make some comments about this.

We -- when Dave Stevens and I were doing things like intravenous miconazole, we would start treatment with, you know, not months and months of toxicology in support of that, but rather maybe a month, and then as we got to the end of that, we would report back to the FDA that things were going favorably. We -- the patient was not having untoward reactions of if they were, what they were, and ask permission to continue on and sort of bootstrap as we go for long-term toxicity studies.

And I'm very interested to know if, for instance, pediatrician -- or pediatrics could be enrolled under that risk-benefit, even though

Page 183

pediatric safety had not yet been established if, in the judgment of all involved though that that was in the patients' best interest or not, or whether or not you'd really have to have the Phase 1 done for these groups before you could get them enrolled.

DR. JANIS BLAIR: Do we have anybody on the panel that can address that?

DR. ANTONINO CATANZARO: This is Tony again. Can I make a comment?

DR. JANIS BLAIR: Yes, you may.

DR. ANTONINO CATANZARO: So I want to go back to question number one and while I agree with you that any one of those groups that are listed are tiny and not subject to -- could not really support a controlled trial, the group that we have a substantial of, as everyone knows, fluconazole at 1,000 milligrams per day is like the community standard, even though it's never been studied. But there are some people who fail that.

And what to do with the failures is a complete mess. So we could study that group, that sizeable group of people who fail fluconazole, we

Page 184

define what that means, and then subject those failures to one of the drugs that we've been talking about. I think that would be a good model to at least talk about.

DR. JANIS BLAIR: Okay, I'm seeing only raise hands of people who have recently spoken, so I'm not sure if you have another point to make or if you forgot to un-raise your hand, so we'll circle back to Neil.

DR. NEIL AMPEL: No, I was un-raising my hand, Janis. Sorry.

DR. JANIS BLAIR: Un-raise your hand then, okay? What about Dr. Bennett?

DR. JOHN BENNETT: Well, I've been hearing what people are saying about the difficulty in studying this disease and one of the problems that I see is that these people come into the trials at different points in their treatment and that's almost an unsolvable, so haven't heard people address that except for the thought of having people that are after they failed 1,000 milligrams of fluconazole, but I'm concerned they're bringing people in at different

Page 185

phases in the trial is -- gives you very heterogenous patient population, so I don't know how to solve that problem, I'm just worrying about it. That's the end of my comment, Janis.

DR. JANIS BLAIR: I agree with that. It makes it very difficult to understand a result. John, have you got a follow-up comment -- Dr. Galgiani?

DR. JOHN GALGIANI: Well, I'm -- Sumathi, you're on the call. Is there somebody at the FDA that could give us some thoughts about the Phase 1 package that's needed to address small groups? Or people going to take longer than the Phase 1 data really supports?

DR. JANIS BLAIR: Yeah, I'll defer to -- oh, go ahead.

DR. SUMATHI NAMBIAR: I can take the call. Hi, Dr. Galgiani. My name is --

DR. JANIS BLAIR: Hi.

DR. SUMATHI NAMBIAR: --- division of anti-infectives. So in terms of the pre -- nonclinical data package that is required to support

Page 186

the studies, I think takes into consideration many factors and what types of toxicities we've seen in the nonclinical studies, what might be the duration of the Phase 1 studies. You know, we can have single-dose studies or we can have multiple-dose study, so the duration of the non-clinical studies that are needed to support each of these studies generally follow what is in the ICH accounting and then there is also additional requirement in terms of marketing applications, for example, for longer treatment durations of 13 weeks, for purpose of the clinical trial, the 13-week nonclinical study might suffice, but for marketing application, there might be need for six- or nine-month studies.

So I think a lot really depends on the compound. It depends on what we know about the class of the drug, what kinds of toxicities we've seen, were they monitorable toxicities, whether they could be mitigated with measures in the protocol, et cetera.

In terms of pediatric, again, a lot really depends on the molecule. Sometimes, we do require studies in juvenile animals before going to

Page 187

clinical trials in children, but that's not always the case.

It should be based on all the information we have with the nonclinical studies and the findings in adult, and then we make an overall benefit-risk assessment and decide how to proceed, so unfortunately, I cannot give you a particular -- a specific answer to your question, but yes, there is some degree of flexibility but we have to take into consideration all the factors and all the evidence before we decide whether it's a go or no go. So I hope that helps.

DR. JOHN GALGIANI: Thank you very much. Janis said she's having a little trouble seeing names, so maybe I'll -- Royce, are you asking another question or making another comment?

DR. ROYCE JOHNSON: Yeah, I am. As regards the heterogeneity issue, I think that can be dealt with. All of us that are seeing patients in a tertiary sense, which is most of the people that are talking, see people that have been on previous treatment and failed. In fact, that's one of the main

Page 188

ways we recruit new patients is somebody that wasn't doing well.

And again, I'm -- despite John Rex and Jack Bennett, both of whom I much admire, I think that having a score system that tells you how sick a person is and whether they improve or don't improve that score solves the problem of heterogeneity to some substantial extent. So you could set a certain score and we had, actually, I didn't talk about it today, thought that the minimum requirement to be enrolled in a trial with the MSG 2020 would be something like a score of 6 so that a 50 percent reduction means you had to drop 3 points.

And whether the person's been on therapy and failed fluconazole and has a score of 12 and we drop it to 6 or whether they've never been on treatment and they have a score of 12 and we drop it to 6, both of those are a success and it's a way of dealing with a heterogenous population.

DR. ANTONINO CATANZARO: This is Tony. Can I make a comment?

DR. JOHN GALGIANI: Go ahead, please,

Page 189

Tony.

DR. ANTONINO CATANZARO: Well, I agree with Royce. I think by far the most common patient that is seen by the members of the cocci community of -- I don't know exactly what to call them, specialists or whatever, by far the most common referral is people who failed on fluconazole. So I agree with Jack, they're going to be heterogenous. But I think that if we shoot for the population that's never seen drugs, we'll have the same problem that we had with the FLEET study. We're going to be -- we're not going to enroll many patients. The majority of the patients that we see are people who failed 1,000 milligrams of fluconazole and we can "standardize" them, as it were, by doing a grade -- score, a Mycoses Study Group score, expanded score to pick up these other factors and then look for reduction. That was the rationale for the original study that Mycoses Study Group did which seemed to work very well.

