FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Tuesday, May 1, 2018

10:00 a.m. to 2:32 p.m.

DoubleTree by Hilton Hotel Bethesda

The Grand Ballroom

8120 Wisconsin Avenue

Bethesda, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Chee, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Nina M. Clark, MD

Associate Professor

Director, Transplant Infectious Disease Program

Division of Infectious Diseases

Loyola Medical Center

Maywood, Illinois

Demetre C. Daskalakis, MD, MPH

Acting Deputy Commissioner

Division of Disease Control

New York City Department of Health and Mental Hygiene

Long Island City, New York

Dean A. Follmann, PhD

Assistant Director of Biostatistics

Chief Biostatistics Research Branch

National Institute of Allergy and

Infectious Diseases

National Institutes of Health (NIH)

Bethesda, Maryland

Michael D. Green, MD, MPH

Professor of Pediatrics, Surgery and Clinical &

Translational Science

University of Pittsburgh School of Medicine

Division of Infectious Diseases

Director, Antimicrobial Stewardship & Infection

Prevention

Co-Director, Transplant Infectious Diseases

Children's Hospital of Pittsburgh

Pittsburgh, Pennsylvania

Barbara M. Gripshover, MD

Associate Professor of Medicine

University Hospitals Cleveland Medical Center

Case Western Reserve University

Division of Infectious Diseases and HIV Medicine

Cleveland, Ohio

Jonathan R. Honegger, MD

Assistant Professor of Pediatrics

The Ohio State University College of Medicine

Division of Infectious Diseases and Center for Vaccines and Immunity

Nationwide Children's Hospital

Columbus, Ohio

Vincent Lo Re, MD, MSCE
Assistant Professor of Medicine and Epidemiology
Division of Infectious Diseases
Department of Medicine
Center for Clinical Epidemiology and Biostatistics
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Joanna M. Schaenman, MD, PhD
Assistant Professor of Medicine
Division of Infectious Diseases
David Geffen School of Medicine at UCLA
Los Angeles, California

Peter Weina, MD, PhD, FACP, FIDSA
Colonel, Medical Corps, USA
Chief, Department of Research Programs
Walter Reed National Military Medical Center
Division of Education, Training and Research
Bethesda, Maryland

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Nicholas A. Kartsonis, MD

(Industry Representative)

Acting Section Head, Antibacterials/CMV

Vice President and Therapeutic Area Head

Infectious Diseases, Clinical Research

Merck Research Laboratories

North Wales, Pennsylvania

TEMPORARY MEMBERS (Voting)

Lindsey R. Baden, MD

(Acting Chairperson)

Director of Clinical Research

Division of Infectious Diseases

Brigham and Women's Hospital

Director, Infectious Disease Service

Dana-Farber Cancer Institute

Associate Professor, Harvard Medical School

Boston, Massachusetts

Joel G. Breman, MD

Senior Scientist Emeritus

Fogarty International Center, NIH

Bethesda, Maryland

Richard C. Condit, PhD

Professor Emeritus

Department of Molecular Genetics and Microbiology

University of Florida

Gainesville, Florida

Debra Dunn

(Patient Representative)

Libertyville, Illinois

Randy Hawkins, MD

(Acting Consumer Representative)

Private Practice

Inglewood, California

C. Rick Lyons, MD, PhD

Director, Infectious Disease Research Center

Chief Scientific Officer, Infectious Disease Super Cluster

Colorado State University

Fort Collins, Colorado

Brett W. Petersen, MD, MPH

Commander, U.S. Public Health Service

Epidemiology Team Lead, Poxvirus and Rabies Branch

Division of High-Consequence Pathogens and Pathology National Center for Emerging and Zoonotic Infectious Diseases

Centers for Disease Control and Prevention

Atlanta, Georgia

Jurgen Venitz, MD, PhD

Professor and Vice Chairman

Virginia Commonwealth University

School of Pharmacy

Department of Pharmaceutics

Richmond, Virginia

FDA PARTICIPANTS (Non-Voting)

Edward Cox, MD, MPH

Director

Office of Antimicrobial Products (OAP)

Office of New Drugs (OND), CDER, FDA

Debra Birnkrant, MD

Director

Division of Antiviral Products (DAVP)

OAP, OND, CDER, FDA

Adam Sherwat, MD

Medical Team Leader

DAVP, OAP, OND, CDER, FDA

Kirk Chan-Tack, MD

Medical Officer

DAVP, OAP, OND, CDER, FDA

Su-Young Choi, PharmD, PhD

Clinical Pharmacologist

Division of Clinical Pharmacology IV

Office of Clinical Pharmacology

Office of Translational Sciences, CDER, FDA

Jules O'Rear, PhD

Lead Virologist

DAVP, OAP, OND, CDER, FDA

Patrick Harrington, PhD

Virologist

DAVP, OAP, OND, CDER, FDA

Laine Peyton Myers, PhD

Senior Toxicologist

DAVP, OAP, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Theresa Eisenman, who you can see to the left.

My name is Dr. Lindsey Baden. I am chairperson of the Antimicrobial Drug Advisory Committee, and I will be chairing this meeting. I will now call this meeting to order. We'll start by going around the table introducing ourselves. We'll start with the FDA to my far left.

DR. COX: Good morning. Ed Cox, director, Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Good morning, Debbie Birnkrant, director, Division of Antiviral Products, CDER, FDA.

DR. SHERWAT: Adam Sherwat, medical team

leader, CDER, FDA.

DR. CHAN-TACK: Kirk Chan-Tack, medical officer, CDER, FDA.

DR. CHOI: Su-Young Choi, clinical pharmacology reviewer, FDA.

DR. O'REAR: Jules O'Rear, virology team leader, FDA.

DR. HARRINGTON: Patrick Harrington, virology reviewer, FDA.

DR. MYERS: Peyton Myers, toxicology reviewer, FDA.

DR. BADEN: Dr. Breman?

DR. BREMAN: Joel Breman, senior scientist emeritus at NIH.

DR. VENITZ: Jurgen Venitz, clinical pharmacologist and professor at VCU.

DR. SCHAENMAN: Joanna Schaenman, infectious diseases, associate professor David Geffen School of Medicine at UCLA.

DR. LO RE: Vin Lo Re, Division of Infectious Diseases, Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania.

DR. DASKALAKIS: Demetre Daskalakis, I'm an infectious disease doctor and the deputy commissioner for disease control at the New York City Department of Health.

DR. CHEE: Cindy Chee, acting designated federal officer for the AMDAC.

DR. BADEN: Lindsey Baden, infectious diseases physician, Brigham and women's Hospital, Dana Farber Cancer Institute, Harvard Medical School, Boston, Mass.

DR. WEINA: Peter Weina, infectious disease and director of research at the Walter Reed Army Institute of Research.

DR. HONEGGER: Jonathan Honegger, pediatric infectious diseases, Ohio State University.

DR. GREEN: Michael Green, pediatric infectious diseases, Children's Hospital, Pittsburgh and the University of Pittsburgh.

DR. GRIPSHOVER: I'm Barb Gripshover. I'm an adult infectious disease at Case Western Reserve University in Cleveland.

DR. CLARK: Nina Clark, infectious diseases at Loyola University in Maywood, Illinois.

DR. FOLLMAN: Dean Follmann, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. HAWKINS: Randy Hawkins, physician private practice, Los Angeles, California.

MS. DUNN: Debra Dunn, patient representative.

DR. PETERSON: Brett Peterson, epidemiology team lead poxvirus and rabies branch, CDC.

DR. LYONS: Rick Lyons, recently retired director of infectious disease research at Colorado State University.

DR. CONDIT: Rich Condit, also retired professor emeritus from molecular genetics and microbiology at the University of Florida.

DR. KARTSONIS: Good morning. Nick Kartsonis. I am the industry rep, and I'm from Merck Research Labs.

DR. BADEN: Thank you all for making the time and joining us today.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that

today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus as a gentle reminder, individuals be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'll now pass it to Dr Cindy Chee, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. CHEE: The Food and Drug Administration is convening today's meeting of the Antimicrobial Drugs

Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for special government employees' services outweighs his or her potential financial conflicts of interest, or when the interest of a regular federal employee is

not substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children's, and for purposes of 18 USC, Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application 208627 for tecovirimat sponsored by SIGA Technologies, Inc., for the proposed indication of the treatment of smallpox disease caused by variola virus in adults and pediatric patients.

This product was developed under the Animal Rule 21 CFR, Part 314, subpart I. This is a particular matters meeting during which specific matters related to SIGA Technologies NDA will be discussed. Based on

the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have makes concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr Nicholas Kartsonis is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr Kartsonis' role at this meeting is to represent industry in general and not any particular company. Dr. Kartsonis is employed by Merck and Co.

We would like to remind members and temporary voting members that if the discussion is involving any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion

will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BADEN: We will now proceed with the FDA's introductory remarks from Dr. Debra Birnkrant.

FDA Opening Remarks - Debra Birnkrant

DR. BIRNKRANT: Good morning. I'd like to welcome everyone to today's advisory committee. Today we will be discussing SIGA's NDA for tecovirimat for the treatment of smallpox submitted under NDA 208627. Tecovirimat is an oral drug that inhibits viral spread to uninfected cells by targeting a viral protein involved in the production of extracellular enveloped virus.

To frame today's discussion, for a disease that was eradicated almost 40 years ago, why would the FDA be interested in helping to set a regulatory pathway for an antiviral to treat smallpox? Well, despite the eradication of naturally acquired smallpox, the causative variola virus remains a possible bioterrorism concern, and it's categorized by NIAID and

CDC as a Category A priority pathogen. Category A pathogens are those organisms or biological agents that pose the highest risk to national security and public health. The fact that no effective drug treatment was identified during smallpox eradication efforts adds to the urgency of drug development.

As background, drug development for smallpox has a number of distinctive features compared to other indications. As I've already noted, the absence of cases and lack of previously known effective drugs, variola virus has a very narrow host range, does not readily infect experimental animals, and generally does not produce disease resembling human smallpox in nonhuman hosts.

Other members of the orthopox genus are closely related genetically but may have very different host specificities and disease manifestations. Bridging the need to have drugs available to treat a potential biothreat and the difficulties in developing such drugs, we convened a workshop in 2009 to discuss animal models of disease and an advisory committee in 2011 to flesh out a regulatory pathway.

What were the recommendations of the 2011 advisory committee? The 2011 advisory committee agreed that smallpox drug development would have to use the Animal Rule, which others in their presentations will elaborate on and I will briefly mention. The advisory committee also reached consensus that activity would need to be demonstrated in reproducible studies in two lethal animal models of non-variola orthopox infection; for example, the nonhuman primate monkeypox and rabbit rabbitpox models, along with adequate human safety data.

Use of a lethal variola model was considered, but the 2011 advisory committee agreed that the nonhuman primate models using variola were not consistently reproducible, did not mimic what is known about human smallpox disease, and presented numerous feasibility challenges due to the worldwide restriction of variola virus research. Exploratory studies that had been conducted with variola were considered supportive. In some, combinations of animal models using other orthopoxviruses were considered to provide the best achievable approximation of likely relevance

to human smallpox.

What is the Animal Rule? The Animal Rule is a regulatory mechanism that may be used to approve drugs for serious disease caused by toxic substances, including pathogens when human challenge studies would not be ethical and definitive clinical trials after accidental or hostile exposure have not been feasible.

The Animal Rule can only be used if these four criteria are met: there needs to be a reasonably well understood pathophysiological mechanism of both disease and treatment; the effect is demonstrated and usually more than one animal species expected to react with a response predictive for humans; the animal study endpoint is related to desired human benefit, usually survival or prevention of major morbidity; and the PK and PD obtained from human and animal studies would allow for an effective human dose selection.

Turning to study design considerations based on the Animal Rule, the primary outcome of interest for human smallpox was assumed to be whether the patients survived the disease, so this was adopted for the animal study primary endpoint. However, in

experimental animal studies, mortality is largely determined by humane euthanasia interventions, so it was important to define and agree upon clinically based euthanasia criteria during study design. Agreement also had to be reached on clinically relevant treatment triggers and on study observations as well as randomization and blinding of treatment assignment.

Important virologic data included strain description, route and quantity of challenge, and assessments of viral burden and resistance. Specifics of resistance pathways, however, will not be discussed by the agency or the applicant today either in the presentations or in the Q and A sessions for security reasons. As in all animal studies, appropriate animal welfare provisions were considered essential.

Recognizing the inherent uncertainties with the use of surrogate animal models for assessing an antiviral drug to treat smallpox and based on the conclusions of the 2011 advisory committee, you will see in the subsequent FDA presentation by Dr. Kirk Chan-Tack and Dr. Su-Young Choi that the applicant has submitted data to support the following:

The mechanism of action of tecovirimat is well established and the drug target is highly conserved across orthopoxviruses. The drug was demonstrated to have broad and consistent antiviral activity in cell culture assays against 7 different orthopoxviruses, including several independent isolates of variola virus. Treatment efficacy was evaluated using to lethal well studied animal models of non-variola orthopox infection with several disease characteristics in each of these models being relevant to human smallpox. And lastly, PK and PD data from these animal studies enabled reviewers to assess the potential for an effective human dose.

That brings us to today's committee meeting where we will be asking our advisors and consultants the following risk-benefit question based on SIGA's data package; that is, based on the available data, does the risk-benefit profile of tecovirimat support its use for the treatment of human smallpox?

Finally, I would like to acknowledge and recognize our dedicated review staff and our colleagues from the Counterterrorism and Emergency Coordination

office along with our sister agencies, including BARDA, NIH, the Department of Defense, USAMRIID, and the Centers for Disease Control and Prevention, who helped to advance the medical countermeasures field.

Thank you very much, and I'll turn it back to our committee chair.

DR. BADEN: Thank you. Dr Birnkrant.

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual presentation. For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you

choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with SIGA Technologies' presentations.

Applicant Presentation - Annie Frimm

MS. FRIMM: Good morning. I'm Annie Frimm, vice president for regulatory, clinical, and quality at SIGA Technologies. We are pleased to be here today to present our drug candidate, tecovirimat, for approval.

Tecovirimat is a novel oral therapeutic agent intended for the treatment of patients with smallpox, an indication for which there are currently no products approved. Tecovirimat works by blocking the ability of the variola virus, which causes smallpox to spread. While naturally occurring smallpox has been successfully eradicated through global vaccination campaigns, there is a concern that smallpox could be used as a bioweapon, and Centers for Disease Control have determined that smallpox is at the highest threat level.

Tecovirimat was developed in close collaboration with the National Institutes of Health, the Department of Defense, and BARDA as an antiviral drug for use in biodefense. It has been purchased for the Strategic National Stockpile as a bioterrorism countermeasure and is currently being held at multiple CDC-managed sites in the United States.

Developing a drug for which there is no human disease population has required innovative clinical and regulatory strategies. With smallpox eradicated, traditional drug development and approval based on human efficacy trials was not possible nor ethical. Therefore, efficacy of tecovirimat was evaluated using the FDA Animal Rule regulations and guidance, which state that FDA may grant marketing approval based on adequate and well controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce a clinical benefit in humans. It is important to note that tecovirimat meets all requirements for the Animal Rule.

In December of 2011, FDA convened a meeting of the Antiviral Advisory Committee, which later became

the Antimicrobial Drugs Advisory Committee, to discuss the types of animal models that should be used to study drugs for the treatment of smallpox. Based on the panel's recommendations, the FDA agreed that the current variola model was not adequate to support advocacy for smallpox for multiple reasons.

The FDA agreed that efficacy should be evaluated in 2 of 3 animal models for smallpox, nonhuman, primates, rabbits, or mice. The agency further agreed that the human dose should be estimated based on animal data and human PK and safety data. Lastly, the panel recommended that clinical studies in monkeypox would not be required.

With FDA concurrence, we chose to conduct our efficacy studies in nonhuman primate and rabbit models. Toxicology studies were conducted in five species, which included mice, rats, rabbits, dogs, and nonhuman primates, and safety and tolerability studies were conducted in human volunteers.

We conducted our animal efficacy and clinical programs in close consultation with FDA and provided our protocols to FDA for review. Additionally, the FDA

had designated tecovirimat for fast track and an orphan drug status.

Our proposed indication is treatment of human smallpox disease caused by variola virus in adults and pediatric patients, and the proposed treatment regimen for this indication in adults is 600 milligrams by mouth, twice daily for 14 days. It is recommended that tecovirimat be taken with food.

Evidence for this targeted indication is based on animal data establishing therapeutic efficacy and human data demonstrating safety. Overall, 6 pivotal trials in FDA-accepted animal models for human smallpox, 4 in nonhuman primates, and 2 in rabbits show that tecovirimat provided nearly complete protection from death and significantly reduced morbidity. Tecovirimat was shown to be generally well tolerated across 12 human trials with a similar safety profile to placebo. Tecovirimat has been administered on a compassionate-use basis to treat a few individuals who had complications resulting from the current smallpox vaccine.

For the rest of our presentation, Dr. Dennis

Hruby, chief scientific officer at SIGA, will discuss smallpox disease and the unmet need in smallpox treatment, review the efficacy data, including the selection of animal models used and selection of the human dose. He will then review the safety data from our animal and human studies, and then conclude with a benefit-risk summary supporting tecovirimat's approval.

We also have additional experts with us today to help answer your questions. All external experts have been compensated for their time and travel.

Thank you, and I will now turn the lectern over to Dr. Hruby.

