FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Thursday, July 12, 2018

8:00 a.m. to 3:35 p.m.

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Kalyani Bhatt, BS, MS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Lindsey R. Baden, MD

(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

Dean A. Follmann, PhD

Assistant Director for Biostatistics

Chief Biostatistics Research Branch

National Institute of Allergy and Infectious Diseases

National Institutes of Health

Bethesda, Maryland

Michael 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 *(via phone)*
Associate Professor of Medicine
University Hospitals Cleveland Medical Center
Case Western Reserve University
Division of Infectious Diseases and HIV Medicine
Cleveland, Ohio

Vincent Lo Re, MD, MSCE
Associate 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

Ighovwerha Ofotokun, MD, MSc
Professor of Medicine
Division of Infectious Diseases
Department of Medicine
Emory University School of Medicine
Atlanta, Georgia

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

TEMPORARY MEMBERS (Voting)

Warren B. Bilker, PhD
Professor of Biostatistics
Department of Biostatistics and Epidemiology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Josh A. Mailman, MBA
(Patient Representative)
Oakland, California

Thomas A. Moore, MD, FACP, FIDSA
ID Consultants, PA
Wichita, Kansas

Michele J. Orza, ScD

(Acting Consumer Representative)

Chief of Staff

Patient-Centered Outcomes

Research Institute (PCORI)

Washington, District of Columbia

Kathrine R. Tan, MD MPH

Division of Parasitic Diseases and Malaria/

Malaria Branch

Centers for Disease Control and Prevention

Atlanta, Georgia

Julie M. Zito, PhD

Professor of Pharmacy and Psychiatry

University of Maryland, Baltimore

Pharmaceutical Health Services Department

Baltimore, Maryland

ACTING INDUSTRY REPRESENTATIVE TO THE ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (Non-Voting)

Ercem S. Atillasoy, MD

(Acting Industry Representative)

Vice President, Global Regulatory Affairs and Clinical Safety

Merck & Company, Inc.

North Wales, Pennsylvania

FDA PARTICIPANTS (Non-Voting)

Edward Cox, MD, MPH

Director

Office of Antimicrobial Products (OAP)

Office of New Drugs (OND), CDER, FDA

Sumathi Nambiar, MD, MPH

Director

Division of Anti-Infective Products (DAIP)

Office of Antimicrobial Products (OAP)

OND, CDER, FDA

Yuliya Yasinskaya, MD

Clinical Team Leader

DAIP, OAP, OND, CDER, FDA

Sheral Patel, MD

Medical Officer

DAIP, OAP, OND, CDER, FDA

Xianbin Li, PhD

Statistical Reviewer

Division of Biometrics IV (DBIV)

Office of Biostatistics (OB)

Office of Translational Sciences (OTS), CDER, FDA

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

(8:00 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 that make noise if you've not already done so. I would also like to identify the FDA press contact, Theresa Eisenman. If you are present, please stand. She's in the back left.

I'm Dr. Lindsey Baden. I'm chairperson of the Antimicrobial Drug Advisory Committee and I'll be chai this meeting. I will now call this meeting to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA on the far left.

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

DR. NAMBIAR: Good morning. Sumathi Nambiar, director, Division of Anti-Infective Products, CDER, FDA.

DR. YASINSKAYA: Good morning. Yuliya Yasinskaya, medical team leader, Division of Anti-Infective Products at the FDA.

DR. O'SHAUGHNESSY: Good morning. Elizabeth O'Shaughnessy, medical officer, CDER, FDA.

DR. LI: Good morning. This is Xianbin Li, a statistical reviewer from the FDA.

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

DR. BADEN: Please remember to turn on and off your mics when you talk. Thank you. This is for the record.

DR. HONEGGER: Jonathan Honegger, pediatric infectious diseases, Ohio State University, Nationwide Children's Hospital.

DR. CLARK: Nina Clark, infectious diseases, Loyola University Medical Center, Maywood, Illinois.

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

MS. BHATT: Good morning. Kalyani Bhatt. I'm with the Division advisory committee consultant's management. I'm the acting DFO for this meeting.

DR. BADEN: Lindsey Baden. I'm at Brigham and Women's Hospital, Dana-Farber Cancer Institute, and Harvard Medical School in Boston, adult infectious diseases.

DR. WEINA: Peter Weina. I'm in infectious diseases at the Walter Reed National Military Medical Center.

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

DR. ORZA: Michele Orza with the Patient-Centered Outcomes Research Institute. I'm the acting consumer representative today.

MR. MAILMAN: Josh Mailman. I'm a patient advocate, a patient representative for today.

DR. MOORE: Dr. Tom Moore. I'm an infectious disease physician at the University of Kansas in Wichita.

DR. BEYRER: Chris Beyrer, infectious diseases, epidemiologist at the Johns Hopkins Bloomberg School of Public Health in Baltimore.

DR. ZITO: Julie Zito, pharmacoepidemiology, University of Maryland.

DR. KARTSONIS: Nick Kartsonis. I'm in adult infectious disease. I help to lead clinical research in infectious diseases and vaccines at Merck and I serve as the industry rep on the committee.

DR. BADEN: Thank you all for making the time to join 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 will 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 topics at hand take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the 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.

Now, I'll pass it to Kalyani Bhatt, who will read the conflicts of interest statement.

Conflict of Interest Statement

MS. BHATT: Good morning. 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 U.S.C., 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 U.S.C., 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 a particular individual's services outweighs his or her potential financial conflict of interest or when the interests of a regular federal employee is not

so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary 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, and for purposes of 18 U.S.C. 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 NDA 210795, tafenoquine tablet, 150 milligrams, sponsored by GlaxoSmithKline Intellectual Property Development, England, for the proposed indication of radical cure, prevention of relapse of plasmodium vivax malaria.

This is a particular matters meeting, during which specific matters related to GlaxoSmithKline's

NDA will be discussed. Based on the agendas 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 made 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 non-voting 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 Company.

We would like to remind members and temporary voting members that, if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest,

participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all participants to advise the committee of any financial relationships they may have with the firm at issue. Thank you.

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

FDA Opening Remarks

DR. YASINSKAYA: Good morning, again. My name is Yuliya Yasinskaya, medical team leader from the Division of Anti-infectives, CDER, FDA. I will provide you a summary and overview for the day.

The subject of today's advisory committee is tafenoquine tablet, 100 milligrams. The NDA is 210795. The indication is radical cure of plasmodium vivax malaria.

The applicant for this application is GlaxoSmithKline. The product was given orphan and breakthrough therapy designations for the indication being sought. The application was also granted priority review. I would like to remind

you that primaquine, 15 milligrams daily for 14 days, is the only approved drug for the radical cure of plasmodium vivax malaria in the United States.

So the proposed dosing regimen for this indication is 300 milligrams, which is 2 100-milligram tablets on the first or second day of appropriate therapy for acute plasmodium vivax malaria, such as chloroquine.

The development program for this indication included 3 randomized, double-blind, controlled efficacy and safety trials and 2 trials compared to tafenoquine, 300-milligram single dose in combination with chloroquine to chloroquine alone. Trial 582, part 1, was a dose-ranging phase 2b trial and 582, part 2, was an independent phase 3 trial.

DR. BADEN: We're going to take a two-minute break to correct an embedded automated feature that's disrupting the slides.

(Pause.)

DR. YASINSKAYA: Going back to the

development program, starting --

DR. BADEN: I think they're still correcting something.

DR. YASINSKAYA: Really?

DR. BADEN: But while they do that, we can have Dr. Tan, who has joined us, introduce herself for the record. Thank you for joining us.

DR. TAN: I am Dr. Katherine Tan. I am the unit chief for the domestic response unit in the malaria branch at CDC.

DR. BADEN: Thank you.

(Pause.)

DR. BADEN: This is a free lesson in PowerPoint nuance for all of us, as we watch experts solve the problem.

So we shall resume and, if the problem persists, we only have a few more slides before we go to the applicant's presentation. And we can make sure there are no other embedded features. So please resume. Thank you. Please resume and try your best to navigate it for four or five more slides. And then we'll address it while the

applicant is presenting.

DR. YASINSKAYA: Sounds good. So going back to the development program, again, 3 randomized double-blind active and placebo-controlled efficacy and safety trials were conducted. Two of the trials compared tafenoquine in combination with chloroquine to chloroquine alone.

Trial 582, part 1, was a phase 2b dose-ranging trial and 582, part 2 was a phase 3, independent efficacy trial. A safety trial, 564, compared a combination of tafenoquine, 300-milligram single dose with chloroquine to a combination of primaquine, 14 days, plus chloroquine. And this trial had provided support of efficacy information.

Three safety studies were also part of the applications and the safety trials were conducted in healthy volunteers and included ophthalmic safety study, thorough QT study, and hematologic safety study in G6PD-normal and deficient individuals.

This slide provides an overview of efficacy

findings in two trials, 582, part 1 and 2, tafenoquine, 300-milligram single dose in combination with chloroquine was superior to chloroquine alone for the relapse-free efficacy endpoint assessed at 6 months.

In part 1, the difference between the two arms was 52 percent, which was statistically significant. In part 2, the difference was 33 percent, which was also statistically significant. In the supportive trial, 564, tafenoquine, 300-milligram single dose in combination with chloroquine, was compared to primaquine-chloroquine combination for the relapse-free efficacy endpoint assessed at 6 months.

For the combination of chloroquine and tafenoquine, the relapse-free efficacy was 67 percent. For the chloroquine-primaquine, it was 71 percent with a difference of minus 3.4 percent. With regards to safety, 493 plasmodium vivax malaria patients were exposed to tafenoquine, 300-milligram single dose in combination with chloroquine. The safety issue that had been

identified in this patient population was hemolysis decreases in hemoglobin and increases in methemoglobin levels.

In healthy volunteer studies, 401 subjects were exposed to tafenoquine at 300 milligrams, single dose. In this patient population, all saw hemolysis decreases in hemoglobin and increased levels of methemoglobin were identified, which were dose dependent and dependent on the level of G6PD.

There were also 2 cases of hypersensitivity identified, and 2 cases of depression, and 2 cases of psychosis in this patient population. Tafenoquine, 300-milligram single dose had no ocular safety or QT prolongation liability.

So for today, my presentation will be followed by the presentation by the applicant and then by presentations by the FDA. Efficacy will be covered by Dr. Xianbin Li and safety will be covered by Elizabeth O'Shaughnessy.

The presentation from the FDA will be followed by clarifying questions. After lunch, we'll have open public hearing followed by

questions to the committee. We have two questions for the committee today. Question 1 deals with efficacy. Has applicant provided substantial evidence of effectiveness of tafenoquine for the radical cure, prevention of relapse of plasmodium vivax malaria in patients 16 years of age and older.

If the committee finds that substance evidence has been provided, we ask the committee to provide any additional recommendations concerning labeling. If the answer to this question is no, we would like the committee to discuss what additional studies or analysis need to be conducted.

For question 1, we ask the committee to vote whether applicant has provided adequate evidence of safety of tafenoquine for the radical cure, prevention of relapse of plasmodium vivax malaria in patients 16 years of age and older.

If the committee finds that such evidence had been provided, we would like you to discuss any recommendation concerning labeling. If the evidence was not provided, we'd like you to discuss

any additional studies or analyses that are needed. Thank you.

DR. BADEN: Thank you, Dr. Yasinskaya.

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's 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 couple things 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 statement, it will not preclude you from speaking. We will now proceed with GlaxoSmithKline's presentations.

Dr. Kleim?

Applicant Presentation – Joerg-Peter Kleim

DR. KLEIM: Good morning, Mr. Chairman, members of the committee, and the FDA. I am Jorf-Peter Kleim and I'm the medicine development leader for tafenoquine at GlaxoSmithKline. I want to thank you for the opportunity to present the data supporting the safety and efficacy of a single dose of tafenoquine, 300 milligram, for the prevention of relapse or radical cure of P. vivax malaria.

There is a global effort to eradicate malaria, which is a significant public health problem around the world. In collaboration with the not-for-profit Medicines for Malaria venture, we are developing tafenoquine as part of our global health program.

Should tafenoquine be approved by the FDA, it will also be an effective option for the orphan population of patients with P. vivax in the United

States. Tafenoquine would assist with malaria eradication efforts as the program aligns with U.S. and global initiatives to end malaria worldwide.

Today, we will demonstrate that a single tafenoquine dose of 300 milligram in combination with standard doses of chloroquine is an efficacious treatment for relapse prevention of P. vivax malaria. Tafenoquine demonstrates this efficacy while maintaining a similar safety profile to the currently approved standard of care.

If approved, tafenoquine would afford high treatment compliance and it would be the first new treatment for prevention of relapse of P. vivax malaria in more than 60 years. While the molecular mechanism of action of tafenoquine is unknown, we do know that it inactivates the dormant liver stage. P. vivax can hide in the liver of infected people and it can be undetectable for weeks or months after initial infection.

The dormant liver stage causes malaria. It relapses in infected patients without the need for another infected mosquito bite. The ability to

relapse not only affects individual patients, but also makes P. vivax more difficult to control and eliminate than other human malaria parasites.

Right now, tafenoquine is the only medicine that inactivates the P. vivax dormant liver stage and prevents relapse. It has to be taken for 14 days and treatment compliance can therefore be difficult. Tafenoquine offers a novel single-dose treatment for relapse prevention.

Tafenoquine is an 8-aminoquinoline and a synthetic analog of primaquine. Tafenoquine is absorbed slowly with maximum plasma concentrations observed after 12 to 15 hours of dosing. It has a plasma half-life of 15 days, which is what provides the potential for more convenient dosing. Tafenoquine was originally discovered by the Walter Reed Army Institute of Research.

Since then, a total of 33 completed or ongoing clinical studies have been conducted, 13 of which support the radical cure indication. Tafenoquine's clinical safety and efficacy are supported by 3 randomized double-blind studies.

The pivotal study is study 582 part 2, with study 582 part 1 and study 564 as supportive studies.

Cases reported in the United States are rare, mostly occurring in returning travelers from malaria endemic countries. Therefore, the 3 studies were conducted outside the U.S. 20 additional studies in other malaria indications were analyzed for safety.

We have not seen any regional or ethnic differences in the clinical pharmacology program, which included more than 400 U.S. subjects. Tafenoquine was granted orphan drug status in January 2013. Based on positive data from part 1, tafenoquine was granted breakthrough therapy designation later that year.

The proposed indication is for the radical cure, that is, the prevention of relapse of P. vivax malaria in patients aged 16 years and older. The recommended dosing administration is a single 300-milligram dose co-administered with chloroquine.

I would now like to provide you with a brief

overview of the data we're going to present today. In the pivotal study, treatment with a single dose of tafenoquine, 300 milligram, co-administered with a standard course of chloroquine resulted in a clinically and statistically significant reduction in the risk of recurrence of P. vivax at 6 months by 70 percent compared to chloroquine alone. Tafenoquine efficacy was consistent in the supportive studies.

The overall safety profile of tafenoquine at the recommended dose was acceptable and broadly similar to a 14-day regimen with primaquine.

The primary safety risk of tafenoquine is the same as that of primaquine, which is that both drugs may cause hemolysis in patients with G6PD deficiency. In alignment with primaquine, we plan to manage this risk with appropriate labeling and G6PD testing before treatment. In fact, applying G6PD testing, there were no cases of clinical hemolysis in our development program.

We also looked at other safety events of interest and there was no increased risk of

clinically relevant events with a proposed single 300-milligram dose of tafenoquine. With this information in mind, here's the agenda for the remainder of our presentation. Next, Dr. Kevin Baird will provide his perspective on the unmet need in the treatment of P. vivax malaria.

Dr. Justin Green will follow with a review of the study designs and efficacy results of all key studies. Dr. Alison Webster will then present the safety results and Dr. Rick Price will conclude with his clinical perspective on the benefit-risk profile.

We also have additional responders with us today to help answer your questions. Thank you. I will now invite Dr. Baird to give his perspective on the unmet need.

Applicant Presentation – Kevin Baird

DR. BAIRD: Thank you, Dr. Kleim.

Good morning. My name is Kevin Baird. I'm a professor of malariology in the Nuffield Department of Medicine, University of Oxford in the United Kingdom.

I am posted in Jakarta, Indonesia, where I serve as the principal investigator for clinical trials of P. vivax aimed at improving the prevention and treatment of this particular and uniquely complex malaria.

Currently, I'm running another clinical trial with tafenoquine as well. By way of conflicts, I have no financial interest in the company, but they have compensated me for my time and travel. This heat map of the prevalence of plasmodium vivax illustrates the most geographically widespread malaria, causing a very significant clinical and public health threat all across the globe.

Although plasmodium vivax has been successfully eliminated in many parts of the world, it may erupt as widespread epidemic malaria, as is now happening in Venezuela and may reappear as stable endemic malaria, where it had once been eliminated, as occurred on the Korean Peninsula.

Absolute numbers of cases are difficult to ascertain. Estimates range between less than 10

million to more than 100 million. But we may be confident in the estimate of 2.5 billion people living at risk of this infection. That's 40 percent of humanity. More than 90 percent of this burden occurs in the Asia-Pacific region.

In the Americas, more than half of malaria cases are caused by plasmodium vivax. During each of the past 30 years, the U.S. CDC has consistently reported hundreds of cases of vivax malaria diagnosed in the United States, almost all of those occurring in travelers or visitors.

While rare, these imported cases sometimes lead to local transmission by American anopheles, mosquitos. There have been 63 such outbreaks of malaria in the United States since 1957 with annual reports of 1 to 32 individuals affected. The most recent report of an outbreak was just last year in a family in Houston, TX.

Although these locally acquired mosquito-transmitted outbreaks frequently involve only a limited number of infected persons, they raise legitimate concerns in the community and require

substantial public health resources to avert broadening of those outbreaks. Plasmodium vivax malaria is a parasitic disease transmitted by mosquitos in the genus anopheles.

Once a patient has been infected, an incubation period of approximately 2 weeks occurs as active liver stages develop without symptoms. In humans, the infection consists of both a liver and a blood stage. It is the subsequent infection of the red blood cells that provoke the symptoms of an acute attack of malaria.

Some of the liver-stage parasites do not immediately develop like that. Instead, they become dormant hypnozoites. These parasites are wholly silent and cannot be detected by any diagnostic means. Days, months, or even years later, hypnozoites in the liver can awaken and cause a renewed attack of acute malaria, called a relapse.

If a patient does not receive specific therapy against hypnozoites, they often suffer 6 or more relapses within the first year. Each one of

those comes with acute illness and opportunity for transmission to the people around them.

The symptoms of acute vivax malaria include daily bouts of shaking chills followed by a spiking fever, accompanied by vomiting, malaise, headache, and myalgia. Although historically regarded as causing a benign and self-limiting course of illness, there is increasing evidence that the severity of disease, overall burden, and economic impact of P. vivax malaria have been greatly underestimated.

Even today, severe and fatal infections occur with delayed or inadequate therapy. Splenic rupture, although rare, has long been recognized as a life-threatening complication of vivax malaria. More recently, a diagnosis of vivax malaria has been associated with severe disease syndromes.

In a review of more than 12,000 cases of vivax malaria in travelers returning to the United States, .1 percent of those cases resulted in death and 1.3 of those were classified as severe. The case fatality rates for severe vivax and falciparum

malaria were statistically indistinguishable.

Vivax malaria is not an inconsequential infection. Unfortunately, a diagnosis of vivax malaria often comes with a very high risk of multiple relapses and thus imposes a clinical threat if the liver stage is not adequately treated.

This graphic illustrates a study of American soldiers returned to the United States after exposure in the Pacific. These data illustrate what may occur without therapy against relapse as primaquine was not available for use until 1952.

Among more than 2,400 diagnosed with vivax malaria, a median of 10 to 14 relapses occurred in each soldier within 2 years, each relapse being an acute attack, and another opportunity for a poor clinical outcome, and onward transmission.

At the time, repatriated soldiers carrying hypnozoites were acknowledged and recognized as threatening the reintroduction of recently eliminated malaria transmission in the United States. This is not just history. Recent work

shows similar trends in relapse and transmission when the liver stage is not effectively treated.

The frequency of clinical attacks caused by relapse has been shown to be greater than 80 percent, causing a serious public health threat from an untreated hypnozoite reservoir. In a study at the Thai-Myanmar border, 98 percent of clinical attacks of P. vivax were actually derived from dormant hypnozoites in the liver rather than new cases, that is, a fresh mosquito bite.

Similar longitudinal cohort studies in Papua New Guinea, illustrated in this graph, the red Kaplan-Meier curve, estimating force of reinfection, versus the blue of force of reinfection and relapse combined. Estimated 82 percent of attacks derived from hypnozoites.

That is the difference between the blue and red curves seen here and assumes 100 percent efficacy of radical cure among those randomized to the primaquine treatment group. Not properly treating this by effective radical cure accounts for most of the morbidity and mortality associated

with acute attacks of vivax malaria in endemic areas.

Plasmodium vivax is thus refractory to conventional elimination efforts. Untreated hypnozoites stream fresh attacks into communities, causing outbreaks, epidemics, or reintroduced endemic malaria in areas which have previously eliminated it.

Suppressive chemoprophylaxis is widely available in the United States, but these drugs have no impact on dormant hypnozoites. Attacks of vivax malaria often occur months after returning from travel. When these occur with seasonally abundant American mosquitos, real risk of outbreaks or even epidemics is incurred.

Achieving radical cure of each diagnosis of P. vivax malaria by successfully eliminating both the blood and the liver stages of this infection is a therapeutic goal with profound clinical and public health benefits. Most antimalarials in the United States are approved and effective for suppressive chemoprophylaxis or for treatment of

only the blood stage of the infection responsible for acute malaria.

The preferred treatment for acute malaria is a three-day regimen of chloroquine. Other treatment options are available for treating chloroquine-resistant vivax malaria or when chloroquine is not readily available.

8-aminoquinlines are the only class of drugs effective against the dormant liver stage. Currently, the only approved 8-aminoquinline is primaquine, which is administered once daily for 14 days. While primaquine is an efficacious treatment, its effectiveness depends on adherence to the full 14-day treatment regimen.

This graphic illustrates a very important fact of primaquine therapy. The upper dashed line shows the risk of relapse after unsupervised 14-day therapy compared to the lower line showing use under directly observed therapy.

Complete compliance with primaquine treatment is reported to be as low as 30 percent when patients are not supervised. It has been

estimated that primaquine efficacy is reduced three- to fourfold when as few as 3 out of the 14 doses are missed.

This problem of poor effectiveness often amounts to inadequate access to safe and effective therapy for vivax malaria. Like all compounds of the 8-aminoquinline class, primaquine can cause hemolysis in patients with a deficiency in glucose-6-phosphate dehydrogenase enzyme, G6PD. This is an identified risk that can be mitigated by G6PD screening before treatment.

The prevalence of G6PD deficiency is high in many malaria endemic areas, averaging about 8 percent. The condition is sex linked. Males carry one copy of the G6PD gene and are either wholly normal or deficient. Females carry two copies and may be homozygous or heterozygous for G6PD deficiency.

Although access to G6PD screening is problematic in rural areas of the developing nations, effective diagnostic tests for G6PD deficiency are readily available in the United

States. Primaquine has been safely used here for more than 65 years.

In summary, without treatment to eliminate the dormant liver stage of plasmodium vivax, patients may suffer from multiple repeated bouts of acute malaria, each clinical event carrying significant risk of a poor outcome and infection of others in their communities.