And then with those failures, then we could do multiple therapeutic regimens. We could take one at a time and compare continuing 1,000 milligrams

Page 190

with itra, with vori, with one of the new drugs, or we could compare it with an azole versus a new drug, which is what I would like to say -- what I would like to recommend, but the point is that the patient population which is problematic, which needs to be solved, which we have plenty of, people who failed 1,000 milligrams.

DR. JOHN GALGIANI: Thanks, Tony. Neil, is your hand up?

DR. NEIL AMPEL: Yeah, it is, John. I wanted to swing it back to the concept of bringing the MSG in and I know Donna Love is on and I thought I saw Dennis Dixon and Pete Pappas, and I wondered if NIAID or even FDA wants to make some comments about giving government support to cocci studies in addition to industry support, and if Pete's still on, what he thinks of that idea. I'm done.

DR. DENNIS DIXON: Well, Dennis is here, while we're waiting for Pete to hear his proposal. And so MSG was really, I think, a model. Was on an island committee for public-private partnerships and how well they worked from 1978

Page 191

forward addressing many of the questions people needed to use available drugs effectively.

And, as has been said, even the cocci studies, I counted 12 of them, and the ITRA versus FLU was the largest and it was the only one that was a randomized prospective controlled trial and even with that and nearly 200 patients, it did not reach a statistical significance for the primary endpoint, so they're all hard, but beyond that, as we moved farther into the '80s and into the '90s and crossed over into the next century, the model began to collapse because of the disproportionate investment of the government versus pharma and because of the changing landscape for the conduct of clinical trials, the expectations, the rigor, and so forth, and the reluctance of industry to contribute the same amount of money when they could go off on their own and fund it with a design that they preferred.

So the last iteration, the last five years of the MSG which was then relabeled the Bacteriology Mycoses Study Group, was the top priority, invasive aspergillosis and people worked

Page 192

exceedingly hard trying to find the company support and a design of the protocol that everybody liked. And I think we had three different names associated with one company with purchases, takeovers, and changes of protocol and the five years ran out before we got to the study.

So I think we began to look at the return on the investment and recognizing that diagnosis was such an issue there, shifted and invested and tried to have a better diagnostic for invasive aspergillosis and created a contract to address that.

And as we collected the samples, it can essentially be a one-stopping for the clearance of a company for an FDA use for invasive aspergillosis, we could not entice big companies to want to touch that and it's sort of what John Rex described yesterday -- he may want to follow up on this again since not everybody was on yesterday's call -- about the huge challenge, not just getting the Phase 3 done, but having that drug get licenses and sustain its return on investment over the next five-year period and how

Page 193

the last five drug companies that tried that for antibacterials have now gone bankrupt.

So we're very concerned about that and about the time we shifted with the MSG to another way to do business, we made big shifts in the entire division for making Phase 1 the point of handoff to corporate sponsors. And so that way, we could do more things for more microbes and we are doing it in a way that may not be familiar to the cocci community of old, and they're the things that Erin Zeituni talked about this morning where we have compartmentalized it into significant support, probably more than we gave to the MSG, in terms of all the preclinical services, to bring as many new compounds forward as possible and Phase 1 to do first in human hoping that that could be moved along for corporate investment, which is ultimately going to be essential to get the drugs licensed.

And then, there are the opportunities for the community to come in with investigator initiated clinical trials, to propose their own in partnership with the community. And we're approaching

Page 194

the in-depth study of the cocci population through the initiative that Donna just sent the community notice of, and that is those consortiums to study cocci patients in clinical perspective and invasive perspective to try and get out some of the very things this group is discussing.

So I think I'll call your attention back to the link for that initiative for groups to work together collaboratively to study in depth cocci patients and look at how you can leverage that information to move forward to a clinical trial. John, do you want to add anything, John Rex, to nature of the problem in antimicrobial development in general today?

DR. JOHN REX: Yeah, sure, Dennis. Thanks. The broad problem is that antibacterials, much more so than antifungals -- antifungals pick it up a little bit as well -- suffer from a real market failure problem. It's the antibacterials, antifungals are space where you invent a new drug, everyone's very proud of you and pleased and tells you it's an important thing to do. As a matter of fact, it's so

Page 195

important that we're not going to use it and -- unless we really, really, really have to.

That doesn't work well for the over -- for keeping a product on the market and the -- an insight that's kind of glaringly obvious in retrospect, just like lots of things, is that initial approval of a new drug is really only about 40 or 50 percent of the way into the lifetime of the drug, and you need several hundred million dollars beyond the point of approval to simply stay in business, keep the lights on, and stay -- break even on a cash flow basis.

A vivid demonstration of this is that of the last 15 drugs approved by the FDA in antibacterial spaces, about 2009, five of them are now -- their company is in bankruptcy and the -- or the equivalent thereof, and the availability of the drug is uncertain. Indeed, it seems not likely that you can get it right now.

So it is a -- this need to deal with the backend problem of sustaining new products in the market is a bigger problem than might appear from just

Page 196

the antifungal universe and has been the subject of a lot of work, and I don't mean to be self-serving, but if you want to learn about it, one way to do it would be to go to my website, AMR.Solutions. there's a newsletter that I put out.

I spend 20, 25 percent of my time dealing with this problem, sort of on a very broad global scale and there's been a lot of work. There -- legislative activities, there's some stuff going on in the U.K. where we have laid out the framework for what needs to be done to cause drugs to come onto the market and stay on the market. The story of cocci is just, in many ways, is a microcosm of the larger problem, antibacterial.