Applicant Presentation - Dennis Hruby

DR. HRUBY: Thank you, Annie, and good morning.

In addition to serving as chief scientific officer at SIGA, I spent over 35 years as a faculty member at the University of Wisconsin, University of Texas, and Oregon State University. Most of my career has been focused on poxviruses, virology, and anti-infective research. At SIGA, we've been working on developing a smallpox therapeutic for more than 15

years, and I'm pleased to be here to summarize this work for you. But first let me start with why we needed treatment.

The variola virus, which is the etiological agent of smallpox, is the most deadly human pathogen in the history of the world. It was responsible for 300 to 500 million deaths in the 20th century alone. It's a significant threat to human health because it's both highly contagious and highly lethal. Rapid spread from person to person can occur through speaking, breathing, or touching. It's estimated that without vaccination or treatment, each person infected with smallpox could infect 5 to 7 others.

Mortality rates are as high as 30 percent of those infected, while all infected experienced significant morbidity. Post-infection sequelae included scarring, encephalitis, corneal ulcerations, and blindness. Fortunately, naturally occurring smallpox has been successfully eradicated through aggressive global vaccination campaigns.

Despite this important public health achievement, there's growing concern that smallpox

could be used as a bioweapon. While there are two publicly acknowledged stocks of the variola virus held by the United States and Russia, experts believe that additional stores of the virus could be in the hands of governments or organizations that might use them to cause harm. Furthermore, the DNA sequence of the smallpox genome is in the public domain and could be synthesized in a laboratory from scratch or created by genetically modifying a similar virus such as camelpox. This possibility was recently validated by experiments in which horsepox virus was created de novo by Canadian scientists.

CDC has categorized variola virus as a Category A pathogen, and it is designated as a material threat by the U.S. government. Thus, with the advent of biowarfare as an instrument of terrorism and the potential to generate the virus de novo using genetic engineering technologies, smallpox can no longer be thought of as a disease of historical impact only.

Let me take a moment to describe the disease progression for smallpox in humans. Following exposure, there's an incubation period of 7 to 17 days

during which no disease is evident and the infected individual is not contagious. During this pre-eruptive phases of the disease, the virus spreads from the primary infected foci to the regional lymph nodes. The virus replicates in lymph nodes and releases a small amount of virus into the bloodstream, primary viremia. These virus particles see the spleen, liver, and reticuloendothelial systems where the virus replicates to high titer.

Release of virus results in a secondary viremia and initiates the prodrome phase of the disease. At this point, the infected individual is contagious. The prodrome is characterized by high fever, excruciating headaches, backaches, joint pain, and abdominal pain, in addition to high levels of viremia. Within 1 to 4 days following the onset of the prodrome phase, the virus spreads through the blood and lymph nodes, seeding capillary endothelial cells and initiating replication in the skin and oral pharyngeal mucous membranes.

After the prodrome in what is referred to as the eruptive phases of the disease, a characteristic

rash begins to form on the extremities and face. Pock development follows, progressing from macules to papules to vesicles, and finally to crusts and scabs. If the individual does not succumb to the disease, the pocks are fully resolved within about 21 days at their initial appearance with residual desquamation and scarring of the affected tissues. It bears repeating that all infected will experience significant morbidity, approximately 30 percent will die, and the survivors will be scarred for life and may experience numerous other disease sequelae.

While vaccination remains the only way to protect against smallpox, vaccines alone cannot address the smallpox outbreak. Unfortunately, there are currently no other therapies other than early vaccination available. Although the vaccine is approved and is currently stockpiled for use in the event of a smallpox emergency, it is not universally available for the general population because of the risk of adverse vaccination reactions, particularly in individuals who are immunosuppressed.

The majority of today's population is not

immune to the variola virus, as routine vaccination ended in the 1970s. A smallpox bioterror attack could have catastrophic consequences on individuals, populations, and perhaps a significant global impact.

The vaccine does not work as a therapeutic treatment in symptomatic individuals. To be effective, vaccination must occur within 3 to 4 days of exposure to smallpox when patients are still asymptomatic. Sentinel cases will not be identified until after the eruptive phase, approximately 10 to 20 days after exposure. Therefore, there's an important unmet need for a medication that reduces morbidity and mortality in symptomatic patients with smallpox and limits its spread in a susceptible population.

Given the potential for an intentional smallpox outbreak and the absence of any post-exposure treatment modalities, a safe and effective small molecule drug is needed to respond in the event of a smallpox emergency.

Turning now to efficacy, 6 pivotal studies in FDA-accepted animal models for human smallpox, nonhuman primates and rabbits show the tecovirimat provides

nearly complete protection from death and reduces morbidity.

Let me start with the nonclinical program. In order to predict tecovirimat's activity against orthopoxviruses in humans, in vitro studies were conducted with 4 human pathogens as well as with three related orthopoxviruses that infect animals. Overall, tecovirimat was shown to be an active nanomolar inhibitor against all the orthopoxviruses tested. Results of the studies showed that tecovirimat targets a highly conserved protein unique to orthopoxviruses, including variola virus.

Tecovirimat inhibited virus spread and plaque formation in cells infected with orthopoxviruses. Tecovirimat showed a dose-dependent inhibition or orthopoxvirus-induced cytopathic effects, and tecovirimat functions by inhibiting dissemination of orthopoxviruses.

Let me walk through tecovirimat's mechanism of action in more detail. Tecovirimat works by blocking the ability of the variola virus to spread. Although infectious intracellular particles are formed,

tecovirimat inhibits further viral maturation by preventing the formation of a secondary viral envelope. In the absence of this envelope, the viral particles remain inside the cell in which they're produced and cannot spread to or infect other cells. By inhibiting envelopment and thereby precluding the exit of viral particles from an infected cell, infection is slowed to a point where the host immune system can clear the virus.

Turning now to the animal models used to evaluate clinical efficacy, as a reminder, efficacy of tecovirimat was based on data from FDA-accepted animal models. Based on the outcome of the 2011 advisory committee convened by FDA to specifically address the issue of animal models for smallpox, three models were suggested to and accepted by the FDA as appropriate for evaluation and demonstration of drug efficacy versus smallpox. These were intravenous infection of nonhuman primates with monkeypox virus; intradermal infection of New Zealand white rabbits with rabbitpox virus; and intranasal infection of BALB/c mice with ectromelia virus.

The agency recommended that two of these models be utilized to demonstrate efficacy and to triangulate the exposure-response relationship in animals with target exposures in humans, and that the most conservative animal model should serve to establish the appropriate drug exposure that would need to be exceeded in order to establish the human dose. The two models that SIGA studied for efficacy and dosimetry where the nonhuman primate and rabbit models.

In addition, the committee discussed various elements that should be included in animal models that are being used to predict human efficacy. These include providing a sufficiently accurate recapitulation of the human disease course; providing a sufficient kinetic approximation of human disease progression; having reproducible and defined disease severity criteria to include quantifiable endpoints; having a defined therapeutic trigger; providing a correlation between clinical observations and outcome; and the drug pharmacokinetics in the infected animal should mirror the human as closely as possible.

When comparing the nonhuman primate model with

the elements necessary for an ideal animal model, it meets all the criteria. The rabbit model also checks most of the boxes except that the disease out course is abbreviated, and the dose-exposure relationship is dissimilar.

Based on scientific literature, monkeypox infection of cynomolgus macaques is a very reliable model that captures many of the aspects of human smallpox. In evaluating the nonhuman primate model for human smallpox for demonstrating the efficacy of antiviral therapeutics, a number of parameters have to be considered.

First, it's important to determine the stage of the disease progression, as it compares to human smallpox, in which treatment could be no longer considered prophylactic but rather considered therapeutic. The most distinctive and unambiguous identification of smallpox was the appearance of a synchronous, centrifugal rash that progressed from an enanthema/exanthema to pustules beginning a few days after severe fever.

Importantly, the time course and associated

pathology of monkeypox virus in the nonhuman primate versus human smallpox is nearly identical from the secondary viremia onward. In the intravenous challenge nonhuman primate model, lesions containing virus appear 3 to 4 days post-challenge and continue to increase in number and progress through stages typical of human smallpox until death.

In this model, a uniformly lethal challenge of 5 times 10 to the 7th platform forming units was used. Therefore, the trigger for treatment would be the first appearance of lesions on day 4. Recent literature also suggests that rabbitpox disease in rabbits closely mimics the steps of smallpox disease in humans. After the initial infection, there's a symptom reincubation period followed by fever and dissemination of virus in the blood and establishment of a secondary systemic infection followed by death.

Following the FDA recommendation at the 2011 advisory committee, the intradermal challenge model was used for evaluation of tecovirimat efficacy. In this model, a lethal viral challenge of a thousand plaque forming units of rabbipox virus was chosen. The

trigger in this model is different from the nonhuman primate model since most rabbits die quickly before developing lesions. The therapeutic trigger used in this model is fever, which is always observed prior to day 4. Therefore, treatment started at day 4 in the rabbit models.

Let me now review the results of the animal studies.

More than 40 preliminary animal efficacy studies were conducted in a number of different species using a number of different orthopoxvirus pathogens in a number of different institutions with the results obtained being fully consistent with pivotal studies.

A total of 6 pivotal, nonclinical studies for non human primates 2nd 2 in rabbits were undertaken to evaluate the efficacy of oral tecovirimat. Five of these pivotal studies were double-blind studies. All pivotal studies were conducted in a step-wise process with the discussion and agreement between the FDA and SIGA on design, endpoints, and analysis.

The efficacy endpoints were the same in all 6 studies. The primary efficacy endpoint was survival

rate. Survival rates were defined as the percentage of animals alive at the day of scheduled study termination. This endpoint is clinically meaningful for the human situation, which is one of the requirements of the Animal Rule.

Supportive pharmacodynamic endpoints representative of morbidity included lesion formation in nonhuman primates only in viral DNA load. I'll review each of these studies in more detail.

Starting with the four conducted in nonhuman primates, which were all randomized placebo-controlled studies, study 26G was conducted to determine the minimum effective dose of oral tecovirimat in cynomolgus monkeys infected with monkeypox virus. 27 animals received placebo once daily or tecovirimat at 0.3, 1, 3, or 10 mgs per kg once daily. Drug was administered for 14 consecutive days starting on day 4.

Turning now to the efficacy endpoint results. Assessment of survival rate demonstrated a significant dose-dependent effect of tecovirimat treatment on mortality. No animals survived a scheduled termination in the placebo and 1 mg per kg tecovirimat groups,

whereas 20 percent, 80 percent, and 80 percent of the animals survived in the 0.3, 3, and 10 mg per kg groups, respectively.

A single animal died in both the 3 and 10 mg per kg dose groups, but their deaths were not attributed to monkeypox. As typical, disease was not evident at necropsy. It's considered most likely that the deaths were due to the complications from anesthesia.

There was also a dose-dependent effect of tecovirimat treatment on lesion counts. By day 3 or 4, all animals in all treatment groups had developed lesions. Lesions became pustular and umbilicated by day 7 to 9 and peaked between days 9 and 12 for all groups, with scab lesions indicative of resolution first noted on day 11.

Animals treated with placebo, tecovirimat at 0.3 mgs per kg, or tecovirimat at 1 mg per kg typically died prior to lesion and resolution. In contrast for animals treated with tecovirimat at 3 or 10 mgs per kg, lesions generally fully resolved between days 19 and 23. Animals receiving tecovirimat at 10 mgs per kg

had significant decreases in total lesion counts compared to placebo-treated animals.

Similar results were observed with regard to viral DNA load. Assessment of viral DNA load revealed a significant dose-dependent effect of tecovirimat on monkeypox virus concentrations in the blood. Animals receiving tecovirimat at 3 or 10 mgs per kg had significantly lower viral DNA load than animals in the placebo group, with the 10 mgs per kg dose confirming the greatest protection against viremia.

Turning now to study 87, in study 87, which was a dose-response study, 24 animals received placebo once daily or tecovirimat at 3, 10, 20 mgs per kg once daily. The doses evaluated in this study were based on the demonstration of efficacy using similar doses in 26G study with the intent of determining tecovirimat exposures correlating with efficacy. Drug was administered for 14 consecutive days starting on day 4.

With regards to the primary endpoint, tecovirimat had a significant effect on survival with no evident dose-dependent trends observed. All animals on tecovirimat had 100 percent survival compared with

no survival in animals receiving placebo. Lesion monitoring in this study was not designed to detect a significant effect of tecovirimat treatment, so let's review the viral DNA load results.

Circulating viral DNA loads decreased gradually in tecovirimat treated animals with no evident dose-dependent differences across tecovirimat 3, 10 or 20 mgs per kg treatment groups. In contrast, by day 6, placebo-treated animals demonstrated a consistent increase in circulating viral DNA load that was maintained until death.

Turning now to nonhuman primate study 37F, which was a repeat-dose study to evaluate the efficacy of tecovirimat in male and female cynomolgus monkeys against a lethal IV challenge of monkeypox virus and to determine the time point at which tecovirimat failed to protect the mortality.

Twenty-one animals were randomized into four groups to receive placebo once daily, starting on day 4 or tecovirimat at 10 mgs per kg once daily starting on either day 4, 5, or 6 for 14 consecutive days. Overall, 83, 83, and 50 percent of animals survived in

the tecovirimat groups initiating treatment on days 4, 5, and 6, respectively. No animals survived a scheduled termination in the placebo group. Tecovirimat treatment initiated on day 4 or 5 after viral challenge conferred greater protection against monkeypox virus infection than treatment initiated on day 6.

Lesion monitoring data demonstrated an effect of tecovirimat treatment on lesion counts with treatment initiated before day 6, conferring the greatest protection against monkeypox virus lesion formation. By day 6, all animals across the four treatment groups had developed lesions. Most lesions were vesicular or pustular.

For all treatment groups, total by the lesion counts typically peaked between day 6 and 9. Animals receiving tecovirimat initiated on day 4 had the lowest median lesion counts compared to animals receiving placebo or tecovirimat initiated on day 5 or 6. Assessment of viral DNA load revealed a significant effect of tecovirimat on monkeypox virus concentrations in the blood with treatment initiated on day 4,

conferring the greatest protection against infection.

Turning now to the fourth and last nonhuman primate study, study 38F was conducted to determine the treatment duration at which tecovirimat failed to protect the mortality and was similarly designed to study 37F. A total of 25 animals were randomized in this study. Assessment of survival rate demonstrated a significant effect of tecovirimat treatment on mortality with treatment for at least 5 days sufficient to confer a survival advantage. 100, 100, and 80 percent of animals survived in the tecovirimat groups receiving treatment for 5, 7, and 10 days, respectively.

For surviving animals treated with tecovirimat, lesions typically continued to resolve until study termination. Animals receiving tecovirimat had fewer lesions and developed scab lesions indicative of resolution on day 6 to 9, or such lesions were rare in animals that succumbed to disease.

Assessment of viral DNA load revealed a significant effect of tecovirimat on monkeypox virus concentrations in the blood. Longer durations of

tecovirimat treatment of 5, 7, or 10 days were associated with the lower limit of quantitation of the virus by study termination.

This forest plot summary shows that overall in studies 26G and 87, tecovirimat treatment at doses of at least 3 mgs per kg successfully inhibited progression of monkeypox virus infection in nonhuman primates and significantly improved survival. Increasing the dose to 10 mgs per kg did not provide additional survival benefit for results in further reductions in morbidity. Study 37F demonstrated that protection was greatest when treatment was started on day 4 or 5. Study 38F showed that at least 5 days of treatment is sufficient to demonstrate a survival advantage.

Overall and consistent with results observed in the nonhuman primate studies, treatment with tecovirimat at doses of 20 to 120 mgs per kg was highly efficacious in rabbits with established rabbitpox virus infection, as indicated by improvements in survival and decreases in viral DNA load. Survival for all doses evaluated was 80 to 90 percent and was significantly

improved relative to placebo treatment or there were no survivors. No dose-dependent trends were observed suggesting that all the doses used were above the dose-response range for efficacy.

In summary, data from 6 pivotal studies in nonhuman primates and rabbits indicate that tecovirimat is efficacious for the treatment of smallpox infection. The five placebo controlled studies demonstrated that a minimum dose of 3 mgs per kg in nonhuman primates and 20 mgs per kg in rabbits was sufficient to reduce mortality.

In nonhuman primates, additional benefit on lesion count and viral DNA load was provided by increasing the dose to 10 mgs per kg, but no further benefit was evident when the dose was increased to 20 mgs per kg.

Let me now turn to the justification for our human dose selection. For smallpox, there's a clearly outlined process for determining the human dose. Triangulation to the human dose is achieved by showing efficacy and PK in two species, animal toxicology, along with safety and PK in humans. In order to bridge

the effective animal dose to the proposed clinical human dose, PK/PD and exposure response analyses were also performed in infected nonhuman primate and rabbits.

Animal studies are used to inform the selection of the human dose by establishing that drug exposures that are safe and efficacious in animals. FDA guidance suggests that where possible, humans should have several fold higher exposure than the most conservative animal model, in our case, the nonhuman primate model.

While toxicology studies were conducted in multiple animal species, maximum safety exposures for tecovirimat were determined in dogs, as this was the most sensitive species. At a dose of 300 mgs per kg, one dog with an exposure of level of 16,500 nanograms per mL, which was 4 times the highest exposure achieved in humans, had a seizure, while others at lower exposure of levels did not. The next lower exposure level were no seizures were observed was at 5,575 nanograms per mL, and this level is used as our maximum safety limit.