While primaquine is efficacious in preventing relapse, poor adherence to the 14-day regimen and safety concerns regarding unknown G6PD status limits its effectiveness and this has important clinical and global health consequences. Therefore, there is an unmet need for a simple single-dose regimen of P. vivax malaria. Importantly, successful attack on the hypnozoite reservoir of P. vivax is likely to result in the collapse of endemic transmission of this parasite. Thank you. I will now invite Dr. Green to the lectern to discuss the efficacy results.

Applicant Presentation – Justin Green

DR. GREEN: Thank you, Dr. Baird.

My name is Justin Green and I'm the project physician for tafenoquine GSK. I've worked on tafenoquine since 2010. I'm trained in infectious diseases and have had a long career in global health.

Because of the treatment gap for radical cure of P. vivax, GSK has partnered with MMV to develop a simple single-dose treatment and I'm pleased to share with you today the key efficacy and clinical pharmacology data from our late-stage radical cure clinical program.

As Dr. Kleim mentioned, the primary evidence supporting the clinical efficacy of tafenoquine is provided by 3 randomized double-blind studies. We've designed a set of studies that allows us to understand the efficacy of tafenoquine given that there is no biomarker of hypnozoite carriage and therefore a chloroquine-only arm is essential for understanding the true efficacy of our drug.

Patients in all groups were treated with chloroquine for 3 days to eradicate the blood stage infection. In addition, we have added a standard

of care primaquine as a benchmark for non-statistical comparisons. Part 1 of study 582 was a fully powered dose-finding phase 2b study evaluating tafenoquine doses between 50 and 600 milligrams.

The pivotal efficacy and the primary focus of today's presentation are the data derived from part 2 of study 582. The design of study 564 is similar to the pivotal study, but was primarily focused on assessing clinically relevant hemoglobin declines. Although there was no placebo arm in this study, recurrence-free efficacy assessments were included as secondary endpoints.

As agreed with FDA, we designed the studies to achieve a safety database of approximately 500 patients. So let's review the rational for a 300-milligram dose, starting with a summary of tafenoquine clinical pharmacology.

Tafenoquine is slowly absorbed following oral administration with maximum concentrations reached approximately 12 to 15 hours post-dose. It should be administered with food in order to

increase systemic absorption and improve GI tolerability. The PK profile is linear up to 1,200 milligrams and the half-life is long, about 15 days, which is a key difference from primaquine.

The PK profile is not impacted by factors such as age, weight, or G6PD deficiency. And finally, it is metabolized slowly with no major circulating metabolites. Now, in part 1 of study 582, with that primaquine standard of care benchmarking arm, we looked at 4 doses of tafenoquine ranging from 50 up to 600 milligrams, compared to chloroquine alone. This determined that both 300- and 600-milligram doses met the pre-specified efficacy criteria for us in part 2.

Although no new safety concerns were identified at either of these two dosages, based on the lack of evidence of any increase in efficacy between 300 and 600 milligrams, the 300-milligram dose was selected for evaluation in the phase 3 studies.

Let's now move to pivotal study 582 part 2. We designed study 582 part 2 assuming a 90 percent

recurrence-free efficacy in the tafenoquine arm with a 30 percent treatment difference to chloroquine alone. However, a greater number of patients were to be enrolled in part 2 than would be required purely to power for efficacy in order to bolster the overall safety database. That's our original sample size with 600 patients.

However, recruitment was much slower than expected, particularly in southeast Asia. We think was due to enhanced elimination efforts in the region. In addition, both phase 3 studies were interrupted due to a global shortage of study-grade chloroquine. Therefore, we negotiated a smaller sample size with FDA, but because of the large original sample size, the study was still powered for superiority above 90 percent.

Now, focusing on the design of our pivotal study, study 582 was a multicenter, double-blind, placebo-controlled study originally designed in 2010. Randomization was center based and patients were allocated to each of the treatment groups in a 1 to 2 to 1 ratio.

A total of 522 patients were randomized into the study. The chloroquine-alone group was the primary comparator used for statistical testing. In agreement with key stakeholders, the comparison to chloroquine alone was thought to be the best design since the clinical equipoise of chloroquine plus primaquine has never been clearly established.

Since primaquine is the standard of care, this treatment group was included as a benchmark for efficacy. All patients were treated with chloroquine on days 1 to 3 to treat the blood-stage malaria infection along with their randomized treatment. Patients were then followed for 6 months with regular visits.

Any patient who experienced a recurrence during the study was provided radical cure with a primaquine-containing regimen. Patients had to have microscopically diagnosed uncomplicated P. vivax malaria, thus without mixed or severe disease at screening. They were at least 16 years of age. Patients had to have a corrected QT interval less than 450 milliseconds and a

hemoglobin concentration of at least 70 grams per liter at screening.

Additionally, because tafenoquine is an 8-aminoquinline, patients could not have a G6PD enzyme level less than 70 percent. The primary comparison in the pivotal study was recurrence-free efficacy of chloroquine alone compared to 300 milligrams tafenoquine plus chloroquine over 6 months. The primary population for all efficacy analyses was the microbiological intent to treat or mITT population.

Now, throughout this talk, the term recurrence is used more accurately to reflect our efficacy assessments. This is because parasite genotyping cannot distinguish between a true relapse of the disease from the dormant liver stage and reinfection from a second mosquito vector.

The primary endpoint was analyzed using two methodologies, a Kaplan-Meier survival analysis using Cox proportional hazards and time to recurrence as recommended by the World Health Organization in their published guidance document,

Protocol in Assessing Antimalarial Drugs.

In a categorical analysis preferred by the FDA, using logistic regression, where all patients who either have disease recurrence or an undetermined outcome are imputed as treatment failures, sometimes this is known as missing equals failure analysis.

Now, let's look at the results. The study completion rate was very high, in fact greater than 95 percent across all treatment groups. The reasons for withdrawals were also balanced, with the most common reasons being loss to follow-up or withdraw by the patient.

Demographic characteristics were well balanced across the treatment groups. The mean age was 35 years old and more males were enrolled, which represents the demography of the disease both in endemic countries and broadly in the U.S. malaria population as well.

The ethnic background of patients in the study reflected the wide geographical spread of the sites and disease. All patients had a G6PD enzyme

level above 70 percent, but of note, we evaluated patients right down to the 70 percent cut-off.

Baseline disease was similar across treatment groups, with the common malaria signs and symptoms present in the majority of patients. The majority of patients reported a previous episode of malaria and there was no difference in P. vivax counts between treatment groups.

Compliance was high in all arms of the study. Specifically, there was 100 percent compliance in the tafenoquine arm and, in this heavily supervised clinical trial setting, compliance with primaquine treatment was also high at 96 percent when assessed by pill count.

So let's first look at the survivor analysis of the primary endpoint. The study met its primary efficacy endpoint with a recurrence-free efficacy rate at 6 months of 62.4 percent in the tafenoquine group compared to 27.7 percent with chloroquine alone. Another way of looking at these data is the comparative risk, referred to as a hazard ratio, a hazard ratio of 0.299 for tafenoquine versus

chloroquine alone actually means that a patient has a 70 percent reduction in risk of recurrence if treated with tafenoquine plus chloroquine.

When we add the primaquine group, we can see very similar rates of efficacy. Thus, the risk of recurrence was also significantly reduced in the primaquine group compared with chloroquine alone. Similar results were observed using the categorical analysis. This also demonstrated that a larger proportion of patients treated with tafenoquine were recurrence free during the first 6 months compared to chloroquine alone with similar results observed in the primaquine group.

This resulted in a clinically and statistically significant reduction in risk of recurrence with tafenoquine. All other sensitivity analyses and secondary endpoints support our primary conclusions. We've undertaken a number of additional analyses throughout the clinical program better to understand why patients suffer recurrences despite being dosed with tafenoquine.

Factors we've considered include gender,

age, body mass, index, region, parasite, genotype, and exposure. Notably, though, PK/PD analyses demonstrated that an AUC above 56 microgram-hours per mL was the greatest predictor of a positive treatment outcome, with greater than 95 percent of patients in phase 3 achieving this exposure.

Given these analyses, our conclusion is that those patients on tafenoquine or primaquine who experienced a recurrence are more likely to have been re-infected, since reinfections and relapses can't be distinguished in individual patients.

Although not part of the pivotal study or primary analysis, we also looked at recurrence-free efficacy in our other key studies. As mentioned earlier, efficacy analyses for 300 milligrams in part 1 of study 582, presented here, corroborate the results of the pivotal study.

In part 1, recurrence-free efficacy at 6 months was 89.2 percent in the tafenoquine group compared to 37.5 percent in the chloroquine group. While study 564 did not evaluate chloroquine alone, which is critical for understanding the underlying

relapse rate, recurrence-free efficacy assessments were included as secondary endpoints.

Recurrence-free analyses at 6 months in study 564 also supported the results of the pivotal study, with similar efficacy rates between the two arms.

So in summary, tafenoquine is an effective treatment for the radical cure of P. vivax malaria. A 300-milligram single dose of tafenoquine co-administered with chloroquine significantly reduced the risk of P. vivax recurrence compared to chloroquine alone.

Across all studies, the recurrence-free efficacy rate in the tafenoquine groups was consistent and significantly higher than that in the chloroquine-alone group. Finally, the reduction in recurrence was numerically comparable with primaquine. Thank you.

Next, I invite Dr. Webster to the lectern to discuss safety.

Applicant Presentation – Alison Webster

DR. WEBSTER: Good morning. I'm Alison

Webster, head of clinical global health at GSK. I'm a physician with more than 25 years experiencing clinical development and have worked on this project for the last nine years.

The safety profile for the 300-milligram single dose is well characterized and similar to a 14-day course of primaquine, 15 milligrams, which is already approved for radical cure. I'll first focus on the safety from the placebo-controlled studies and then look in more detail at adverse events of special interest across various development programs.

I'll then touch on our proposed post-approval plans. Let me first review the overall safety exposures with tafenoquine. More than 4,000 subjects have been exposed to tafenoquine across various development programs, including more than 800 subjects exposed to a 300-milligram dose, 483 patients with P. vivax receiving 300 milligrams single dose in combination with chloroquine in the phase 2 and 3 studies, of whom 317 were enrolled in the placebo-controlled studies 582 part 1 and part

2.

For the purposes of this presentation, I will focus on these placebo-controlled studies in malaria patients and will present the additional safety studies that support the 300-milligram single dose.

The incidence of adverse events was similar between the treatment groups with no evidence that tafenoquine exacerbates the effects of chloroquine. It was a slightly higher incidence of serious adverse events in the tafenoquine group. There were no fatal SAEs and no adverse events led to withdrawal in any of the groups.

Adverse events leading to discontinuation of study drug were similar in the tafenoquine group and chloroquine-alone group and lower in the primaquine group. This shows the adverse events across the entire 6 months of the study. Several adverse events are more frequent in the chloroquine-only arm. These symptoms, such as headache, pyrexia, and chills are likely to be related to malaria relapse and retreatment, which

happened more frequently in the chloroquine-only arm.

To attempt to remove this potential confounding effect, we therefore also looked at AEs occurring in the first 29 days of the study before the first documented P. vivax recurrences.

Pruritis was the most common adverse event in all treatment groups. This is a well-described side effect for chloroquine. The incidence of dizziness and decreased hemoglobin were higher in the tafenoquine group compared to the chloroquine-alone group. I'll return to these later.

The majority of adverse events that led to the continuation of study drug in the tafenoquine group were evens that met the protocol, pre-defined stopping criteria for changes in hemoglobin.

The protocol defined a serious adverse event of hemoglobin decline regardless of severity or seriousness in order to ensure thorough evaluation of hemoglobin changes in the phase 3 studies in real time. Therefore, we pre-defined that any hemoglobin decrease of 30 percent or 30 grams per

liter from baseline or a decrease in absolute hemoglobin to below 60 grams per liter would be recorded as an SAE.

In reality, none of these patients experienced events that would otherwise meet the criteria for seriousness such as being life threatening or prolonging hospitalization. And all patients recovered without any intervention. Additionally, none of the hemoglobin-related adverse events reported as severe.

Decreased hemoglobin was the most common serious adverse event and the only SAE reported in more than one subject in the tafenoquine and chloroquine group. QT prolongation, a well-recognized adverse effect of chloroquine, was observed less frequently in the tafenoquine group than in the other groups.

Excluding SAEs of hemoglobin decrease, the incidence of SAEs was similar between treatment groups. Let me now turn to adverse events of special interest. There were no clinically meaningful differences between the tafenoquine

group and the chloroquine-alone group with respect to hematologic ophthalmic, psychiatric hepatobiliary, or renal and urinary adverse events.

On the right, you can see the relative risk of experiencing a particular event between the two groups. The risk of experiencing nervous system adverse events was estimated to be lower in the tafenoquine, primarily driven by the incidence of headache.

This is likely due to the increased rate of P. vivax malaria recurrence in the chloroquine-alone group as previously highlighted. I'll now go into more detail on some of these areas of interest. In the placebo-controlled studies, you'll see that the changes in hemoglobin over time are very similar between chloroquine, tafenoquine, and primaquine groups.

None of the tafenoquine-treated patients had a hemoglobin value below 70 grams per liter. We looked in some detail at the patients experiencing these protocol-defined SAEs of 30 grams per liter hemoglobin decline. While we've observed these

hemoglobin declines in G6PD-normal patients, these were not due to drug-induced hemolytic events since there was no evidence from any laboratory markers.

In fact, our data suggests that the underlying infection and subsequent rehydration could be contributing factors in most cases. Importantly, all declines resolved without intervention.

Furthermore, the hemoglobin nadir in patients who experienced a protocol-defined SAE, was in much the same range as those without an SAE, further highlighting the conservative nature of the SAE definition. Hemoglobin declined with a 300-milligram single dose was also studied in the safety study 564 and compared with primaquine. The same definition of hemoglobin decline as described previously was used in this study.

Study 584 showed no clinically relevant declines in hemoglobin. Few patients met this endpoint in either treatment group and there was no meaningful difference in the proportions between the tafenoquine and primaquine groups.

Similar to what was seen in the placebo-controlled studies, there was no evidence from other laboratory markers that these declines were due to hemolysis. No tafenoquine-treated patient had a hemoglobin below 70 grams per liter or required a blood transfusion.

The majority of hemoglobin drops in both treatment groups were less than 20 grams per liter and recovered with no clinical sequalae.

Moving to ophthalmic events, across the primary studies, there was no evidence of retinal toxicity or any corneal changes associated with vision changes for the 300-milligram tafenoquine single dose. Adverse events associated with ocular changes were infrequent and similar across the treatment groups.

All events were mild or moderate in severity and all resolved. There were no ophthalmic SAEs. All of the events had onset within the first 29 days. In addition to these evaluations in malaria patients, we conducted an assessment of ophthalmic safety in healthy volunteers using more sensitive

techniques.

We conducted study 807 in healthy volunteers to look specifically for retinal toxicity and other ocular safety parameters for the tafenoquine 300-milligram single dose. In total, 330 tafenoquine-treated subjects and 168 placebo-treated subjects were followed for 90 days for safety.

There were no changes in ophthalmic safety parameters using the very sensitive techniques of ocular coherence tomography and fundus autofluorescence. AEs related to eye disorders were actually less frequent in the tafenoquine group compared to the placebo.

Moving on now to CNS adverse events, no serious CNS events have been reported in the more than 800 individuals who have received the proposed -- the 300-milligram single dose. All CNS events were mild or moderate and resolved. Additionally, no patient withdrew from the studies or discontinued drug due to a CNS adverse event.

Let me first show the CNS adverse events

reported over the entire 6 months' follow-up from the placebo-controlled studies. The overall incidence of CNS events was higher in the chloroquine-alone group, mainly driven by headache. There was a low incidence of psychiatric adverse events, similar in all three groups.

Insomnia and anxiety were the only events reported. All were mild or moderate and all resolved. For the reasons previously mentioned, with the confounding effects associated with the chloroquine group, here I'm showing the CNS AEs just for the first 29 days.

In this period, the overall incidence of CNS events was similar across the treatment groups. The incidence of dizziness was higher in both tafenoquine and primaquine groups compared to the chloroquine-alone group and this will be reflected in proposed labeling.

As previously highlighted, insomnia and anxiety were the only psychiatric adverse events that were reported. In these malaria patients, the use of a single 300-milligram tafenoquine dose

given with chloroquine for radical cure has a low risk of CNS effects.

Across the various tafenoquine development programs comprising both studies in radical cure and in healthy volunteers, there were a limited number of psychiatric adverse events of potential concern.

Of more than 1,100 patients receiving a single dose of tafenoquine, 4 individuals experienced such a psychiatric adverse event. Importantly, all cases resolved. All received a dose of tafenoquine greater than 300 milligrams and 3 of the 4 had a history of pre-existing psychiatric disorder.

While no causal relationship can be established, given that we have observed these events, we are proposing a cautionary statement be added to the label for patients with a history of serious psychiatric disorder.

Tafenoquine is not associated with clinically significant hepatobiliary events. Transient sporadic reversible increases in liver

transaminases were observed in all clinical studies. There was a similar incidence of ALTs 3 times the upper limit of normal in all three groups. There was a low incidence of ALTs more than 5 times the upper limit of normal in any group.

A similar incidence of bilirubin elevations, more than twice the upper limit of normal, were observed across the groups. No cases of Hy's law were observed. As shown in the table, 2 patients fulfilled the laboratory criteria, but each had clear evidence of an alternative cause.

The first is a 27-year-old female diagnosed with hepatitis E on day 89, the second a 29-year-old male who reported use of concomitant herbal medicines. A thorough QT study was conducted to assess the effect on QT prolongation. 300-, 600-, and 1,200-milligram doses were compared to placebo.

There was no effect of the tafenoquine 300- or 600-milligram doses on QTc prolongation and the 1,200-milligram supratherapeutic dose fell within the safety margin set in regulatory guidance.

The maximum effect the QT interval with the 1,200-milligram dose had an upper bound for the 90 percent confidence interval of less than 10 milliseconds. In a separate drug-drug interaction study, study 491, co-administration of tafenoquine with chloroquine did not demonstrate an additional effect for tafenoquine on the QTcF interval prolongation observed for chloroquine.

Likewise, no differences were observed across the placebo-controlled studies. 2 cases of hypersensitivity were observed across the development program, both in a study of healthy volunteers. A delay in onset of the events post-treatment and the duration of symptoms were not consistent with anaphylaxis.

Importantly, both subjects recovered, having received antihistamines and steroids. Alternative explanations were not identified. Proposed labeling will also include a precaution for hypersensitivity.

The evaluation of the 300-milligram single dose provides reassuring safety data. However, we

are proposing post-approval activities that will enhance pharmacovigilance, including monitoring for CNS and hematologic events.

We're exploring a CDC collaboration for active follow-up of the U.S. patients by protocol who will be treated with tafenoquine. We also plan to conduct observational studies of real-world tafenoquine use in endemic countries and to participate in a collaboration with the WHO, MHRA, and Bill and Melinda Gates Foundation called Smart Safety Surveillance, with the aim of strengthening pharmacovigilance capabilities in low- and middle-income countries.

In summary, the safety profile for the 300-milligram single dose of tafenoquine is well characterized and similar to 15 milligrams of primaquine for 14 days, which is already approved for this indication in G6PD-normal patients.

There was no evidence that tafenoquine exacerbates the effects of chloroquine. The known risk of hemolysis in G6PD-deficient patients can be appropriately managed by mandating G6PD testing in

the proposed label. As expected, in G6PD-normal patients, there were no clinical hemolytic events.

The observed hemoglobin declines recovered without intervention. There was no evidence of retinal toxicity. Furthermore, with the 300-milligram single dose, CNS side effects have been mild to moderate and resolved.

Thank you. Dr. Price will conclude with a benefit-risk assessment.

Applicant Presentation – Richard Price

DR. PRICE: Thank you, Dr. Webster.

Good morning, everyone. My name is Rick Price. I'm professor of global health at the Menzies School of Health Research in Australia and professor of travel medicine at the University of Oxford in U.K. I'm an infectious diseases physician and a clinical researcher with a program primarily focused on the epidemiology and management of plasmodium vivax.

I'm not paid by the pharmaceutical industry and declare no conflict of interest except for the reimbursement of my travel costs. I'm here because

I believe that tafenoquine represents a huge advance in malaria therapeutics, both within the United States and the global community. Let me tell you why.

Dr. Baird highlighted the main challenge in treating plasmodium vivax. It's the parasite's ability to form hypnozoites in the liver, coupled with our inability to provide an effective and reliable radical cure of vivax malaria.

In areas with high relapse periodicity, patients have recurrent bouts of malaria every 3 to 4 weeks, sometimes extending for months and even years. Each episode of malaria is associated with hemolysis and frequent relapses can thus rule out result in a cumulative risk of severe anemia.

Now, severe anemia is associated with both direct and indirect morbidity and mortality. The more malaria episodes you have, the greater the incident density of the disease. And as you can see from this figure derived from Papua, Indonesia, patients dying had a much greater instance of malaria compared to those surviving. And most of

those episodes were due to vivax malaria, represented here by the green bars.

Clinical trials generally quantify the risk of the first occurrence and they're so likely to underestimate the main benefit of radical cure, which is its reduction of multiple episodes of malaria, hence killing hypnozoites effectively, particularly in low-resource settings, can potentially reduce both morbidity and mortality.

Since the 1950s, we have relied on primaquine for the radical cure of plasmodium vivax. And this quote is taken from 1963, when there was a huge enthusiasm for the arrival of the drug, recommending intensive research, develop safe and effective radical cure with a single or 3-day regimen.

However, progress with primaquine has been appallingly slow and we are a long way off that goal. After 55 years, we still don't know the optimal dosing regimen. In areas where G6PD testing is unavailable, clinicians are reluctant to prescribe primaquine, prioritizing the treatment of

acute symptoms rather than preventing subsequent infections.

Perhaps the greatest challenge is that patients are unlikely to complete a prolonged course of treatment, especially when their acute symptoms resolve rapidly. The WHO and CDC currently recommend a 14-day course of primaquine. Now, the efficacy of this regimen depends on the total dose ingested by the patient.

Several studies have explored the effect of endurance, total dose, and treatment efficacy, and here's a recent example from Ethiopia. In this clinical trial, treatment was partly supervised and, yet, despite supervision, almost a third of patients had an incomplete course. An incomplete course was associated with 20 percent lower efficacy.

In the patients with unsupervised treatment, the efficacy was even worse. Dr. Green showed us the results of the tafenoquine versus primaquine randomized trials and tafenoquine has a very similar efficacy to a standard supervised 14-day

course of primaquine.

Interestingly, in study 582 part 2, adherence to 14 days' primaquine was greater than 90 percent, much higher than I would have expected, a likely reflection of the intense study environment and these carefully conducted GCP phase 3 trials. In my opinion, the true effectiveness of chloroquine plus primaquine would be much lower, whereas for a single-dose regimen, the observed efficacy will differ very little if at all from that in reality.

So the clinical efficacy of primaquine in the trials presented by Dr. Green represents the best-case scenario. True effectiveness studies are incredibly difficult to undertake, mainly due to reaction bias when patients are being observed. Now, we tried to explore effectiveness in Papua, Indonesia and, over a 10-year period, gathered data routinely collected for more than a million patients. 46,000 patients were treated with an unsupervised 14-day course of primaquine.