So thanks, Dennis, for calling that out and I think it's -- the reason it's important for the community to know about it, you can leverage it, you know. To the extent you can connect the story here to the kinds of solutions being used, it actually helps all of us because our political leadership has been being updated, but they've begun to learn these ideas and if you learn to speak to them using the language

Page 197

that we have developed over time about antimicrobials as being the fire extinguishers of medicine, antimicrobials as preparedness, COVID gives us a great lesson here.

You know, a year ago, no one would've paid anything for an anti-SARS, coronavirus drug, but now people would pay trillions of dollars. So there's a lot of really good lessons here for the community to pick up on. Over.

DR. DENNIS DIXON: A lot of the --

DR. JOHN GALGIANI: Hold on --

DR. DENNIS DIXON: I'm sorry, is that --

DR. JOHN GALGIANI: Was that Pete that wanted to make a comment? Don't hear him. I would like to maybe think about the biology here. I think there's some good news about the dimorphics in cocci in particular that probably, if we found a better drug for cocci, it would not be put on the shelves. We would be using it because -- for a couple reasons. One is, we need it. And the other is because I don't think that you acquire resistance to drugs in the

Page 198

dimorphics like you do in transplant units where you're doing a lot of prophylaxis or ICUs where you're selecting new colonizing organisms.

I think cocci is a point source infection and you're left with that infection until you control it and so it's hard for that fungus to develop resistance in a closed space, and so I think there would be lots of reasons to encourage use of better therapies if they were developed for cocci.

But the point that Dennis was making in terms of getting buy-in from industry, I would like to see -- and I think that's for prophylaxis studies or empiric trials has its own special set of issues, but in terms of industry being willing to work with the investigators and allowing the design to emerge through an honest broker like MSG, with the analysis being done by the statistical support of the central group for cocci, would that be actually an easier problem than to try to figure out how to model or posture a indication for the immunosuppressed patient populations?

Anyone have some thoughts about that?

Page 199

Neil.

DR. NEIL AMPEL: Well, John, I don't have thoughts, but I want to throw it back to Dennis. So, Dennis, I heard what all the problems were but following up on John, so what is our solution, because we don't have, at this time, really well-designed, well-controlled trials and I think everyone has spoken today how difficult that would be simply with industry support.

So what mechanism, if not reinvigorating MSG to assist in that, what mechanism might you use? Over.

DR. DENNIS DIXON: Okay, I have the name of that group, so I would start with the Coccidioidomycosis Collaborative Research Centers which are listed on concepts cleared web page with NIAID as a simple couple sentence explanation about them, the whole thing won't be public until we are finalized, posted for advertisement, and I would suggest you call in to me, to Erin Zeituni, to Baoying Liu or any of the others associated with this meeting to tell you what opportunities we have to work with

Page 200

you on each of those points, including the submission of trials.

And visit our resources in our webpage for opportunities in the area.

DR. JOHN GALGIANI: But Dennis, the wonderfully exciting idea for cocci centers coming forward, I am so looking forward to that process play out, but can I ask you, that you have been -- when you roll things back to Phase 1, why not reexamine that, whether or not you want to allow for some diseases -- and I would like to think we'd be talking about cocci -- that it wouldn't stop at Phase 1, that you could -- I could imagine some really interesting Phase 2 trials with adaptive designs that would be cutting edge that would be, you know, we move the field forward in design as well as getting some results.

What about that as being either -- the cocci centers, as I understand it -- I haven't seen an RSA yet, but I believe it's going to not support clinical trials. It may collaborate with others doing clinical trials, but you're not going to be -- funding budget for the clinicals within the centers

Page 201

themselves.

DR. DENNIS DIXON: The norm is now Phase 2s. There are exceptions. I think with something like the collaborative research centers, the intent is to have people dig down to solve some of these problems where there could maybe be something too good to leave sitting at the curb.

DR. JOHN BENNETT: Will there be strong active input into that decision-making process?

DR. DENNIS DIXON: Could you repeat your question?

DR. JOHN BENNETT: That concept sounds really good from a governmental point of view. I just wonder if we're kind of thinking about the benefit of the Mycoses Study Group, one of the strong benefits was the intimate relationship that included clinicians and academics in the decision making process. And I'm wondering if that's going to be part of the program you're planning.

DR. DENNIS DIXON: We really can't comment on what it's going to be other than what's been posted on the web, and then when the solicitation

Page 202

is published, it will say exactly what it's about.
DR. JOHN BENNETT: Well, I'm just thinking about the FLEET project and how it originated. And Dennis was intimately involved in that and it was a wonderful "gift" to the community of $10 million, but the decision making process in bringing that study from the $10 million to actually doing it, did not -- it had academic input, but it didn't -- it was not effective input. And I think that the result of that was not successful.
DR. DENNIS DIXON: Well, thanks for that opinion.
DR. JOHN GALGIANI: But Dennis, what I hear, if I understand you correctly, you're saying that if somebody had an idea for a Phase 2, that the policy is not so rigid within DMID that it couldn't be discussed, with the possibility it might actually be explored.
DR. DENNIS DIXON: I think that's a safe statement. That's what we mean by case-by-case decision making and certainly, look where COVID went. Nothing is exactly like COVID, thank goodness.

Page 203

DR. NEIL AMPEL: So Dennis, this is Neil. Just to come back, the problem I have with the cocci collaborative groups doing broad pharmaceutical studies, let's just say the RFA comes out to University of Arizona has one and UC Davis has one. To me, that's not solving the problem, because those are going to -- that's siloing the problem where we really want all those medical centers involved, so if we're going to do therapeutic trials, we want every center that sees cocci patients and particularly those that are very involved, and I guess that's why I'm having trouble. I don't see that as the solution to the problem.
DR. DENNIS DIXON: There's nothing more I can give you at this point because the policy of the division is what it is and we'll work with you any way we can to move things forward iteratively.
DR. JOHN GALGIANI: I'm noticing that there's a lot of people on this panel, many of whom haven't said much yet. Tom Patterson, are you there? Maybe not.
DR. TOM PATTERSON: Hello.