Tecovirimat was very well tolerated at supratherapeutic doses when administered daily for 3 months to mice and nonhuman primates. Comparison of Cmax, Cmin, and AUC exposures associated with maximal efficacy in nonhuman primates and rabbits indicate that nonhuman primate is the most conservative model for estimation of the human dose, as higher exposures were required in this model for maximal efficacy. Thus, the human dose estimation is based on nonhuman primate exposures.

PK/PD modeling was performed to identify the PK critical parameters most closely correlated with survival and to determine the exposure-response relationship. Cmin was determined by both the FDA and SIGA to be the most critical parameter to predict efficacy.

PK data from humans at 600 milligrams twice-daily studies were analyzed to ensure that drug exposures in these subjects are within the safety and efficacy ranges. Cmin in the fed subjects were several fold higher than efficacious exposures in nonhuman primates achieved by dosing at 10 mgs per kg

and fasted drug administration still provides excess exposure. Cmax should be below the maximum safety exposure as defined by the toxicology study in dogs. The 600-milligram, twice-daily dose was predicted to meet these criteria.

Based on highest efficacious dosing and exposures to nonhuman primates, along with human PK data, tecovirimat at 600 milligrams twice daily was established to achieve exposure levels in humans that exceed efficacious exposure in nonhuman primates by several fold.

Let me now review tecovirimat's clinical safety profile. In human studies, tecovirimat was shown to be generally well tolerated with a similar safety profile to placebo. The overall safety of tecovirimat has been evaluated in 788 subjects in 12 clinical studies. Safety and tolerability were evaluated in healthy subjects as well as in subjects with renal or herpetic impairment. There was 1 pivotal study, 3 supportive, multiple-dose studies, and 8 supported single-dose studies.

In this presentation, I will focus on the data

from our pivotal study 008, which was a randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability, and pharmacokinetics of tecovirimat administered at 600 milligrams twice daily for 14 days to adult volunteers.

This trial, while excluding subjects with end-stage morbid conditions, reflected American population at large, including subjects with various comorbid conditions taking various therapies. A total of 449 subjects were administered tecovirimat or placebo. During our pivotal study, there were a total of 359 adult volunteers who received tecovirimat . Approximately 94 percent of subjects in each group received 80 percent or more of their prescribed doses.

Overall, administration of tecovirimat at 600 milligrams twice daily for 14 days was generally well tolerated. There were a total of 449 subjects included in the safety population with approximately three-quarters of the subjects coming from the tecovirimat arm.

The proportion of subjects that experienced at least one adverse event was similar among the groups,

with 37 percent in the tecovirimat arm and 33 percent in the placebo arm. Very few subjects had severe AEs, and one subject had a fatal SAE determined not to be related to study drug.

AEs leading to discontinuation were low in both groups with a 2 percent discontinuation in each group. The most commonly reported AEs were comparable between tecovirimat and placebo, with a difference in incidence being less than 3 percent. The most frequent AEs were headache and nausea.

Next, let's look at the adverse events by severity. In our pivotal study, AEs of severe or greater intensity or infrequent, the only severe AE reported in more than one subject was a headache, which was reported in two subjects. The incidence of AEs leading to discontinuation was low in both the tecovirimat and placebo groups. Of AEs leading to discontinuation in the tecovirimat arm, the most common were nausea and pyrexia. There was one death in pivotal study 008. The subject receiving tecovirimat at 600 milligrams twice daily died from a fatal SAE of a pulmonary embolism. This was determined to be

unrelated to tecovirimat .

Tecovirimat was provided for emergency use under U.S. emergency investigational new drug applications. There were 5 cases in the U.s. that included one pediatric case and 4 adult cases. There was also one case in Europe where tecovirimat was provided for compassionate use. All patients survived with no new clinically important safety signals associated with tecovirimat.

In summary, tecovirimat is generally well tolerated with a similar safety profile to placebo. At the proposed oral adult dose of 600 milligrams twice daily, the incidence of AEs was similar to the incidence of AEs amongst subjects receiving placebo. Most AEs were mild or moderate and resolved without sequelae. The most common AEs in subjects receiving tecovirimat were headache and nausea. Across all studies, there were 5 SAEs in 2 subjects. None were related to tecovirimat. The incidence of AEs leading to treatment discontinuation was low in all clinical trials.

I would now like to conclude with a summary of

the benefit-risk profile for tecovirimat. The threat of smallpox as an instrument of biowarfare of bioterrorism is real, and it must be addressed. Currently, vaccination is the only available option to protect Americans against a smallpox infection, but it has limitations. As we heard earlier, the smallpox vaccine is associated with a risk of adverse events and is currently stockpiled for use in the event of emergency only. Additionally, it does not work in symptomatic individuals.

With the majority of the population not immune to the variola virus, vaccines alone cannot help prevent a spread, and a biological attack would be devastating making the availability of an effective smallpox treatment an essential requirement. Tecovirimat will help fill this need by providing the first and only effective antiviral treatment for smallpox.

In two animal models, tecovirimat was shown to be efficacious as measured by the survival endpoint. Based on demonstration of therapeutic efficacy in animals, tecovirimat is predicted to be efficacious in

symptomatic individuals and can be administered post-exposure.

Population PK/PD models were developed to bridge the effective animal dose to a dose expected to be safe and efficacious in humans. The proposed dose of 600 milligrams twice daily was confirmed as the optimal dose by pharmacokinetic and safety results in pivotal clinical study 008, which is considered to represent the adult general population.

Overall, tecovirimat is generally well tolerated in humans, and the risk of tecovirimat administration are minimal. Most adverse events are mild or moderate and self limited in nature with the most common being headache and nausea.

Based on the some of the data, the important public health benefits of tecovirimat 600 milligrams twice daily far outweighs its risks. The seriousness of smallpox with severe morbidity in all infected and mortality rates noted as high as 30 percent underscores the need for therapeutic treatment that will prevent the progression of this deadly disease post-exposure.

Tecovirimat was shown to significantly reduce

mortality and morbidity in animals with minimal risk observed when administered to humans. Considering the safety profile of tecovirimat demonstrated in clinical trials and the efficacy demonstrated in animal models, the benefit-risk profile of tecovirimat is favorable and supports its use for treatment in smallpox. Thank you.

DR. BADEN: Thank you, Dr Hruby.

We will proceed with the agency's presentations and do the clarifying questions together to both groups.

Dr. Chan-Tack?

FDA Presentation - Kirk Chan-Tack

DR. CHAN-TACK: Hi. Good morning. My name is Kirk Chan-Tack. Dr. Su-Young Choi and I will be presenting the highlights of the FDA's assessment of the animal efficacy pharmacokinetics and dose election and clinical safety on behalf of our multidisciplinary review team. We'll begin with an outline of our presentation starting with a brief recap of the tecovirimat basics, followed by a summary of the 2011 Antiviral Drug Advisory Committee meeting.

We'll then proceed to discuss the tecovirimat development program for the treatment of human smallpox, notably the animal efficacy, the pharmacokinetics and dose selection, and the human safety. And then we'll conclude our discussion with the agency's assessment of the available data to meet the FDA's Animal Rule requirements.

To begin with the basics of the product under question today, tecovirimat is an oral capsule. Its mechanism of action is that it inhibits viral spread to uninfected cells by targeting an orthopox protein, the P37 protein, that's involved in the production of the extracellular enveloped virus. Its antiviral activity is only against orthopoxviruses.

The next four slides will summarize the agency's perspective as presented at the 2011 advisory committee meeting, and the committee's conclusions were in accord with the agency's perspective.

The Animal Rule requirement number 1 outlines that there should be a reasonably well understood pathophysiological mechanism of toxicity of the substance and its prevention or substantial reduction

by the products. The agency and the committee agree that because smallpox was eradicated over 30 years ago, the pathophysiology of variola virus infection is not fully understood, making it difficult to know which elements of variola virus infection and pathogenesis in humans are most important to recapitulate the animal model of variola virus infection.

It was acknowledged that this requirement cannot be wholly met, but the uncertainties can be addressed, to the extent feasible, if data from at least two lethal animal models of non-variola orthopoxvirus infection are attained to evaluate drug efficacy.

The second requirement of the Animal Rule is that the effect is demonstrated in more than one animal species to react with response that is predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well characterized model for predicting the human response.

The agency and the committee agreed that the scientific limitations of the available nonhuman primate variola model preclude definitive efficacy

assessments and uncertainty exists whether an adequate variola model can be developed. And therefore, the FDA and the advisory committee agreed that data from a combination of other lethal animal models using surrogate orthopoxviruses, such as the nonhuman primate monkeys with monkeypox virus, the rabbit with rabbitpox virus, and mice with ectromelia virus could be used as evidence along with or potentially instead of animal studies using variola virus.

The third requirement of the Animal Rule is that the animal study endpoints is clearly related to the desired benefit in humans, that being generally the enhancement of survival and prevention of major morbidity. The agency and the committee agreed that the primary endpoint of survival should be used, and euthanasia should be based on prospectively defined criteria.

As discussed previously by the other presenters, prospectively defined criteria are important because, in animal efficacy studies, mortality is based on humane euthanasia criteria. At the time of the 2011 meeting, the applicant appeared to

have met this requirement in one lethal animal model of non-variola orthopoxvirus infection, that being the nonhuman primate monkeypox virus model.

The fourth requirement of the Animal Rule is that the data or information on the pharmacokinetics and pharmacodynamics of the product, or other relevant data or information, in animals and in humans allows for the selection of an effective dose in humans. The agency and the committee assessed that the tecovirimat program had at that time collected PK/PD in the nonhuman primate monkeypox virus model and needs similar information in the second animal model. The applicant's plan post-advisory committee meeting was to conduct studies using the rabbit/rabbitpox model as the second animal model.

A summary of the animal efficacy follows in the next four slides. In the nonhuman primate monkeypox virus model, cynomolgus macaques were challenged intravenously with 5 by 10 to the 7 plaque-forming units of the monkeypox Zaire 1979 strain. Disease in this model is rapid, causes systemic viremia, and disease signs such as fever,

rash, and skin lesions that resemble the features of human smallpox.

Mortality is nearly universal in non-treated animals with a mean time to death or moribund disease requiring humane euthanasia at approximately 14 days post-challenge. The appearance of skin lesions, which first occurs 3 to 4 days post-challenge, was selected as a clinically relevant trigger for initiation of tecovirimat treatment.

The conclusions from the efficacy studies in this model are that the applicant completed four randomized placebo-controlled studies; 3 or 4 were double blinded with tecovirimat started at the time of lesion onset. A statistically significant treatment benefit over placebo was demonstrated for the primary endpoint of survival when tecovirimat was dosed at 3, 10, and 20 milligrams per kilogram per day for 14 days, starting at day 4 after virus inoculation.

Efficacy was observed at 3 milligrams per kilogram, and for the purpose of human dose selection, a nonhuman primate dose of 10 milligrams per kilogram per day was used to provide exposures that exceed those

associated with the fully effective dose. Inspections confirmed the studies' quality and integrity, and the studies in this model appeared sufficient to constitute one of two acceptable models to meet the Animal Rule requirement for approval.

Moving on to the rabbit/rabbitpox model. In these studies, 16 week old New Zealand white rabbits were challenged intradermally with 1,000 platforming units of the rabbitpox Utrecht strain. The disease in this model is rapid and universally fatal and is consistent with what is known about variola virus infection of humans, in that only a very low-challenge dose is required to cause severe disease. The disease signs include fever, changes in respiration rate and erythema, edema, scabbing and necrosis at the injection site. Systemic viremia is observed by 3 to 4 days post-challenge and increases to high levels until the time of death, which occurs approximately 6 to 9 days after lethal challenge.

Fever, which consistently occurs by day 4 post-challenge, was selected as a clinically relevant trigger for the initiation of tecovirimat treatment,

and the conclusions from those efficacy studies in the rabbit/rabbitpox model are displayed here. The applicant completed two randomized, double-blinded studies, 1 of 2 being placebo controlled, with tecovirimat started at the time of fever onset.

A statistically significant treatment benefit over placebo was demonstrated for the primary endpoint of survival when tecovirimat was dosed 20, 40, 80, and 120 milligrams per kilogram per day for 14 days starting at day 4 after inoculation.

Efficacy was observed starting at 20 milligrams per kilogram. And for the purpose of human dose selection, a rapid dose of 40 milligrams per kilogram per day was used to provide exposures that exceed those associated with the fully effective dose.

The inspections confirmed study quality and integrity, and the studies in this model also appear sufficient to constitute one of the two acceptable models to meet the Animal Rule criteria for approval.

Now I'd like to turn the podium over to Dr. Su-Younhg Choi who will discuss the pharmacokinetics and dose selection.

FDA Presentation - Su-Young Choi

DR. CHOI: Good morning, everyone. In this section, I will outline the information needed to select the effective dose in humans under the Animal Rule and our rationale for accepting 600 milligrams twice daily for 14 days as effective human dose for tecovirimat for smallpox infection treatment.

To select an effective dose in humans under the Animal Rule, the following information is needed. First ADME, which is absorption, distribution, metabolism, and excretion, and the pharmacokinetic profile of the investigational drug in animals and humans should be characterized.

The exposures associated with efficacy in animals to study should be determined. Also, the effects of the challenge agent induced disease or condition on the pharmacokinetic of the investigation or in animals should be determined. And the relationships between exposure parameters, such as AUC, Cmax, and Cminimum, and the primary endpoint, which was survival for tecovirimat of at least 3 doses in dose-ranging finding study should be determined. The

applicant conducted a series of in vitro, animal, and healthy volunteer studies to collect information listed here.

There are several ways to select an effective dose under the Animal Rule, and for tecovirimat, the review team has concluded that the use of a conservative approach is acceptable. Under this approach, first, the fully effective dose in animal models should be selected. Then conservative approach means that human doses should provide exposures that are higher than those associated with the fully effective dose in animals ideally by several fold if the drug's safety profile allows. We recommend this approach due to inherent uncertainty in animal models for smallpox.

Tecovirimat dose-response relationship for survival is summarized in this slide. As previously presented by the applicant and by Dr. Chan-Tack, in both animal models, tecovirimat demonstrated survival benefit over placebo. In nonhuman primates, the efficacy, survival benefit, was observed from 3 milligram per kilogram per day, and 10 milligram per

kilogram per day was selected as the fully effective dose in nonhuman primates. For rabbits, 40 milligram per kilogram per day was selected as the fully effective dose. Based on the available pharmacokinetic information in humans as well as animal models, 600 milligrams twice daily for 14 days was selected as an effective dosing regimen in humans.

Tecovirimat plasma concentrations in nonhuman primates and rabbits at the fully effective doses and humans at the proposed dosing regimen are compared in this slide. The graph on the left side shows the tecovirimat time concentration profile on day 1, and the graph on the right side shows the time concentration profile at steady state.

On both days, in humans receiving the proposed dosing regimen shown in red, tecovirimat concentrations are higher than those associated with the fully effective dose in nonhuman primates, which is shown in black, and in rabbits, which is shown in green. Also, to achieve the maximum efficacy in both animal models, higher tecovirimat exposures are required in nonhuman primates as compared to rabbits. Therefore,

pharmacokinetic parameters were mainly compared between nonhuman primates and humans.

The tecovirimat key pharmacokinetic parameters in nonhuman primates and humans are compared in this table. On day 1 and day 14, at the proposed dosing regimen, in humans, Cmax and AUC values are about 2-fold higher and Cminimum values are about 4-fold higher as compared to those in nonhuman primates at the fully effective dose, 10 milligram per kilogram per day.

In addition to comparing pharmacokinetics between animals and humans, there are things to consider when selecting a human dose under the Animal Rule. First, the effects of infection on the study drug's PK should be characterized. For tecovirimat, there was no significant PK differences between uninfected and infected nonhuman primates.

Also, the differences in protein binding between animals and humans should be considered. For tecovirimat, plasma protein binding was 88 percent in nonhuman primates and 80 percent in humans. Therefore, there was no need to adjust doses based on the

differences in protein binding.

While several fold higher exposures are recommended in humans as compared to those exposures associated with fully effective dose in animals, doses higher than 600 milligrams twice daily were not pursued for the following reasons. First, at 600 milligrams 3 times daily, some subjects may reach Cmax concentrations associated with an adverse event, which is seizure observed in dogs, which will be explained later in the safety section. Also, for doses above 600 milligrams, exposures increased less than a dose proportional manner.

We also reviewed the effects of food and the intrinsic/ extrinsic factors to determine whether a different dosing regimen is recommended for a certain patient group. As for effects of food, food increased absorption of tecovirimat, therefore we recommend to take tecovirimat under fed conditions. In fact, the key clinical studies were conducted under fed conditions.

However, some critically ill patients may not be able to take drug under fed conditions, so even

under fasted conditions, tecovirimat exposures are still comparable to those associated with the fully effective dose in nonhuman primates.

As for specific populations, based on the currently available data at this time, no dose adjustment is necessary based on renal or hepatic function, sex, age, weight, or race. The potential for drug interactions is characterized. Tecovirimat is a weak inducer of CYP3A and weak inhibitor of CYP2C8 and 2C19. Tecovirimat is metabolized by UGT1A, therefore inhibitors or inducers of UGT1A can alter the pharmacokinetics of tecovirimat.