You can see from the figure that both low-

and high-dose primaquine regimens had very similar risk of recurrence compared to those patients who were treated without primaquine. In multivariable analysis, the effectiveness of primaquine in this real-world setting was at best just 10 percent. Now, that's appalling.

Would the effectiveness of a 14-day regimen be better in the United States, United Kingdom, or Australia? Maybe with appropriate patient education, but probably not a lot better. We don't have reliable data on primaquine adherence in the United States, but as a guide, only half of patients prescribed a 7-day course of antibiotics actually complete their treatment.

So adherence to a 14-day antimicrobial regimen is likely to be poor even in the United States. Dr. Webster has presented the safety profile of tafenoquine. It's excellent and very similar to that of primaquine.

Now, it's worth noting the huge experience we have with primaquine. Over 36 million individuals have been exposed. The predominant

reported symptoms are gastrointestinal and can be alleviated by taking tablets and with food.

In a comprehensive WHO report, 219 SAEs were identified and almost all were due to severe hemolysis. Importantly, there were no hemolytic SAEs in patients known to be G6PD normal.

There's been one report of a neuropsychiatric SAE in a 55-year-old man in the United States with malaria, treated with chloroquine and primaquine. And he developed depression and psychosis after the second dose of primaquine, but it resolved within 24 hours on stopping both drugs.

Other adverse events are very hard to attribute confidently to either primaquine, the disease, or concomitant medications. Symptoms such as headache and dizziness are very commonly seen in patients with malaria. There have been 14 days associated with primaquine use, again almost all related to severe hemolysis.

Reassuringly, the overall mortality associated with primaquine is very low. So in

summary, the post-marketing surveillance of primaquine, a drug very similar to tafenoquine, is extremely reassuring. For both tafenoquine and primaquine, the predominant concern remains that of drug-induced hemolysis.

But this can be avoided by excluding patients with G6PD deficiency. In G6PD-normal individuals, the benefits of radical cure far outweigh the risks since malaria's an intraerythrocytic infection and causes significant hemolysis even in the absence of an 8-aminoquinline.

This recent large pooled analysis highlights that primaquine is associated with a small non-significant greater drop in hemoglobin at day 3. However, crucially, it prevents relapses and thus a further bout of parasite-induced hemolysis. Hence, patients treated with radical cure actually have a significantly faster hemoglobin recovery and a higher hemoglobin at day 42.

So in summary, radical cure is essential for the control and ultimate elimination of vivax

malaria. In low-resource settings, I am convinced that radical cure has the potential to reduce direct and indirect morbidity and mortality, but we will need a large clinical trial to prove that.

The adverse effects of both primaquine and tafenoquine are well identified and manageable. In reality, the current WHO strategy for the radical cure of vivax malaria is broken. We have to find a way to fix it and we are looking at a number of options, shortening the course, text reminders, media campaigns, education, et cetera. You know how difficult it is.

But the arrival of tafenoquine provides a very welcome alternative both within the United States and globally. The ability to provide radical cure with a single dose of tafenoquine is a phenomenal achievement and, in my opinion, represents one of the most significant advances in malaria therapeutics in the last 60 years, so thank you.

I'll now invite Dr. Webster back to the lectern to take your questions.

Clarifying Questions

DR. BADEN: I would like to thank the applicant for a whirlwind of data in an hour. That is fabulous and greatly appreciated.

What I'll ask of the committee is, can committee members indicate to myself and Ms. Bhatt if you have questions? As we've done in prior meetings, what I'll try to do is ask follow-on questions to a theme so we're not jumping between themes, so that if you have a follow-on question to a particular theme, let me know as well and we'll try to build on a theme while I manage the time so we can get through as many questions as possible.

We have a little over a half an hour. If we can't get through all the clarifying issues at this time, we'll resume clarification discussion after the agency's presentation.

What I'd like to also just clarify is, when you do ask a question, state your name for the record and direct the question to a specific presenter. We already have many questions on the list. I will start with the first question. All

right. And I have a question about efficacy, Dr. Webster.

This comes from in part the presentation of Dr. Baird, where they were able to distinguish on slide CO-18 relapse from reinfection, yet in your studies, you were unable to do this. Can you help me understand why certain investigations are able to do this and others are not, as that's obviously an important question of efficacy?

DR. WEBSTER: I think the clarification is that, on an individual patient basis, it's not possible to identify an individual recurrent episode as to whether it is a relapse or reinfection on the basis of genotyping, but perhaps I could invite Dr. Baird to speak about his analysis of the data.

DR. BADEN: Because it looks like, in the Thai-Myanmar and the Papua New Guinea data, they were able to do that.

DR. BAIRD: Thank you. I'm Kevin Baird. I'm with the Oxford Clinical Research Unit in Jakarta, Indonesia. The answer to the question is

as Dr. Webster alluded and this is the difference between being able to ascertain the source of an infection in an individual patient versus in a population.

So what Dr. Green explained is completely accurate. We cannot know in any individual study subject whether the recurrence that they're experiencing has come from the liver or from a fresh mosquito bite. We can't know that. In this particular study that's up on the screen right now, what the investigators did very simply was to randomize cohorts to treatment.

They could then ascertain at a population level what the infection pressure from hypnozoites appeared to be. And it's very simply the difference between the blue lines and the red lines that you see here.

DR. BADEN: Thank you. Dr. Moore?

DR. MOORE: Pardon me. I actually have three questions, all very brief. Just a quick question -- how do you pronounce the trade name that we're going to be using?

DR. WEBSTER: Krintafel.

DR. TAN: Krintafel, thank you. I've tried to look for the dates of the clinical trials that we were discussing. I mean, tafenoquine has been around for a very long time, but I apologize. Perhaps I overlooked it. Would somebody be able to provide the dates that the clinical trials were executed, the 582 and 564?

DR. WEBSTER: Could I ask Dr. Green to confirm the exact dates? Thank you.

DR. GREEN: Justin Green, clinical. Yes. So part 1 of study 582 was conducted in approximately 2012 and took us about 12 months to recruit those subjects. And then studies 582 part 2 and study 564 were run concurrently between about 2015 and about in May 2017. Thank you.

DR. MOORE: Thank you. And then one last question regarding safety, Dr. Webster; the issue really for tafenoquine as I understand it in my mind, anyway, has been the Australian defense forces have been using tafenoquine for weekly prophylaxis for quite some time.

It seems to have been a very safe drug with the exception of some issues with psychiatric events. I know those data were not presented today, but it's on my mind about the question of whether these soldiers had PTSD versus tafenoquine-associated problems.

I just want to say thank you for presenting the data. The psychiatric safety data were somewhat reassuring, but just to be clear, the three individuals that were discussed, that were mentioned had psychiatric problems with tafenoquine. Did I understand that correctly that they did have underlying psychiatric illness or not?

DR. WEBSTER: The 4 subjects that I presented here -- 3 of them had pre-existing psychiatric conditions. 1 did not, which was a mild episode of depressed mood.

DR. MOORE: Thank you.

DR. BADEN: If no follow-on, then Dr. Clark?

DR. CLARK: This may be a question for Dr. Green. I had a question about diagnosis. Were

only blood smears done for diagnosis? Or were there any more sensitive tests done? And how often were they performed?

DR. WEBSTER: Dr. Green, could you respond? Thank you.

DR. GREEN: Justin Green, clinical. Yes. So we used slide read. We did a large amount for our slide readers in our endemic sites before they were allowed to do slide read, both too thick and a thin film. We had two independent readers and a third reader if there was an inconsistency between those. We also had a significant amount of quality assurance with an external slide read done on a percentage of those slides.

We did not use other sensitive techniques during the study. We did, as you know, use some parasite genotyping subsequent to the study and we also have a collaboration with Sanger in Cambridge looking at parasite genotyping in a more academic way.

DR. CLARK: Were there routine smears done or was this for symptoms? Or how did --

DR. GREEN: Thank you, yeah, sorry, your second question. So there was fairly intense follow-up within the first month of our subjects being in the study, initially 3 days as an inpatient or in a clinic, and then 3 visits in the first two weeks, weekly visits, and then monthly scheduled visits the whole way out to 6 months.

Irrespective of symptoms, they would have a smear done at that point. Independent of that, unscheduled visits would occur. The subjects were counseled if they got any symptoms of recurrent malaria, principally fever and headache. They would come back to the clinic and part of that work-up would be an additional smear.

DR. CLARK: Thank you.

DR. BADEN: Dr. Follmann?

DR. FOLLMAN: Thank you. I have questions about the proposed post-marketing studies. So three questions -- one is how many individuals in the U.S. have P. vivax infection that are treated. And could you hazard a guess as to how many that you would enroll in this study? And then also, are

you planning on looking at just tafenoquine alone or are you also planning to look at people who are treated with primaquine to provide a kind of comparison for the psychiatric and safety issues you've mentioned?

DR. WEBSTER: So to answer your first question, based on the efficacy we have, we anticipate around 200 subjects annually in the U.S. with P. vivax malaria. And I'd like to ask Dr. Hardaker to explain to you all post-marketing plans.

DR. HARDAKER: Dr. Liz Hardaker, clinical safety at GSK. So we've committed to a post-registration safety surveillance study in the U.S. We propose to use an active surveillance model, so we will follow up every tafenoquine-exposed patient. We're exploring collaboration with the CDC and we'll monitor patients throughout the reporting period annually and then after a 5-year period.

Beyond the U.S., we are going to do some implementation studies, so we're going to do a

stepwise introduction into low-, middle-income countries, where there's a higher disease burden, but less pharmacovigilance infrastructure. And in those studies, there will be some comparison with primaquine.

We will say proposed beyond those studies to do active surveillance, using some specialist slides that we'll have routinely follow up all patients. So we'll have both a numerator for events and also a denominator so that we can study the rates of events.

DR. BADEN: Dr. Follman, did you say you had three questions?

DR. FOLLMAN: Well, I thought I asked them. One was how many are in the U.S.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: Just specifically about the hypersensitivity, what was the denominator for those two patients? Was it just the ones that had the malaria or was this the, like, 4,000 exposed patients, for instance?

DR. WEBSTER: These are two cases of

hypersensitivity throughout the entire safety database.

DR. BADEN: Thank you. Dr. Weina?

DR. WEINA: I'm trying to ascertain the issue of compliance because, of course, tafenoquine has this real advantage over primaquine, but you had unusually high compliance in 582 part 2. Was that because of directly observed therapy or just based on pill count?

DR. WEBSTER: Dr. Green, could you respond, please?

DR. GREEN: We did not use directly-observed therapy in any of our treatment studies. What we did was, we enhanced the ability of sites with the principal investigator to help individual subjects or patients in the trials with compliance.

So as I spoke to Dr. Clark earlier on, there were visits after the three days of inpatient when there was delivery of the medicine in front of the patient, visits at day 5, 8, 10, and 14 on those days and in some cases in between days. There would be reminders dependent on what the local site

wanted to do.

So there was a very heavy kind of resource used to get that level of compliance. We assessed by pill count on each visit, but we just presented the final pill count for you.

DR. GRIPSHOVER: Just a quick follow-up on that -- so was that different from part 1 and part 2?

I think you said, part 1, that part of why the primaquine arm didn't look as good was because of the adherence. So did you specifically add those extra when you went to part 2 of the study?

DR. WEBSTER: Yes, we did.

DR. BADEN: Ms. Orza?

DR. ORZA: Dr. Orza. My question got asked and answered by someone else. Thank you.

DR. BADEN: Thank you. Dr. Gripshover?

DR. GRIPSHOVER: I have one more question about the hypersensitivity. So because the drug has such a long half-life, it looks like 10 weeks or more, how long were those patients required to be treated with steroids and antihistamines?

DR. WEBSTER: Just to clarify, the drug has a half-life of approximately 15 days.

DR. GRIPSHOVER: But there's one side that looks like you have levels up to 10 weeks. Right?

DR. WEBSTER: The drug will be detectable for several half-lives, yes. No, the patients responded in the anticipated time frame, rapidly, to steroids and antihistamines.

DR. BADEN: I guess the question is, did they have a day of treatment or did they require steroid antihistamines for weeks if I understand the question correctly?

DR. GRIPSHOVER: Because it's still around, you know.

DR. BADEN: How long did they require the supportive care?

DR. WEBSTER: Dr. Green, could you answer that, please?

DR. GREEN: Justin Green, clinical. So both subjects attended the ER, were diagnosed with the hypersensitivity. We treated with oral steroids and antihistamines for about 7 days or less.

DR. BADEN: Thank you. Mr. Mailman?

MR. MAILMAN: Yes. Josh Mailman. This is for Dr. Price on slide 71. You had one of the reasons that, 55 years later, clinicians are reluctant to describe PQ is because of the testing for G6PD. Since this is still a requirement in this drug, how does that change or what percentage of you think this not being a radical cure 55 years later is for that?

DR. WEBSTER: Before asking Dr. Price to respond, could I just clarify that we do have an effort to produce high-quality point of care diagnostic tests for G6PD deficiency in endemic countries, which will be available at the time that tafenoquine is used in endemic countries, but could I just ask, then, Dr. Price, to response to your question?

DR. PRICE: Thank you. Dr. Price from Oxford. It's a very good question and I'm referring to endemic environment. I work with 17 malaria endemic countries and the reality is that G6PD deficiency kits are often not available.

There is a lot of anxiety and the reality is that, even though this is national policy on the ground, in the clinic, patients don't see that necessity. They don't see the benefits and the patients don't see the benefits because it's future events. So if you're frightened of treating because you can't rule on G6PD deficiency, the easiest thing is not to give it.

DR. BADEN: I think Dr. Tan had a follow-on or a different line of questioning.

DR. TAN: It's a different question.

DR. BADEN: Okay. Then Dr. Weina has a follow-on.

DR. WEINA: We all know what happens in clinical trials that is not necessarily reflected in the reality once something gets out on the street. And speaking about this fear, there are going to be people who are going to prescribe tafenoquine even in individuals who may be G6PD deficient because they've never been tested. What type of labeling would you suggest as a recourse for somebody who does that?

DR. WEBSTER: We will be contraindicating in G6PD deficiency, so we're not anticipating use in G6PD-deficient patients.

DR. BADEN: I guess there are two sides to that. One is if they know they're G6PD, another if their G6PD status is unknown. And so would it then be contraindicated in an unknown G6PD status?

DR. WEBSTER: Yes, because we would mandate that patients are tested for G6PD deficiency before prescribing.

DR. BADEN: Thank you. Dr. Beyrer?

DR. BEYRER: Thanks. I think this is a question for Dr. Green, just really the issue of the slow accrual in the 582 trial, if you can speak to that, and if you think that, that had any bearing on study outcomes. It was variable at the sites as well.

I'd also be interested to know if it varied much by the sites, seeing as it was a multi-site trial, multi-country trial. So the question is about the slow accrual in the 582 trial that was eluded to on one of the slides, actually number 28,

but not really explained in detail, so I want to know more about the slow accrual.

DR. GREEN: Justin Green, clinical. So we had a number of sites, 13 sites in overall, but 8 sites in that particular study. And we found, particularly in southeast Asia, that we had slower recruitment than we anticipated, given a relatively embedded clinical trial infrastructure with the principal investigators that we used in Cambodia and Thailand in particular, but also in the Philippines.

We believe that there has been quite substantial efforts on malaria elimination, particularly in those middle-income countries. Additionally, because of the efforts because of ACT resistance in Cambodia, there's also increased resources looking at treatment of all malarias.

So we believe that, along with the stochastic seasonality of malaria, which is that some years you get more and some years you get less, particularly that was an issue for recruitment in southeast Asia, although we did

still get over 20 percent of our subjects from that region. The principal recruitment was actually from Latin America, where we actually had less issues in terms of recruitment within hollow endemic areas within the Amazon. Thank you.

DR. BADEN: A follow-on? Presumably, any redesign in the study occurred fully blinded to treatment allocation to outcome. Correct?

DR. WEBSTER: I'm sorry. Could you --

DR. BADEN: Yes. The study design was 600 and you wound up enrolling less. My inference -- but I just want affirmation -- is that was done fully blind.

DR. WEBSTER: Yes. It was.

DR. BADEN: It was done based upon the accrual issues and then statistical reassessment?

DR. WEBSTER: Yes. And it was done in discussion with the FDA.

DR. BADEN: Thank you. Follow-on, Dr. Green?

DR. GREEN: Mike Green. This is a follow-on not to your question, but the one before, which was

trying to get a sense if the accrual was variable between centers. And I guess the inference would be if it was different in one versus the other and not part of the original design, was efficacy different between geographic areas.

So I wonder if you did any internal analyses to determine whether there was site-to-site variability and response.

DR. WEBSTER: We did look at efficacy by region and consistently showed benefit for tafenoquine versus chloroquine, consistently across all of the regions.

DR. BADEN: Presumably no center effects?

DR. WEBSTER: Could I ask Dr. Rolfe to respond to that, please?

DR. ROLFE: Hi. I'm Katie Rolfe from statistics at GlaxoSmithKline. We didn't look at center effects. Some of the centers were very small, hence us grouping centers by region when we did our analysis.

DR. BADEN: Dr. Tan?

DR. TAN: So this question is probably

directed towards Dr. Green. I'm thinking one way that the U.S. population may differ from the study population is BMI and weight. It is not unusual for us to see primaquine in those greater than 70 kilograms.

So I'm curious if, in your study population, you had anyone on that higher weight range. And I know this isn't quite fair because I don't think you presented this data, but I am curious about the efficacy on the upper weight limit.

DR. WEBSTER: I can share with you the exposure data by BMI.

You can see that the exposures are very comparable between those with BMIs above and below 30. And you can see on the right-hand side of the graph this actually includes all of our data across the healthy volunteer studies, which would include more than 400 subjects in the U.S. That does cover a wide range of BMIs and showing that 300-milligram dose achieves the exposures that we target for 56.4 microgram-hours per mL.

DR. BADEN: If you can leave that slide up,

just a follow-on, presumably post hoc you determined the 56.4 threshold. Are any factors identifiable as to who fell under that threshold that might inform future use?

DR. WEBSTER: Well, just to clarify, that exposure threshold was identified from an analysis of the dose response in phase 2. Could I ask Dr. Goyal to respond to your second question?

DR. GOYAL: Navin Goyal, clinical pharmacology at GSK. So yes. As Dr. Webster mentioned, we looked at multiple factors and exposure was the only one which showed to be a significant predictor of efficacy.

DR. BADEN: But were there any factors that predicted the exposure falling below the presumed efficacious threshold?

DR. GOYAL: No. None of them did that. Thank you.

DR. BADEN: I will ask a follow-on question of my own on efficacy. If I understand it correctly and I think it was already commented on that a single dose of tafenoquine had detectible

levels out to 10 weeks. Then, one might infer the differential exposure in the primaquine group and the tafenoquine group in terms of period at risk without drug on board and so the primaquine group presumably has drug on board through 2 to 3 weeks while the tafenoquine group has drug on board through 10 or more weeks.

So therefore, is it comparable time frame or period at risk between the two groups that you're comparing in terms of relapse and how do you deal with that?

DR. WEBSTER: Dr. Green, would you like to respond to that?

DR. GREEN: Justin Green, clinical. So it's true that the tafenoquine will be on board for longer than the primaquine. Even the carboxy-primaquine metabolite is not long lasting.

But we think that the activity of tafenoquine is against the hypnozoites. We do not have data as to its ability, for example, to stop a blood stage infection or sporozoite challenge at the 300-milligram dose, so we don't have that

information and we feel that the activity that we're seeing is actually related to its anti-hypnozoite activity alone.

DR. BADEN: So you think the activity is exclusively to the hypnozoite, not to the other forms?

DR. GREEN: We believe, at this dose, that that's probably the correct assumption. Higher doses have been shown to be prophylactic against multiple malaria parasites, but we don't know, for example, with this dose, what the prophylactic activity would be

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

DR. WEINA: Any concerns about the development of resistance at that low level based upon the fact that reinfection can take place and you have low levels kind of hanging around for a long time? Have you looked at laboratory studies trying to induce resistance or anything, detected any resistance?

DR. WEBSTER: In this use, where we're

giving tafenoquine for radical cure, we're obviously looking at the effect on the hypnozoite. We know that there are relatively small numbers of parasites present in the liver, so those are not the typical circumstances with parasite forms that are not actively replicating, where you would tend to see resistance emerge.

But when given for radical cure for any blood-stage parasites, chloroquine is also being administered, so there is dual therapy for the blood stages. We haven't done --

DR. WEINA: So the answer is no.

DR. WEBSTER: We haven't done any specific studies to look for resistance.

DR. WEINA: Thank you.

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

DR. GREEN: This would be really a follow-on to the previous question. So I'm going to presume you don't have any data about longitudinal efficacy, so this is a treatment trial. They get treated for their sentinel event and, if they got

recurrences, I presume they were treated with standard therapy, so they got primaquine plus chloroquine, so we don't know whether this drug will work with your next episode of infection or the episode after that.

Again, the concern with the long low levels in blood and the potential impact on the blood phase parasite at the time of infection for selecting resistance and the ongoing circulation of that potentially in the population.

DR. WEBSTER: So in this clinical program, yes, we looked for the first incidence, the first recurrent episode and anyone who subsequently relapsed would be treated with standard of care. So we haven't studied redosing with tafenoquine. But we do know that relapses following tafenoquine are very unusual, within two months of dosing, by which time levels would be less than 10 percent of the cmax achieved on the initial dose.

DR. BADEN: Ms. Orza, a follow-on question?

DR. ORZA: Yes, Michele Orza. I had two questions, part of which already got answered. The

first was whether you have -- because you said that relapses can occur even years later, whether you have any data on any of the patients beyond the 6 months in terms of a relapse.

Then the other question was about whether you have any data on people who have been treated multiple times with tafenoquine for perhaps reinfection if it's endemic in these areas.

DR. WEBSTER: No, we haven't. To answer your first question, no, we don't have any information on patients after 6 months. I think we acknowledge that 6 months is already quite a long period of time to keep patients in a clinical trial when they're fit and well and going about their daily business. So we thought that was realistically the longest we could follow subjects for.

Just to reiterate, no, we don't have any information on retreating patients for a further episode of vivax malaria for radical cure.

DR. BADEN: Follow-on, Dr. Kartsonis?

DR. KARTSONIS: Yes. The question I had is,

do you have any data with regard to administering the tafenoquine beyond the 3-day period where chloroquine is administered? I'm trying to think about it in a real-world situation. If somebody couldn't get this, could they administer it a little later, especially since the effect is more on the hypnozoite phase?

DR. WEBSTER: No, we don't have any data. Within the clinical trials, they could be treated on the first or second day of chloroquine therapy. I think, logically, would they expect it still to work? But we don't have any information.

DR. BADEN: In your study design, you were anticipating 90 percent efficacy. You saw 70 percent efficacy. Why do you think there is that decrement and why is it only 70 percent effective? Any hints? Is it all reinfection?

DR. WEBSTER: In a nutshell, that's our assumption. Yes.

DR. BADEN: Dr. Zito?

DR. ZITO: Yes. I'm just wondering about if a clinical trial beyond 6 months is not very

feasible, what will be accomplished by the post-marketing surveillance 5-year study?

DR. WEBSTER: Could I ask Dr. Hardaker to clarify our plans for post-marketing?