Page 204

DR. JOHN GALGIANI: Tom? Good. You've been intimately involved, as we heard, with doing the animal studies on various antifungals for development for NIAID. Do you want to make any comments about how successful that process has been and do you think it could be done differently or are you happy with the way it's set up?
DR. TOM PATTERSON: It has been a very successful partnership. I think it's really helped spur drug development and I think you heard from our industry partners in those earlier talks that those studies were able to give pretty critical data that would otherwise be maybe outside their range at this point in time with their development, so cocci would've kind of gotten kicked to the curb. And instead, they really got a real boost when they were able to show activity in those models. And so I think it was an example of where the preclinical investment by the NIH was able to really spur drug development.
And I think the same things can continue with even smaller companies moving forward, you know, and so we'll have to see how much support

Page 205

that continues. It's important for the community to reach out to the government and let them know that they find it useful, but I think it is an important process to do and has really been helpful so far in getting drugs moved ahead, and even in the regulatory paths, you can -- you heard from, this morning, how those could be useful in helping lead to approvals.
DR. JOHN GALGIANI: Good. I see Dr. Hope is logged in. Dr. Hope, are you there? Maybe not. I happened to --
DR. WILLIAM HOPE: Yes, I'm here.
DR. JOHN GALGIANI: Yes, I see your name. You recently were having to grapple with a patient with Valley Fever. Was this workshop helpful to you in terms of seeing where we could go better?
DR. WILLIAM HOPE: Well, I'm listening from a place that, of course, doesn't see this disease except for the one that I mentioned this morning, John. I guess the only comment that I have, sort of listening to a disease that I don't look after previously and I don't study, although I have worked with Laura Kovanda and David Stevens recently on the

Page 206

model, but the preclinical models have obviously been truly difficult and characterized by pretty significant variability, but something that I haven't heard all day is that triazoles are the mainstay of treatment of this disease and we know that there's extraordinary variability (inaudible) sort of curious that people haven't been more interested in sort of understanding from a pharmacological perspective why fluconazole fails, why you say it's fungistatic, where the space are that emergence of resistance. I asked them to break out compliance (inaudible) about penetration of these drugs into complex tissue base.

So there's sems to be a lot of basic science here that could help unravel some of the issues. There's been quite a clinical discussion all afternoon. So that's, I guess, my only perspective from somebody very much from the outside.

DR. JOHN GALGIANI: Thank you. I see John Rex has got his hand up.

DR. JOHN REX: Hi. I'm coming off mute. Dennis, coming back to you for a second. I want to think out loud and actually I think that

Page 207

Elektra Papadopoulos is on who is somebody I know has thought a lot about PROs, and I'd like to point -- ask the question of whether or not this community could get interested in developing a PRO, focus on how people feel. Maybe it's arm on the phone Jack, that's be fun, but the idea that an endpoint that we all agree is reasonably useful across the range of cocci syndromes would be a tool that everybody would get advantage of it.

And Royce, I do really appreciate what the MSG did, what you guys did with the points scoring system. The -- my general understanding in this area is that things like cocci Comp. Fix titer or CSF white count would be new to this category of biomarkers and while you and I as docs pay a lot of attention to them, if we want to use them as endpoints in a trial that enables regulatory action, we'd have to go to a lot of trouble to prove how they connect to the outcome of the disease and like with HIV, where we know what it means to have a certain quantitative viral load.

We'd have to do the equivalent that

Page 208

here and I think that's probably a much heavier lift than any of us can envision; whereas, I'm actually struck by the idea that there might be a way to measure things that patients really care about with tools -- there's been a lot of work on these general purpose PROs in the past 10 years.

I'm not an expert on it, but I am really quite surprised that -- and it puzzled me how much stuff is out there. So that's a call for maybe a group action. That can be something that would be a big community benefit. Over.

DR. JOHN GALGIANI: Yeah, the QID which we heard about earlier today which was -- has been involved, I think, within the FDA and NIH, that is more -- correct me if I'm wrong, those who know more about this -- is more for professionals talking to each other about their experiences. I guess what John's talking about is to get the patient feedback and what FDA -- are they working on that, also or would it need to be a new opportunity rather than the QID.

ELEKTRA PAPADOPOULOS: Are you able to

Page 209

hear me?

DR. JOHN GALGIANI: Yes.

ELEKTRA PAPADOPOULOS: Oh, great. Okay. Yeah, I did hear my name so I thought I could just chime in a bit from a regulatory standpoint on the patient reports outcome questions and I think we've heard expressed multiple times that our goals with our endpoints is really to assess the clinical benefit on how patients feel, function, and survive and so we know that there's a need for outcomes that are reliable, valid, and responsive and that we need to take into account what really matters to the patients.

And that begins with listening to the patients and how do they discuss their condition, the treatment, what are the therapeutic gaps, and what really matters to the patient, what are things that a drug can treat that would impact their disease and also help them to feel better or function better, what would it be that they would most like to see improved, and then really factoring these explicitly into the endpoints.

Page 210

And I've heard -- there's been a lot of discussion about the challenges of heterogeneity and I think that there is a potential possibly to find certain symptoms that cross individuals that could be relevant across a broad variety of individuals and that patients could self-report so we would have a way of hearing the patient voice and how they're feeling and functioning and to take, really, and say adults and adolescents, those who are able to provide self-report.

And I think, you know, we've also heard about the length of the trial, the need to be parsimonious in the measures. I think minimizing missing data is also going to be very important, so having something that's feasible, that the patient is indeed compliant with is going to be important.

And then we've also heard about the need for different language translations for that target population. So it's a lot, I think. I think having some good clinical outcome assessments that could be used to support approval would be a bit boost to drug development.

Page 211

Very often, if there are good outcome assessments and there's regulatory agreement, then that's an incentives for drug development, and so the agency, of course, we will always provide advice to individual companies in the context of their drug development programs and there's also another regulatory pathway for looking at clinical outcome assessments and other drug development tools which is the qualification pathway and so that may be another very good avenue to have a tool that could be reviewed by the agency where we could provide advice and that could be usable across drug development programs and made publicly available and it wouldn't need to be necessarily de novo drug -- a de novo PRO or COA development.