In summary, the FDA review team agrees with the proposed dosing regimen 600 milligrams twice daily for 14 days under fed conditions as the effective dosing regimen of tecovirimat for the treatment of smallpox infection.

The last topic in my section is pediatric dosing regimen. Conducting a clinical trial in healthy children with no clinical benefit is considered unethical. Therefore, pediatric dosing regimen is determined solely based on modeling and simulation.

The FDA review team conducted population pharmacokinetic modeling and simulation to determine the pediatric dosing regimens that are predicted to produce compared with tecovirimat exposures to adult.

FDA recommended pediatric dosing regimen is summarized in this table. For pediatric patients weighing 40 kilogram and above, the recommended dosing regimen is 600 milligrams twice daily, which is the adult dose. For patients weighing 25 kilograms to less than 40 kilograms, we recommend 400 milligrams twice daily for 14 days. For patients weighing 13 to 25 kilograms, the recommended dose is 200 milligrams twice daily.

For patients weighing less than 13 kilograms, we do have specific dosing recommendations, however, this requires subdividing capsules by caregivers. So the information will be available in product labeling upon the successful completion and review of the human factor study to ensure that instruction for dividing capsules is easy and clear to follow for caregivers.

Now I'll turn it over to Dr. Chan-Tack for safety information.

Presentation - Kirk Chan-Tack

DR. CHAN-TACK: Next, we're going to a discussion of the human safety. The human safety database; as part of drug development under the Animal Rule, an adequate human safety database is required. The size and composition of the human safety database that is necessary to support drug approval depend on the proposed indication, the toxicity profile, and/or the extent of the agency's experience with a particular drug class. For a drug intended for treatment of life-threatening diseases or conditions, greater unknown risks or greater uncertainty about undefined risk may be acceptable when the drug offers a clear benefit for those patients.

For tecovirimat, a minimum database of 300 individuals at the intended treatment dose and duration was recommended. A database of at least 300 individuals allows for reasonably reliable detection of adverse reactions occurring at a rate of 1 percent or greater.

Onto study 008. This was the phase 3, double-blind, randomized, placebo-controlled

multicenter study in healthy adults who were randomized 4 to 1 to receive tecovirimat 600 milligrams BID for 14 days or placebo. There was an initial PK, i.e., the lead-in cohort of 40 subjects; 20 received drug under fed conditions and 20 fasted, and the breakdown was tecovirimat 32 subjects versus 8 subjects in the placebo group.

There was expanded cohort of fed subjects that constituted a target enrollment of 382 of whom 306 would receive tecovirimat and 76 in the placebo group, for an overall target of 338 tecovirimat recipients and 84 placebo recipients. The target enrollment was achieved, and the demographics for these subjects are displayed on this slide, the 359 tecovirimat recipients, 90 placebo recipients, to total 449 in the phase 3 study. And as you can see, the treatment arms are well balanced with respect to sex, age, race, and ethnicity.

The disposition of these subjects are presented here. As you can see for tecovirimat versus placebo, the treated population, i.e., the 359 tecovirimat recipients and 90 placebo recipients, are

the population that was used in the safety analyses. The completion rates were high, 93 percent and 94 percent, respectively, and the rates of discontinuation due to adverse events, which is one of our key elements of the safety review, was low and comparable across arms at 2 percent, respectively.

The following slide presents a summary of the safety events, and we'll spend a few moments walking through them. For subjects with any adverse event, 37 percent in the tecovirimat group versus 33 percent in the placebo group. And of note, the majority of these events, approximately 80 percent, were grade 1 in intensity.

In terms of grade 2, 3 or 4 events, those were relatively infrequent at 8 and 9 percent, respectively. Grades 3 or 4 were fewer at 1 percent, respectively, in both arms. Regarding related adverse events, 20 percent in the tecovirimat group versus 17 percent in the placebo group experienced said events, and for related events that were grade 3 or 4 in intensity, they were infrequent at less than 1 percent in the tecovirimat group and zero in the placebo group.

Of the serious adverse events, there was also one subject in the tecovirimat group and none in the placebo group, and this event was not related. The asterisk there shows that the subject with the serious adverse event was also the subject who died, and this subject will be discussed very soon. Discontinuation of study drug due to adverse events, as noted before, was low and comparable at 2 percent in both groups.

The following slide presents a high level summary of the adverse events all grades that were related to tecovirimat that occurred with greater than 2 percent frequency and at higher rates in tecovirimat than placebo. As you can see, the most frequently reported related adverse events are headache with 12 percent versus 8 percent; nausea, 5 percent versus 4 percent; abdominal pain, 2 percent versus 1 percent; and vomiting 2 percent versus zero percent.

A bit more about the subject who had the serious adverse event and the death, this subject was in the tecovirimat group. She was a 46-year-old female with a history of irregular menstruation, a history of deep venous thrombosis that had occurred 4 years prior

to her study participation. Concomitant medications included Depo-Provera that she took every 3 months.

She completed 14 days of tecovirimat, had no adverse events prior to the event. The laboratory abnormalities were limited only to a grade 1 glucose elevation at day 15. However, 7 days post-completion of dosing, she developed acute shortness of breath and chest pain while at home. The subject was talkative when the emergency medical services arrived, however, pulseless electrical activity developed en route to the hospital, and the subject died. The autopsy findings showed extensive pulmonary embolism and no other significant findings. The toxicology report was negative, and the cause of death was determined to be due to pulmonary embolism.

The clinical narrative was reviewed in detail, and the agency agrees with the investigator's assessment that these events of SAEs and death were unrelated to study medication. Of note, the subject had preexisting risk factors, that being a history of deep venous thrombosis and concomitant oral contraceptive use that predisposed her for pulmonary

embolism. It should also be noted that Depo-Provera is contraindicated in subjects with a current or past history of thromboembolic disorders.

With regards to the potential role of the drug, there was no thrombotic signal that was observed in tecovirimat nonclinical studies, and when considering the pharmacokinetic aspects of the product, tecovirimat and its metabolites is not expected to increase the medroxyprogesterone, i.e., the Depo-Provera, concentrations.

The active component of Depo-Provera is mainly metabolized by the CYP3A4, and as noted, tec**o**virimat is a weak inducer of the CYP3A substrates. Based on in vitro studies as well as drug-drug interaction study that evaluated the effects of tecovirimat at 600 milligrams BID on the PK of index substrates, tecovirimat and its metabolites did not inhibit CYP3A4 at clinically relevant concentrations. Therefore, tecovirimat and its metabolites is not expected to increase the medroxyprogesterone concentrations. In fact, it may decrease said concentrations due to enzyme induction by the metabolites of tecovirimat .

The discontinuations due to adverse events were infrequent across groups, and those six others in the tecovirimat group who discontinued due to adverse events are briefly summarized here, one being the first subject who had a grade 1 one abnormal EKG that resulted in discontinuation on treatment day 5. Of note, that subject remained clinically asymptomatic.

There was one subject who had grade 1 abdominal discomfort, dry mouth, and dysphoria, and disturbance in attention that resulted in continuation on treatment day 3; one subject with grade 3 headache, grade 1 fever, grade 2 diarrhea, and grade 1 nausea who discontinued on treatment day 3; one subject with grade 1 nausea who discontinued on treatment day 8; one subject with grade 1 palpable purpura who discontinued on treatment day 2; and the 6th subject had grade 1 erythema pruritis, facial swelling that led to discontinuation on treatment day 2. The last two subjects will be covered on the following slide.

The subject with palpable purpura is a 58-year-old Caucasian female with a history of depression and hyperthyroidism. The concomitant

medicines, levothyroxine and sertraline. This subject had grade 1 palpable purpura on treatment day 2. Of note, this subject had an isolated grade 2 AST that was on day 15 and no changes in renal function and no proteinuria throughout treatment.

The drug was discontinued on treatment day 2, at which point the subject had received a total of 4 doses. No other interventions were made, and on day 15, the investigator noted a fading rash, palpable purpura, and the event was considered resolved on day 16.

The other subject with facial erythema, pruritis, and facial swelling was a 37-year-old Caucasian female with a history of ulcerative colitis on no concomitant medicines. That subject developed grade 1 facial erythema, pruritis, and facial swelling on the morning of treatment day 2. Drug was discontinued on day 2 after the subject had received a total of 2 two doses. There were no other interventions, and the events resolved on day 5.

We'll move on to a brief description of the nonclinical adverse events of interest, that being

seizures. In the nonclinical development program, the maximum tolerated dose study in dogs showed that a single oral administration resulted in seizures and deaths in one dog at 300 milligrams per kilogram. Findings at the 100 milligram per kilogram cohort consisted of tremors, face twitching, focalization, licking, and excessive salivation.

Based on these nonclinical data, the applicant selected a Cmax of 5,575 as the maximum allowable exposure level for humans. The human PK at 600 milligrams BID in study 008 showed a geometric mean value for Cmax at 2106, and you can see that the exposures are well below those associated with the CNS toxicity observed in the dog study.

Within study 008, EEGs were assessed at various time points for subjects in the lead-in cohort and in the PK subset of the expanded study, which led to a total of 65 subjects in the tecovirimat group and 16 in the placebo group who underwent EEG evaluation. There were no seizure events, and there was the one discontinuation due to abnormal EEG as discussed previously.

The summary of the human safety is that the successful completion of study 008 yielded a safety database for tecovirimat of approximately 300 subjects for the proposed treatment regimen that is consistent with the FDA's Animal Rule guidance. Tecovirimat 600 milligrams BID for 14 days was generally safe and well tolerated when assessed and administered to healthy adult subjects.

As we conclude our presentation, we provide the agency's perspective on whether the Animal Rule requirements have been successfully met for tecovirimat, and we will frame them within the discussion of the Animal Rule requirements that were presented at the top of this presentation.

Animal Rule requirement number 1, that being that there is a reasonably well understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product. The agency's perspective is that because smallpox was eradicated nearly 4 decades ago, the pathophysiology of variola virus infection is not fully understood.

This will requirement will not be wholly met, but the uncertainties have been addressed, to the extent feasible, via studies demonstrating broad antiviral activity and similar potency of tecovirimat against orthopoxviruses, including variola virus, and clear survival benefit into well-studied lethal non-variola orthopoxvirus animal models.

The second Animal Rule requirement is that the effect is demonstrated in more than one animal species that is expected to react with the response predictive for humans unless the effect is demonstrated in a single animal species that represents a sufficiently well characterized animal model for predicting the response in humans.

The agency's perspective is that the scientific limitations of the available nonhuman primate very old model precludes definitive efficacy assessments and uncertainty exists whether adequate variola model can be developed. The applicant has successfully demonstrated the efficacy of tecovirimat in two well studied, lethal, non-variola orthopox animal models, those being the nonhuman primate

monkeypox virus model and the rabbit/rabbitpox virus model.

On to the third Animal Rule requirement being that the animal study endpoint is clearly related to the desired benefit in humans, that being generally the enhancement of survival and the prevention of major morbidity. The agency's perspective is that these studies used a primary endpoint of survival. Euthanasia was based on prospectively defined criteria, and the applicant's nonhuman primate monkeypox virus and rabbit/rabbitpox virus studies confirmed a treatment using a primary efficacy endpoint that is clearly related to the desired benefit in humans.

The fourth Animal Rule requirement is that the data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and in humans allows for the selection of an effective dose in humans. The agency's perspective is that the applicant has collected PD and PK data in both the nonhuman primate monkeypox virus model and the rabbit/rabbitpox virus model that enabled the selection of an effective dose in humans.

The exposures in healthy humans are significantly higher than those associated with the fully effective doses in either nonhuman primates or rabbits, and the agency agrees with the proposed human dosing regimen of 600 milligrams BID in adults, which brings us to the end of our presentation, and we'd like to thank the committee for its attention. And I'd like to thank the entire multidisciplinary review team for all the work throughout this entire process.

Clarifying Questions

DR. BADEN: Thank you, and I'd like to thank both the agency and the applicant for very thorough and comprehensive presentations. For those in the back, there are seats up front if you would like to sit.

To the committee, we will now open the floor to questions, both clarifying of the presentations and exploratory of the data. When asking a question, please express if it's to the applicant, or to the agency, or both.

Are there any clarifying questions or discussion? In terms of our process, please indicate if you have a question to myself or Dr. Chee. We will

have a running list. When a question is asked and answered, if there is a follow-on for the same theme, please let me know so that we can develop the themes appropriately and try to fully explore a given line of concern.

We will start with Dr. Schaenman.

DR. SCHAENMAN: Joanna Schaenman from UCLA. I have a question for the applicant regarding the animal models. I think it's clear why the nonhuman primate model was used. I was interested, however, to learn more about the choice of the rabbit model over the mouse model, which you mentioned in your briefing documents has also been studied. And I would also like more information about the comment in the slide that the rabbit model dose-exposure relationship was dissimilar.

These slides are not numbered, but it was early on in Dr. Hruby's presentations. So I'd just like more information about what is meant by that?

DR. HRUBY: Correct. Well, I can answer the first part for question. After the 2011 advisory committee, both the rabbit and mouse models were

identified as having potential to support regulatory studies. Unfortunately, neither of them had been reduced to practice to support those. So some time was required to identify the appropriate challenge strain, grow it up, validate it, and then infect animals, determine the dose and the natural history to support those. Our BARDA colleagues spent considerable time and effort reducing the rabbit model to do so, so that we could do our studies.

Unfortunately, to date, the mouse model has not been reduced to practice. It has proven very difficult to identify and isolate the challenge strain. Every time they get a clonal isolate, it seems to lose virulence, and so it is not yet available to support those regulatory studies. What I can tell you is a non-pivotal studies, we have been in both the ectromelia as well as vaccinia and cowpox models in the mouse, and they do in fact work quite well.

I'll ask Dr. Grosenbach to address your second question.

DR. GROSNBACH: Good morning. I'm Doug Grosenbach, the senior director of pox virus research

at SIGA, and I oversaw the conduct of the animal efficacy studies.

The question was how were the pharmacokinetics different in rabbits versus the nonhuman primate and why were these dissimilar from the human; is that correct?

DR. SCHAENMAN: From your slide dose/exposure, relationship dissimilar.

DR. GROSENBACH: That's correct. The FDA put up a nice slide in which they showed that the Tmax and Cmax for the rabbit model was quite a bit delayed versus what we saw for the nonhuman primate and for the human. And in addition, there appears to be some level of induction. So when we were comparing exposures at steady state, we use the date 14 exposures. And you may have noticed that they were much, much lower than the nonhuman primate, whereas the FDA used the 7-day exposure as the steady state, and that was more similar but still lower than the nonhuman primate.

So because of the Tmax/Cmax issue as well as induction, we considered that to be dissimilar enough from the human that the nonhuman primate was preferred.

DR. BADEN: A follow-on, I have a follow-on question. In both the monkey, NHP and the rabbit models, the choice of the challenge strain in the monkeypox -- it was the Zaire 79 strain, what was the basis of the choice of the challenge strain for both models?

DR. HRUBY: Again, I'll ask r. Grosenbach to address that.

DR. GROSENBACH: The Zaire 79 strain had been demonstrated previously to be a lethal human virus causing severe disease in an outbreak in the Congo in '78 and '79, as well as having also been used in numerous animal studies and becoming well established as the model agent for these types of studies. This included sequencing, virulent studies, and purity studies. So this was produced under well-controlled conditions and is available and recommended by FDA for these studies.

DR. BADEN: And the rabbit?

DR. GROSENBACH: And you asked about the rabbit. Historically, rabbitpox Utrecht is one of two strains that have been available for these studies.

Rabbitpox Utrecht is much more virulent than this other strain that is no longer used. The strain that we used was very well characterized, clonally isolated sequence and then grown under controlled conditions, tested for purity, et cetera. And this also comes at the recommendation of the FDA to use for these types studies.

DR. BADEN: Dr. Lo Re also has a follow-on.

DR. LO RE: Just a follow-on. Could you clarify further how you selected the sample sizes for each of the different animal studies? I noticed that the sample sizes were different, and I just wanted to get some sense as to what were the assumptions that you had put into your calculations to come up with the efficacy differences.

DR. HRUBY: I can give you the general answer, and then I'll ask somebody else to give you the specific answer. In general, we attempted to use group sizes of animals sufficient to give us statistical significance while being very mindful of using as few animals as possible to achieve our scientific ends. To answer the question about statistics, I'll ask Dr.

Richardson-Harman to discuss that, please.

DR. RICHARDSON-HARMAN: Hello. Nicola Richardson-Harman, president of Alpha Statconsult, statistical consultant for SIGNA Technologies. The question concerning how many animals were used in the animal studies, the NHP efficacy studies were powered to find at least a 75 percent increase in survival rate to be significant when compared to the placebo.

The tests that we used was the Fisher exact one-sided test with an alpha level of 0.05.

DR. BADEN: Dr. Venitz?

DR. VENITZ: Thank you. I have questions for Dr. Hruby on some of the slides that you presented regarding exposure. My first question relates to slide number 51 where you are summarizing the exposures in the two models. Are those steady-state exposures?

DR. HRUBY: Those are steady-state exposures.

DR. VENITZ: On day 14?

DR. HRUBY: On day 14.

DR. VENITZ: Are they corrected for plasma protein binding?

DR. HRUBY: I don't believe so, not in this

graph. But we have the data available if you'd like to see it.

DR. VENITZ: Okay. Then on the next slide, slide 52, this is where I'm getting very much interested in the food effect. So you're obviously demonstrating -- and this nonhuman significant food effect. Can you give me a reason what caused the levels to go up in presence of food?