DR. HARDAKER: Dr. Liz Hardaker, clinical safety. I wonder if I could just ask you to re-ask the question. I didn't quite follow it. Yeah. I didn't quite follow the question. I wonder if you could repeat it for me.

DR. BADEN: Please use the microphone.

DR. ZITO: Yes. I was just thinking more broadly, if length of clinical trials beyond 6 months is not feasible, what will be accomplished by a 5-year post-marketing surveillance study?

DR. HARDAKER: In the U.S., we plan to follow for 5 years. That's the commitment that we have undertaken. However, in the endemic countries, we were establishing some active surveillance centers who will be specialist pharmacovigilance sites.

Although we planned to do early and delayed follow-up, these sites I guess would also be seeing

the same patients again and I think would be able to monitor for that.

DR. BADEN: Thank you. Yes, Dr. Honegger?

DR. HONEGGER: I have three questions, actually not very related. The first one is about the post-marketing or maybe labeling recommendations for monitoring patients who receive the study drug in terms of hemoglobin specifically. Is there going to be a specific recommendation for frequency or timing of hemoglobin monitoring?

The second question is about resistance.

DR. BADEN: If the three questions are not directly linked, you probably should do one and answer it.

DR. HONEGGER: I'll stop.

DR. WEBSTER: Dr. Hardaker, could you respond to that, please?

DR. HARDAKER: So could you repeat the question?

DR. HONEGGER: Do you anticipate specific guidance on when physicians should monitor the hemoglobin in patients who receive the study drug?

DR. HARDAKER: We are not anticipating hemolysis. We're using the 70 percent threshold, so the label will recommend the 70 percent threshold, which we've seen in our studies and have proved to be reliable. But obviously, if clinicians do experience hemolysis despite using that threshold, then we hopefully will be able to detect that through routine pharmacovigilance and obviously follow up to monitor to understand how that serves them.

DR. BADEN: Is your question more along the hemoglobin decline that was seen and what type of monitoring on therapy would the hemoglobin decline that was observed should clinicians be aware of assuming they were all G6PD competent?

DR. HONEGGER: Yes.

DR. HARDAKER: The patients were entirely asymptomatic and none of the patients needed any intervention. So even if there is a decline, we don't anticipate the patients needing any further support, but were situations to arise where that was the case, we would hope to pick that up in

pharmacovigilance. But we're not recommending hemoglobin monitoring.

DR. HONEGGER: Thank you. In terms of resistance, is it correct that this class of drugs generally has not been shown to induce resistance in vivax?

DR. WEBSTER: Most of the studies around resistance are in blood stage infections and we know that tafenoquine is not cross-resistant with chloroquine against P. falciparum blood stages, for example, but clearly monitoring for resistance in the hypnozoite is very challenging, not possible to do in vitro or in vivo, but using primaquine as by analogy, there really is no clear evidence of primaquine resistance after 60 years of use.

DR. HONEGGER: Thank you. My last question, I think I know what you're going to say, but in terms of the use of a placebo arm for this when there is already a standard of care where you use primaquine, can you just talk a little bit about the thought behind that and the ethics of the decision to use a placebo?

DR. WEBSTER: Yes. We believe the use of a placebo was the most robust way of clearly demonstrating efficacy in radical cure. And therefore, it was essential to use placebo in the clinical trials. We did consider doing a noninferiority study, but even in those circumstances, we believe that a chloroquine-alone arm would have been important. We discussed the study design with key external partners who agreed that this was the appropriate way forward. And the studies were approved by all the appropriate ethical ethics committees.

I know this is something that Dr. Price has actually considered in the past as well, so I'd like to invite him to comment.

DR. PRICE: Thank you. Dr. Price, Oxford University. It's an excellent question and one that we should always be very wary of. One of the challenges of determining efficacy is the background relapse pattern which vary from location to location.

So without a placebo arm, it's extremely

difficult to show the overall efficacy. If you didn't have a placebo arm, you could actually have noninferiority of two products which were equally useless. And that has been shown in the past. We have repeatedly put this through ethics and done a large multicenter clinical trial enrolling 3,000 patients and we passed that through American ethics, through Oxford ethics, through Australian ethics, and through ethics in seven countries.

So I can go on talking. We're also published on the ethics of this and I think it's entirely appropriate that it was a placebo arm.

DR. BADEN: But I think, if I understand your question, Dr. Honegger, specifically withholding -- I understand the scientific value, the statistical value, but in the group of patients who had primaquine withheld, what is the justification?

DR. PRICE: Two justifications; the justification firstly is that several countries where we're working, actually primaquine isn't part of policy, so therefore it's not ethically

challenging. In those places where it is part of policy, you are closely monitoring people. You're not actually declining or withholding it. It's withheld temporarily because people will be treated at the end of their treatment course and also they will be extremely closely monitored during that period.

It's also unethical to bring people into a clinical trial if you can't make the appropriate conclusions at the end of that.

DR. BADEN: Thank you. Dr. Green, did you have a follow-on? Ms. Orza, a follow-on?

DR. ORZA: Michele Orza. About the decision not to power for noninferiority, could you speak to that?

DR. WEBSTER: So there were a number of issues in designing a noninferiority study and one was our uncertainty about establishing appropriate recurrence rates for a primaquine control arm, which varies from site to site, and there is not reliable data in order to make the appropriate estimate for efficacy against which to compare.

Then the second reason is, it would clearly have increased the sample size, which would have exceeded the feasibility for us to actually conduct those studies in terms of the number of clinical trial sites that are in malaria endemic regions that have the capability to conduct studies to the appropriate standards for a phase 3 study.

DR. ORZA: How many more patients would it have required?

DR. WEBSTER: I can show you a sample size estimation here that was based on an assumption for 80 percent efficacy. With an equal 1:1 randomization, it's just under 700 subjects. With an unequal 2:1, it's above 700 and then, including a chloroquine comparison arm as well, we estimated more than 1,000 subjects, which would have been exceedingly difficult for us to enroll.

DR. BADEN: Dr. Clark?

DR. CLARK: Thanks. In thinking about potential reasons for tafenoquine other than reinfection, I'm not sure if it's known whether severity of disease could affect the liver stage

and the burden of organisms. It seemed that most patients in these studies had malaria before and were maybe partially immune and then, in thinking about the U.S. population, where that may not be the case, I was just wondering whether there could be a difference in efficacy based on that.

DR. WEBSTER: I think that's a very sensible suggestion in the hypnozoite burden within the liver, may actually be a factor, but unfortunately, it's not anything that we can study, but logically, with a lower hypnozoite burden, then perhaps we would expect an efficacy rate that was closer to 90 percent rather than the 70 percent we observed.

DR. CLARK: It seemed like, from the symptom list, many of these infections were not severe. Was it looked at in terms of the advocacy in the more severe infections if there were. Was there a significant population there?

DR. WEBSTER: Patients with severe malaria, i.e. fulfilling the WHO criteria for severe, were excluded from the study because they would have required parenteral treatment. I could perhaps

just ask Dr. Green what we know about parasite counts at study entry.

DR. GREEN: Justin Green, clinical. Yes, sir. Actually, in part 1 of study 582, we stratified individuals by a parasite count of based on at 7,500. We saw absolutely no difference in efficacy of the drug between those two groups, so we actually dropped that. That was something in the literature. We don't believe that parasite count at baseline, which is based on blood stage infection, has any bearing on your hypnozoite burden, which is related to the number of times that you've been bitten by an infected mosquito.

DR. BADEN: Along the lines of your inclusion of parasite count, I think your upper limit of 100,000 and I was curious as to why there was a ceiling for inclusion.

DR. GREEN: Yes. Justin Green again. So we have that just purely because that then fulfills the WHO criteria of severe malaria, but in actual fact, in vivax malaria, the parasite counts, because it's an infection of very young red blood

cells, is often much lower than that. The median parasite count is about 5,000.

We actually saw nobody with a parasite count above 80,000. Thank you.

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

DR. GREEN: Yes. This is a follow-on to both of the last two questions. Given that your study really excluded people with severe malaria, I would imply from that, that the proposed labeling would only be for not severe malaria due to this vivax. Is that correct?

DR. WEBSTER: The indication will be for treatment, for radical cure, so prevention of relapse when given with the appropriate treatment for the acute infection.

DR. BADEN: Dr. Orza, did you have a follow-on question? And I apologize for my incorrect moniker earlier. I was given incorrect information.

DR. ORZA: It's not a follow-on. Is that okay?

DR. BADEN: A new direction? You're on now.

DR. ORZA: It's a question about real-world use outside the U.S. and whether the people who we're concerned about their ability to adhere to the regimen for the PQ would also be people we would be concerned about if they had, because of the long half-life of the TQ, people who we would be concerned about having an adverse event in day 7 through 14 and their ability to get that seen to.

DR. WEBSTER: Could I ask Dr. Hardaker to comment on our risk management plan?

DR. HARDAKER: Yes. It's Dr. Liz Hardaker, clinical safety. So we are very aware that, in the low- and middle-income countries that carry the highest burden for malaria, there is a challenge in terms of pharmacovigilance and therefore we are developing a strategy in collaboration with the national regulatory agencies and the national malaria control programs to develop pharmacovigilance hotspots where we will be following both early and late events, so they'll be followed up at key time points.

We're also working in collaboration with the WHO, and the Bill and Melinda Gates Foundation, and the MHRA to use tafenoquine actually as an example along with two other products to develop effective strategies for pharmacovigilance in these countries. So we will be doing everything that we can.

DR. WEBSTER: Perhaps also, just to add, irrespective of the half-life, tafenoquine with the long half-life, primaquine with a short half-life, we have actually seen very similar safety profile to primaquine in our phase 3 clinical program, so we're not anticipating that there are going to be excessive adverse events.

DR. BADEN: Thank you. Dr. Green, you had an additional question?

DR. GREEN: Yes, just very quickly. Can you let us know if there are either in place or plans for a pediatric evaluation of this product for this indication?

DR. WEBSTER: Yes, I can confirm that we do have a pediatric development plan. We have a study

ongoing with a pediatric-friendly dispersible formulation, which we anticipate will take us 2 years to complete. The tafenoquine is active against the hypnozoites of vivax. Any reason to believe it would not be active again, the hypnozoites will volley? Or is it purely a vivax compound?

DR. WEBSTER: We have no information.

DR. BADEN: There are some data in the literature for primaquine and certain hepatic isoenzymes that impact activity such as 2D6. Do you have any information on how that impacts tafenoquine's activity?

DR. WEBSTER: We do. I would ask Dr. Green to respond to that, please.

DR. GREEN: Thank you. We were aware of this information, which came naturally between part 1 of study 582 and we did a retrospective analysis there and found no evidence of CYP2D6, which is the one that you're referring to in terms of its effects on efficacy for tafenoquine, but like other literature reports, we found a small suggestion of

that with primaquine.

We then did prospectively look at this in study 582 part 2 and study 564, particularly in study 582 part 2, where there were more poor metabolizers of 2D6, who actually showed no effect of tafenoquine within the context and the small numbers of poor metabolizers suggested that, again, primaquine might be associated with a lower treatment outcome. And that was not what we observed with tafenoquine.

DR. BADEN: Did you observe that with the primaquine-treated --

DR. GREEN: Yes. With poor metabolizers particularly, with primaquine, the numbers were small, but it did appear that there was a greater chance of treatment failure with poor metabolizer status with 2D6, whereas with tafenoquine, we did not see that.

DR. BADEN: So if I understand the mechanism correctly, primaquine is activated or at least that's what suggested. Is tafenoquine not? Is there a different activity profile in vivo?

DR. GREEN: Yes. So we've done a number of both in vitro and in vivo. Tafenoquine is slowly metabolized. There are no major circulating metabolites and so our hypothesis would be that 2D6 for tafenoquine is unimportant in terms of its activity.

DR. BADEN: Tafenoquine was given single dose or any repeat dosing in this line of investigation?

DR. WEBSTER: So it was given as a single dose, but I just wanted to clarify, did you mean any patients needing re-dosing following --

DR. BADEN: A safety issue with tri-fluoridated compounds. There are some safety issues associated with the accumulation of fluoride and whether or not exposure to some of the other aspects of the chemistry might have side effects that you may or may not have been able to detect. And we've seen this with some other compounds where fluoride accumulates over time and has a toxicity profile and would you be in a position to detect that.

DR. WEBSTER: We haven't done repeat dosing of the single dose, but clearly tafenoquine has been dosed long term in prophylaxis studies. I'm not aware of what safety profile one might expect with fluoride accumulation.

DR. BADEN: Periostitis, the variety of described side effects.

DR. WEBSTER: To my knowledge, no, we've not seen those events

DR. BADEN: It is 10:40. We have received a lot of information and are very appreciative of the applicant for bot presenting and responding to our many queries. We'll now take a 10-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break, amongst yourselves, or with any member of the audience. We will resume at 10:50 sharp.

(Whereupon, at 10:39 a.m., a recess was taken.)

DR. BADEN: It's 10:52. We shall now resume and we'll proceed with the FDA's presentations. And I think we'll start with Dr. Li's comments.

FDA Presentation – Xianbin Li

DR. LI: Good morning. I'm Xianbin Li, a statistical reviewer from the Division of Biometrics IV Office of Biostatistics. I will be discussing the FDA's assessment of efficacy of tafenoquine in the treatment of plasmodium vivax malaria.

We will review the three studies in support of efficacy of a 300-milligram single dose of tafenoquine, which I have abbreviated as TQ for the radical cure of P. vivax malaria in patients 16 years of age and older.

Co-administration with another faster-acting schizonticide, chloroquine, CQ, for 3 days is required for treatment of P. vivax malaria, as this combination targets both blood and liver hypnozoite stages of infection. The three studies were multicenter, double-blind, double-dummy, randomized studies.

Study 582 contained the two parts. Part 1 was a dose-ranging study that also came in placebo and active control. Part 2 was a confirmatory

portion and it contained the 300-milligram single dose of TQ and both a placebo and active control.

The two parts were independent and distinct. And they were considered as two separate studies. Study 564 was an active controlled study. The three studies supported the efficacy of TQ.

I will discuss the results from those trials separately. For some analyses discussed, we have used different analyses and populations than those used by the sponsor. Because of that, I will report FDA's analysis of results.

Note that the differences between FDA's and applicant's result are minimal and do not impact the overall conclusions of the studies.

Study 581 part 1 was a dose-ranging study to evaluate the efficacy, safety, and tolerability of TQ and to find an optimal dose for part 2. This part was conducted in Brazil, India, Peru, and Thailand. Eligible patients were randomized to one of 6 groups, 4 TQ groups, including the 300-milligram single dose on day 1 or day 2, primaquine, PQ, an active control group once daily

for 14 days, and CQ alone. All groups received CQ on days 1 to 3 for blood-stage infection.

CQ was chosen as a control group or a placebo-equivalent group, as it does not have any activity in preventing the relapse of hypnozoites once blood levels have declined sufficiently. Therefore, it allowed a test of superiority to confirm and quantify efficacy. All drugs were given early.

The main inclusion criteria included a positive smear for P. vivax, parasite density between 100 and 100,000 per microliter and age greater than or equal to 16 years. The main exclusion criteria included subjects with mixed malaria infections, subjects with severe P. vivax malaria, or subjects with a G6PD deficiency.

The primary efficacy endpoint or relapse-free efficacy 6 months post-dosing -- this was the final initial clearance of parasitemia undetectable from two smears, slides 6 to 12 hours apart with no presence of P. vivax asexual-stage parasites within 6 months.

The FDA's analysis population for all efficacy analyses was the ITT population, defined as all randomized subjects. So analysis method for the primary efficacy analyses included a Kaplan-Meier survival analysis and a log-rank test for time to relapse.

To control the possible inflation of the type I error due to multiple treatment groups, a closed testing approach was used, that is, hypotheses were tested in order from the highest dose to the lowest dose.

Baseline characteristics were comparable across groups. This table contains the result of the primary efficacy endpoint, relapse-free efficacy, at 6 months for all 6 groups. The TQ 600 group had the highest relapse-free efficacy at the 6-month. A comparable proportion of subjects were censored due to lack of baseline parasites, use of an antimalarial drug, or lack of a 6-month assessment in the CQ-alone group and in the TQ 300-milligram group.

Here, I'm going to report on the results for

only the CQ-alone group and the TQ 300-milligram group. Those estimates and a confidence interval are for relapse-free proportions at 6 months from a Kaplan-Meier analysis. There was a statistically significant difference in time to relapse and in relapse-free proportions at 6 months, as indicated by the p value from a log-rank test and the confidence interval for difference in proportions.

Those remained significant even with a stepwise comparison to control for multiple comparisons. The survival analysis assumes censoring as non-informative. When you consider sensitivity analysis, considering censoring as a failure, the results reach a similar conclusion.

The Kaplan-Meier curves for the CQ group, the blue line, and the TQ group, the red line, indicate the difference in time to relapse.

Subgroup analysis showed consistent treatment results across age, gender, race, weight, country, and a baseline parasite count. In addition, in the CQ and CQ plus TQ 300-milligram groups, their relapse-free proportions at 4 months

were similar as those at 6 months.

In conclusion, although the first part of the study was designed to find the optimal dose to evaluate in part 2, the selected 300 TQ group given with CQ did demonstrate statistically significantly improved efficacy compared with the CQ-alone control group.

The second study, study 582 part 2, had a similar design as part 1. The trial was conducted in centers in Brazil, Ethiopia, Cambodia, Peru, Philippines, and Thailand. Subjects were randomized 1:2:1 to one of the 3 groups, CQ alone, placebo, CQ plus TQ, given on day 1 or 2, the 300-milligram dose, CQ plus TQ once daily for 14 days. All subjects received CQ on days 1 to 3.

The third arm was to provide a concurrent benchmark. The inclusion and exclusion criteria were very similar to those in part 1.

The primary efficacy endpoint was recurrence-free efficacy after 6 months. This required initial clearance of P. vivax parasitemia, defined as 2 negative asexual P. vivax parasite

count with at least 6 hours between counts, no positive counts in the interval, and no presence of P. vivax asexual stage parasites from initial clearance to day 201.

The microbiologic ITT, micro-ITT population, included all randomized subjects who received at least 1 dose of study medication and had a positive parasite smear of P. vivax at baseline. The analysis method in this part included a Kaplan-Meier analysis and a Cox proportional hazards model with region and treatment as a covariate for time to relapse.

Baseline characteristics were comparable across groups. The observed recurrence-free proportions at 6 months were comparable between the TQ group and the PQ group at 68 percent and 64 percent, and higher than that in the CQ-alone group at 26.

The proportion of subjects censored was the same across groups. There was a statistically significant difference between the TQ and the CQ-alone group, as indicated by the p value from a

log-rank test and a confidence interval for the difference in proportion.

A Kaplan-Meier curve for the CQ group, the blue line, and the TQ group, the red line, indicate the difference in time to relapse. The Cox proportional hazard model showed similar results, that the TQ group had a statistically significant reduced risk of recurrence compared with the CQ-alone group as indicated from the confidence interval and the p value.

The survival analysis, when considering censoring as treatment failure, also reached the same conclusions. In addition, subgroup analyses showed consistent treatment results across age, gender, weight, race, region, and baseline parasite count.

Additional early treatment endpoints were collected in this trial. The results for those early endpoints were similar across all treatment groups, showing that TQ did not impact the efficacy of CQ. Proportions of subjects with parasite clearance was very high. The median time to

parasite clearance was comparable across groups.

The fever clearance proportion and a median time to fever clearance were comparable. The result for gametocyte clearance was very similar as well. This table shows the result at 4 months as a secondary analysis. In the CQ plus TQ group, the relapse-free proportions at 4 months were about 8 to 9 percent higher than those at 6 months. The difference in relapse-free efficacy at 4 months was also statistically significant.

In conclusion, study 582 part 2 demonstrates that there was a statistically significant reduction in risk of recurrence at 6 months in a CQ plus TQ group compared with CQ treatment alone.

The last study I will discuss is study 564. The primary objective of this study was safety. It was conducted in five countries and was active-controlled. Subjects were randomized 2:1 to either CQ plus TQ or CQ plus PQ group. As with other trials, CQ was administered on days 1 to 3. This study did not contain a CQ-alone group.

The inclusion and exclusion criteria are

very similar as in the previous trials. No primary efficacy endpoint was defined. FDA's analysis focuses on the recurrence-free efficacy 6 months post-dosing, which was defined as having a positive smear at baseline, initial clearance, and then no positive smear results by day 201.

Initial clearance was defined as two negative asexual P. vivax parasite count with at least 6 hours between the counts and no positive counts in the interval.

The primary analysis population for all efficacy analyses was micrologic ITT, defined as all randomized subjects who received at least 1 dose of blinded study medication and had a microscopically confirmed P. vivax parasitemia.

The statistical method was the same as in study 582 part 2. Notice that there was no plan to assess noninferiority in this trial. I will report the results from a comparison of recurrence-free proportions.

Baseline characteristics were comparable across groups. The observed proportions of

recurrence-free efficacy at 6 months was similar between the two groups. The proportions with recurrence and the proportions who were censored were similar as well.

The difference in recurrence-free proportions was negative 3.4 percent. The 95 confidence interval was minus 16 to 9.8 percent. This implies that TQ could have had as much as 16 percent lower recurrence-free efficacy than PQ. I had mentioned earlier the sponsor did not plan to assess this study using noninferiority.

However, if we use the two previously discussed studies to estimate treatment effect of PQ, a conservative estimate would be 26 percent over CQ alone. Based on this margin, TQ could be considered non-inferior to PQ because a low limit would exclude a margin of minus 26 percent.

In conclusion, this study supports efficacy of TQ. In conclusion, the efficacy of TQ, 300 milligrams, single dose, were evaluated from 3 clinical trials. All three trials were randomized, double-blind, double dummy, active control. CQ was

used to clear the initial blood-stage infection in all subjects in all 3 trials.

The two trials using CQ alone as a control group demonstrate a statistically significant treatment effect for the proposed regimen for the radical cure prevention of relapse of P. vivax infection. The trial using CQ plus PQ group as a control group indicated that the treatment group produced similar efficacy results supporting the efficacy of the product.

This concludes my presentation. Thank you very much for your attention.

DR. BADEN: Thank you.

Dr. O'Shaughnessy will present the safety data from the agency's perspective.

FDA Presentation – Elizabeth O'Shaughnessy

DR. O'SHAUGHNESSY: Good morning. I am Elizabeth O'Shaughnessy, the safety reviewer for this indication. I would like to present some of our analysis of the safety data and I must say our safety analyses are in general agreement with the applicant's analysis.

This slide is just a high-level view of the pharmacokinetic properties of tafenoquine, which were presented earlier. I'll just make a few points. The absorption of tafenoquine is increased when taken with food and it was taken with food in the clinical trials.

Its long half-life has implications for safety because the symptoms of an adverse reaction are kind of curtailed by stopping the drug. And tafenoquine, which welded be used in conjunction with chloroquine, chloroquine also has a long half-life, a median half-life of about 40 days.

With regard to drug-drug interaction studies, there were no clinically significant PK interactions between tafenoquine and other antimalarials such as chloroquine and artemether-lumefantrine.

So again, for the umpteenth time, these are the clinical studies that we looked at for the safety review. There were 3 double-blind randomized trials. After tafenoquine plus chloroquine in studies, these are in studies 582

part 1 and 2 in 564. Patients in these trials had G6PD enzyme levels greater than 70 percent of normal. Safety evaluations will also be presented for 3 studies in healthy subjects, a thorough QT, an ophthalmologic safety, and a study of the hemolytic potential of tafenoquine, which will be referred to later as study 027.