There could be existing tools that could be brought to bear and so I think it would be a good conversation to have, and I just -- yeah, so I think that concludes my brief remark.

DR. JOHN GALGIANI: Thank you. I see Tom Walsh has his hand up. Tom? Are you on mute, Dr. Walsh?

Page 212

DR. TOM WALSH: Oh, no. Okay. John, are you able to hear me?

DR. JOHN GALGIANI: I am.

DR. TOM WALSH: Okay, very good. John, I wanted to comment with regard to preclinical and then also a strategy that might be helpful for support. Number one is, in terms of compounds that seem to be (OVERLAPPING VOICES OBSCURES) at a preclinical level.

One of the features that seems to stand out is, one, the potential microbicidal or fungicidal activity certainly posaconazole seemed to have that, the large volume of distribution, if we look at the data, certainly that's been presented with olorofim, for example. It seems to be also -- it seems also to have similar properties. One would also imagine that ibrexafungerp, large volume of distribution, 5 liters a program, and also apparently fungicidal.

Those agents certainly may rise to the level preclinically with appropriate dosing strategies to taking on the most serious patients. And if you look at -- if we look at the most serious patients,

Page 213

which is really where people are devastatingly compromised, the posaconazole trial actually for the salvage study, had 73 percent response rate where patients were just utterly not responding and I think as I recall, about 6 of the 17 had widespread -- had disseminated disease as well.

So if one has to decide, well, what might be logical extensions, translationary from the preclinical data because you only have X number of compounds, the Y number of patients, at least those properties seem to stand out in contrast more to a flu, which -- fluconazole which may not have those properties, but the other consideration, then, is well, who might be interested in supporting when industry obviously as has been wisely stated some degree of reluctance about further support, but there may be some considerable interest in military.

With all the maneuvers, there is -- Demosthenes Pappagianis' paper came out. He estimated that there may be as much as 4 or 5 percent serologic conversion. Frequency of serious infection was low, but nonetheless there are cases I'm aware of that came

Page 214

out of the -- especially in the armored command -- that came out of training. So I would raise the question, would the military, given its exposure, also maybe CDMRP, the Congressionally Directed Military Research Program, which does offer grants for -- in further support might be interested in clinical trial development.

DR. JOHN GALGIANI: Thank you, Tom. Tony Catanzaro and Dave Stevens, I think both of your have had some experience trying to engage with military. Do either of you want to weigh in on that?

DR. ANTONINO CATANZARO: I actually have a DoD grant right now but it -- they're very particular. They tell you what they're interested in and then you apply for it and I have a TB grant, but I've never seen anything about cocci. I work closely with the Navy Balboa Center and they had a lot of TB patients and they're interested, but they don't have any funding that I'm aware of.

DR. JOHN GALGIANI: Well, we in the formalin-killed serial vaccine, there was a lot of attempts to get military involvement and indeed, the

Page 215

Lemoore Naval Hospital was one of the study sites for that vaccine trial in humans. But in general, my experience with the military is that if you don't have -- and this actually is reflecting comments I got from David Danley who was a career military person at Ft. Dietrich that said if the -- if a treatment for Valley Fever or a prevention of Valley Fever is not a written in the requirement in the user's manual for the military, that is if you don't have a requirement to have such a vaccine, in order to have a military, then you're just not going to get any priority.

We've had sympathetic interests at regional military bases for periods of time, but then they rotate every two or three years and you start all over again. So I think I could imagine how we could do that with the military, but I haven't seen the push to get it as a military requirement. Dennis. Dennis Dixon, are you there? You had your hand up.

DR. DENNIS DIXON: It looks like my line is muted.

DR. JOHN GALGIANI: Dennis, are you --

DR. DENNIS DIXON: I was muted by

Page 216

somebody else, but now I'm unmuted. So I wanted to return to how we're looking at the problem and I think when the MSG ended, people wanting MSG back and so the MSG isn't back. There are no plans to bring it back. What is there and is available can do some of the things that group did but not through an infrastructure support basis.

So for example, Tony or others who would like to leverage the CSG for particular kind of study, for particular problem, it could be looking at the 1,000 milligram fluconazole failures and putting them into some sort of study that you could do at an early stage clinical investigation. There are new ways to do that; that's why I encourage reaching out to the bacteriology and mycology group team and either have the ways to reach us and so you could write or a group could write a clinical trial planning grant and there's a certain amount of money, up to, I think it's $150,000 to develop a protocol.

So that could be the part where the experts get together, some up with the idea, map out the basics of a protocol. That's competitively

Page 217

reviewed and funded against all the other people who don't have infrastructures who are trying to do that, and they do get funded and they're successful.

After that, if you've got the protocol and it looks like there was traction, there's the option to apply for an investigator initiated clinical trial grant that can conduct probably the kinds of study you're looking at to do, so there are ways to get there if you can work with the system to try them.

MAN 1: That's very encouraging.

DR. DENNIS DIXON: -- extra layer -- they do work through that extra layer of peer review. It's time consuming and peer review is generally more frustrating than it is gratifying, but it is a way to get there, just like other contract and grant support throughout the NIH.

To take a look at the resources that are there. Understand them better and see how they might be used to advance and leverage your interests.

The response to standard review and then you work through that, because that's quite stilted in the interactive potential. It's very

Page 218

difficult to work through the standard review process through (inaudible) who have worked with the reviewer. I think that they rotate, so if you use that system or do you use a different system?

DR. DENNIS DIXON: A number of these grants have been funded to other groups, bacteriology. I can't remember if we had any recent ones. I think we've had some in mycology, too. Baoying would know that, who spoke this morning. So people do get through it. It's not like having a multimillion-dollar contract aware that you can make all the decision on yourself moving forward; it is a way to go, and it has worked for some people. And it could work for you.

DR. JOHN GALGIANI: Dr. Bennett, I see your hand's up.

DR. JOHN BENNETT: It seems to be -- can you hear me, John, okay?