DR. HRUBY: I'll ask Dr. Corrado to address that.

DR. CORRADO: I'm Michael Corrado, an infectious disease physician and fellow of the Infectious Disease Society of America. I've been involved with SIGA for the last 14 years on the clinical development of tecovirimat .

Would you ask the question again, please?

DR. VENITZ: I'd like to know what causes the effect of food. Why do the levels go up in presence of a meal?

DR. CORRADO: I'm afraid I can't give you that answer, but I can tell you that a fatty meal and the more fat in the meal increases the plasma absorption,

and therefore the bioavailability of tecovirimat.

DR. VENITZ: So if you then look at the left-hand part of that figure, it obviously shows that the trough levels do go up, but you also increase the variability quite a bit. In other words, your concurrent food that you're now proposing to be used as part of the standard regimen does on average increase the trough level, but it also spreads it out in the population.

DR. CORRADO: That is correct, and you'll experience higher Cmax with that as well.

DR. VENITZ: Right, but one of the reasons why I bring that up, in one of the public comments, and I think in one of your, compassionate use cases, a patient achieved what was referred to as suboptimal doses and/or levels, and the doses needed to be increased. Can you comment on that?

DR. CORRADO: Yes, I'll have Dr Hruby comment on that.

DR. HRUBY: If you read that case, you'll know that that individual was very ill and had a number of problems. He experienced septicemia, had his limbs

removed, and was on many, many medications, and he was not eating. And you're correct that when we gave the perceived or proposed dose, we did not get appropriate blood levels, for reasons we don't know, but we have theoretical reasons. We increased the dosage to get it up above Cmin until he began to eat and get healthier.

DR. VENITZ: So how would that be relevant in the future for labeling of this product if it gets to the market?

DR. HRUBY: We think it's appropriate for the vast majority of the U.S. population. The 600 milligrams twice daily taken with food as recommended will give an exposure level that will be above Cmin and below the safety.

DR. VENITZ: Okay. Then my last question, you pointed out when you discussed this that you believe that Cmin is the most important metric to base your doses on. Can you explain that?

DR. HRUBY: I'll ask Dr. Grosenbach to explain that.

DR. GROSENBACH: In doing the PK/PD studies, we evaluated Cmin, Cmax, AUC, and all of these at

steady state, and it was determined that by the receiver operating characteristics analysis approach, the PK parameters Cmin and AUC, they had the highest sensitivity of 92.9 percent and specificity at 94.9 percent for survival prediction in nonhuman primate model, which is why they were selected as the key parameters.

DR. VENITZ: Then my last question, did you then see an exposure response on Cmin? In other words, for the various treatments in the NHP, did you see increasing Cmin actually did increase survival?

DR. GROSENBACH: Yes, we did. In doing PK/PD studies, although we're using the 10 mgs per kg dose, which has an associated Cmin of 169, by that approach, it was determined that a Cmin in excess of 29.7 -- just pulling that out of my head, but that's correct -- provided a hundred percent survival. So the Cmin is a clear indicator of survival efficacy in the nonhuman primate.

DR. VENITZ: Okay. Thank you very much.

DR. BADEN: Dr. Breman?

DR. BREMAN: I'm interested in the

hypoglycemia reported in some patients on table 18 in the material sent to us relative to I guess experiment 10.2, titled Adverse Events in Supportive Multiple Dose Studies. So the question may be addressed to both the company and FDA because on their page 14 and 15, they talk about safety events, headache, nausea, but they don't have blood sugar results as you did.

Now, true, 10 hypoglycemia patients in 78 events were reported with the drug given at 600 BIDs, but the fundamental question is does this drug have any impact on a gluconeogenesis or the insulin pathway, something we should be more aware of? The discussion of the dog is classic hypoglycemia seizure. I don't know how many dogs were given the drug, but you might share with us your thoughts and any experiments or knowledge.

DR. HRUBY: I'll ask Dr. Corrado to comment on that and then ask the FDA to add their comments if they like.

DR. CORRADO: Thank you, Dr Hruby.

Mike Corrado. In fact, dogs that had plasma exposure levels below the one dog, which had 16,500,

did not experience seizure, and we have no knowledge that they had become hypoglycemic.

In terms of the humans that had hypoglycemia, once again, we don't know of any interaction with the islet cells of tecovirimat causing expression or secretion of insulin from the islet cells or any effect on gluconeogenesis.

We did do a drug interaction study with repaglinide, which would be affected by tecovirimat in theory because of its mild effects on cytochrome CYP2C8. And in fact in that study, we did see some hypoglycemia a down to about 50 nanograms per milliliter. Those subjects responded to sugar candy and eating in terms of normalizing their hyperglycemia.

I will point out one interesting aspect. These were normal volunteers in that study, and Kuzma has shown that normal people with normal islet cells when exposed to repaglinide have a 61 percent increase in insulin secretion over diabetics. So how much of that was due to the fact that they were normal with normal islet cells or the effect on repaglinide is difficult to know, but such patients should be watched

carefully when receiving tecovirimat.

DR. CHAN-TACK: Dr. Su-Young Choi, and I also have some to contribute to that question. So with regards to those findings, one of the many aspects that muddy the ability to access their contribution was that, as stated, this was done in healthy volunteers, so therefore between them being healthy volunteers, the dose of repaglinide that was used, the timing of the dose with respect to dose of drug versus dose of tecovirimat, all these confounders kind of coalesce to perhaps overestimate the findings that were shown.

DR. BADEN: Thank you. A follow-on question?

DR. HAWKINS: Yes. Dr. Randy Hawkins. So just a question whether -- and it's for both -- any concern that other commonly used diabetic medications might result in significant hypoglycemia? Some of the other very common ones are not metabolized through that C2A pathway. Just concerned.

DR. HRUBY: Dr. Corrado?

DR. CORRADO: Thank you. Mike Corrado. I'm not aware of any that would -- the ones that would be affected through the same CYP pathway would also

include rosiglitazone and pioglitazone, but I'm not aware of any that are not through that pathway that would be affected.

DR. CHOI: So based on the data available, it seemed like the hypoglycemic cases were primarily due to repaglinide itself rather than drug interaction. The drug interaction was like a 30 percent increase in AUC in repaglinide, and that 30 percent increase, I don't believe all of a sudden increased the risk of hypoglycemia that much. It's rather due to the fact that the repaglinide was given to subjects with normal blood glucose levels and that reduced the glucose levels.

So for actual diabetic patients who are on a stable regimen of repaglinide, I don't expect all of a sudden that hypoglycemia is getting worse. So it's just due to the fact that study was conducted in healthy volunteers with normal glucose level.

DR. HAWKINS: Sorry. Just a clarification. So these are not diabetics who were on the repaglinide as part of their treatment regimen?

DR. CHOI: So the study was conducted in

healthy volunteers.

DR. HAWKINS: Are they healthy volunteer diabetics?

(Laughter.)

DR. CHOI: No. Based on their current blood glucose level, they were within the considered normal range.

DR. HAWKINS: Why did you select that drug to add to their regimen then? I'm just confused about that.

DR. CHOI: So that's --

DR. BADEN: It's probably better for the applicant to respond as to why those substudies were done.

DR. CORRADO: The CDC has guidance about doing drug-drug interaction studies, and we chose a drug that we knew our product, tecovirimat, had an effect on that CYP system. So we chose a drug that also would be affected by that CYP system.

DR. HAWKINS: Thank you.

DR. BADEN: Follow-on? If it's a follow-on.

DR. GRIPSHOVER: Well, it's about the healthy

volunteers. I just have one question. What defines healthy?

I noticed in your healthy volunteer study, half of the people screened out, but I don't think -- at least I didn't see anywhere what the eligibility criteria were. And there was a good demographic mix, but I didn't see about any comorbidities. Are there nomads [indiscernible] completely in normal, healthy volunteers, the better definition?

DR. HRUBY: Dr. Corrado can comment on that for you.

DR. CORRADO: Thank you. You're speaking about the 008 study, correct? These were volunteers in that they obviously volunteered for a disease that they did not have, so in that regard, they were volunteers. However, they could have had comorbid conditions and many of them did. The criterion was that the comorbid condition was controlled and that the comorbid condition would not affect their participation in the study nor their longevity for us to follow them throughout the course of the study.

DR. GRIPSHOVER: So do we know those --

DR. BADEN: Please use the microphone.

DR. GRIPSHOVER: Do we know those comorbidities? Did you collect it? And also, do you know why the 300 screened out?

DR. CORRADO: The comorbid conditions, as you saw, some were hyperthyroidism and history of anxiety and insomnia. But the most common one was hypertension, well controlled as defined by a systolic blood pressure of 140 or lower, and a diastolic blood pressure of 90 or lower. You might not consider that normal today, but that was the definition for the study. Some subjects, a few had diabetes, but again, they were under control.

With regard to the reason that people screened out, their perhaps inability to stop smoking for the trial, stop using coffee for the trial. Their participation, they may not have wanted to have stayed in this study for the entire time, or they had conditions that were not under control.

DR. GRIPSHOVER: Do you have a list of the eligibility criteria?

DR. CORRADO: We can get that for you. I don't have it right here.

DR. BADEN: Dr. Clark, do you have a follow-on?

DR. CLARK: Yes. Thanks. So in volunteers, did any have a history of seizure disorder. And related to that, is there anything known about CSF levels in humans?

DR. HRUBY: Dr. Corrado?

DR. CORRADO: I will answer the first part of that. The only seizure history that we permitted was febrile seizure during childhood. so if they had adult onset seizure activity or recent seizure activity, they would have been excluded. Regarding CNS penetration, I'll have a Dr. Grosenbach.

DR. GROSENBACH: Although your specific question was human CNS levels, I don't know what that is. In our animal studies, we did show that the brain exposure did occur, at least in our mouse models, and the brain to plasma ratio was 0.35.

DR. BADEN: Dr. Follmann?

DR. FOLLMAN: This is a question for the FDA.

So the Animal Rule that you went through lists for different requirements. I was curious, is there a requirement or plans or suggestions for studies in the event of an outbreak, sort of postmarketing studies like they have for accelerated approval, or is it just these four that are what you require?

DR. SHERWAT: Thanks for the question. I can cover that for you. The applicant must conduct postmarketing studies, like field studies as you indicated, to verify and describe a drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical as in the case of an outbreak.

Applicants must include as part of their application a plan to approach postmarketing study commitments in the event that such studies become ethical and feasible. The applicant has done so, and we're actively working with them to reach consensus on the study design.

DR. FOLLMAN: Okay. So that's still, I guess, preliminary. You haven't settled on anything, but you're aware of this, and you're working towards that

goal.

DR. SHERWAT: That's correct. We've reviewed a draft protocol, and we're working back and forth on reaching consensus.

DR. BADEN: Dr. Clark, do you have another line of questions?

DR. CLARK: Thank you. I did. On the animals that died, the nonhuman primates and rabbits, was there any evidence they died of things other than the infection itself or the procedure? I'm specifically thinking about hypercoagulability with the patient that was presented who died.

DR. HRUBY: Dr. Grosenbach?

DR. GROSENBACH: So to the animals that were treated with placebo, to the best of our knowledge, they all died of severe monkeypox or rabbitpox disease, and this was evident as a very high viral load, lesion counts, fever, et cetera. For animals that were on treatment that died, there were some that died of severe disease both in the nonhuman primate and in the rabbit models.

Not all of them though. There were some

animals that died of procedural issues. For example, the gavage procedure in rabbits is quite traumatic, and there were two animals that died from that. And then as well in the nonhuman primates, as presented in our core presentation, 2 nonhuman primates died of what were considered to be complications of anesthesia, and these were study pathologist determined outcomes.

DR. BADEN: Dr. Kartsonis?

DR. KARTSONIS: The question I had for the applicant was what can you tell us about resistance development of tecovirimat and specifically the genetic barrier? And in the animal studies that you did, maybe the ones that were shorter duration, do you have any evidence of resistance development that might have occurred over time?

DR. SHERWAT: So I can start by answering -- so as Dr. Birnkrant mentioned, we're not going to be covering any specifics on the resistance pathway for reasons of security, but I think you had a -- did you have a second question that didn't relate to specific pathways?

DR. KARTSONIS: I guess the question was did

we see any resistance development in the animal models?

DR. HRUBY: We have done genomic sequencing on all the animals that failed. We've yet to see one where we believe resistance is the primary cause for death.

DR. KARTSONIS: Thank you.

DR. BADEN: Dr Weina?

DR. WEINA: Pete Weina from Walter Reed. I know that the FDA had commented that monkeypox human trials weren't going to be required. I guess the question becomes has this ever been used in monkeypox and humans? I mean, there is a clinical trials.gov, a trial that was opened in 2014. There's a lot of problems with monkeypox in humans. I can't believe that if this works, it wouldn't be used in monkeypox in Africa for outbreaks. I understand at least the reasoning that was listed originally about not doing a monkeypox human trials because of where it's occurring, but medical research and material command has done some pretty interesting studies in some pretty interesting places, and they seem to be a partner in the development here.

DR. SHERWAT: So I guess I can start with that. Thanks for your question. So to paraphrase it, is your question more, is there an interest potentially if the drug is approved with doing monkeypox studies or is your question, should the approval span the spectrum of variola and monkeypox?

DR. WEINA: I guess both. First of all, the last time that the database was updated was last year, so I don't know if it's been used at all in humans and monkeypox, and for security reasons or anything may not have been reported. But also the fact that since we do have a clinical trial that's open for both smallpox and monkeypox, I assume that the off-label use of this or potential marketing of it down the road for WHO or a variety of other reasons will probably open up, including monkeypox. So I guess both questions.

DR. SHERWAT: So why don't I start by saying that the tecovirimat development program focused on generating adequate data to support an indication for the treatment of smallpox in the Animal Rule as we outlined today. There are concerns related to the use of the Animal Rule to support an indication for the

treatment of monkeypox.

The Animal Rule applies to new products for which field trials to study the product's effectiveness are not feasible. And as you outlined, we understand there are significant challenges involved in the study of naturally occurring monkeypox virus infection, but also as you've just outlined in your comments, the conduct of such a trial remains a possibility.

So that would make it difficult for us from a regulatory perspective to approve it under the Animal Rule if there's the possibility of conducting trials and interest in doing so.

DR. WEINA: Well, I guess as with just about everything that we do here, a lot of times we may approve it for indication X, but it's also used off label for indication Y, Z, and A through N.

DR. SHERWAT: Right. So I would also note that even if tecovirimat is not approved for the treatment of non-variola orthopoxvirus infections like monkeypox, there's a mechanism in place to provide tecovirimat as needed for treatment. It would probably be better for the applicant to provide more details on

that specific mechanism.

DR. HRUBY: What I can tell you is that we could go through all the reasons why doing clinical work in Africa was not feasible in the past, and I agree that that's improving as we go forward. I participate in the WHO advisory committee for variola virus research each year, and monkeypox is part of that discussion. So they are certainly aware of the drug and its potential utility against both smallpox and monkeypox.

I know they are making preparations to perhaps do a field trial, and we have participated in those discussions, and we'll continue to do so going forward.

DR. BADEN: I guess an extension of Dr. Weina's question, I understand the difficulties of such a trial and whether or not it's feasible, however, your position on expanded access or EIND access in the context of monkeypox infection.

DR. HRUBY: I'll ask Annie Frimm to discuss that.

MS. FRIMM: Annie Frimm, vice president of regulatory, clinical, and quality. We have, as you

noticed, given that drug and compassionate use cases under several EINDs. We would continue to make that available if there was a need, but I don't think that's why we're here today. I think we're discussing the NDA, but, yes, SIGA is well aware that there may be needs, and we are willing to provide our drug as needed.

DR. BADEN: Thank you. Dr. Honneger?

DR. HONNEGER: We can anticipate that if there's an outbreak, pregnant women might be exposed, and there's obviously no human studies in that. I was noted that on page 37 of the briefing document, it said that 9 out of 22 maternal rabbits who did not have infection died when they were given the drug. Is there any explanation for mechanism and interest in testing this in other animal models before it's given to the first pregnant patient?

DR. HRUBY: Dr. Corrado will discuss that with you.

DR. CORRADO: Thank you for the question. Mike Corrado. In fact, you're correct. In the highest dose level of a 100 milligrams per kilogram, and to put

it in reference,
for an 80-kilogram human, a 600-milligram capsule would be something like 7 milligrams per kilo. So at the 100 milligram per kilo, we did see 9 of the 22 dams died. They stopped eating. They lost weight. And if you've done rabbit work, you know they're very sensitive to that. At 30 milligrams per kilo, those rabbits did not have mortality.

The fetus born to even the highest dose treated dams, we saw no gross abnormality in those fetuses. With respect, though, to your really fundamental question, and that is if there were an outbreak, pregnant women would be infected. I will give an opinion as an infectious disease physician, that I'm not now speaking for either SIGA nor obviously for the FDA, I would not hesitate to use it.

If you look at the CDC report from July of 2002 on emerging infectious diseases, it's the best review of pregnancy and variola disease that has been published. And that report, which is out at Tubingen University in Germany, looked at pregnant women from the 18 [00s] and 1900s up until World War II. And in

that review and those studies, the mortality in pregnant women was a bit higher than the normal population, and it doesn't surprise you because pregnancy is a mild immunodeficient state. And the fetal loss in those women was about 40 percent.