Study subjects received single doses of tafenoquine from 100 milligrams up to 1,200 milligrams in these studies in safety assessments. And these were useful because they did not have confounders such as underlying disease or the presence of chloroquine.

So with regard to exposure in the phase 2b/3 clinical trials, overall 483 patients were exposed to tafenoquine, 300 milligrams, single dose plus chloroquine. 264 patients were exposed to primaquine plus chloroquine. And 187 patients were exposed to chloroquine alone.

Exposure to tafenoquine in the three healthy volunteer studies is summarized in this slide. 528 patients were exposed to tafenoquine in these three

studies. The thorough QT study enrolled 260 subjects who were G6PD normal and 156 received single doses, tafenoquine capsules, from 300 milligrams to 1,200 milligrams.

Study 027 was an open-label dose-ranging study of the hemolytic potential of tafenoquine capsules, 100 milligrams, 200 milligrams, and 300 milligrams, single dose in healthy subjects. There was a G6PD-deficient cohort in this study, which included 27 heterozygous females with G6PD enzyme levels in the 40 to 60 percent range and another group with females with a level greater than 60 percent. And then there were 24 females in the G6PD normal cohort.

The ophthalmology safety study was a randomized placebo-controlled study conducted primarily to investigate any retinal effects after the tafenoquine 300-milligram single-dose and 330 healthy subjects were exposed to tafenoquine in the study with 168 in the placebo arm.

This is an outline of the safety review. It will cover common adverse events in the studies,

serious adverse events, and adverse events of special interest associated with quinoline antimalarials, which include the following categories, hematologic, neurologic, psychiatric, cardiac, and ophthalmologic.

In the vivax malaria trials, this is the overview of the adverse events. Approximately two-thirds of patients experienced adverse events and the frequency of these events were similar across the treatment arms. The frequency of serious adverse events was also similar at 5 or 6 percent and, at 3 arms, there were no deaths.

No patient withdrew from a trial due to an adverse event and 3 percent or less discontinued 1 of the components of the regimen that they were randomized to. So this is a graph of the common treatment-emergent adverse events across study 582 part 1 and 2 and 564.

The gray bars depict chloroquine and primaquine plus chloroquine is in blue and tafenoquine plus chloroquine is in red. And as you can see from the X axis, the difference is between

treatment groups for many of the adverse events. What is it, a few percent or less?

Headache, pruritis, and dizziness were the most common adverse events across the three treatment arms. And as we know, pruritis is a known side effect associated with chloroquine. If we look at the tafenoquine plus chloroquine in red bars, dizziness, and decreases in hemoglobin were more common in the tafenoquine plus chloroquine group than the chloroquine, suggesting an association with tafenoquine.

Back pain and myalgia were also common, but in association with tafenoquine, these events were less obvious. Insomnia, which is associated with other quinoline antimalarials at similar rates across the 3 treatment groups, which is around 3 percent. And finally, if we look at chloroquine again in the gray bars, headache, pyrexia, chills, and diarrhea were more common. And some of these symptoms, such as headache, pyrexia, and chills, are probably associated with a higher number of recurrences of vivax malaria in these patients.

In the 3 clinical trials, serious adverse events included decreases in hemoglobin levels, QT integral prolongation, and one possible case which was called a drug-induced liver injury. 3.7 percent of patients in the tafenoquine 300-milligram arm experienced decreases in hemoglobin as compared to 1.5 percent approximately in the other two treatment groups.

QT prolongation was observed in less than 1 percent of subjects with tafenoquine compared to 3 percent in the chloroquine group. And 3 patients in the chloroquine arm were discontinued because of QT prolongation under ECG. And the patients were asymptomatic.

As we know, QT prolongation is listed as an adverse event in the drug labels for some quinoline antimalarial drugs. There was 1 case of possible drug-induced liver injury in a patient with vivax malaria in the tafenoquine plus chloroquine group. This patient we already discussed under hepatic adverse events.

Elevated transaminases and bilirubin levels

at baseline associated with vivax malaria occurred in all treatment groups. And elevated transaminases post-baseline were observed in the tafenoquine plus chloroquine group and I'll give you some examples from study 582 part 2.

Two patients had elevated transaminase less than 5 times the upper limit of normal on treatment which resolved and both patients recovered. And then the other patient was also described by the applicant, which this patient was a 29-year-old patient with vivax malaria who had elevated ALT and bilirubin levels at baseline, which declined on treatment. And then his ALT began to rise around day 8 and, at day 22, his ALT levels were 10 times the upper limit of normal.

The patient said that he had taken herbal medications after he was discharged from the hospital and, once these herbal medications were stopped, his ALT levels returned to normal and, by day 42, he was within the normal range. However, I guess one cannot rule out an effect of tafenoquine plus chloroquine in this patient because of their

long half-lives.

I've only shown patients with elevated transaminases potentially related to the study drugs. Other significant post-treatment elevations in ALT were associated with concurrent viral hepatitis, a relapse from vivax malaria.

With regard to cardiac and renal treatment-emergent events in the tafenoquine plus chloroquine group, there was really no significant events. Less than 5 percent of patients in any of the three treatment groups had an increasing QT greater than 60 milliseconds and an interval greater than 400 milliseconds. And patients were asymptomatic.

In the thorough QT study, there was no effect on prolongation of the QT interval with the tafenoquine, 300-milligram and 600-milligram doses. And the maximum dose of 1,200 milligrams, which is 4 times the recommended dose, did not prolong the QT interval to any significant extent. Elevations in creatine from baseline were mild and transient.

The following slides describe safety data from 3 healthy volunteer studies that evaluated

tafenoquine doses from 100 up to 1,200 milligrams. So in the thorough QT studies, adverse events, which I outlined in red, occurred with greater frequency in the tafenoquine 300-milligram versus placebo and these included nausea, vomiting, headache, and dizziness.

If you look at the nausea in the first row, this increase from 10 percent to 33 percent is the dose of tafenoquine increased from 300 milligrams up to 1,200 milligrams, which suggests that nausea is associated with tafenoquine.

There are transient mild reversible elevations and hepatic transaminases in this study. The next study talks about serious adverse events in the thorough QT study. The 2 cases of hypersensitivity have been discussed in detail by the applicant and I'm not going to dwell on this slide.

I'd just mention that the CPK elevations were associated with patients who did not follow protocol instructions and participated in strenuous physical exercises during this study.

This is 027. They studied the hemolytic potential of tafenoquine capsules. Thought it would be interesting to look at some of the adverse events in this study because there's a G6PD-deficient cohort and you will see their hemoglobin levels later.

Decreases in hemoglobin was the most common adverse event in the study and dizziness and headache were not reported in the tafenoquine 100-milligram arm in this study. In the ophthalmology safety study, there were no deaths or serious adverse events. Headache, nausea, dizziness, somnolence, and dysplasia were reported. There were no significant decreases in mean hemoglobin levels.

I will discuss the ocular findings later. So now to move on to switch to adverse events of special interest, which are associated with quinoline antimalarials, I apologize. I'm going to show you a lot of tables back to back.

As mentioned previously, decreases in hemoglobin levels were more frequent in patients

treated with tafenoquine, 300 milligrams plus chloroquine, 3.7 percent, then patients with primaquine plus chloroquine and chloroquine alone. And the following tables describe hemoglobin decreases during the first month post-treatment in the clinical trials and a similar pattern emerges.

This is study 582 part 1, which was a dose-ranging study of 50 milligrams of tafenoquine up to 600 milligrams. 2 to 4 percent of patients had drops in hemoglobin from baseline greater than 2.5 grams, which was a pre-specified cut-off for a serious adverse event in the trial.

Most patients had drops in hemoglobin to 1.5 grams or less, which was not considered clinically significant and all patients recovered without medical intervention such as blood transfusion. The decreases in hemoglobin were associated with small increases in reticulocytes over time across all treatment groups.

In study 582 part 2, 5 percent of patients experienced drops in hemoglobin of greater than 3 grams, again which was this pre-specified cut-off

for a serious adverse event as compared to 2 percent of patients treated with primaquine plus chloroquine or chloroquine alone. The patients were asymptomatic.

The maximum decline was in a patient who dropped their hemoglobin 4.2 grams with a baseline level of 15.6 grams. In this trial, the subjects in the chloroquine recovered their baseline hemoglobin levels around day 22 post-treatment in subjects in the tafenoquine plus chloroquine and primaquine groups returned to the baseline hemoglobin levels are higher around day 29.

An increase in reticulocyte counts, small increases, were observed associated with the decrease in hemoglobin levels. So this is study 564. 2 percent of patients experienced drops in hemoglobins greater than 3 grams. In this study, the maximum drop in hemoglobin was in a patient who dropped their hemoglobin 5.3 grams from a baseline of 19.2.

In the thorough QT study, the majority of patients experienced decreases in hemoglobin levels

of less than 2 grams. Obviously, there was no chloroquine in this study. And actually, this also included patients in the moxifloxacin and placebo groups.

The hemoglobin declines in tafenoquine were the same as placebo. In this study, there were no significant changes in reticulocyte counts, haptoglobin, or indirect bilirubin. Small increases in reticulocyte counts and indirect bilirubin were noted for the 1,200-milligram dose.

In study 027, in the G6PD normal group, hemoglobin declines were small, less than or equal to 2. We know that primaquine can cause hemolysis in individuals with G6PD deficiency. And in this study, a greater proportion of patients in the G6PD and G6PD-deficient group are in the lower half of the graph.

In this study, a greater proportion of patients in the G6PD-deficient group treated with tafenoquine experienced declines of hemoglobin greater than 2 grams as compared to their G6PD normal counterparts. However, the numbers in this

study are quite low.

In the G6PD-deficient group, mean reticulocyte counts were higher in the tafenoquine 300-milligram group and primaquine groups as compared to the G6PD normal cohort and mean haptoglobin levels decline from baseline in the tafenoquine 300-milligram and primaquine groups.

All of these patients recovered without blood transfusion. Methemoglobin levels for this study are not shown, but 3 G6PD-deficient patients who received tafenoquine has met the hemoglobin increases of greater than 5 percent. The normal would be less than 2. No subjects had clinical signs of symptoms of methemoglobinemia.

So we looked at methemoglobin in the clinical trials and this slide shows elevations in methemoglobin greater than 10 percent at any post-baseline visit by treatment arm as well as the maximum value for methemoglobin percent and patient symptoms.

I would like to point out that there is an error on the slide. The numbers and percentages

are incorrect for the study 582 part 2 in the middle row. It should be 2 percent for tafenoquine, 7 percent for the primaquine group, and 4 percent for the chloroquine group. However, the conclusion remains the same, that methemoglobin levels greater than 10 percent occurred more frequently in patients who had received primaquine plus chloroquine.

But maximum increases from patients who had normal levels of baseline was just a couple of percent. These levels greater than 10 percent must have been transient, as patients were general asymptomatic and there was no reports of cyanosis or other symptoms of methemoglobinemia.

So in summary, for the hematologic findings, the nadirs in hemoglobin levels were not in the anemic range in the G6PD normal patients and patients recovered without medical interventions such as blood transfusion.

Decreases in hemoglobin were accompanied by reticulocytosis without significant changes in haptoglobin or indirect bilirubin. I would suggest

that patients who present with anemia should be monitored for hemoglobin levels.

The decreases in hemoglobin were probably related to underlying vivax malaria and rehydration may have contributed. Elevations in methemoglobin levels were observed, but were more frequent in the primaquine plus chloroquine arm and patients were asymptomatic.

There was a small number of patients with G6PD levels less than 70 percent of normal, which was difficult to draw any conclusions from.

I am now going to switch to the neurologic adverse events that we observed. The most common neurologic adverse events associated with tafenoquine and chloroquine in the phase 2b/3 clinical trials were dizziness and headache. And these adverse events were generally mild and self-limiting.

With regard to psychiatric adverse events, these included anxiety and insomnia, which were transient. Insomnia caught similar rates at approximately 3 percent in the tafenoquine plus

chloroquine and primaquine plus chloroquine treatment groups.

There was 1 case of depression or depressed mood in the primaquine arm. As we know, insomnia is associated with the quinoline antimalarials, at least some of them.

This is just a more detailed look at the psychiatric cases, which were described earlier. So there were 2 male patients in the clinical development program who experienced an episode of psychosis following doses of 350 milligrams and 500 milligrams. 1 patient had a history of psychotic episodes and the other patient had a recent diagnosis of schizophrenia.

There were 2 cases of depression or depressed mood. In clinic doses greater than 300 milligrams, 1 healthy subject with no psychiatric history developed depressed mood on day 4 following a single dose of 600 milligrams and his symptoms resolved within 3 days without treatment.

One patient with vivax malaria who had a history of depression and diazepine use was

hospitalized for depression at day 88 post-tafenoquine. And he was discharged within 2 days and received a psychiatric referral. It is not known when his symptoms started in relation to tafenoquine.

In the ophthalmology study, ophthalmologic adverse events were infrequent across in the clinical trials. In the safety study, a comprehensive look at a significant battery of tests were used to look for retinal toxicity. No retinal toxicity or other significant ocular abnormality were observed with the tafenoquine 300-milligram dose and our ophthalmology consultants looked at the data and found no significant ocular risk from the use of tafenoquine 300-milligram single-dose.

So in summary, we found that tafenoquine was reasonably safe and plus chloroquine was reasonably safe and well tolerated, nausea, dizziness, headache, pruritis, and insomnia were relatively common adverse events in the patients with vivax malaria. These events were less common in the

healthy volunteer studies except for nausea.

Hemoglobin declines of greater than 3 grams were seen in some patients who were G6PD normal. Looking at hemoglobin levels where it can be done would be important in patients, especially those who present with vivax malaria and anemia. Caution is advised in patients who have a history of psychiatric disorders. And finally, there were no ocular adverse events and no QT interval prolongation. This completes the safety presentation. Thank you for your attention.

Clarifying Questions

DR. BADEN: Thank you very much to both of our presenters and the agency for giving a careful analyses of the datasets available. One clarifying question about the datasets you had available. If I understand from the applicant's presentation, they have about 4,129 people exposed.

Presumably the safety dataset that you looked at was all exposed, not just those in these three studies. Is that correct?

DR. O'SHAUGHNESSY: I focused on the three

studies.

DR. BADEN: Can you pull the microphone toward you?

DR. O'SHAUGHNESSY: I focused on the 3 clinical studies and the three healthy volunteer studies.

DR. BADEN: Studies, okay, but not all exposed?

DR. O'SHAUGHNESSY: Not all exposed.

DR. BADEN: Thank you. We will now begin questions from the panel members. Remember to state your name for the record before you speak and direct questions to a specific presenter.

So we'll start with Dr. Moore.

DR. MOORE: I'm sorry, Elizabeth. Would you be able to give those numbers again on slide 24, the ones where they were an error regarding the hemoglobinemia rates? I didn't quite catch that. And by the way, thank you for an excellent and very thorough presentation.

DR. O'SHAUGHNESSY: I just looked at subjects who had any elevation in methemoglobin

greater than 10 percent at any time post-baseline. The applicant can correct me if my numbers are incorrect. So that's what I looked at. And there were a greater proportion of patients in the primaquine plus chloroquine group who had levels greater than 10 percent.

DR. MOORE: Right, but I apologize. You said that the numbers in the slide were incorrect and you gave them corrected specific ones?

DR. O'SHAUGHNESSY: The corrected ones, yes. I had 2 percent for tafenoquine, 7 percent for primaquine, and 4 percent for chloroquine.

DR. BADEN: That's 582 part 2.

DR. O'SHAUGHNESSY: That's 582 part 2 in the middle row of the table.

DR. MOORE: Got it. And you wouldn't happen to have the numbers in addition to those percentages?

DR. O'SHAUGHNESSY: I have them somewhere. I will get them for you. If I remember correctly, the primaquine is 19. And I don't quite remember the numbers for tafenoquine and chloroquine, but I

know that primaquine is 19.

DR. MOORE: That's okay. I'll try to rely on my rudimentary math skills.

DR. O'SHAUGHNESSY: I'll give you the numbers.

DR. MOORE: No, no. It's fine. Thank you very much. Appreciate it.

DR. BADEN: Just a question about the drop in hemoglobin. Is there a mechanism that is understood as to why the hemoglobin has dropped 2 to 3 grams percent since there isn't hemolysis?

DR. O'SHAUGHNESSY: I don't think we have a mechanism. Our clinical microbiologist was discussing whether there was some shrinkage in red cells with tafenoquine. I think she would like to comment on that.

DR. BADEN: If you can go to the microphone, state your name.

DR. BALA: Thank you. I'm Shukal Bala, the clinical microbiologist for this application. Yes, there was an in vitro study where human red blood cells were shown to have shrinkage of the size. It

was done by flow cytometry and the [indiscernible] size characters were reduced. And there were some changes in the membrane as well. It's based on a published study.

DR. BADEN: As we ask clarifying questions, clarifying questions to the agency, questions may come up that the applicant is in a position to better explain. What I would ask is if the applicant can keep a running list and then, after we've completed our clarifying questions to the agency, we can ask you to clarify any other issues that get raised during this part of the discussion.

Dr. Clark?

DR. CLARK: This is a question for Dr. Li. In the FDA briefing document, there was mention of a meta-analysis done for parts 1 and 2. And I was just wondering if it was assessed as part of that subgroups in terms of efficacy based on, for example, gender, or weight, or race.

DR. LI: We conducted a meta-analysis meaning for the efficacy in order to interpret study, observe study. We did subgroup analysis for

each study and we have slides. Let me find a number, slide 1.

Yes. This is the subgroup analysis for part 1. And this graph shows the estimated difference in the confidence interval for subgroups. We also have a similar result for part 2, but we did not conduct a meta-analysis for these two parts combined.

DR. BADEN: In these analyses of efficacy, did you look for center effects or that was not deemed necessary?

DR. LI: We did analysis by country, but we did not look at centers because sometimes the sample size is so small it's hard to interpret the results.

DR. BADEN: Dr. Follmann?

DR. FOLLMAN: The TQ group here that is the 300-milligram dose --

DR. LI: TQ, yes. We focused on the 300-milligram dose only in the slide.

DR. BADEN: Do you have more questions, Dr. Follmann?

DR. FOLLMAN: Not related to that.

DR. BADEN: If there are follow-on questions, please do get mine or Ms. Bhatt's attention.

DR. FOLLMAN: So my question was brought up before actually and has to do with the exclusion criteria, where people with severe P. vivax were excluded. I was wondering why that was and it seems like those people would just be at risk of relapses, people with non-severe P. vivax.

So you might want to logically give them the drug, but we don't have any data for it, so why were they excluded? And would people logically wait, like a couple weeks after they're successfully treated, and then give them tafenoquine?

DR. BADEN: So I guess the agency can give their perspective and we'll wait until after the agency discussion to go back to the applicant for those clarifications. I don't know if the agency has a strong opinion on the severe exclusion criteria.

DR. O'SHAUGHNESSY: For severe patients, you would have to give them intravenous treatment, so you wouldn't start with oral therapy. I would think that would be the reason for excluding them.

DR. FOLLMAN: So you couldn't treat them, I guess, when they're getting the blood stage cleared up, but in principle, like two weeks later, if they were successfully treated, they might benefit.

DR. O'SHAUGHNESSY: That's true. That's possible.

DR. BADEN: A corollary to Dr. Follmann's question is -- and this, Dr. Kartsonis raised before -- is there any reason to believe this has to be given with chloroquine or can it be given separate from chloroquine when the patient is appropriately stabilized?

DR. O'SHAUGHNESSY: It wasn't studied that way, but I'm sure it could be used just like primaquine is. Dr. Green, would you like to comment?

DR. BADEN: We'll ask that question again to them when we come back to their clarification.

DR. O'SHAUGHNESSY: Sure. I'm sure it could be used like primaquine.

DR. BADEN: Dr. Tan has a follow-on.

DR. TAN: This is a follow-on question related to severe malaria, actually mostly a comment and also the question about why this wasn't studied in severe malaria.

I think the concern with tafenoquine in severe malaria is that hemoglobin drop. And so you have a very ill patient already with severe malaria. And while their studies in uncomplicated malaria showed no symptoms due to this hemoglobin drop, I would imagine it may be different and have different consequences in a patient with severe malaria.

Then the second kind of more comment and thought is that, in patients who are treated with IV artesunate, there is a recognized post-artemisinin and delayed hemolysis that happens after that IV treatment. And so if you were to give tafenoquine with that, what would the consequences be? So there are some questions

related to giving patients with severe malaria tafenoquine.

DR. BADEN: Fair enough. But just to drill down a little bit to help educate the group, what if the tafenoquine were given a day plus 10, a chloroquine-tafenoquine combination, but it's given a day plus 10, not day plus 1, again as terminal prophylaxis? Wouldn't the hemoglobin drop be more manageable at that point because the acute treatment would be done?

DR. TAN: So in a patient with severe malaria, they would get artesunate and then the tafenoquine. The PADH-post-artemisinin and delayed hemolysis is observed between 1 to 3 weeks after the artemisinin. And so that would overlap with the levels of the tafenoquine.

DR. BADEN: Thank you. Dr. Orza?

DR. ORZA: I have one general question and then some specific ones, but I'll get back online for those. And my general question comes from the fact that this is not my home committee and so I don't fully appreciate the context for considering

this drug, but to what extent are we supposed to focus almost exclusively on approval in the U.S., for use in the U.S.?

If we are to focus on that, how unusual is it to have no data on patients in the use where it will be used in this kind of arena. Maybe it's typical for this kind of drug. And to what extent should we be conscious of the fact that this is also part of the pathway to WHO pre-qualification and much wider global use as the sponsor has indicated and be considering all of the other issues that, that brings in, just would appreciate some framing.

DR. BADEN: I suspect Dr. Cox may assist with how to frame those issues.

DR. COX: Yes. So we are asking the question with regards to approval for the U.S. We recognize that, for drugs for tropical diseases, what we do here in the U.S. has implications for the world, so that's also clearly recognized when we're looking at these products.

Your question about not having U.S.

patients, so if we look back at malaria drugs, because of the places in the world where malaria occurs and the very, very limited number of patients, which are imported cases here in the U.S. for the most part, we typically see that for diseases such as malaria, other tropical diseases, the data that we have from patients with malaria is going to be from ex-U.S. [ph].

So that's something to think about and think if that impacts your decision or your recommendation for today. So it's something to consider. And you heard some of the questions when folks were asking about BMI and trying to understand how the BMI of the patients in the trial related to what we might expect for BMI here in the U.S., recognizing that exposure is an important thing to think about.

When we look at data from ex-U.S., you know, we at the FDA look at the data. And we try and make the assessment of, is the data that we have from ex-U.S. relevant to the U.S. population and, if we think so, why.

So that's something else to consider and you can see that that's important because we are approving the drug for the U.S. population. And then I think your third question was about the WHO pre-qualification process. So I guess what I would say there is that, again, that's the recognition that what we do here in the U.S. with regards to a product that will be used globally has implications for other parts of the world.

Certainly, we would think that it would have implications for what the WHO might do and then may also have implications for regulators in affected areas and could also be a resource that they might consider as they're evaluating the product, too. So hopefully I've gotten most of your questions, but I'll pause there and make sure I have.