DR. JOHN GALGIANI: I can. Thank you, John.

DR. JOHN BENNETT: Okay. It seems to me the best hope for a cocci drug is to have a drug

Page 219

that has broader use than cocci, so that industry support of that drug has to be based upon other indications, but with a well-done cocci study, the drug will also be used for cocci.

Approval for cocci, I wouldn't know about that, but the drug isn't approved for -- posaconazole's not approved for cocci, yet you're using it. So the question is, can we have a drug that has broader usage and then we can design a study for cocci that gets people with the knowledge they can use it and here's how to use it for cocci.

But I'm a little concerned about drug nikkomycin. If its major use is only for cocci, you need to say that. but if its major use for cocci, I don't know how industry would be able to support that drug. So tell me I'm wrong, John.

DR. JOHN GALGIANI: I'm not sure you are wrong. I wish I could tell you you're wrong. But there is evidence suggests that it would be synergistic with other drugs against such things as aspergillus. So the concept that we have sort of entertained primarily is the path to get the drug

Page 220

approved would be primarily for cocci and if that were to occur, then that would open up some post-marketing trials, Phase 4s, to look at outcomes for other diseases. There's also activity assessment in blasto, but I think those are modest markets given the size of the markets and other therapies.

But I think the idea of synergy with the azoles -- sorry, with echinocandins, for example, would be an exciting possibility for other diseases besides cocci. But that doesn't -- it's hard to put that into a development plan to get it to its first indication.

DR. JOHN BENNETT: So maybe if a drug like olorofim got an indication for treatment or prevention or both of aspergillosis and had a good enough market size, yet its use for cocci could be an important side effect, if you will, but it's not what makes the drug economically viable. It's another indication, but we could still use it for cocci if we could figure out a good way how to study that or some other drug that has a broader indication.

DR. JOHN GALGIANI: Dr. Ampel, II see

Page 221

your hand's up.

DR. NEIL AMPEL: John, can you hear me?

DR. JOHN GALGIANI: Yeah.

DR. NEIL AMPEL: So the question, the two issues. Dennis, the mechanism you proposed would be drug by drug and that really doesn't solve the issue. There might be multiple. We need, really, a mechanism where we can study a lot of drug and if we had to submit for funding drug by drug, I'm not sure that's the solution.

The other point I want to make as a clinician, so we all think -- and I talk about this at ID week -- fluconazole is probably not the best drug to use in Valley Fever and the new triazoles seem to be better and we all try every day when we see cocci patients to get them moved over, and the problem is, it's very difficult.

For example, TR posaconazole costs on the order of, I think, $7,500 a month and so frequently requires prior approval, which is frequently denied by insurance companies, so without studies that get us to FDA approval, this was pointed

Page 222

out before I spoke, it really impacts clinical care and it's particularly a problem if we think that fluconazole may not be the best drug to use.

It was just the first drug -- the first triazole, anyway, that we used. And so how do we move that? We need a mechanism, even for drugs, as Jack was saying, that are already available. They're still very difficult to use because of our current insurance system. Over.

DR. JOHN GALGIANI: Laura Kovanda, I see your hand's up.

LAURA KOVANDA: Yes.

DR. JOHN GALGIANI: Hi.

LAURA KOVANDA: Thank you. I was just going to add that it seems like a perfect opportunity with multiple different drugs, I guess, in line to do studies would a master protocol be an opportunity for, say, the Cocci Group or the NIH to pull together, including some ideas like John Rex has with the PRO type outcomes and a way that could maybe help facilitate getting trials cone. Thank you.

DR. JOHN GALGIANI: I don't know if

Page 223

Dennis or Jack, do you still have questions or you just didn't put your hand down.

DR. DENNIS DIXON: -- figure out how to do that. My arm's getting tired anyway.

DR. JOHN GALGIANI: Well, we're a little close -- we're about 10 minutes away from the allotted time. We have certainly time for additional comments. Is that Thomas Walsh?

DR. TOM WALSH: Yes. Are you able to hear me?

DR. JOHN GALGIANI: Yes.

DR. TOM WALSH: Sorry, John, it's difficult to ascertain as to whether the phone is activated. Just in reflection on the refractory study -- the refractory cases of posaconazole where large challenges, although it may, as was noted, never really lead to an indication, but may inform the usage and expand the comfort or especially of bolstered by adequate preclinical data.

One might envision if one did have a study group that would be, as Laura suggested, a universal templated protocol that then could evolve

Page 224

small studies particularly for refractory patients where the challenges are especially great or those refractory or intolerant, where there's clearly tangible benefit, for those patients to be studied in a systematic way would not necessarily even have to be randomized.

We talked extensively yesterday about refractory historical controls or contemporaneous control, so it may be difficult given the wide variability, but rather than having extremely -- relatively large study such as the flu and itra, one may be able to understand and use compounds in a much more focused way, smaller populations, difficult to treat with patients being their own control and response much like the posaconazole study where potentially in a relatively short span of time, you can have potentially great candidates from olorofim to ibrexafungerp to other candidates, study in a short span of time or a novel study design.

DR. JOHN GALGIANI: Thank you, Tom. Pete Pappas? Are you on mute?

DR. PETER PAPPAS: -- hear me?

Page 225

DR. JOHN GALGIANI: I can now.

DR. PETER PAPPAS: Okay, good, good. I've just been listening to the comments. I'm in Montana so it's been kind of in and out.

DR. JOHN GALGIANI: A little louder, Pete?

DR. PETER PAPPAS: Oh, I'm sorry, excuse me. I said I am out state and I'm kind of in a remote area, but if you can hear me okay, let me know.

DR. JOHN GALGIANI: You're kind of weak.

DR. PETER PAPPAS: Yeah --

DR. JOHN GALGIANI: -- tell you that before.

DR. PETER PAPPAS: Okay --

DR. JOHN GALGIANI: That's better.

DR. PETER PAPPAS: People have said that before. Is that better? Is that better?

DR. JOHN GALGIANI: Yeah, that is better.