Looking at the mortality in the mother's, looking at the fetal loss, looking at the safety of the drug, even though I understand we don't know about its use in pregnancy, the risk-benefit, I would not hesitate to use it.

DR. SHERWAT: Did you want the perspective from the agency on that as well?

DR. BADEN: Please.

DR. SHERWAT: Okay.

DR. McMILLAN: Dave McMillan, pharm tox reviewer at FDA. I'd just like to follow up with that. While we acknowledge that there were some maternal toxicities that were present in the embryofetal development studies in rabbits, it's very difficult for us to really comment on what the relevance of that is to humans. Generally, these studies are really performed to evaluate the effects on the fetus, and we

did not see any fetal effects or fetal toxicities in the embryofetal development studies in either rodents or in rabbits.

DR. SHERWAT: Dr. Choi also has a comment on this.

Actually, could I clarify? There was an earlier question related to the most important parameters, and they were discussing Cmin. Sorry, I tried to get your attention, but Dr. Choi wanted to have a brief follow-up if that's okay with you.

DR. CHOI: So the question, AUC versus Cminimum, which is more associated with efficacy. Based on exposure/response relationship analysis, the relationship between exposure parameters or variable rates [sic – endpoints] were evaluated, and both AUC and Cminimum are well correlated with efficacy between the two parameters.

While it is possible that one parameter is more important than the other, based on the currently available data, it cannot be precisely determined whether AUC or Cminimum is more important than the other because animals were all dosed once daily, so in

each animal, AUC and Cminimum values are well correlated. So based on the analysis, both are important.

During the product development, we probably emphasized importance of Cminimum because, first, it is often associated with higher variability. So to make sure that Cminimum values are high enough, it's important. And second, based on other antiviral programs, not tecovirimat, we often see maintaining concentrations above a certain threshold is critical to avoid developing resistance. That comment is actually from other programs, not from tecovirimat. For tecovirimat, both AUC and Cminimum are well correlated with efficacy.

DR. BADEN: Dr. Venitz, any follow-on?

DR. VENITZ: No, I appreciate that follow-on.

DR. BADEN: Thank you. Then, Dr. Green?

DR. GREEN: Thank you. Mike Green. During Dr. Hruby's presentation of the mechanism, he made a comment -- and I think he was trying it a little bit more simplistic for everyone to understand, that the drug slows down the process of the release of the virus

into the body, allowing the immune system to then sort of handle it in slowing down a process that might be otherwise overwhelming.

I know that that's probably not exactly correct in terms of either what you said and my understanding of it or maybe the process that is. But it does raise the question of how this drug might work in a compromised host setting, which might be one of the places that it would be of interest. And in particular if it was used off label for patients with vaccinia, it would be very important.

So I wonder if you have any data on how this works in the presence of immune suppression or if there are any plans to potentially do an animal model with immune suppression to understand the limitations of this drug in that setting.

DR. HRUBY: I'll give you the general answer, and if the details aren't sufficient, I'll ask Dr. Grosenbach to amplify. We have done studies in both immunocompromised mice and immunocompromised nonhuman primates and can show that as long as the animals retain any portion of the immune system, either

some humoral immunity or some T cell immunity, that they are protected by the drug, and they develop a protective immune response. If they are completely immunoincompetent, the drug protects them against disease, but you'll have to remain on drug until the virus is totally clear at a much later date or other therapies can be used.

Now we've had two examples in humans. Two of our compassionate use cases were individuals that were vaccinated, and then shortly thereafter diagnosed with leukemia and aggressively treated with chemotherapy to ablate their immune system. We together with other types of therapies were employed, kept these infections in check for long periods of time, 70 days in one case and 60 in the other. And what we could show is that when their immunity began to return -- you can start to see T-cell counts coming back, they in fact cleared the virus.

So that's what we know about immunocompromised situations.

DR. GREEN: Thank you.

DR. SHERWAT: Dr. Baden, would it be alright

if the agency provided a perspective as well?

DR. BADEN: Please?

DR. SHERWAT: Dr. Harrington is going to discuss this.

DR. HARRINGTON: We basically agree with the sponsor's perspective on this issue. They've conducted a number of studies in mice and in nonhuman primates and have shown that tecovirimat has activity in immune deficient animal hosts, but its activity is limited in animals that are severely immune compromised, such as lacking T and B cells. It can help to control the viral infection, but ultimately it does appear that some component of the immune response is necessary to help clear that viral infection.

DR. BADEN: Thank you. We are getting close to 12:15. One question for the applicant, the agency noted that there were 30 grade 2 or greater adverse events in the -- I think it's the 008 study. The four grade 3 or 4 you presented, if you would be able to prepare a slide of the 26 grade 2's just so we're aware of the spectrum of grade 2 or better adverse event.

DR. HRUBY: We'll prepare that during the

lunch hour and have it ready for you.

DR. BADEN: And if you can do that with placebo versus active just so we can see the nature of the adverse events greater than grade 1.

It is now 12:14. We will break for lunch. We will reconvene again in this room in one hour, at 1:15. Please take any personal belongings you may want with you at that time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves with the press or with any members of the audience. Thank you. See you in one hour.

(Whereupon, at 12:14 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

Open Public Hearing

DR. BADEN: It is 1:15, time to resume. We'll resume with the open public hearing element, and then get back to the clarifying questions and the formal evaluation of the question

Both the FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentations. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral comments to advise the committee on any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the

beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of issues before them. That said, in many instances and for many topics, there'll be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. KNAPP: My name is Kieren P. Knapp, DO. I'm a family physician from a small town of 1200

people, about 80 miles north of here. I'm board certified in family medicine. I'm here to give a personal encounter with this. My financial arrangements are I'm not in the office today, and I may or may not turn in my mileage. And that's as far as the financial arrangements go.

(Laughter.)

DR. KNAPP: Unfortunately, this doesn't do much good if I don't have the use of the clicker because the pictures are very important. So if I get somebody to do that while my 10 minutes is running down, I'd be very appreciative.

This began on May 10, 2011 when a patient called me in the office with a concern that she had a pimple on her chin that was beginning to look very strange and had great concern. So she described it as looking like a wet belly button. Growing up in the era I did, there were two things that came to my mind, one of which was vaccinia, the other one was anthrax. I did have her come into the office on the 11th after having her quarantine herself in the house. At that time cultures were obtained and the PCR, and the PCR

came back as positive for vaccinia orthopox.

Again, is there anything to do with this clicker? It does not work. Okay. The pictures are really important for this.

On May 13th, the Pennsylvania Department of Health did manage to help me get an EIND started for compassionate care for the tecovirimat. On May 14th, the CDC decided that they would be able to transport VIG, vaccinia immune globulin to the area to be given to the patient, and this was given on May 14th.

Within the time period until the arrival of the compassionate use for tecovirimat came through, the patient did have a decrease in her headaches and fever, but unfortunately, as you can see on the screen --

(Laughter.)

DR. KNAPP: -- the lesions were decreasing -- or increasing, rather, in number and size. She still had the other symptoms.

On May 19th, we started tecovirimat at 400 milligrams per day for 14 days, and within 5 days not only was there significant resolution of the lesions, but the patient was symptom free. The PCR at that time

that was attained was also virus free. And again, since the pictures are not there, the lesions were resolving within a month's time. There was a little bit of redness, and by 2 months time, she was then exceptionally [indiscernible] scar free. And for those of you who are my age, who were walking around with a little patch on your arm, that is very impressive considering the number of lesions and location on this patient's face.

So without a question in my mind, this was very beneficial for this patient. The VIG was good for the fever and the headache but did nothing to progress the disease as I saw it.

Does this mean we're going to get something or not? Oh, there we go.

Again, this is my case running down the timeline. So basically at this point, since I've gone through this, the thing that is most important are these pictures. And if you'll notice, I believe it's probably the fourth one over, was on the day that the VIG was given, and the fifth or sixth over is when the tecovirimat was started.

As you get to the bottom of the page, there's very significant resolution of the rash, from the standpoint of vaccinia, if any of you had seen those reactions when you were growing up. There's a whole generation who hasn't, but they were very significant, and this is very amazing to me.

So that basically concludes what I have to present. If I were to be involved in the Zombie Apocalypse and I had a choice between the two, this would be my choice.

(Laughter.)

DR. KNAPP: If this is the point where if there are any questions, I'll be glad to answer.

DR. BADEN: Thank you.

DR. KNAPP: Nothing?

DR. BADEN: Will speaker number 2 step up to the podium and introduce yourself. Please state your name and any organization you're representing for the record.

DR. SMITH: I'm William Smith. I'm the medical director of Volunteer Research Group, the phase 1 unit at the University of Tennessee in Knoxville, and

we did the lead-in protocol in this study. My transportation has been paid for, and we had a clinical grant where we did the initial study.

I was asked to just talk today about our experience regarding adverse events and to sort of expand a little bit on the bland tables. We had 40 subjects in the lead-in group. They were healthy on no meds. There were 14 headaches in the group, which is the same side effect that's predominant in the group as a whole. All of these were classified as mild. Many of them were what the subjects would attribute to either sleeping in a funny position in the beds in the study unit are to caffeine withdrawal.

An interesting fact with those at our location is that most of these headaches occurred in the evening. I'm not sure why, but they were not the usual morning headaches that we frequently see in our study subjects, but all were for mild. I think one of them required some Tylenol, and all the others just put a cold compress or just made us aware they were having a little headache.

There were 4 adverse events we had that were a

little unusual, and I wanted to explain them because did not feel any of these were drug related. One of the subjects had a panic attack, and this was the very first subject that we dosed. There were 4 or 5 representatives of the company, and the CRO, and some of the vendors for the equipment that all just had to be in the room. And the subject gave permission for this but with everybody standing around looking at him, he lost it and had a full blown panic attack. It resolved fairly quickly when everybody left the room, but his heart rate was up at 140 and he was very anxious.

Another subject complained of difficulty hearing, and this was bilateral and persisted for several weeks. But this also happened at the same time the subject was complaining of a sore throat, and that persisted for several days and almost for sure was secondary to a viral illness and in no way related to the drug.

Another one of the subjects had vertigo, but this subject was someone that had a history of prior episodes of vertigo, and we did not feel that this was

related to the drug.

Another subject had an itchy rash, and this looked like a typical contact dermatitis, allergic kind of reaction. And on questioning, she had switched detergents in her laundry 2 days before. She went back to her old detergent, continued dosing, and the rash resolved.

That was really all I wanted to say, was how mild the side effect profile was that we saw in this. And we do a lot of early phase work, and this was toward the much more benign side of the projects that we're involved in.

DR. BADEN: Thank you. Will speaker number 3 step up to the podium and introduce yourself. Please state your name and any organization you're representing for the record.

DR. McFADDEN: My name is Grant McFadden. I'm a professor of virology at Arizona State University, and I'm the director of a center devoted to immunotherapy, virotherapy, and vaccines. My way to this meeting was paid by the sponsor organization, and I jumped at the chance, mostly to give a perspective of

the development of this drug from the early days.

I come with three virtual hats. My number one hat is I'm a member of the poxvirus community of scholars, and I've studied poxvirus pathogenesis for the majority of my professional career. Also hat number two, I'm the co-editor in chief of the journal PLOS Pathogens, which is devoted to microbial pathogenesis and the studying of pathogens, and the deconstruction of antimicrobial strategies. The people who read this journal and the authors are intensely interested in the issue of antimicrobials, and we all understand how hard this process can be.

The third virtual hat I wear is I'm also a member of the WHO oversight committee that has been paying attention, very close attention, to the development of this and other countermeasures against variola. One of the mandates of that committee is to oversee all research with live variola, including the development of antivirals and other things. And as a member of that committee, I've also watched year-in, year-out as the development of this drug progressed through the various scales of development and finally

regulatory processes. And every year, we got to listen to the interplay between what the FDA regarded as the Animal Rule and the company's attempt to come to terms with those mandates.

So having said all of that, the only thing I wanted to communicate is, number one, having been in this field for a while, I know how hard drug development is. The field is littered with failures, and I actually jumped at the chance to come here and just comment, actually, to both the sponsor and also to the FDA, to compliment them because this has been a hard slog.

I can tell you for sure, listening to the reports of both sides through the WHO committee, I've lost count of the number of times when I said to myself -- and listening to the debate and the things that had to be accomplished in order to make this meeting possible, I lost count of the number of times I said to myself, "Boy, I'm glad that's not me."

This has been a struggle, but at the same time, I think the FDA should be proud of the fact that after all that, after the multiple Animal Rule morphed

into I guess what we call triangulation now, they've come up with a process that makes sense, that I think those of us in the academic community can look at this process and tell our peers that the entire process has been fair and straightforward, and the public can have confidence in the final decisions. The documentation, the packages that have been put together that are made public are very impressive, and it's a nontrivial task to actually get to this point.

So those are my basic comments. I just wanted to compliment both the developers and the FDA for a job well done. Thank you.

Clarifying Questions (continued)

DR. BADEN: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. We will continue the clarifying questions that we paused for lunch, and we will start with Dr. Lo Re. Remember to note if it's to the agency or the applicant, or both.

DR. LO RE: Thank you, Dr Baden. This question is for the agency. We're being asked to

assess the risk-benefit profile of this drug, and as I see it, the safety was assessed in 300 healthy human volunteers, which seems to be based on a decision to allow for the detection of adverse effects of at least 1 percent or greater.

One of my struggles is that we're being asked to assess this new drug's risk or safety based on a relatively small sample size. And I just wanted to get a sense from the agency if they have any, perhaps, triggers for safety for additional studies, know, particularly in light of the palpable purpura, the hypersensitivity reactions going forward or for other candidate drugs that are going to be evaluated under the Animal Rule.

DR. SHERWAT: I can start. I would note that the 300 number is a minimum. That number is predicated on not seeing what we would consider to be a red flag signal in the clinical studies. I'll turn it back to Kirk if you want more details about the specific cases that were seen for example, the palpable purpura case, and to go over some of those details. But I wouldn't target the 300 as being what we're asking for all

these. That's what we're requiring as a minimum, assuming that we don't see an initial signal of concern.

Did you want additional information on any of the specific other cases, the discontinuation or the death?

DR. LO RE: I felt that both the applicant and the agency had gone over those fairly well. I just wanted to get a sense of -- here, we're really looking at only 359 healthy -- the use of the drug in only 359 individuals, and we're being asked to weigh does the risk outweigh the benefits; is the profile acceptable for use in potentially a widespread outbreak situation.

I'm just have a sense of what is at some point the level of concern from the agency that would trigger a desire to evaluate the safety of the drug in larger samples, given that if this ever has to be used, it's going to be used widely, and certainly much rarer side effects than 1 in a 100 are going to become manifest.

I'm just trying to appreciate what is the trigger in terms of the current profile or in general, theoretically, that the agency would say we need to

have more healthy volunteers or perhaps other subgroups of races, comorbidities, to go forward with establishing perhaps a wider profile.

DR. SHERWAT: I would say that one issue I know we had discussed earlier was the field trial that's a requirement with approval. So if the drug is approved, if there is an outbreak, that field trial would have to be conducted in order to generate more information. Now, the numbers of that may not be such that you're going to pick up very rare events, even in that setting, and the design may not be such that they're able to do that. It may not be a placebo-controlled trial for ethical reasons with a potentially approved drug.

With respect to what specific signals we would see in the safety study, in the development safety study, to trigger requiring additional subjects to enroll, to be able to pick up a signal, it's hard to say. I mean, we really have to wait to see the signal. It's a combination of both what we see from the preclinical studies as well as what we're seeing in the clinical studies.

As of to date, we've not seen a signal that makes us concerned enough that we feel like we need to go beyond the 300 in order to make a benefit-risk judgment, particularly based on the serious and life-threatening nature of the disease in question.

DR. BADEN: A follow-on. The two adverse events, palpable purpura and the facial swelling pruritis, is it the sense that one of those may have been anaphylaxis? Do you have a better characterization of what you think is going on and the risk it may imply, both to the agency, and then potentially, the applicant may want to weigh in?

DR. CHAN-TACK: Sure. For the subject with the palpable purpura, it's unclear reading through the narrative whether or not that was the most appropriate descriptive term. Photographs weren't available, nor were other -- it may have more been akin to a rash per se, so not really along the lines of the hypersensitivity reaction that you're describing.

With regards to the subject who had facial erythema, pruritis and facial swelling on day 1 of dosing, that one is more concerning for an angioedema

type presentation, and all of these issues will be addressed in the labeling.

DR. BADEN: Does the applicant have any comment on those two events?

DR. HRUBY: We do not.

DR. BADEN: Follow on? Please.

DR. HAWKINS: This is Dr Hawkins. In the mouse studies, there were some mild liver toxicity and there were histopathology results given. In the normal population studies, were there any liver function or other markers of hepatic function that were monitored or followed?

DR. SHERWAT: Are you directing it to us or to --

DR. HAWKINS: The applicant?

DR. HRUBY: Dr. Corrado?

DR. CORRADO: Thank you. During the pivotal safety trial, there was no suggestion of elevation in transaminases and LDH, or any of the other liver function studies that we did follow.

DR. BADEN: Thank you. I had noted that at the end of the morning session to the applicant to

provide some follow-up. So I'd like to give the opportunity to follow up on the questions that were left to you at break.

DR. HRUBY: Thank you. Dr. Grosenbach will deal with the first one, and then Dr. Corrado will do the other two.

DR. GROSENBACH: The question was whether or not the values that we presented to you for our PK parameters were for total protein versus unbound fraction.