DR. ORZA: Yes, thank you very much, just one follow-up in terms of other kinds of differences that there might be in the U.S. population. I mean, if this is largely returning travelers or visitors, in the U.S. population, in addition to the BMI differences and possibly the

fact that this will be their first infection.

Might also be things like maybe they were taking prophylaxis ineffectively. Probably, they're taking other medications. I mean, the average person in the U.S. is taking something like, I don't know, three or four medications. And so we don't have any data on those sorts of things. Right, in the U.S.?

DR. COX: So I think you're asking about the issue of drug interactions. And I'll look to our clin pharm folks to see if there's anything that they may be able to add to your question. Hang on just a second.

DR. WEI: Tracey Wei, the clinical pharmacology reviewer from the FDA. So regarding to the drug-drug interaction, I think just regarding to the effect of the other drug on the PK, of the tafenoquine, because the tafenoquine according to the applicant's data, tafenoquine undergoes a minimal hepatic metabolism and also the minor renal elimination, so we don't expect there would be some clinically significant drug-drug

interaction with regards to the metabolism of tafenoquine.

Also, there is clinical data that shows that there's no clinically relevant drug-drug interaction of the tafenoquine between the commonly used antimalarial drug, including the chloroquine and also artemisinin combination therapy. And regarding the effect of the tafenoquine to the PK of other drugs, the clinical study demonstrates that there's no clinically relevant GDI effect between the tafenoquine to most of the CYP enzyme substrates. I hope that answers your question.

DR. ORZA: Thank you.

DR. BADEN: Dr. Cox, if I hear you correctly, studies don't have to be done on U.S. patients, but we need to be persuaded that the data generated are convincing for the efficacy, safety claims, and we think it reasonably applies to how it might be used in the U.S.

DR. COX: That's correct. Thank you.

DR. BADEN: Dr. Weina, are you at a follow-on comment?

DR. WEINA: I just had one additional comment there. I think that one of the other things that we have to consider with this, even though
it's not necessarily a U.S.-based population is that the drug, especially a drug like this, is potentially going to be used in an eradication effort worldwide.

When it comes down to funding, for example, USAID money is preferentially used in U.S.-approved drugs rather than in U.S.-non-approved drugs and that's a very important thing to consider as well when we're taking a look at this drug.

DR. BADEN: Agreed, Dr. Weina, but I'm not sure. I mean, the data still need to be compelling that there is a clinical benefit.

DR. WEINA: I'm not disagreeing with you at all on that.

DR. BADEN: There may be additional potential benefits, but we are evaluating the data before us, that we think there is meaningful efficacy with reasonable safety.

DR. WEINA: Absolutely, but I guess from my perspective, I'm also looking at it from the fact that we have a lot of people that go into harm's way, if you will, that will be potentially using drugs like this as well, that may not necessarily be treated here in the U.S.

DR. BADEN: Agreed. Treating U.S. citizens may not just be on U.S. territory. And whether U.S. citizens are really different than other citizens may be another question, but if it's effective, it's effective and can be used in that vein. Dr. Green has a follow-on question?

(Dr. Green gestures no.)

DR. BADEN: If no other follow-ons, then I think Dr. Honegger?

DR. HONEGGER: Dr. Honegger. I have a clarifying question on table 21 from Dr. Li. My general understanding is that the early response to treatment was good in all arms on these trials, efficacy trials, but the fever clearance percents are in the 30s.

So I just was wondering if you could clarify

when was fever clearance determined, at what time point, because I would expect it to be closer to 100 percent.

DR. LI: I think, at the very beginning, patients had very frequent visits. So they might capture the time to fever accurately at the very beginning, but later on, they did not have very frequent visits, so I would like to defer this question to the sponsor. They might be more familiar with the study design for the early part of the study. Thank you.

DR. BADEN: We'll get back to that after we're done with this segment. I think Dr. Beyrer is next.

DR. BEYRER: Thanks, Chris Beyrer. This is a question for Dr. Li again. In the presentation of the data that you showed, that basically is a kind of post-hoc noninferiority analysis, it looked to me as though the confidence interval's wrapped around 1 and the test for noninferiority was met, but then you didn't present a p value or a statistical test around that confidence interval.

When we've spoken about the numbers, I don't think I heard it clearly. Maybe you could just -- I think it's actually on that handout that I have. The font size is too small to see which slide it is for me, anyway. But it's the noninferiority test slide. You know the one that I'm referring to?

DR. LI: Yes. We did meta-analysis from part 1 to part 2 to derive a margin. It's 22, 23 percent. Then from this study, we conclude the low confidence interval limit meets the defined margin from part 1 and part 2.

So it's the issue, inferiority, if we used treatment effect from part 1 and part 2, but we did not report the p value for the two comparisons. We just reported numerical results, but internally, we can think we interpreted, admit the noninferiority margin if we use the margin from part 1 and part 2. Thank you.

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

DR. NAMBIAR: Sorry. We were just

discussing. And maybe the sponsor or applicant can correct us, but there are some healthy volunteers who were enrolled in U.S. sites, so there is some exposure data in U.S. subjects.

DR. BADEN: Okay. We will clarify that. So I'm back in line. Follow-on, Dr. Moore? Then we have Dr. Zito?

DR. ZITO: Julie Zito. I wanted to raise the issue of the psychiatric adverse events and how the labeling will be, for example, in post-marketing surveillance. Will there be efforts to screen patients for prior psychiatric events? Because it could make a good deal of difference in the acceptability of the drug among all the patients in programs.

DR. BADEN: So your question is, post-marketing, is the labeling post-marketing surveillance?

DR. ZITO: Both, both.

DR. COX: Yes. So this is an area, too, where I think we're looking for your advice. If you have particular recommendations on this -- and

you've heard some of what the sponsor's talked about with regards to their proposal for post-marketing, and certainly we do follow drugs in the post-marketing period because we learn more as drugs get out into larger numbers of patients in a more heterogeneous patient population.

So we appreciate your comments, and any advice you have on that, we welcome.

DR. BADEN: If I understand the data, there were two schizophrenic episodes, one of which was a new diagnosis. Was that new diagnosis predating or postdating the use of the tafenoquine?

DR. O'SHAUGHNESSY: It was predating.

DR. BADEN: So the new diagnosis predated treated exacerbated; whether relationship or not is always hard to know, and that all 4 identified, the two depressions, the two psychoses were all in a higher than the 300-milligram dose, because I thought I --

L17; There are higher, but one dose was 350 milligrams, which was --

DR. BADEN: 50, yes. One was 350, but they

were all greater than the 300-milligram dose.

DR. O'SHAUGHNESSY: That's correct.

DR. BADEN: Both of the psychoses had a pre-existing psychosis.

DR. O'SHAUGHNESSY: Yes.

DR. BADEN: Just a lot data presented, to make sure that was clear. Then Dr. Green?

DR. GREEN: Yes. I'm just looking for clarification of what breakthrough therapy designation means and what implication it might have on our thinking and our recommendations.

DR. BADEN: Dr. Nambiar?

DR. NAMBIAR: So breakthrough designation is one of many designations we can give products. This is based on preliminary clinical evidence that suggests that the product that's in development offers some benefit over currently available therapy. So it's based on clinical data, and it has to be preliminary clinical evidence. It doesn't have to rise to the level of being statistically significant, which would be needed for approval.

So it's a designation that's given to products in development. What it provides for sponsors is more frequent interactions with the agency. But the approval mechanism doesn't change, so our standards for approval do not change. The applicant still has to provide adequate evidence to support effectiveness and obviously enough information to support the safety.

DR. GREEN: Does it impact at all on sort of -- and for this particular set of studies, at least one of them, they renegotiated the population size due to difficulties in accruing. And so are you all differentially flexible when they had that because of the preliminary data that supports or no?

DR. NAMBIAR: No. So that's really not necessarily based on whether or not the product has got breakthrough therapy designation or not. I think it was a scientific sound decision, and I think we had conversations with them. So I think that's irrespective of whether or not there is breakthrough designation.

DR. BADEN: Dr. Moore? New question, then, Dr. Orza?

DR. ORZA: I had two questions. One was about the special safety studies and they were single blinded. And I was just wondering if that was typical and, if so or if not, if there's any opportunity for that to have affected the findings, and then I can wait for the answer to that for my second one.

DR. O'SHAUGHNESSY: Are you talking about the ophthalmology safety study?

DR. ORZA: Yes, the ophthalmology one and I think it was the cardiovascular one.

DR. O'SHAUGHNESSY: The QTc study?

DR. ORZA: The QT, yeah, QTc study.

DR. O'SHAUGHNESSY: Honestly, I don't actually know the answer to that question. I might have to defer that to the applicant.

DR. BADEN: Did you have another question, Dr. Orza?

DR. ORZA: In the larger safety database -- and maybe this has to go to the

sponsor, too -- of the over 4,000 patients, is there any longer-term data on any of the ophthalmologic, or hematologic, or hepatologic, or any of those?

DR. O'SHAUGHNESSY: There is ophthalmology data for the multiple-dose studies and longer-term studies that I don't have with me, but I think the sponsor can answer.

DR. BADEN: Dr. O'Shaughnessy, just the reason you focused on the data you focused on is those with a single dose.

DR. O'SHAUGHNESSY: Yes.

DR. BADEN: The multiple dose is for another time because that is a different use?

DR. O'SHAUGHNESSY: Correct.

DR. BADEN: I just want to make sure why certain data were looked at and certain were not. So all of the single-use data, you evaluated?

DR. O'SHAUGHNESSY: Yes. I focused on single dose.

DR. BADEN: Single dose, thank you. Dr. Moore?

DR. MOORE: Minor question, and I don't know if FDA or the sponsor could answer this, so just a quick question about the methemoglobin levels, but obviously the levels get bumped up with various drugs, but the question I have is with regard to the tafenoquine.

I know what the maximum methemoglobin level was in the treatment. Is there a minimum level? Was there a minimum level that was seen of elevation?

DR. BADEN: So what you're saying is, most people had zero, some people had some, which was above zero, and the highest was the 13.4 percent, I think that I saw.

DR. MOORE: Correct. I didn't see 0.

DR. BADEN: But I assumed 0 was in the majority of the -- but that's my assumption.

DR. MOORE: No. No, no. What I'm saying is, all patients treated with tafenoquine, or primaquine, or chloroquine will have some bump in methemoglobin. I'd like to know what the lower limit or the lowest number. I need to know the

range. I'd like to know what the lowest level raised was in the study.

DR. O'SHAUGHNESSY: I saw increases from baseline of 1 to 3 percent, but I don't know what was the lowest level a patient had.

DR. MOORE: That's fine. Yes. That's fine. I mean, just a minor increase in 1 to 3 percent is adequate. Thank you.

DR. BADEN: Dr. Clark?

DR. CLARK: This question is for Dr. Cox or Nambiar and I just wanted to clarify that the number of patients that made up the safety analysis for those treated for malaria, which is about 500 or so. That was endorsed by the FDA. And how do you arrive at that number generally, of what you think is enough to look at safety?

DR. NAMBIAR: It's not like we'd really have a magic number. Typically, when you look at the design of the studies and the overall development program, the number of patients that you need in these studies to be able to demonstrate efficacy is sort of -- and if that number falls within a

reasonable safety database, we are okay. I mean, 300 is the bare minimum. And in our guidances, we do say, especially for unmet need programs, you need a minimum of 300.

So in this instance, we felt getting a safety database of around 500 at the proposed dose would be adequate. And this is an analog of primaquine, so we do have a fair amount of experience with humans having seen primaquine. The safety concerns were not any different from what is known for the antamin or quinoline 8-aminoquinline.

So I think we take all that into consideration and make a decision around the safety database. Larger is better, but I think we also have to consider feasibility.

DR. CLARK: Thank you.

DR. BADEN: If I understand Dr. Nambiar, the basis of that is, you need about 3X to see an event rate, so 300 gives a chance of seeing a 1 in 100 event rate as just a rule of thumb.

(Dr. Nambiar nods yes.)

DR. BADEN: So 600 is a 1 in 200 event rate

to have a chance of seeing it. So I have a question for Dr. Li. The applicant has suggested that a blood level of 56.4 may be a marker of activity. What do you make of that analysis and that potentially being a threshold of interest?

DR. LI: I do not have the answer. Probably our colleagues in clinical pharmacology might have an answer for this question.

DR. ZHUANG: This Luning Zhuang, pharmacometric surveyor from FDA. So regarding this exposure or breakpoint, we consider, because it's coming from the exposure response analysis, we consider it as an exploratory analysis. There is no solid evidence to support this exposure breakpoint.

DR. BADEN: Along those lines, the applicant also mentioned the metabolism question and that the issue of metabolism for primaquine may be different than tafenoquine. Did you have a chance to see those data and do you have any perspective on the metabolism and activity question?

DR. ZHUANG: So my colleague, Tracey Wei

will give the answer.

DR. WEI: Tracey Wei again. So yes. We had a chance to review the data regarding the status of the C2D6 metabolizer on the efficacy for the tafenoquine. So we agree with the statement from the applicant.

DR. BADEN: You also agree that tafenoquine is exclusively active against the hypnozoite and not the other forms and therefore the exposure and treatment should not be different, given the 10 weeks of tafenoquine and the 3 weeks of primaquine exposure.

DR. BALA: Actually, there are some in vitro studies and animal studies. In vitro studies, P. vivax, erythrocytic phase was tested. And when I looked at the 50-percent inhibitory concentrations, they were similar to what's seen for falciparum.

I think the highest I saw was about 35 microgram per mL. I may be wrong on that. So yes. It is active against the erythrocytic phase. There are a lot of animal studies using other species of

plasmodium which infect whether rodents or non-human primates and it is effective against all stages of the parasites, which include sporozoites, liver stages, gametocytes, back stages, and --

DR. BADEN: So then should there be concern that 10 weeks of tafenoquine exposure may impact, relapse differentially then 3 weeks of primaquine exposure in terms of the primary efficacy outcome.

DR. BALA: Well, that's a little difficult to answer in this situation because subjects, when they are treated before administering radical cure therapy, there are no parasites in the blood actually. The blood parasites are in the liver and that's a little hard to study at that stage.

DR. BADEN: Dr. Green?

DR. GREEN: Just speculating, then, if this agent or if this drug has activity against the blood phase and being freshly induced. And at 9 weeks, you have a level, but it's very low. And we ask this of the sponsor as well. In your thinking, does this raise the risk for resistance?

DR. BALA: Yes. Repeated doses are due to

the long half-life. Yes. That's a possibility. But I do want to clarify one thing, that the activity of tafenoquine is slower than that of chloroquine or some of the artemisinin class of drugs.

DR. GREEN: You said slower?

DR. BALA: Yes, it's slower

DR. BADEN: Thank you. Mr. Mailman?

MR. MAILMAN: This is a kind of follow-on from Dr. Orza, but this is to Dr. Cox. You know, when I first looked at this package and was seeing something for malaria and designated as an orphan drug, it was kind of an interesting thing because, if you look at worldwide, right, we're talking 2.5 million living at risk of infection.

Understanding that this went through orphan drug designation, what would have been different if we were looking at not an orphan drug designation and what other things would we have seen?

DR. COX: So I'll try and answer what I think are key elements of your question. So the standards of approval are the same. The orphan

drug designation is based upon the number of cases in the United States. And, clearly, there's not much malaria in the U.S. It's an orphan disease.

You are absolutely correct. From a global perspective, this is a huge infectious disease problem. So let's see. I'm trying to figure out, have I gotten all of the elements of your question. Just help me there for a sec.

MR. MAILMAN: Yes, you've gotten the elements. I mean, instead of seeing 200, if you saw that this was in 20 million, would you have required more testing, more patients? What would you have seen? What might you have seen differently? Because this looks like it's going to be used in a more global sense than just the 200.

DR. COX: Right. So the development program, if we look at drugs for malaria, the studies are ex-U.S., and they've put together a reasonable package of studies, recognizing that there's a large disease burden outside of the U.S.

So I don't know that much would change here if you will. Certainly, if there were malaria in

the U.S. -- fortunately, there is not -- then we might see patients enrolled in the clinical trials with malaria from the U.S. sites, not just from the healthy volunteer or the QT studies. So I don't think it would change that much. I can't tell you much about it.

MR. MAILMAN: Maybe that's what I'm trying to get at. If we had the same amount of cases as India, would you have been satisfied with the number of studies that we're seeing here?

DR. COX: So if we had an equal burden of disease of malaria in the U.S.?

MR. MAILMAN: Or India or some of the other South American countries that are indicated here in the heat map.

DR. COX: Yes.

MR. MAILMAN: Would you have been satisfied if you were sitting there?

DR. COX: So in that case, we would have strongly encouraged. If there were an equal burden in this hypothetical scenario, if there were an equal burden of cases in the U.S. of malaria as

there were in other parts of the world, we would have strongly encouraged that there were studies in the United States that enrolled patients in the United States.

My expectation of that incidence, too, is that the company probably would have also tried to, even without our encouragement, enroll patients in the United States, recognizing that they're coming in or their intention is to come in with an application to the United States. So that's my hypothetical answer to your hypothetical question.

MR. MAILMAN: But would they have been in the 500- to 700-patient range?

DR. COX: So back to the size of the safety database, yes. So as Dr. Nambiar has correctly answered, we look at the nature of the disease, the severity, the practical implications for enrolling the trial. And if you look at more severe illnesses, we're ranging somewhere from, say, 300 patients for the most severe illnesses for the greatest degree of unmet medical need to somewhere up in the, say, 700 range as we get to other

serious infections with some degree of unmet need.

As the disease process or the infection becomes less severe and the benefit conveyed by the product is less, that's where you're going to want more safety.

So if you go to a type of infection where you may just be, for most patients, speeding up the time to resolution such as a less severe bacterial upper respiratory tract infection, there, you'd probably want more safety because you want a greater degree of certainty for an area where the benefit is less. But I think with the disease process we're looking at here, given the severity of malaria and relapsing of malaria, this is the range that we would generally ask for with regards to a safety database.

MR. MAILMAN: That's what I was really looking for. Thank you.

DR. COX: Sure.

DR. BADEN: If I understand you correctly, Dr. Cox, you're also leveraging a compound that's very similar that's been used for 50 years.

DR. COX: We do, yes. The general knowledge about other similar chemicals that had been administered, that are approved and have been used, certainly, yes, is helpful to us as we evaluate safety and safety databases, and what we know about either a class of drugs or a type of molecule that's been used, so that's also considered.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: Yes, another question for the FDA about this point again about distinguishing reinfection from relapse. And I don't mean to overemphasize it, but the sponsor mentioned that you can't distinguish those with genotyping assays if they have them, but I just was wondering if there are regions, like first, if they actually sequence the genome and variable parts. Could you distinguish that or is it truly indistinguishable?

DR. BALA: The tools we have for distinguishing relapse an equal distance from new infection for vivax are not really well standardized. There are a few labs which are trying to do it. But again, one of the limitations

is, you can do it against the erythrocytic forms, but against the liver stage, then, the question of how one gets the specimen will come up. And doing invasive procedures may not be very practical there.

DR. BADEN: Dr. Orza?

DR. ORZA: So for use in the U.S., if this were to be approved, it would actually, for the patient and the clinician, be a choice, right, between TQ and PQ because of the availability here of the G6PD, if I have it right, testing? And so what we're trying to choose between, if we assume that the safety profile is similar, except for the fact that the TQ stays in your system for such a long time that you effectively can't stop taking it.

We have, I think, an open question about whether the efficacy is equivalent. I mean, it's potentially because we didn't demonstrate noninferiority. It could be as much as 22, 23 percent inferior. But it has this trade-off where it's much easier, adherence will be better. So

what I as a clinician or I as a patient am trying to choose between -- and so I was just wondering if there is any data either on FDA's part or the sponsor's part or any thoughts about how you would guide that kind of a choice.

DR. COX: Dr. Orza, I'm recognizing you're from PCORI, so I understand the context.

DR. ORZA: Patient outcomes is literally my middle name.

DR. COX: Right, right. I understand the context of your question. So let me try and just give you a few pieces that I hope will be helpful.

So when we look at a particular drug application, we're looking at that application based on its merits to see whether it's safe and effective. The drug doesn't have to be the best among all those that are out there. It just needs to be safe and effective and can be an option among treatments that would be available.

I think you're rightfully bringing up that physicians in their practice of medicine, with the individual patient before them, may be weighing a

variety of different factors when they're making a decision for a particular patient as to which among different options they may choose.

We do recognize, too, the value of having options because with patients, there may be different considerations when you're looking at practice situations and making therapeutic choices.

Certainly in the world of antimicrobials, the issues of resistance and other drug interactions issues with allergies, having options can certainly be a valuable consideration so that physicians are in the position to be able make those choices as to what might be most appropriate for their patient.

So hopefully, that helps some with your question, but I'll stop there and make sure that I'm addressing what you're asking.

DR. ORZA: It helps a little bit, but it's an option, but for example, with allergies, if they're allergic to one, they're likely to be allergic to the other because they're so similar.

I mean, they're, in so many respects, so similar that really the trade-off comes down to this benefit of a single dose versus multiple doses and the adherence challenges with that.

Otherwise, I think, as a patient or as a clinician, I probably would like a little more reassurance about the noninferiority. And that's where we seem to be kind of lacking conclusive data on the efficacy from.

DR. COX: Dr. Li can show the slide again if that would be helpful. And recognize, too, that the wideness of the confidence intervals is in part driven by the size of the study, too.

DR. LI: Please show slide 29. The low margin is 16 percent with the noninferiority margin of 26 percent from the previous two studies. So this drug, TQ, could be as much as 16 percent worse than PQ because of these small samples.

DR. ORZA: Your additional analysis, where I think you counted the missing data as failures, went as low as 22 or 23 percent. Right?

DR. LI: No, that's the treatment effect for

PQ from the first two trials. So the effect could be 20 percent. I mean, that's an effect of PQ. It could reduce recurrence by 26 percent. That's the treatment effect.

This trial could be 16 percent worse. So it's within the margin. We can conclude it's noninferiority if it would be on the 26 percent margin.

DR. BADEN: Dr. Follmann, I think you have a follow-up.

DR. FOLLMANN: Yes. I just wanted to follow up. So this, too, is a study where we just have two arms and so it's natural to think of noninferiority, even if that wasn't pre-specified. But when I was thinking about this, I didn't do the calculation, but the other studies, 562, I guess part 1 and part 2, also had TQ and a PQ arm. And if I was serious about noninferiority and going in that direction, I would have combined all those studies in some kind of a meta-analysis to try and get essentially a tighter confidence interval.

So it, from my perspective, 16 is too wide,

really. We have all this other data. Why not bring it to bear on the noninferiority issue? And just I think a little more of a technical comment; I think the 26 percent you're talking about relates to the so-called margin or the bar four, which we conclude noninferiority. And so that's based on how much a better, I guess, PQ would be than placebo. It's based on that kind of calculus.

DR. BADEN: But I think also, agreed, there are more data that could be brought together to make a tighter confidence interval.

DR. FOLLMANN: Right.

DR. BADEN: But you then have what's the meaning of recurrence and the ability to treat that as well as the issue in a study setting of high compliance with the PQ. That may or may not play out in general use. So there are many moving features to these data, at least for me, to be able to interpret it cleanly as noninferiority.