DR. PETER PAPPAS: Okay, good. Just a couple of reflections on this, you know, the comments

Page 226

that were directed to Dennis and all -- and so forth. For - at the risk of being self-serving, obviously, I think that not only cocci but the rest of the fungal pathogens constitute a public health issue and I do believe that one way of getting these addressed is through a uniform group that brings to the table statistical integrity, being -- protocols being really ferreted out in a fashion that we used to do, and I do think, following Jack Bennett's lead and others, this is really a great way to do studies.

That said, much has changed in the last decade or so and that is that these -- while we have now lots of compounds, those compounds are oftentimes brought to research through smaller groups, smaller -- venture capitalist groups. They really can't tolerate the delay that is inherent in our traditional way of developing protocols and going through the NIAID and so forth, and so on the one hand, I love the idea of a centrally organized, especially for biostatistical and trial design purpose.

On the other hand, I don't know that the tolerance is from industry as to whether they can

Page 227

tolerate very long delays where things have to go through a series of subcommittees and committees at the federal level, beyond the FDA. So we need to remember that as well.

I do think this is a big enough public health issue, not just cocci, but the whole area of mycology in general, that we should be able to justify putting together a study group that at least provides infrastructure in biostatistical support and integrity so that we can help all of these compounds and these entities develop sound studies that really address needs.

All of this has been addressed, many of you throughout the day, Neil and others have underscored this but I just wanted to kind of put my two cents' worth in because it's important to remember how we also caused a lot of heartburn on the part of our corporate colleagues who just couldn't wait for us to move forward and we just weren't moving forward fast enough. That's all I wanted to say.

DR. JOHN GALGIANI: Thank you, Pete. Well, we're close to the allotted time. This would be

Page 228

the time, if anyone else had some additional comments to make, to make them. Are there any shows of hands? I see none. Dr. Stevens. David, are you on mute?

DR. DAVID STEVENS: Okay, can you hear me now?

DR. JOHN GALGIANI: Really can, loud and clear.

DR. DAVID STEVENS: Okay, great. No, I just had a little comment and I thought the discussion about continuing collaborative clinical studies was really most important and I didn't want to in any way divert or interrupt that, but I did have a couple comments about nikkomycin Z. first, we studied nikZ against blastomycosis and published our results and the -- it's a very impressive drug against blastomycosis in the laboratory.

And in the course of those studies, we gave huge doses to mice because it was a dose ranging study, and never actually found any toxicity that we could see and I think we were up to, if I can remember, the range of 1,000 milligrams per kilogram. But David Larwood was very modest because currently in

Page 229

our laboratory, we've been studying disseminated cocci which had never been studied before in models with nikZ and David's been very involved in those studies.

And it is very active against disseminated cocci as well and although that, unlike the blasto studies, that hasn't been published but it has been presented in part and as an abstract it's available from the cocci study group from the meeting of this year and we've gone on to do some of the kinds of studies that Richard Hector did with CNS cocci and also find it to be very active against central nervous system cocci, and the thing that's different -- I'm sure David would've liked to have mentioned this more -- but maybe he was kind in terms of not trying to let the cat out of the bag, but the dosing has been by not lavaging which is what we did in our published blasto studies, but leaving in the water for -- that the mice are drinking and we monitored how much they were drinking and we could calculate what their dose was based on that and that has been very effective both against disseminated cocci and against CNS cocci and I think where that leads is the possibility of maybe

Page 230

developing a delayed release form which would make it very convenient, get around problems about the half -- any problems that there are about the half-life.

So I just wanted to interject that when we were talking about nikZ and hope that's useful information.

DR. JOHN GALGIANI: Thank you, David. David Larwood, did you want to add something to that? Unmute?

DAVID LARWOOD: Unmute. Hello. Better?

DR. JOHN GALGIANI: Much better.

DAVID LARWOOD: Sorry about that. Yeah, I actually wasn't going to talk about it because we have some publications that we're developing, but since we're talking about it, Richard Hector did some studies in the last '90s where he used -- infused a rate -- IV infusion of nikkomycin against injected Candida albicans and showed very good results.

And so I looked at that and I said, how can we do this in humans. Extended release formulations are very expensive and time consuming to

Page 231

develop and since I'm a chemist working on the molecule, I looked at the properties. I said, I think we can do this dosing in water that David just talked about and it worked. The first experiment worked fabulously well and we're doing some more of these, and like he says, the upper tox limit seems to be unreachable.

But the model that I was looking at and it seems to be proving out nicely, is this is a simulation of an extended release formulation, so we're saving a million dollars in a year to just do some screening studies so it's working out quite well. We're anxious to try it in more model diseases.

DR. JOHN GALGIANI: Great. And so we're down to the last two minutes. Tom Walsh, do you have any final thoughts you want --

DR. TOM WALSH: Are you able to hear me, John?

DR. JOHN GALGIANI: Yes.

DR. TOM WALSH: Okay, thank you. I think in listening to all of the outstanding presentations in this vast body of expertise and

Page 232

experts that are here, I think the time is right and well poised to bring everyone together, new compounds, great expertise, and the concepts for following Dennis Dixon's path, especially building on the foundation of the exciting idea of the Coccidioidomycosis Centers of Excellence.

It would be just a wonderful, logical extension going with the R34s, clinical trial R01s, and with novel study design whether it's in the refractory patients, disseminated CNS, or in advanced pulmonary disease, I think we're on the threshold of a major advance in clinical research in coccidioidomycosis.

DR. JOHN GALGIANI: Thank you, Tom. Appreciate those words. And I think we are out of time, so I thank everybody for their comments and the wrap-up will be done by Sumathi Nambiar. Dr. Nambiar is currently the director, Division of Anti-Infectives at the FDA. Sumathi.

DR. SUMATHI NAMBIAR: so, thank you, Dr. Galgiani. You can hear me okay?

DR. JOHN GALGIANI: Yes, I can.