It's not coming up, so I will let you -- okay. So what was reported to you was total protein, and what I'm showing you here is those original values along with the unbound fraction. For example, the question was did the 169 nanograms per mL as a Cmin in nonhuman primates, what was that as in terms of the unbound fraction. And you can see the unbound fraction is 20 nanograms per mL.

The take-home point from this is that there is more protein pound drug in animals, in nonhuman primates and rabbits, than there is in human. So in the human, there was more drug that is

pharmacologically available, and it actually is in favor of the dosing that was conducted in humans.

DR. CORRADO: There were two additional questions regarding the clinical safety trial, and the first pertains to the criteria for entry to the study. Of course, inclusionary and exclusionary criteria can be lengthy, so I will just highlight some of them while showing them to you.

In entry, there were 18 to 80 year olds, and in fact we did enroll subjects from 18 to 80 years of age. And you will notice that we required that they discontinue alcohol, nicotine, and all caffeinated products prior to entry, which may have been, as already reported, one of the aspects leading to some of the headaches.

Next slide. In terms of the exclusionary criteria, obviously we excluded women who were either pregnant -- and we did pregnancy tests on all of them -- or who were currently breastfeeding. At this time, we did not know that less than 1 percent of tecovirimat makes its way into mother's milk; and in addition to that, people who had an active malignancy

or malignancy under treatment, or who had a seizure episode, as I had mentioned, other than febrile seizures. And we looked for people with -- the next slide -- people who had ECG abnormalities and who had QT intervals using the Fabricius method of greater than 450 milliseconds per second and if they had a current fungal, viral, or bacterial infection, if they had HIV, and these are the primary exclusionary endpoint.

I will also say that we excluded people who were on concomitant medication that might in theory have been affected by tecovirimat therapy based on their disposition vis a vis the cytochrome P450 system. So that gives you an idea of the major inclusion and exclusionary criteria.

The second question pertains to those adverse events that were considered of moderate severity. Just as way of background, we used the HIV division's criteria for grading adverse events, 1, 2, 3, 4 and 5, 1 being mild; 2 being moderate; 3 being severe; 4 being life threatening; and 5 ending in death. And when we look at those slides, these are the adverse events. And by and large the ones -- of course dental caries,

it happened. But among those that might be -- and this is regardless of drug relationship. But other than the broken arm, and the dental caries, and the common cold, when you look at these adverse events, they pretty much look like the ones that were mild as well.

So the pattern of adverse events, whether you look at the mild or you look at moderate, look to be the same, and they look to be the same between both tecovirimat and placebo.

DR. BADEN: A follow-up question on this image. This time period that was assessed was the 2 weeks on drug for a month for 6 months. What is the time frame that AEs were collected?

DR. CORRADO: Adverse events were collected throughout the entire dosing period. Subjects were given a diary to take home and complete and to return, and that was up until 28 days post last dose.

DR. BADEN: Thank you. Other follow-on questions from those, follow-on from the morning? Dr. Breman?

DR. BREMAN: Breman. I've got a question tied to the last point made by the doctor on the right

there -- no, you.

(Laughter.)

DR. BREMAN: I can't see your sign, Dr. Weina.

First of all, human monkeypox has less than 1 or 2 percent case fatality rate. And smallpox, even in the worst situation, has about a 30 percent case fatality rate with 50 percent or higher in the very young or the very old.

So the studies here, which depended greatly on mortality, would not apply to the studies of natural smallpox because you would need a very -- or monkeypox, certainly, because most of the patients survived. But there is opportunity now, as was mentioned this morning, with these increasingly large monkeypox outbreaks in Africa -- and you're well aware of that, and we heard from Dr. McFadden who is following this closely with the orthopoxvirus research group -- establishing protocols with your statisticians for what's going on. And you could find out tolerance and much more information.

Not that this is linked directly for the topic we're talking about to date, but for beneficial

clinical application and getting information in groups that are now exposed to human monkeypox would very be very, very advantageous to the field and to the populations that are under peril, including our own, because we have had importations of human monkeypox and outbreaks in our country in the early 2000s, following importations of pet Gambian rats into the country with big outbreak in the Midwest.

This point was raised this morning. I'm sure you're cognizant of this, and I see this as an opportunity to get real clinical information on a problem that's growing because vaccinia protects against human monkeypox, as you know. And these populations like in central Africa, like our own, are fully non-immune due to lack of vaccination.

DR. HRUBY: Well, I'd have to comments. We totally agree with you. First of all, with regard to the utility of our drug in smallpox, we think it will have an important role. One, we think it will greatly reduce the lethality that, as you pointed out, could be as high as 50 percent.

The other thing we believe, based on the

reduction and lesions in viral load, is that one would expect a reduction in morbidity in the human patient, and reducing the number of lesions, the number of scars, number of post-infection sequelae, we think that's an important effect of the drug.

With regard to monkeypox, yes, this is an important area that we're monitoring and are looking forward to the opportunity or participate in. Some of the problems currently are the patients are primarily children. They typically present at the clinics at a point when they are actually convalescing and getting better, so it'll be a little difficult to ascertain the efficacy of the drugs. Certainly we can get information about the safety, but there's also some incidence of transit monkeypox from the primary patient to family members. And if the proper study were designed, it's possible we can begin to see some effect at that level. So we will continue to monitor the situation and work with federal agencies so that we can get that information in the future.

DR. BADEN: If committee members have questions, please let Dr. Chee or myself known, and

we'll add you to the list.

Dr. Gripshover?

DR. GRIPSHOVER: Hi. I guess this is a question for the applicant. I was just curious. I think you explained well why we have the 600 BID, but the duration of therapy of 14 days, since the one study showed that shorter might be alright, and theoretically if 7 days were as good as 14, you could treat twice as many in an outbreak with the stockpile. So the question was why you went with 14 days as your length of therapy.

DR. HRUBY: Two reasons, and I'll give you the first reason. The first reason is we anticipate that we're going to see patients at various stages in disease, and we want to give enough drug for a long enough period of time to ensure that they are all protected since the drug seems to have a relatively safe profile. And there's actually a rationale for the 14 days as well, which I'll Grosenbach to provide.

DR. GROSENBACH: The immune response to smallpox is known to provide protection from later infection as well as immune response to the vaccine.

Cellular immune responses in smallpox were not well characterized, but the humoral immune response was. And what was noted was that within about the first week of the appearance of the rash or a lesion, that there were a complement-fixing antibodies, hemagglutination-inhibiting antibodies, and then finally, there were neutralizing, virus-neutralizing antibodies.

So in more severe disease, the virus-neutralizing antibodies came up later. So by treating for 14 days and controlling disease, you allow for the formation of protective antibodies to form, which does occur within that 14-day period.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: I had a follow-up question for FDA. This topic came up earlier, and you did touch upon it. And the question is regarding the insert, the package insert, and the labeling. We've talked a little bit about potential off-label use, and I just wanted to have a clear idea of how the package insert would be informative and exactly what viruses would be mentioned to be sure that potential prescribers would have enough information to prevent inadvertent use, and

that those who were interested in off-label use would have the proper resources to get in touch with before potentially prescribing the medication.

DR. BIRNKRANT: I don't think at this point we can comment on product labeling as the application is still under review. However, we do feel that our labels, although complicated, they are quite clear. They express all of the data we feel are necessary for physicians and other healthcare providers to make an appropriate risk-benefit assessment whether or not to use the drug.

DR. SCHAENMAN: The comments will just be restricted to variola then, if that's what the indication is.

DR. BIRNKRANT: In general, I think our labels reflect the conditions and indications that were studied.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: I have two questions, one, just real quickly, about adverse events. Was there any discrepancy between men and women and having a frequency of adverse events that seem to be

attributable to the drug?

DR. BADEN: To the agency or to the applicant?

DR. HONEGGER: To the applicant? Sorry. Thank you.

DR. HRUBY: Dr. Corrado?

DR. CORRADO: As you know, about 60 percent of the people in the pivotal study were women, and there was no difference that we could ascertain in terms of the frequency or the type of adverse events between men and women.

DR. HONEGGER: Thank you. My second question relates somewhat -- again, it's kind of off label. The question we're going to be asked is about use for treatment. And all these animals were symptomatic, but one could expect that in the case of a potential exposure, that it would be temptation to treat before patients are symptomatic, and use of the drug is post-exposure prophylaxis.

I don't know if it will be documentation of viremia in exposed patients or what the definition of infection will be, and also the -- this is to the applicant, I guess -- the questions about whether there

are any studies about treatment early on and how that affects development of immunity, which seems to be important. Treating early after vaccination might prevent the development of immunity. Treatment shortly after an exposure and other infections sometimes prevents seroconversion.

These are just questions that maybe aren't directly affecting our decision today, but I think they're important to think about. And I wondered if the company could comment about that.

DR. HRUBY: I can. Obviously, we would like to treat as early as possible in the course of smallpox. Unfortunately, with today's technology, the best diagnostic tool we have as lesional smallpox, there is in fact a diagnostic kit available to determine if you have a rash lesional disease identified as smallpox. The interesting area would be earlier in the program phase I described, and to date, there is not an approved diagnostic to go into that period and say whether or not your symptoms are due to the flu or do to smallpox, unfortunately. So right now, we're seeking approval for rash illness.

With regard to your other question, we have, as I mentioned, done lots of animal studies. And in general, what I can tell you is the earlier we intervene in disease, the more effective the drug is. If we intervene earlier, say, in an nonhuman primate before onset of lesions, we'll get complete protection, virtually no lesions, and very low viral load. If we go early enough so that we don't get any viral stimulus whatsoever, we've not looked at the immune situation, but I agree with you. In the absence of sterilizing immunity or sterilizing the blood, you probably won't get a good immune response.

DR. BADEN: Dr. Daskalakis, you have a follow-on question?

DR. DASKALAKIS: From the public health perspective, I would imagine that the post-exposure prophylaxis question is really important. I want to just sort of press you further and see have these animals studies really been done to look at the effect of post-exposure treatment, not waiting for any sign of infection. So no evidence of by viremia, nothing, just exposure happened and drug started at various times.

Has that been done yet at all?

DR. HRUBY: Certainly. Our earliest experiments, we're always doing, of course, exposing to drug before you infect or exposing at the time of infection. And if you do that, you get very, very effective inhibition.

DR. DASKALAKIS: Can you comment on how effective?

DR. HRUBY: A hundred percent, provided you stay on therapy, continue therapy.

DR. DASKALAKIS: Yes.

DR. BADEN: Dr. Weina a follow-on?

DR. WEINA: I just wanted to comment and make sure that we were clear on the point. You brought up the issue of diagnostics and everything, and the reality is that this is so highly infectious, that post-exposure prophylaxis is going to be a knee-jerk reaction to anybody at any time if you've got anybody who's been diagnosed. So anybody who's within eyeball shot of somebody who's got a diagnosed case of smallpox is going to be getting this drug if it's approved.

DR. BADEN: Dr. Honegger, a follow-on?

DR. HONEGGER: Yes. Thank you. People who have studied these outbreaks would know if this is relevant or not, but I was curious if you treat an animal shortly after infection and they survive, -- and it sounds like they all do -- and then you re-expose them to the virus, are they protected or not in challenge studies. Because that could happen in the real world, that people get treated early after an outbreak, and they don't develop immunity, but the virus is still in the community.

DR. HRUBY: We've done that experiment, and the answer's yes. But perhaps taking the experiment one step farther, we've actually shown in both mice and nonhuman primates that if we infect with the lethal challenge, wait 3 days, and then vaccinate and treat with drugs simultaneously, the drug protects the animals from disease and lethality. They recover. If we allow the animals then to rest a couple of months and challenge, they've also developed protective immunity.

So we believe if you get enough viral replication in the presence of the drug, you will get

immunity. Now, in the course of a natural infection, you would never quite know if they had enough of an antigenic stimulus or not.

DR. BADEN: Dr. Gripshover, did you ever follow-on?

DR. GRIPSHOVER: [Inaudible - off mic].

DR. BADEN: Microphone, please?

DR. GRIPSHOVER: You said how long you left the animals on in your post-exposure, because you said sort of indefinitely, but in the --

DR. HRUBY: Typically, in all of our animal therapeutic regimens, we give it for 14 days.

DR. GRIPHOVER: Okay. And in your post-exposure as well you are doing presently.

DR. HRUBY: Yes.

DR. BADEN: I have a question for the agency. In thinking about the risk-benefit, we have triangulation data suggesting activity in 2 animal models and human PK, but there is no circulating disease. So help myself and the committee way the benefit in the context of no actual disease.

DR. COX: We brought the committee here today

to talk through some of these issues. The idea here is this is something that would be stockpiled should there be an event. We all certainly hope that there is no smallpox release, but at least when I think about it, I'm thinking in terms of should there be an event, should this be used in the setting of using it for treatment of smallpox, that in essence is the benefit-risk, at least as I think about it.

So it is the benefit-risk for the indication, for the treatment of smallpox in patients, should there ever be a release, and we certainly hope there is not.

DR. BADEN: Dr. Weina, a follow-on?

DR. WEINA: Yes, and I think that the question becomes when we look at -- or at least in my mind for risk-benefit, comes down when we actually look at the question that we're being asked to comment on, and that is for the treatment of smallpox.

That's a very different risk-benefit ratio than if we're talking about orthopox writ large, because some of the evidence that we're being given is for vaccinia, which is not smallpox. And the trials in the animal data had been done with rabbitpox and with monkeypox,

which is not smallpox.

So it's a very different risk-benefit ratio. So when we're talking about -- the question that's before the committee, it says specifically smallpox, but all of our evidence is everything but smallpox.

DR. COX: So you're correct that the evidence is from a variety of different orthopoxviruses, but it is for the indication of treatment of smallpox, and it is that we're using that evidence from the other orthopoxviruses to support the smallpox virus treatment indication. So the indication that you should be thinking in terms of is the treatment of smallpox virus.

DR. BADEN: Based on the Animal Rule as you've framed it.

DR. COX: That's correct.

DR. HRUBY: And I'd like to comment on that question if I might. We actually believe the data package you're looking at is actually compelling that it will work against smallpox. As the FDA indicated earlier, the target protein is 98 percent conserved amongst the orthopoxviruses and smallpox. The protein

has exactly the same function in the life cycle in variola virus as it in vaccinia. It prevents EEV, and if you do that, it's known in all these viruses they become avirulent.

We've shown that the drug itself works against variola virus in tissue culture. Our colleagues at CDC have tested already against 7 different strains. Each one is inhibited with EC50 in the nanomolar, and perhaps most importantly -- we've not shown it; it was alluded to in the FDA presentation -- we have actually, although the model has limitations, tested our drug in three animal challenges in nonhuman primates infected with variola. Lethality was variable, so we couldn't use that as an endpoint. But in each and every one of those experiments, if we went in at 2 or 4 days post-infection, and at 4 days these animals are heavily lesional, we saw reductions in lesions and reductions in viral load. So we're quite confident this drug will work in variola the way it works against the other orthopoxviruses.

DR. SHERWAT: Can we provide a perspective as well?

DR. BADEN: Please.

DR. CHAN-TACK: If we can put up FDA backup slide number 3, please. Our perspective shares a strong overlap with that mentioned previously, which includes the clearly established virus-targeted mechanism with a highly conserved viral target and the 98 percent identity conservation across the orthopoxvirus family; its broad and consistent antiviral activity against orthopoxviruses, including several independent isolates of variola a virus. And that treatment efficacy was clearly demonstrated using two well-studied animal models of non-variola orthopoxvirus infection, each of which contributes several relevant characteristics of that approximate, the human smallpox condition.

The PK and PD data from the animal studies enabled the selection of an affected human dose, and then also within the risk-benefit assessment, the safety and tolerability of the product at these doses, which are several fold higher than those associated with the animal efficacy data also factors into our consideration.

DR. BADEN: Dr. Green, you have a follow-on?

DR. GREEN: Yes, and this is primarily to the agency, but it might be to the applicant as well. I guess I'm trying to get an understanding of, in your vision, who will be prescribing this medication. Is this something that the public health service, either at the county, state, regional, national, CDC, et cetera, will be providing, or will I potentially be writing a prescription for this and sending a patient to my local CVS or Rite Aid to get this medication? I think it's the former, but I just want to get clarity if you have a vision on this.

DR. SHERWAT: I think We'll let the applicant respond to this initially, and we can provide find clarification if needed.

DR. HRUBY: At the present time, the drug will be supplied exclusively to the Strategic National Stockpile. It's our vision that as a physician, if you come in contact with a rash illness you suspect to be smallpox, CDC has an algorithm on their website and a hotline to help walk you through and distinguish that patient from other types of rash illnesses. Then I

believe you will make a call to CDC, and a triage decision will be made as to whether the drug is dispersed for your patient.

DR. BADEN: Sorry. I have a follow-on, Dr. Hruby. You noted that 9 different variola strains were assessed, so there were 9 different lineages, disparate, and it had a similar activity.

DR. HRUBY: The number was 7, but yes.

DR. BADEN: Seven.

DR. HRUBY: Yes.

DR. BADEN: But they were distinct lineages of variola, and there was consistent activity across those lineages.

DR. HRUBY: Yes. Those represented both variola major
and variola minor strains.

DR. BADEN: Thank you.

Dr. Weina, you had a follow-on question?