DR. FOLLMANN: Right. So you're putting it, I think, about issues of generalizability and how it will work out in the field and so on, whereas

I'm focused on the narrow question, is that confidence interval over there, 16 to 10, but the best summary of how similar they are based on the research program that they did?

I think it makes sense to also keep in mind the other studies, which showed dead-on similarity, basically.

DR. BADEN: Agreed.

DR. BEYRER: This is getting back to my original question, which is just, the confidence interval here wraps around 1, obviously, so it could be 16 percent inferior. It could be 10 percent better. That's the range and that's why I was asking you about a statistical test for this, a p value, for example.

DR. LI: We created the confidence interval. We focused on the low limits, so we did not compute the p values for the test.

DR. BADEN: But Chris, Dr. Beyrer, to make sure I understand, there are two different questions. One is, is it non-inferior, so is the 95 percent confidence interval above a lower

boundary. The other, if you're comparing treatment A to treatment B, to say one is better or worse than the other; if it's noninferiority, then is there noninferiority margin for which we want to have confidence it's above, which from these data would be above a 20 percent minus, but not above a minus 10 percent.

But then to Dr. Follmann's point, there are two more datasets that could be combined to make a tighter 95 percent confidence interval to at least have more confidence in this type of assessment. Am I capturing your concern properly?

(Dr. Beyrer nods yes)

DR. BADEN: I'm not sure there's an answer or at least not from us. We may hear something from the applicant after lunch.

DR. COX: Dr. Li, we may not have done that analysis, analyzing the additional datasets, but it may be something that the applicant has done.

DR. BADEN: And can bring to us after lunch as a digestive.

(Laughter.)

DR. BADEN: So Dr. Moore?

DR. MOORE: I just had one point and that was that points raised to questions about resistance to tafenoquine for patients where the drug would persist in the blood, I think of greater concern is really the resistance to primaquine, which has already been documented, well documented, in southeast Asia, more to the point, that non-compliance with a primaquine is a major risk for development of resistance, much more so than tafenoquine, if I may, in my opinion, people who have it in their system and don't necessarily need it anymore.

DR. BADEN: Fair enough. An issue that troubles me and I just am interested in the agency's view of it -- the advantage of this compound is the long half-life, single dose, incredibly attractive. However, they did have 2 cases of hypersensitivity. How do we help weigh that, given the potential consequences of hypersensitivity if it goes unchecked or not in a position to have a healthcare response.

So I'm just curious as to your evaluation of those two episodes and how you think about the hypersensitivity concern.

DR. O'SHAUGHNESSY: I guess the first point to make would be those 2 cases are from, as far as I know, the entire development program, so that would be 2 out of, I guess, over 4,000.

DR. BADEN: Four thousand.

DR. O'SHAUGHNESSY: They're interesting cases because they occurred 13 to 15 days after the drug was taken. And both patients ended up in the ER and both patients got prednisone and diphenhydramine and recovered.

The symptoms, at least in 1 patient, lasted for about 7 days. So they are concerning and it will be described in the label, but it will be different, I guess, for physicians to mitigate because the patient is already out of your care maybe at that point. So he's of concern to us.

DR. BADEN: In a detailed evaluation of those two cases, which I suspect would be --

DR. O'SHAUGHNESSY: Yes. We had an

allergist look at them.

DR. BADEN: There was no other concomitant factors, allergies. There was nothing else that we should --

DR. O'SHAUGHNESSY: I would say there is a mitigating case for 1. The patient had an antecedent upper respiratory tract infection. And the allergist who saw the patient in the case narrative did suggest that it might have been allergic urticaria due to that upper respiratory tract infection.

In the other case, the asthmatic patient didn't really have any other reason to have this allergic reaction that we could find in the case narrative.

DR. BADEN: But the patient was asthmatic, pre-existing asthmatic?

DR. O'SHAUGHNESSY: The patient was asthmatic, yes.

DR. BADEN: On therapy or baseline anti-depressives?

DR. O'SHAUGHNESSY: I don't think we got a

list of their concomitant medications at the time, but the cases looked similar. They both had urticaria. They both had angioedema and then other symptoms.

DR. BADEN: Dr. Green?

DR. GREEN: Do you know the incidence of urticaria with primaquine?

DR. O'SHAUGHNESSY: I do not.

DR. GREEN: I'm going to presume that it's happened.

DR. O'SHAUGHNESSY: I presume it has happened.

DR. GREEN: Right, because if we're doing this side-by-side comparison --

DR. O'SHAUGHNESSY: Sixty years, I would imagine.

DR. GREEN: -- of the advantages of a day versus 14 days of therapy and, if we're going to be worried because there's hypersensitivity that occurs in a couple of cases, it would probably be worthwhile to again, even though these aren't a side-by-side comparison except for the safety

study, the third one, maybe the sponsor knows that data.

DR. BADEN: We'll ask the sponsor for it, but again, Dr. Green, to push you a little bit on that, if someone has an allergic reaction to a medicine that I cannot remove for another 6 weeks versus will be out of their system in days, that might make a difference in how one manages depending on the severity of the reaction because, unfortunately, once you give this drug, there may be 10 weeks of antigenic stimulus.

DR. GREEN: If you're looking for me to respond, obviously, we're looking at benefits versus risks. And if we look at the issues of compliance versus non-compliance and then the benefits or the risk.

I mean, again, so obviously this is of concern, but it does need to be weighed with the frequency that it could have happened with the other medication. And it would be nice to know the absolute rate of this. We know some events in a population. We don't know the universe.

So obviously, that could make us want to have more observations post-marketing.

DR. BADEN: Agreed. Dr. Tan?

DR. TAN: I just have a new question for FDA. For the cases of vivax in the U.S., only about 40 percent receive primaquine. And I don't know if that's a practice issue or supply issue. I do remember in 2011 there was a shortage of primaquine that extended into 2012 and we've had issues with medications when there's only one supplier. Do any of you know the current status of primaquine manufacturing in the U.S.? Are we dependent on one manufacturer for our only option?

DR. COX: We can check, and we'll get you some more information about that. You do raise the point of drug shortages, and we do encounter drug shortages, and it can create some difficult situations.

There have been shortages in the past of sterile injectable drugs, and we'll also check. We have a drug shortage webpage at FDA that lists the current shortages.

So the issue of diversity of supply and options becomes very important in a situation where there may be a shortage of one agent or sometimes even when there's multiple manufacturers. If one has a major market share, it's not possible in the short term for the other manufacturers to make up for that lost supply.

So diversity of suppliers for an agent is helpful in having a diversity of agents, if you will, so that if one agent becomes unavailable -- and the situation becomes particularly challenging for lower-volume use products, which ones are approved in the U.S. And you can see that there are obviously market considerations for circumstances where the disease burden in the U.S. might be small.

That might be a situation where the degree of attractiveness for a number of manufacturers is also going to be extremely small because the amount of product that would be used in the U.S. is limited.

So I've talked a lot, but your question

about drug shortage is diversity of supply, and diversity of options can certainly be an important consideration for patients.

We'll check the drug shortage website and see what we find on primaquine and also the currently approved manufacturers, and we'll let you know in just a minute.

DR. NAMBIAR: Yes. So I think we have what they call the Orange Book that lists all the currently available products, and it does seem like there might be more than one supplier for primaquine.

DR. BADEN: Good. It is 12:35. It is time for lunch. We will now break for lunch. We'll reconvene again in this room in 45 minutes at 1:30. Please take any personal belongings. Committee members, remember there should be no discussion of the meeting during lunch, amongst yourselves, with the press, or any member of the audience.

I'll also ask the applicant to prepare any responses and clarifications based upon the issues raised.

(Whereupon, at 12:35 p.m., a lunch recess was taken.)

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

(1:31 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:30, and we should resume if everyone can take their seats. We'll now resume after lunch with the open public hearing session.

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 presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a 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 of 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 the issues before them.

That said, in many instances and for many topics and a variety of opinions. One of our goals today is for this 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. SLUTSKER: Good afternoon. I'm Dr. Larry Slutsker. I'm director of malaria for PATH and I'm representing PATH. I don't have any financial connection with the sponsor. Thank you very much for this opportunity to provide some perspective on this new drug application for tafenoquine.

I'm speaking today on behalf of myself and Dr. Richard Steketee also with PATH. Together, we've both been chief of the malaria branch at CDC and now work together at path. And we spent more than 60 years in public health and epidemiology and more than 50 years collectively directly involved in malaria research and program implementation and evaluation.

So as you know and as you've heard, there's been great progress against malaria over the last decade. Much of this has been against p. falciparum and the progress against P. vivax has been far less apparent. P. vivax, as you've heard,

was initially and long ago thought to be a relatively benign infection. And it's become increasingly evident as we've learned more that it's an important public health issue and lead to life-threatening complications and increased mortality, nearly 10 million cases occurring globally annually with an estimated 5,000 deaths and over 2 billion people living in areas of risk.

As you know, vivax poses special challenges because, unlike falciparum, it causes relapses months or even years after the primary infection due to reactivation of the dormant stages in the liver of the hypnozoites and epidemiologic studies of estimated relapses account for a vast majority of ongoing P. vivax transmission, well more than 50 percent, so preventing relapses by killing hypnozoites providing radical cure becomes a key critical strategy for reduction of transmission and eventual elimination of vivax.

Currently, we only have primaquine as an 8-aminoquinline that's effective against hypnozoites and primaquine, as well as tafenoquine, has a risk

of severe hemolysis in those patients who are administered these drugs with severe gp6d deficiency. The current standard regimen for primaquine is to receive a daily for 14 days.

This prolonged treatment regimen poses significant adherence challenges with estimates from some studies that up to 75 percent of patients may not complete a full 14-day regimen. So with its single-dose regimen, the 8-aminoquinline-tafenoquine would provide really a game-changing opportunity to deliver radical cure with directly-observed therapy.

Tafenoquine administration also does pose a risk of hemolysis in patients with severe G6PD deficiency. And so it's recommended to be administered only after testing for G6PD deficiency. And work is already underway to link G6PD testing with tafenoquine use to assure this safe route of cure.

So the capacity to deliver this single dose directly observed therapy radical cure with tafenoquine can have an enormous impact, both

clinically and from our malaria control and public health perspective.

First, patients with documented vivax, who are tested for G6PD and documented not to have a severe deficiency will be assured to receive safe radical cure through the provision of DOT tafenoquine. They'll be much less likely to suffer additional morbidity from vivax relapses.

Secondly, deployment of and high coverage with a program of safe radical cure based on G6PD testing and single-dose tafenoquine can have a major impact by reducing vivax transmission and provides strong momentum to accelerate towards vivax elimination, infected areas.

The radical cure can end the potential of ongoing transmission for many subsequent relapses. Of note, many of the world's malaria endemic countries have both falciparum and vivax. And as they achieve substantial progress in their control efforts, falciparum is the first to disappear, as it has no relapsing stage of course.

At this time, nearly all the countries on

near-term track for elimination are at the point where they must address and eliminate their viva transmission to be successful. Finally, of note, in the United States, about 150 to 200 cases of recorded vivax are reported annually and, among these individuals, less than half reportedly receive radical cure with primaquine.

The current availability of G6PD testing coupled with a potential for a single-dose radical cure, which tafenoquine could dramatically improve, be curative management for these U.S. travelers.

So in summary, we strongly support the approval of tafenoquine for the proposed indication of radical cure, prevention, and relapse of P. vivax. We think this approval would represent a major step forward and a potentially game-changing opportunity in the fight against vivax malaria and we're very pleased the FDA and its advisory committee is considering this important drug. Thank you.

DR. BADEN: Thank you. Will speaker number 2 step up to the podium and introduce

yourself? Please state your name and any organization you are representing for the record.

(No response.)

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

MR. BLUMENFELD: Good afternoon. My name is Josh Blumenfeld. I'm managing director for a global policy and advocacy, Malaria No More, and I'd like to make clear that I'm not being compensated by an outside organization for my time or travel to this meeting today.

I'd also note that I'm the furthest thing from a scientist or a clinician. I have the great misfortune of being a lawyer. But I'm also an advocate and I'm here to talk in that capacity. So Malaria No More is a U.S.-based global advocacy organization. We envision a world where no one dies from a mosquito bite.

Every day, we work to mobilize the political will, the commitment, the funding, and the

innovation needed to achieve malarial elimination, which we think would be one of the greatest humanitarian accomplishments of our lifetimes. So I should note that we're privileged to live in a country that eliminated malaria in 1951.

As many of you all know, the CDC is located in Atlanta because its first mission was to eliminate malaria from the American south, yet as has been discussed, some Americans still suffer from malaria in the form of imported cases. I would also note that many of our war fighters, our men and women in uniform, also suffer from malaria. Indeed, malaria's one of the top infectious disease threats facing our men and women in harm's way.

So I understand you've heard about the devastating global disease, the progress we've made, and the challenges we face. Let me highlight a little bit the current and historic leadership role the United States has played in the global malaria effort, thanks to the generosity of the American taxpayer and frankly the unique bipartisan commitment of the Congress and of successive

presidents.

In 2018, the U.S. spent $775 million on the president's malaria initiative. We're the largest bilateral donor to malaria efforts in the world through PMI, which operates in 27 countries in Africa, Southeast Asia as well as here in the Americas. In 2017, PMI procured 40 million bed nets, 41 million anti-malarial treatments, and 43 million RDTs.

The U.S. also procured more than 10 million preventative treatments for pregnant women. Our leadership has been equally critical in multilateral form, particularly the Global Fund, where the U.S. is also the largest contributor, having spent $1.35 billion in 2018.

The effects of our leadership have been astonishing. PMI and the Global Fund have been instrumental in saving 7 million lives since the year 2000. Of course, our collective work is far from over. The WHO has set ambitious elimination targets and milestones.

By 2020, the world is striving to eliminate

malaria from at least 10 countries. Kyrgyzstan and Sri Lanka were certified malaria free in 2016. Just last month, Paraguay was certified and Algeria, Argentina, and Uzbekistan are on track for later this year.

By 2030, the WHO has set a goal of eliminating malaria in at least 35 countries and reducing malaria mortality rates by 90 percent. So as you've heard, vivax is the second leading cause of malaria worldwide. It's the predominant cause of malaria outside of Africa, where the vast majority of the burden is in Africa, of course. But outside of Africa, it's responsible for 64 percent of cases in Asia and in south America. It affects women and children under five in some of the most densely populated regions of the world, including India, which has the highest burden of any country outside of Africa.

It's also prevalent in southeast Asia, particularly along the Thai-Cambodia and Thai-Vietnamese border, where the specter of malaria drug resistance is threatening all of our global

success.

As you've heard, though vivax is often mischaracterized as benign, it can indeed cause serious illness. And perhaps most challenging for the elimination effort is that the parasite can go dormant in the liver and appear asymptomatic in patients for years evading detection.

So currently, there is only one approved treatment that can address vivax and that's primaquine. And we all know that that's clinically effective, but in the real world, an application that takes 7 to 14 days is highly unrealistic, particularly in hard-to-reach populations.

So tafenoquine, the drug being considered today, is a true innovation. It's a safe single-dose radical cure treatment. That could have a tremendous impact on preventing relapse, lowering morbidity and mortality, and helping the world and the United States government and its taxpayers achieve our ambitious elimination targets in Asia and the Americas.

Simply put, there is simply no reason for

anyone to die from malaria. It's entirely treatable and preventable. This is a disease of poverty. In our view, the swift approval of this drug will prove to be another crucial tool to help us achieve this dream within our lifetimes. Thank you.

DR. BADEN: Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SLUTSKER: Good afternoon. I'm reading this statement on behalf of Professor Krudsood from the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

"This letter is in support of the approval of tafenoquine, an 8-aminoquinline. It is a single oral-dose drug therapy for the treatment of liver-stage P. vivax malaria, replacing the role currently played by primaquine, 14 days.

"My name is Professor Srivicha Krudsood and I've been working at the Faculty of Tropical Medicine, Mahidol University, Thailand, on the

clinical management of malaria and anti-malarial clinical trials for over 20 years.

"Our group published our first paper evaluating the efficacy and safety of WR238605, tafenoquine, in the prevention of P. vivax relapse in 1999. Since 1996, 6 tafenoquine studies have been conducted at the faculty on the use of tafenoquine as an anti-hypnozoite to treat P. vivax malaria.

"The results of these studies have revealed high cure rates. The studies also found tafenoquine therapy to be well tolerated by normal G6PD patients. For the purposes of malaria elimination, P. falciparum malaria is now showing markedly reduced incidence, especially in southeast Asia. By contrast, the regional incidence of P. vivax malaria is on the increase.

"The currently recommended therapies for P. vivax infection in southeast Asia are for the blood stage, chloroquine-artemisinin-based combination therapies infection for 3 days, for the liver stage primaquine for 14 days. The proposed

recommended therapies for P. vivax in Thailand are blood stage, chloroquine, artemisinin-based combination therapy for 3 days, liver stage, tafenoquine, single dose.

"Besides our findings of anti-malarial efficacy in liver stage P. vivax malaria, tafenoquine has a long half-life and tafenoquine therapy offers the benefits of ease of administration and ready treatment adherence. Since it can be administered as a single dose compared with the current 14-day primaquine regimen with the attendant risks of non-adherence to the full treatment course, one of the most challenging issues in the clinical management and elimination of malaria hinges on adherence to treatment.

"Tafenoquine, a potent anti-hypnozoite, administers a single-dose therapy, offers an efficacious solution to this problem and promises to help transform our goal of malaria elimination into a practical reality.

"In summary, I support the approval of tafenoquine single-dose therapy for the treatment

of liver stage P. vivax malaria in conjunction with chloroquine or ACT for 3 days. Thank you."

DR. BADEN: Thank you. Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. DOW: There should be some slides for this presentation.

Good afternoon. I'm Geoff Dow, the CEO and majority shareholder of 60 Degrees Pharmaceuticals, the company that is the sponsor for tafenoquine for malaria prevention.

Seventeen years ago, I got falciparum malaria. I can assure you personally it's a medical emergency and folks who have no prior exposure to the disease. In the U.S., 96 percent of the malaria burden is in returning travelers who failed to comply with malaria chemoprophylaxis.

One of the key factors involved in that is the ability of the traveler to comply with prescribed medications. Tafenoquine with its long half-life and for the malaria prevention

indication, the potential ability to administer the drug once a week.

We believe, in the future, in the event the drug is approved, that it will make the compliance with prophylaxis much easier for travelers. That same benefit means we can give the drug as a single dose for radical cure and, for the record, 60P fully supports the dedicated efforts of GSK and MMV over the years to bring this product to where it is.

With that said, we have concerns about the way the labeling discussions are being handled with respect to psychiatric events. Because of the logistical issues that will impose in the future, both for military use of the drug and eventually for mass drug administration in the context of elimination.

So with that as background, 60P urges the advisory committee to recommend approval of tafenoquine for radical cure and in 2 weeks' time for malaria prevention as rapidly as possible, to do so without specific warnings in relation to

neuropsychiatric events, because we don't think these warnings are supported by evidence, and to do so with reference to the label for primaquine, the drug from which tafenoquine is derived. We'd further recommend that you do this, keeping in mind that the duration of exposure is not associated with an increased risk of psychiatric events.

I just want to point out a couple of differences in the two indications. We've heard about radical cure earlier today. For malaria prevention, it involves the administration of a 3-day load and the 200 milligrams weekly for up to 6 months, for a total cumulative dose of 5,200 milligrams in asymptomatic individuals at risk of contracting P. falciparum, P. vivax malaria.

We also would like to remind the committee that tafenoquine is an analog of primaquine, not any other quinoline. And you can see here from the structure where the core congener of primaquine is substituted with three blocking groups that confer the long half-life.

Similarly, Primaquine is a very different

molecule structurally and in terms of mechanism of action from other quinolines. It's activated to unknown oxidative species that confer a potent effect against liver-stage parasites and that's derived from it being an 8-aminoquinline as opposed to the amino alcohol side-chain on mefloquine, which mimics the structure of neurotransmitters and associated with an increased frequency of neuropsychiatric events relative to standard of care and a different profile in terms of anti-malarial activity.

This morning, Rick Price covered the prior review of primaquine for radical cure and emphasized the fact that there's very little PQ-attributable neurotoxicity. And most of the adverse events are associated with hemolysis and GI distress.

The FDA's label sensibly reflects this literature consensus. What you may not know is, you can use primaquine for up to 12 months for prophylaxis without any increase in the risk of psychiatric events relative to placebo. That's

reflected in the CDC's recommendations for primaquine for prophylaxis.

With tafenoquine, we've seen that the drug has a benign profile relative to the standard of care and chloroquine for radical cure with a very low event rate of psychiatric events. This is also case with tafenoquine when administered weekly for up to 6 months for a cumulative dose of 5,200 milligrams. You can see that the rate of adverse events overall is very similar to placebo in a non-deployed population.

It's only when you move to a deployed situation with the attendant increased risk of physical and psychiatric injury that you begin to see an increase in the adverse events. In these three conditions, the treatment-related incidence of neuropsychiatric events leading to discontinuation is benign and the common adverse events that are increased by TQ are not neuropsychiatric in nature.

Finally, although reference was made to some important psychiatric events in GSK's dossier, it's

important to remember that these are very rare and, as GSK has stated in its briefing document, there's no causal relationship with prior psychiatric mental health history.

So with these facts in mind, this is the summary of this talk. I'd like to thank the agency for the opportunity to present here today and congratulate GSK on the progress that has been made so far with tafenoquine after what we all acknowledge has been 40 years and a lot of blood, sweat, and tears getting to this point.

Congratulations.

DR. BADEN: Thank you. Will speaker number 6 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. BLUMENFELD: Good afternoon, again. My name is Josh Blumenfeld, and I'll be reading a statement on behalf of APLMA, which is based in Singapore, and they were unable to attend today.

"My name is Marie Lamy, and my testimony is on behalf of the Asia-Pacific Leaders Malaria

Alliance or APLMA. APLMA supports the approval of tafenoquine as a new radical cure for the treatment of relapsing P. vivax globally.

"APLMA is an affiliation of Asian and Pacific heads of government formed to accelerate progress against malaria and to eliminate in the region by 2030. APLMA was created in 2013 to mobilize political commitment and broker tactical policy financing solutions to expedite the elimination of malaria.

"We convene partnerships in support of better access to new and priority anti-malarial commodities from treatments to diagnosis to diagnostic tests and vector control solutions. APLMA would like to highlight the public health -- for the Asia-Pacific region, a region that holds over 90 percent of the global burden of P. vivax.

"P. vivax accounts for half of the total malaria burden in the Asia-Pacific region, where the strains exhibit some of the most aggressive relapse behaviors. Recurrence and relapsing

malaria is a major driver of transmission and, the more episodes of P. vivax there are, the greater the negative impact of the morbidity and mortality rates in the region.

"P. vivax can have the fatal outcomes if left untreated associated with anemia, respiratory distress, and even renal dysfunction. The current treatment, primaquine, a 14-day treatment, is underused and reported adherence even in clinical trial settings.

"P. vivax is also widely resistant to first-line treatments in the Asia-Pacific region, hence the need for new treatments. As expressed at the World Malaria Congress in Melbourne, Australia last week by world experts on P. vivax, the promise of tafenoquine as a single-dose radical cure is revolutionary not only in terms of patient adherence, but also in terms of reducing the risk of resistance.

"This is particularly relevant in settings where regular follow-up with patients was a challenge due to poor geographic accessibility to

public health services. The malaria community is aware of the challenges to contend with when introducing a new treatment.