Page 233

DR. SUMATHI NAMBIAR: Okay, thank you. I just want to thank all the presenters and panelists. We had a very interesting day discussing different aspects, so coccidioidomycosis. I do have the difficult task of trying to summarize the discussions that took place today.

I want to apologize up front if I've missed any of the important points. Meeting materials with recording and transcripts will be available online after the meeting and you should have access to all the details.

So today's workshop we had two sessions followed by a very interesting panel discussion. At the first session, we discussed epidemiology, clinical manifestations, and development resources. I think the main points there were about the changing epidemiology of the disease, the risk factors, and disease manifestation and I though it was also noted that there is an opportunity to here to collaborate with sites outside the U.S. in Central and South America and trial relationships with some of these sites worked well.

Page 234

We had a discussion around animal models. One studied murine models and I think also discussion around rabbit (inaudible). Was also mentioned of the natural pulmonary infection in dogs and I thought that was very interesting, the discussion with enrollment of pets.

We had Dr. Zeituni presented the support that NIAID can provide and a lot of this came up a lot of this came up again during the panel discussion. Dr. Zeituni described the established mechanisms available to support the development of promising products and also mentioned the initiated with Coccidioidomycosis Collaborative Research Centers which was discussed by Dr. (inaudible) during the panel discussion and Dr. Zeituni also provided instructive examples of engagement with pharmaceutical sponsors helping to advance drug development.

A sincere thanks to Mr. Purdie for having joined us for this workshop and represented the patient. It was a very important discussion and Mr. Purdie highlighted the importance of including the patient's voice and use the patient centered endpoint

Page 235

to capture how a patient feels, functions, and survives, a theme that came up again during our panel discussion and also the importance of measuring a quality of life. A point he made that I thought was interesting was the potential opportunity to harness the rich database of patients they have access to that we could use to advance endpoint development.

In Session 2, clinical trial considerations for the treatment of coccidioidomycosis, we heard about regulatory considerations into the trial development endpoint and available incentives for the treatment of coccidioidomycosis.

We heard about trials that have been conducted over the years by the Cocci Study Group and also the lessons learned from the nikkomycin Z development program.

For future trials, the discussion around the use of patient reported outcomes and maybe scoring systems at end points. Dr. Johnson discussed the MSG 2020 scoring system with one each for meningeal and nonmeningeal disease. We heard from

Page 236

colleagues from industry and collectively their perspective raised some concerns such as difficulties in actually conducting these trials with regard to identifying and enrolling patients, the need for the long duration of follow-up, et cetera.

It was mentioned potential use of the PROs with an endpoint. David raised the concern about financial constraints including the small market base and then there was also a call for potentially streamlining clinical development programs.

Dr. Ampel discussed the cocci study group consortium which could potentially help the cocci related treatment study, but said he cannot address all aspects of cocci drug development and presented a proposal for future collaboration to design and implement treatment trials for cocci.

The panel discussion was, again, very interesting. We had three questions, but needless to say, the discussions went way beyond those three questions, which is fine, because I think all the points raised were very valid.

If I can at really high level

Page 237

categorize, really, to topics, the discussion around pros and cons of having the Mycoses Study Group model. I think there were differing opinions on that with -- opinion that had served us well and is a good model to move forward, understanding that over time the needs have changed and there might be a need to revisit and make some adjustments to that approach.

With regard to special population, there's a recognition that immune compromised patients are certainly very small numbers for each of these special populations, immunocompromised patients particularly solid organ transplant patients might be a larger group such that they could be enrolled in the trial but a point was made that it might also provide an opportunity to assess pharmacokinetics in these patients, address drug-drug interaction issues, how one can dose the drug in hepatic, renal impairment, et cetera.

It was emphasized that we need good nonclinical date to support these studies including extended duration studies. There was discussion around biomarkers and imperfections of serologic

Page 238

endpoint and a call for maybe additional work to look into the aspects of cellular immunity, a topic for more research.

There was some discussion around endpoints and I think outcomes. A lot of focusing, again, on patient reported outcomes. I think one key point we heard that this a heterogenous disease.

There will be varied manifestations by there should be a common thread across the different clinical entities which is about making the patient feel better and whether or not one can use some of the existing tools to capture that outcome and I think a point was also made about potentially using technology to capture data with an example multiple sclerosis having been used -- where such technology was used.

I think all of those are very good positions. There was certainly a discussion around the importance of nonclinical work and how that has certainly helped streamline programs and identify some of the new molecules that might have a role in the treatment of cocci.

And I'm sure I've missed some points, but I think at a very high level, those were the main points I heard, and I think in terms of next steps, I think there's a lot of work for all of us to do as a community to be able to advance the drug development for patients with coccidioidomycosis. I think we heard that there are certain mobile techniques to be done on developing endpoints.

Elektra from the FDA provided some thoughts on the kinds of things we need to look for those who are interested in developing patient reported outcome measures.

I think a further discussion is needed on potentially a network of trial sites and how best we can collaborate to make drug development feasible and also to potentially include sites and experts outside the United States and I think for us at the agency, we have to consider options to streamline clinical trial programs both with regard to trial population, release times, duration of follow-up, et cetera, so I think with that, I hope I've covered the key discussion points that took place over the course of the day and again, apologize if I missed any point that any one of you made, but they'll all be captured in the transcripts and the recording.

So with that, again, I want to thank every one of you for participating and maybe turn it over to John for a little concluding remarks. John, are you on? Okay, pardon me. John is -- had to step away. All right, on behalf of everybody at the agency I want to express my sincere thanks to each one of you, panelists, presenters, for having shared your thoughts. I think these discussions were extremely helpful.

As I said, we've all got our work to do and we do hope that we can continue these conversations and find a path forward for drug development for patients who need these treatments. With that, thank you vey much and everybody have a good evening and we'll be in touch. Take care.

DR. JOHN GALGIANI: Sumathi, this is John. Let me just add my thanks. I was involuntarily unmuted and muted again, but thanks everyone for a great day. We've really gotten a lot of ideas from everyone. Thank you very much.

Page 240

Page 241

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

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

b

i

p

u