DR. WEINA: I was just going to comment though, I think we're all in violent agreement here about the fact that the risk-benefit for this thing for smallpox seems to weigh in benefit of having it. I

just think that the question of the orthopox out there and what other uses this thing will have is an important one from the standpoint that we're not going through this exercise to get it approved to put it into the national stockpile because it's already there. So we're not doing this exercise unless I'm mistaken. Yes? No?

DR. COX: Approval is a very important step in a product's life cycle, so I wouldn't underestimate that.

(Laughter.)

DR. WEINA: No, absolutely right. But I mean if we already have --

DR. COX: That's step one.

DR. WEINA: But if we already have it and we already have it stockpiled just in case there's smallpox, the approval isn't just to get it into the stockpile, right?

DR. COX: But having an approval enables the product to -- it's been found to be safe and effective. It makes it much easier to use the product should you ever need to use it. So the approval is a very big

step. Even though the product is already in the stockpile, I would not in any way undervalue the importance of approval for the product that is in the stockpile and any future acquisitions they may choose to do or not.

So that's one thing. And it's not uncommon for a product to be approved. And then should there be an opportunity to further study the product for other indications, that's also a possibility. Doing studies in monkeypox, we talked about some of the challenges, but maybe there's a possibility there, too. Approval is an important step, and we have you here to be part of that discussion today.

DR. BADEN: But our charge today is the question at hand, not the --

DR. COX: That is correct.

DR. BADEN: -- many interesting follow-on questions that interest all of us.

DR. COX: Yes.

DR. BADEN: We have a focused charge today.

DR. COX: That is correct. Yes, the question today focuses around treatment of smallpox.

DR. BADEN: Dr. Daskalakis, you have a follow-on?

DR. DASKALAKIS: I just wanted to follow up on Jonathan's question about post0exposure prophylaxis one more time.

Can you talk about that mouse study, the idea of starting immediately after a lethal exposure, then vaccinating, and then seeing immune responses after vaccination? I'm just wondering how somehow you can vaccinate with a live virus, and then still have pretty hardy immune responses if you're actually also treating the virus that's in the vaccine.

DR. HRUBY: Well, it's an interesting situation. Remember, if you're waiting 3 days, these animals have fairly high viral loads at that point. And because of the mechanism of action of this drug, you're not inhibiting replication; you're inhibiting spread. So you have lots of virus inside of infected cells that present all the viral antigens in the context of the cellular histocompatibility antigens. So you get a full-blown immune response under those situations.

DR. BADEN: But that's likely when you have lytic infection. If you were to be on drug and abort initial infection, you may not elicit the immune response --

DR. HRUBY: If you are a drug prior to --

DR. BADEN: -- to exposure.

DR. HRUBY: -- getting substantial replication, yes.

DR. BADEN: Do you have follow-up?

DR. DASKALAKIS: Do I follow-up? In the mouse model that you talked about, you had drug given soon after exposure, and then you said you vaccinated and you saw a response to the vaccine; is that right?

DR. HRUBY: I'll ask Dough to comment.

DR. DASKALAKIS: So my question is how did the vaccine response happen if the drug's active against that virus as well?

DR. GROSENBACH: So there are a couple of experiments that we've done that address your question. The first is that if we do a legal challenge and immediately treat with drug, a hundred percent of the mice are protected and there's no evidence of disease

whatsoever. If you do a later rechallenge, lethal rechallenge, a hundred percent of the mice are immunologically protected. So obviously there's a very robust immune response in the presence of the drug after lethal challenge.

The second part of the question is what happens if you vaccinate a mouse and immediately treat with drug, can you still have enough antigen presentation to the immune system that is protective? In our mouse studies, we have seen that we have 100 percent protection when there is a later lethal challenge when you vaccinate in the presence of the drug.

DR. BADEN: Dr. Sherwat, did you have a comment?

DR. SHERWAT: Dr. Harrington's going to follow up on that.

DR. HARRINGTON: I do want to follow up a little bit. I think the concept of making sure you're looking at immunity following either an established infection or a lethal challenge is different from the question of what is the effect in a situation where

you're giving somebody a sublethal or nonlethal infection like you would with the vaccine itself. And the sponsor's correct that some of their studies have shown that there really isn't any interference with the vaccine. But there were a couple of studies in nonhuman primates that did demonstrate that if you co-administer, starting at the same time, vaccine plus tecovirimat, that tecovirimat may impair the immune response to the vaccine.

Now, ultimately, the long-term clinical significance of that impairment is unclear, but there is some evidence from one nonhuman primate study in particular that showed that it did impair the immune response to a monkeypox virus challenge about a month later.

DR. BADEN: MVA is an example of it doesn't go into a lytic phase, but there's an antigen load delivered.

Dr. Green?

DR. GREEN: I think I heard the answer to my question to get clarity. So if you give lethal poxvirus, whichever is the appropriate one for the

animal that you're using, You wait 3 days before lesional disease and you give them drug treatment, you will make them live and they will develop immunity. And then I heard earlier that you said if you give a lethal challenge and then you give simultaneously, or around the same time, the vaccine and antiviral therapy, they live and they get immunity. And I think I just heard the last of these, which was if you give vaccine alone without the previous lethal dose and the antiviral at the same time, that you may or may not get immunity

I just wanted to clarify that because I think that's the first time that we sort of heard that, and I think it's fine. I think the interesting thing here is if in an outbreak scenario, whoever's going to be making these decisions, if they're going to give antiviral therapy or alone, or if they're going to give vaccinia and antiviral therapy. But that's not what this committee was asked to think about, nor do I think we necessarily have that expertise.

DR. HRUBY: I think the unifying answer to all of that depends on viral load. You obviously have to

have enough replication of virus to have enough antigen to get good immune stimulation. And as was pointed out in many of these animal challenges, you're giving 5 times 10 to the 7th particles, so you're giving already a high viral load.

DR. BADEN: Dr. Breman?

DR. BREMAN: Can you go back to the last slide that was on? I'm interested in the systems used to test this drug against variola. These were in vitro studies?

DR. HRUBY: We've done both.

DR. BREMAN: Can you give us more information? How many isolates were tested? What types of systems?

DR. HRUBY: Our colleagues at CDC in tissue culture tested 7 isolates of variola as to their sensitivity, and they were all sensitive in tissue culture with EC50s and the nanomolar.

Over the years before we had the guidance in the 2011 advisory committee, we had actually done three experiments in nonhuman primates infected with variola virus. It's not a very good model, and there's a lot of deficiencies. But what we did see is we saw clear

evidence in these preliminary studies that we inhibited both lesion count and viral load in the infected animals in the presence of tecovirimat.

DR. BREMAN: And in the in vitro studies, in the pox presentation, whatever it was, the chorioallantoic membranes or whatever you were testing, did you find reduction or elimination of a pox?

DR. HRUBY: You can give more details on this, Doug.

DR. GROSENBACH: The assays that were conducted against variola in vitro were an EC50 assay, so this is a cytopathic effect based assay or a color metric assay, which evaluated various doses of drug. And what we saw is that the cytopathic effect due to variola infection was reduced in the 10 to 60 nanomolar range.

DR. HRUBY: In tissue culture cells.

DR. GROSENBACH: In tissue culture cells. This is monolayer tissue culture cells.

DR. BADEN: Other questions or comments from the committee members?

(No response.)

Question to the Committee and Discussion

DR. BADEN: Seeing none, we will now proceed with the question to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Can we bring forward the question?

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the

record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

Of we can display the question. I'll read the question. Based on the available data, does the risk-benefit profile of tecovirimat support its use for the treatment of human smallpox?

Any questions about the wording of the question --

(Laughter.)

DR. BADEN: -- so we can have clarity from the agency?

(No response.)

DR. BADEN: If there are no questions or comments concerning the wording of the question, we will now open to discussion, which we've already had. So if there are no other questions, then we shall move to the vote.

Any aspects of the voting or -- okay. So voting will now begin. I guess I'll read, please press the button on your microphone that corresponds to your

vote. You'll have 20 seconds to vote. Please press firmly. After you have made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. CHEE: For the question, we have 17 yes, zero no, and zero abstain.

DR. BADEN: Shall we go around with the discussion as to your comments? Shall we start with Dr. Breman? Any comments about your vote?

DR. BREMAN: No comments. My vote is yes.

(Laughter.)

DR. VENITZ: Jurgen Venitz. I voted yes. I think based on the presentations and the discussions that we had today, it's reasonable to conclude that the drug is effective. I think the way the human dosing regimen was estimated is reasonable as well. So given what we know following the rules of the Animal Rule, I voted yes.

DR. SCHAENMAN: I feel similarly, And I want to mention, as was mentioned earlier, to thank the

sponsor for including a wide range of ages, genders, and ethnicities in the safety trial.

DR. LO RE: This is Vin Lo Re. I voted yes. I felt that with no approved products for the treatment of smallpox and concern that smallpox can be used as a bioweapon and limitations of the current vaccine, I thought there was enormous unmet need for antiviral therapy for smallpox. And I think that this drug fills that enormous need, antimicrobial armamentarium.

I think recognizing the challenges in the developmental strategy under the FDA Animal Rule, I thought that the applicant met all of the regulatory considerations for efficacy, and I thought that the applicant met the requirements for safety that were requested by the agency.

Based on the data from 359 healthy volunteers, there were no serious safety signals that were identified. However, I would express caution that with such a small sample size, potentially serious and important adverse effects occurring at a frequency less than 1 percent might be missed. And I would encourage continued study to evaluate the safety of this drug in

additional samples of patients and other relevant subgroups. I would hope that the drug would never have to be used on a wide scale, but if so, I think it would be prudent to have an even better understanding of the spectrum of adverse effects before wide scale administration.

DR. DASKALAKIS: This is Demetre Daskalakis. I also voted yes for many of the same reasons. I feel the Animal Rule requirements were all met. I feel that the sponsor was extraordinarily responsive to previous committee's recommendations and have achieved all of the goals of those and I think demonstrated in small studies their safety. And as the person who would be the incident commander in New York City if there were a smallpox release, I'm very grateful for this to be added to the armamentarium.

I do, however, want to go a bit off path on this question and say it's probably really important to share information about post-exposure prophylaxis because undoubtedly that is how we're going to use it, and that also means a broader distribution of the drug and potentially more opportunities for observing any

adverse events. But otherwise, I think this is a great addition to the antiviral armamentarium, so thank you.

DR. BADEN: Dr. Baden. I also voted in favor. I think the applicant is to be applauded for their diligence and persistence over the last 10-15 years in systematically developing the data set that is so transparent and easy to understand. I think from the agency's standpoint, a couple of considerations.

As noted, the safety data are limited. That's by its nature and that will have to be accrued as opportunity arises. The dosing in many groups have not been studied, and that also will have to be accrued as the opportunity arises. And then for both the agency and the applicant to consider the application for the orthopoxviruses, which are beyond the scope of the question today, but is a natural extension of the virology and the animal models.

DR. WEINA: Peter Weina, Walter Reed. I voted yes, and I just want to clarify to the narrow question of the treatment of smallpox. I think the sponsor as well as the FDA should be applauded. I'm sure that the progress of this seem glacial at the time that you're

doing it, but now that you look back at the tremendous accomplishments that you've provided, it really is a certain amount of satisfaction.

I think we're missing, though, a huge portion of this that the use of this drug is not going to be just stockpiled and stuck away in a corner for smallpox use. This is going to be used with all the orthopox. I think there certainly is a different threshold for this drug when you're using it with smallpox that has a mortality rate of at least 30 percent, probably more, cut loose in a naive population used as a bioweapon. But the problem is that there's a lot of monkeypox out there, and it's increasing more and more and becoming more and more of a problem. Vaccinia is becoming more of a problem, especially when guys like me get deployed to Iraq and we get 35 smallpox vaccinations in a row because nobody can seem to remember the last time you got one, even though you still have the lesions from the last one.

So there are a lot of complications, so it's going to be used in orthopox. And I would urge you to take a look at the opportunities, to take a look at it,

because monkeypox in some of these outbreaks have got mortality rates up to 15 and 20 percent recently. I know everyone keeps quoting 1 percent, and that may be the historic in the past, but that's not the recent outbreaks. So I think we need to look at that because this drug is going to be used for everything I think but smallpox, or hopefully everything but smallpox.

DR. HONEGGER: Jonathan Honegger. I also voted yes, and like said, I appreciate all the work of the applicant and the FDA in developing a rational way to tackle this problem. And I felt that the Animal Rule criteria and the way that they were met made sense to me. Thankfully the efficacy data appeared unequivocal.

Like everyone, this seems like the actual use of this should be heavily studied maybe more so than most approved drugs. I want to mention pediatrics obviously hasn't been modeled really, so we really need to study the dosing and effects of the drug in pediatrics as well as in pregnant women. Also, development of immunity and the actual effects on outbreak control when this drug is used in real world

will be important.

DR. GREEN: Michael Green, Pittsburgh. I also voted yes, no surprise. This is the first time I've been to an FDA advisory committee meeting where both the agency and the applicant were arguing to the committee that this product should be approved.

(Laughter.)

DR. GREEN: When you speak together, it's pretty powerful. I think this is a clear scenario where the risk of not providing treatment is self-evident and the risk of treating with this agent, while not fully defined, seems unlikely to be significant in the vast majority of treated patients. Clearly, there are scenarios where the data are not full. Even if we're treating smallpox pediatrics, here are the two peds people sitting next to each other, and we don't have the data on dose, nor do we have the data on toxicity, particularly if we go down to small children.

I think, as was just mentioned by Peter, understanding its role with vaccinia would be important. Many of us at this table were around when

about 15 years ago or so they talked about giving everybody vaccinia virus who were medical providers, and we all had to learn the side effects. There's a lot of eczema out there. So I think opportunities in thinking about that would be really important.

Having said that, I also want to applaud the agency for having the visionary wisdom to develop something like the Animal Rule for a scenario like this, and then also compliment and thank the applicant for staying with us to give us really a drug for an otherwise highly fatal, potentially bioterrorist agent. Thanks very much.

DR. GRIPSHOVER: Hi. Barb Gripshover, and like everyone else, I voted yes for many of the same reasons that have already been said. I want to applaud again both the applicant and the agency for developing this drug and developing the Animal Rule so we can test the drug in otherwise fatal illness. I think there is clear evidence that it works and certainly appears safe in the patients studied so far and would hope that we would collect more information if we ever need it. Hopefully, we don't need it for smallpox, but looking

at it for other uses as well.

DR. CLARK: Nina Clark. I voted yes, and I would just echo the other comments. I think the applicant did a great job of making the data clear and fulfilling the criteria of the Animal Rule, and echo the comments on collecting more safety data and efficacy if it ever is used in various populations, including immunosuppressed patients.

DR. FOLLMANN: I'm Dean Follmann. I voted yes. I thought it was a very clear and compelling case made both by the sponsor and the agency. I thought it was very well done. I will look to this myself as a way to sort of navigate the Animal Rule and how I might apply it in other situations that I come across.

DR. HAWKINS: Yes. Dr. Randy Hawkins. I also voted yes. I just wanted to state that I appreciate the discussion from all the parties beyond the question before us. It was very stimulating. Thank you.

MS. DUNN: I'm Debra Dunn, and I am the patient representative. And I just want to thank the applicant and the FDA for their diligence in this. And I can tell you as a mother and representing the

patients out there, I know that I would do anything to get my hands on this if I knew that there was a smallpox outbreak. And I just know that I can sleep at night knowing that it is stockpiled somewhere.

(Laughter.)

MS. DUNN: So I'm very grateful. I think as a mother, as a daughter, and just as a human being, knowing that someone that I love and care about may be infected with us, it's pretty scary, so thank you for your work.

DR. PETERSON: Hi. Brett Peterson, CDC. I think that the data presented here today provides persuasive and compelling evidence that tecovirimat has the potential to provide significant benefit for the treatment of human smallpox, and for these reasons, I voted yes. And I would further add that, personally, I do believe, as has been stated by a number of others on the committee, that there is room for further study of this drug for other orthopoxviruses that are currently causing naturally occurring infections throughout the world. Thank you.

DR. LYONS: I'm Rick Lyons. I voted yes. I

just want to particularly thank the FDA and this applicant for hanging in there with the Animal Rule. Having lived it for 15 years myself, I know that it wasn't without pain on both sides, so I really appreciate the effort of the FDA to hang in there. And this is just an outstanding example of the Animal Rule as far as I'm concerned and can become a template for other companies. So thanks to both the applicant and the FDA.

DR. CONDIT: Rich Condit. I voted yes. I've been following this story since the very early days of discovery of the drug, and it's really a remarkable story to come to this point. I just want to support everything, all the positive stuff that's been said, and congratulate the applicant and the FDA for their cooperative work together to bring us to this point.

DR. BADEN: Thank you. Before we adjourn, are there any last comments from the agency?

DR. BIRNKRANT: Well, as has been mentioned, we have been working together with the applicant for many, many years, and I'm personally quite satisfied and gratified with today's vote. Not only does it

reflect the hard work not just from the applicant but also from the FDA. I think we had mutual goals to try and have a safe and effective product for a potential biothreat, and I think based on the discussions today and the comments from our esteemed committee, that we've reached that goal. So thank you very much.

Adjournment

DR. BADEN: Thank you.

Panel members, please take all your belongings with you as the room is cleaned at the end of the day. Please leave your name badges on the table so they can be recycled. All other materials will be disposed of. The meeting is now adjourned.

(Applause.)

(Whereupon, at 2:32 p.m., the meeting was adjourned.)