"The role of tafenoquine will require strong pharmacovigilance systems to monitor events in country. To address this, APLMA and the World Health Organization facilitate the regional regulatory partnership for malaria elimination.

"One of the objectives of our RRP beyond expediting the registration of new drugs through reliance mechanisms is to build the capacity of the regulatory authorities in low- and middle-income settings, including strengthening pharmacovigilance systems.

"The deployment of tafenoquine will need to happen in concurrence with G6PD deficiency screening, new point-of-care handheld G6PD test are currently in the last phase of development and these will be crucial to mitigate the risk of hemolysis.

"Through the RRP, APLMA is working closely with the product development partnerships of these

new tools to ensure an efficient and safe joint roll-out plan. Regulators across the Asia-Pacific and members of the RRP have expressed keen interest in the new promising treatment and are eagerly awaiting the recommendation of both the U.S. FDA and the Australian Therapeutic Goods Administration on its approval for use.

"We encourage the Antimicrobial Drugs Advisory Committee members to strike a balance between encouraging prospects of tafenoquine as a radical cure, its benefits for public health, and the acknowledgement of potential risks in rolling it out in low- and middle-income settings.

"In summary, APLMA supports the approval of tafenoquine as a key tool in the elimination of malaria in the Asia-Pacific region and a crucial scientific advancement and weapon in the battle against malaria globally. Thank you for your attention."

DR. BADEN: Thank you. Will speaker number 7 please step up to the podium and introduce yourself? Please state your name and any

organization you are representing for the record.

(No response.)

DR. BADEN: Will speaker number 8 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. NEVIN: Thank you, members of the committee. I am Remington Nevin, executive director of the Quinism Foundation. My qualifications are described in the docket submission that you should have before you. I have no financial relationships with the sponsor.

So tafenoquine is an 8-aminoquinline. Our experience with the toxicity of this class of drug dates to when these were extensively tested among members of the U.S. military during the World War II era drug development program. U.S. military interest at the time was focused on development of a causal prophylactic drug as a replacement for quinacrine, a scolicidal drug with known CNS toxicity.

Some of the early work was documented in

this publication, one of the lead authors of which was Leon Schmidt, who saw much of the pre-clinical safety testing of drugs of the 8-aminoquinline class. His reports from this era describe extensive neurohistopathological testing of various 8-aminoquinlines in rhesus monkey.

This work was summarized in a series of three seminal papers, which Schmidt published after the war, which concluded that all of the nearly 140 members of the 8-aminoquinline class studied were uniformly neurotoxic.

As Schmidt noted, drugs of this class produce rather remarkable and highly specific lesions in the central nervous system as shown here. During this era, a modest overdose of an 8-aminoquinline in clinical use proved fatal and, on careful neurohistopathological testing and autopsy, such neurotoxic effects were confirmed in man.

At the time, the military's leading candidate for causal prophylaxis, named pentaquine, was thought to be well tolerated during can testing, causing mostly gastrointestinal

complaints.

However, subsequent neurotoxicity testing in rhesus monkey demonstrated a similar pattern of injury among members of this class, including to the dorsal motor nucleus, involved in innervation of the gastrointestinal system.

Further work on pentaquine was subsequently abandoned. It may well have been this abortive experience with pentaquine that led Schmidt to caution that a detailed search for central nervous system lesions with drugs of this class was highly desirable.

Our foundation has grave concerns that the critical lessons of this era have been overlooked by the sponsor. Tafenoquine is known to be neurotoxic in vitro. Testing of 8-aminoquinline in non-primates, including rats, is known to be insufficient to rule out clinically significant CNS toxicity.

As a lipophilic quinoline, tafenoquine can be expected to share the neuropharmacokinetic heterogeneity of mefloquine, meaning as with

pentaquine, any neurotoxicity identified in pre-clinical testing at any dose would have significant implications for the safe use of this drug. Unfortunately, definitive pre-clinical neurotoxicity testing in primates was never performed prior to clinical testing, thus exposing thousands to a risk of severe and potentially permanent CNS adverse effects.

Our submission details evidence why such effects cannot be ruled out with current data and why gastrointestinal effects must be considered prodromal to serious adverse effects such as those alleged by several surviving veterans of tafenoquine clinical trials, which are expected to be discussed at a pending Australian Senate inquiry.

The foundation is concerned that FDA's consideration of this NDA without the benefit of this potentially critical information and we note for the record that timing and location of this meeting has likely precluded attendance by these surviving Australian veterans.

Lastly, I note the foundation is concerned that the proposed dose of the tablet, oddly chosen at 150 milligrams rather than 300 milligrams, will facilitate a significant higher dose of off-label use, as has occurred with primaquine in response to likely CYP2D6-linked treatment failures and that such unapproved use will significantly increase the risk of unrecognized CNS toxicity.

Now, our foundation recognizes the vital, global need for new effective treatments for malaria, but limit highlight the larger picture that I trust the committee will consider carefully. This is a graphic depicting the global burden of disease with mostly communicable disease in red and the mostly non-communicable disease, including mental illness, in blue. In 2010, the global burden of morbidity due to malaria was roughly comparable to that caused by depression and anxiety, which are known lasting adverse effects of mefloquine.

Here, we can see this for comparison. The outcome that we must protect against is that,

through our efforts to decrease the global burden of morbidity from malaria, particularly through mass drug administration in areas of poorly developed pharmacovigilance infrastructure, that we unintentionally replace morbidity from malaria with mental health morbidity caused by neurotoxicity.

With the evidence presented today, the sponsors cannot rule out this occurrence should tafenoquine be deployed globally as intended. Given our concerns for the safety of tafenoquine, our foundation recommends non-approval of this NDA.

However, we recognize that this NDA has been eagerly anticipated. So we therefore make the following additional recommendations should the drug nonetheless be approved.

First, as with mefloquine, we recommend a boxed warning. FDA has suggested the drug not be used in those with a history of psychiatric symptoms, but we would emphasize a more important warning, that as with mefloquine, psychiatric and neurologic symptoms be considered prodromal and given susceptibility to the dorsal motor nucleus,

that gastrointestinal symptoms also be considered prodromal and a contraindication to further use.

The potential for permanent adverse effects must also be emphasized. Second, before this drug is deployed globally, questions about its safety must be resolved. We there recommend restricted distribution to preclude export during an initial post-approval period. And third, we would also recommend the FDA require completion of phase 4 neurotoxicity testing in rhesus monkeys per the methods of the World War II era studies.

The foundation believes strongly the committee should not have to make this decision without adequate safety data. So to incentivize future sponsors, we would recommend against awarding of a PRV in this instance. Thank you very much.

DR. BADEN: Thank you. Will speaker number 9 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. NEWMAN: Hi. My name is Dr. Robert

Newman. I'm a pediatrician and epidemiologist. I stand before you today as an independent specialist, not representing any organization. I've not received any remuneration to be present nor will be receiving any reimbursement of costs and I have no financial ties to the sponsor.

Again, I'm a pediatrician, epidemiologist, and I've spent the majority of my career, more than 25 years, working in global public health and most of that time on malaria. Why? Because, as a young physician, I moved to Mozambique and I was just overwhelmed by the burden that I saw out there.

I just knew that we could do much more as a society to counter the scourge of this disease. Following that experience in Mozambique, I spent nearly a decade working at the U.S. Centers for Disease Control. At some point, I occupied the role that Dr. Tan occupies today, in charge of the National Malaria Surveillance System, where I saw that this disease does actually affect returned U.S. travelers. It's not just a global problem.

After that, I led the CDC team of the U.S.

President's malaria initiative and then ultimately wound up as the director of the WHO Global Malaria program. Why am I telling you this background? Because I think that, in these roles, I have been exposed to what this disease really means globally, the tremendous burden that it exacts on societies.

At WHO, I recognized with my team that vivax was being ignored. Yes, falciparum remains the number 1 killer in terms of malaria, but the vivax was under recognized as a global public health problem. We set about issuing new guidance for plasmodium vivax. We ensured that the global technical strategy for malaria that went to the World Health Assembly in 2014 included stronger language about the importance of doing more about vivax. In that strategy, it was clearly articulated that the development and adoption of innovative solutions will be essential to target the hypnozoite reservoir of P. vivax.

That was approved by the World Health Assembly, that strategy. So why the unwavering commitment to do more about vivax malaria? You've

heard today from so many speakers that this is really a serious disease, what proportion of the world's population is affected, how many people, how many cases there are a year, and that people actually die from this disease.

You know, when I was a medical student, people used to say, "Plasmodium vivax doesn't kill you, but you wish it would," that you felt so terrible, your fever was so high that you just wished you would die.

But what we know now is not only do you wish, but in fact, for many people unfortunately, that is a reality, that this is a disease that kills many more people than we had understood. And throughout my career, I've lived in the Americas. I've lived in Africa. I've lived in Asia and I've witnessed the toll that this exacts, not just on individuals, but in societies as a whole. Many of the people who are affected by malaria, including P. vivax, are the most marginalized.

They're living beyond the reach of healthcare services. So we know the challenges of

treating vivax today. Getting people to take 14 days of primaquine is unrealistic in so many of the settings where we really need to affect a radical cure.

For any of us, as a physician, I can admit that 14 days of a medicine is nearly impossible for me to take. Imagine coupling that challenge with living in the margins of society and trying to complete a treatment like that.

So when we think about what this offers today, tafenoquine is a game changer. You heard that phrase earlier. The ability to go from 14 days of treatment to a single treatment is not only transformative for individuals, but it's transformative for national malaria control programs that are actually trying to eliminate vivax malaria.

I just spent six weeks actually working. I've been working in Asia and talking to national malaria control program managers across the Asia-Pacific. And people are hungry for this new medicine. People recognize that their inability to

eliminate vivax malaria is in large part coupled to our inability to get people to take 14 days of primaquine.

If we really were to have an approved medicine that allows us in a single dose to affect a radical cure, that changes overnight what national malaria control programs can achieve across the world. And vivax, which we always think of as the stubborn last kilometer, last mile, the challenge to actually eliminating malaria. I think, with the approval of this medicine, we'll actually leap frog falciparum and will become a parasite that national malaria control programs can tackle and can eliminate.

So I'm here today because I believe passionately that we need to do more to tackle the problem of vivax malaria and that tafenoquine is a medicine that, if approved, has the potential to transform not only the ability to definitively cure patients, but the ability of national malaria control programs to eliminate this parasite once and for all from their countries. And that's not

just a public health goal because, as we all know, malaria and poverty go hand in hand.

If we really want to help the countries that are burdened by vivax malaria to accelerate their development, this is a step in that direction. Thank you very much.

Clarifying Questions (continued)

DR. BADEN: Thank you.

The open public hearing portion of the meeting has now concluded and we will no longer take comments from the audience. At this point, I'd like to go back to further discussion, especially asking the applicant to respond to issues raised during the second part of the morning. So Dr. Webster, can you please leave that discussion or share the responses?

DR. WEBSTER: Thank you. Yes. There were a number of firm points raised during the discussion that we thought would be helpful for us to come back to you. And so there was a question around the issue of resistance and I'd like to ask Dr. Price to give his perspective on that, please.

DR. PRICE: Thank you. Dr. Price from Oxford University. The panel raised some important questions over a long half-life antimicrobial and selection of resistance. I don't believe that there's clear evidence of vivax hypnozoites acquiring resistance to primaquine. Indeed, there are treatment failures in eastern Indonesia, which are associated with the Chesson-like strain, but that's confounded by CYP2D6 mutations, which probably account for 95 percent of those drug quality in the high relapse periodicity in that region of the world.

We don't have an ex-vivo model to confirm that, though. Transmission dynamics are very different for vivax. Chloroquine resistance took nearly 40 years longer to acquire and there are a number of reasons for that. So you can never say that resistance wouldn't occur, but with the combination treatment of chloroquine plus tafenoquine, I think resistance will be low despite the long half-life.

DR. BADEN: What I would like is, you

respond to each of those issues. If committee members have any follow-on questions, we just ask them as the issue is raised. So I would look to see if there is any follow-on. If not, then on to the next point.

DR. WEBSTER: Yes. So a question was raised about fever clearance time and I'd like to ask Dr. Green to respond to that.

DR. GREEN: Justin Green, clinical. There was a question around the low N, the number for fever clearance time. So just to be clear, the entry criteria for the study required a history of fever in the previous 48 hours and a large number of subjects would not have had fever at the time that they were consented, and went into the study, received chloroquine, and obviously underwent screening.

However, if we take study 582 part 2 as an example, of those individuals that did actually have documented fever at the time of initial screening, all of those cleared their fever within 48 hours, which is how we got that number, but in a

smaller number of individuals. Thank you.

DR. BADEN: Again, any follow-on question, please let me know. If not, we'll go to the next comment or clarification.

DR. WEBSTER: There was another question concerning blinding in the healthy volunteer studies. I'd like to ask Dr. Green to respond to that, please.

DR. GREEN: Yes. Thank you. In our healthy volunteer studies in the clinical development program, we actually had single blinding in two of those studies that was alluded to. Both of those studies -- one was the cardiac study and one was the ophthalmology safety study.

So just the ophthalmology study primary endpoint was actually read far from the unit at a later date by individuals who were masked as to treatment allocation. And so the primary endpoint to that data, they were actually unable to know the treatment allocation. In addition, our TQT study was also read by a vendor, cardiac specialist vendor, looking at QT and other parts of the ECG at

a different site.

Again, those individual readers were blinded to treatment allocation of people within the study.

DR. ORZA: So it effectively was double-blind? Is that what you're saying? So who was not blinded?

DR. WEBSTER: Dr. Green?

DR. GREEN: Even though those studies were technically single blind, that's all that we can claim. Quite a lot of work was done at the sites in order to ensure that the minimum number of people within the study had access to the randomization code.

Usually, the pharmacy gave the nurses or the staff in the unit the treatment were actually the only people that knew what the treatment allocation was; so even the physicians that were looking after them, when there was an adverse event that they were very worried about where they needed to actually ask the pharmacist what treatment that individual patient had gotten. Yes.

DR. BADEN: Thank you.

DR. WEBSTER: There was a question about whether we had any longer-term follow-up, longer than 6 months following a single dose. No, we can confirm we don't have any follow-up that's of a longer duration.

Then there were some questions around the hypersensitivity cases. I perhaps could give some context in that both of the hypersensitivity, the urticaria cases, occurred in the same healthy volunteer study. And just to give some context, there was actually additionally one placebo patient who experienced urticaria in that same study.

The patient who had asthma, who experienced the hypersensitivity, who did not disclose the history of study entry; there was a question about what medications that patient was receiving. I can confirm that they were receiving inhaled corticosteroids and beta-2 agonists, so the subjects' concomitant medications were recorded as Advair, salbutamol, and budesonide.

Then there was a further question about whether these types of reactions are known for

primaquine. We know that primaquine is labeled for rash and pruritis. And when we consult the WHO Uppsala safety database, there are reports of hypersensitivity, urticaria, Stevens-Johnson syndrome, anaphylactoid reactions, and toxic epidermal necrosis.

There was a question about --

DR. BADEN: I think Dr. Moore is --

DR. WEBSTER: I'm sorry.

DR. MOORE: Just a follow-on question, so the issue was, if I remember Dr. Green's question earlier, what's the likelihood, that is, how common is that. My recollection from the WHO is that all those reactions are exceptionally rare.

DR. WEBSTER: They are not frequent, yes, from a very large number of patients potentially exposed, but then of course we are comparing post-marketing data with clinical trial data.

DR. BADEN: Thank you.

DR. WEBSTER: There was a question about the number of U.S. subjects enrolled in our clinical trials. I can confirm that there were 425 U.S.

healthy volunteers enrolled in our clinical pharmacology program in 6 studies

DR. ORZA: What were the inclusion and exclusion criteria for those healthy volunteers in terms of concomitant medications, or other conditions they might have, or anything that would speak to when this is actually used in the U.S. population coming back with malaria that would make them at all representative.

DR. GREEN: Thank you. Typically, phase 1 safety studies have a fairly narrow set of inclusion and exclusion criteria. And therefore, all patients are not on regular medication when they come into those studies. But in actual fact, except for one study where we had the partner drug had a weight restriction, we didn't actually have a weight restriction on those, which is why we actually have a fairly wide range of BMIs with equivalent exposure, either side of a cut-off of 30, which is one of the cut-offs for BMI in terms of obesity.

DR. WEBSTER: Then finally, there was

interest from the panel in understanding what efficacy we would show relative to primaquine if the data from all three studies was combined and I'd like to ask Dr. Rolfe, our statistician, to show that to you.

DR. ROLFE: Hi. I'm Katie Rolfe, the statistician from GlaxoSmithKline. I'm going to show you a slide here with the results of pooled analysis of our three primary studies. So you can see on this slide the difference in the percentage of subjects on tafenoquine, on primaquine, that experienced recurrence, so a difference of zero would just be no difference between the two treatment groups.

What we saw was a difference of 1 with a confidence interval around that from minus 5.9 to 8.0, so potentially subjects could have been 8 percent worse than primaquine in terms of recurrence, but similarly, they could have been almost 6 percent better. So if you were thinking of a noninferiority, for example, 10 percent, which I know is commonly looked up, and it would have sat

within that margin.

DR. BADEN: Just to clarify, the data you pooled are all those who received the 300-milligram dose?

DR. WEBSTER: Yes, the 300-milligram dose across those three studies.

DR. BADEN: Three studies. Dr. Follmann, any questions?

DR. FOLLMANN: No

DR. BADEN: That's all the questions. That's all the clarifications. Any other questions from the committee members or clarifications for either the applicant or the agency? Dr. Honegger?

DR. HONEGGER: Just one more question for the sponsor in terms of the use of this drug; I understand there is some chloroquine resistance among vivax in certain parts of southeast Asia and maybe other places really. I wanted to ask what was known about the incidence of chloroquine resistance at the study sites?

Then two, in the future where this drug is used with other agents besides chloroquine for the

treatment of the erythrocytic phase, what is known about or speculated about safety and efficacy in those cases?

DR. WEBSTER: Perhaps I can answer the second question first. We don't have clinical trial data, obviously, with anything other than chloroquine, but we do have drug-drug interaction data, which shows no clinically significant effect on pharmacokinetics in either direction, so we know that the drugs can be safely used together and would anticipate that the drug would have the same efficacy if given in combination with an ACT as it does with when given with chloroquine.

I'd like to ask Dr. Green if he could respond to your first question.

DR. GREEN: Background rates of chloroquine resistance -- so all of the countries that we were working in had documented cases of chloroquine resistance. However, we defined in our protocol prospectively and also measured chloroquine and desethyl-chloroquine in all individuals that had a recurrence of malaria.

The definition that we used was before day 33. In only 1 case did we find true evidence of chloroquine resistance, which was one subject on chloroquine only from Brazil.

DR. BADEN: Just further clarification; the studies were all done given CQ and TQ together. Any reason to believe that TQ without CQ can work just as well? Because I can imagine a lot of use will not be during the acute phase, maybe after the acute phase. So any data on it as monotherapy post-acute infection and, if not, any reason to believe it wouldn't work well in that setting or have different adverse events or side effects of concern?

DR. WEBSTER: Yes. We have no data, so I have nothing to share with you on that point, but no reason to believe that it wouldn't work if administered sometime later.

DR. BADEN: You would expect the same efficacy and safety given sometime later as given concomitantly?

DR. WEBSTER: Yes.

DR. MOORE: If I may, this is Dr. Moore. If I may, I actually think it's reasonable to assume that the adverse event would be less because, when you give primaquine long after chloroquine is given, the studies show that the adverse events are less.

DR. BADEN: I'm not worried about less.

(Laughter.)

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

DR. ORZA: I was just wondering whether the sponsor had, in terms of trying to make some trade-offs, especially with respect to global use, whether you had estimated the numbers needed to treat and the number needed to harm for death from malaria, relapse, and then for harm, a serious adverse event or death from the treatment.

DR. WEBSTER: We have looked at number needed to treat. Perhaps I could ask Dr. Green to respond to that, please.

DR. GREEN: So specifically, when we read out our studies that I presented today, the number

needed to treat was three, so you need to treat three individuals within the context of that to prevent one relapse.

DR. ORZA: To prevent one relapse or to prevent one death?

DR. GREEN: Well, we haven't had any deaths in our clinical program. We've done some very provisional look at modeling in terms of, for example, the rates of G6PD if somebody inadvertently took and had a hemolytic event because it was an off-label use, and deaths, and so on, and we think that the drug has an extremely good risk-benefit within that setting. I do not have that information to show you today.

DR. ORZA: Do you have number needed to harm for a serious adverse event?

DR. WEBSTER: No, we haven't looked at that.

DR. BADEN: Any other questions or comments from committee members for the agency or the applicant?

(No response.)

DR. BADEN: If not, I will follow the

schedule. We now get a 10-minute break, and we will resume at 2:35. And then I'll have the committee discuss a lot of the issues that have been raised to better put things in perspective, from our perspective and for the agency, so 10-minute break, 2:36.

(Whereupon, at 2:26 p.m., a recess was taken.)

DR. BADEN: One last round of clarifications. Some questions were asked about drug shortages, and I think Dr. Nambiar has a couple of clarifications associated with those questions earlier.

DR. NAMBIAR: Thank you, Dr. Baden. I think Dr. Tan had asked if they added the number of suppliers for primaquine. So there's at least 4, and it's not on the drug shortage list.

DR. BADEN: Dr. Green?

DR. GREEN: So I have a question to the agency and it's probably to one of the pharmacologists. During the public comment period, we heard one speaker talk to us about the

biochemical differences between mefloquine and TC. Another speaker tried to invoke the strong similarities. And I wonder if someone from the agency could just provide us comment on how they interpret the potential relatedness versus not relatedness of the two products.

DR. McMASTER: Thank you. Owen McMaster, pharm-tox reviewer. So I actually have some slides. I don't know. And next slide, next slide, and next slide. So we did in fact look specifically at this product. There was, of course, a concern whether or not this tafenoquine was actually similar. There had been published reports of brain damage and potential neuropsychiatric effects in soldiers.

So we looked pretty carefully at the sponsor's studies, looking at potential neuropsychiatric effects. And they did two studies which zeroed in on this issue. The first study was a single-dose study in rats, which looked at the effects, and then the second study was a multiple-dose study where young animals were dosed up to

adulthood and then allowed a recovery period and after which they were evaluated.

The single-dose study went up to 500 milligrams per kilogram, after which they did neurofunctional assessments. And this is what they looked at. They looked at locomotor activity prior to dosing and then locomotor activity and functional observation battery at the time participants.

I listed this because I wanted to make clear that it was pretty detailed in the different parameters that were evaluated to try to get at whether or not tafenoquine was actually causing anything which could possibly be interpreted as neuropsychiatric.

So for example, reactivity to handling, ease of locomotion, arousal, auditory assessments, pain perception, et cetera. So while not very clean and obviously not perfectly representing neuropsychiatric findings, the kind of data we get from these functional studies will give us an idea of whether or not, for example, the animals are

more anxious than they normally would be expected to be.

Motor activity was also evaluated in 60-minute sessions and it was broken down into 5-minute segments, whether they looked at horizontal and vertical movement of the rats. The oral juvenile study; as I said, young rats were dosed into adulthood.

They were submitted to both the motor activity and also the neurobehavioral function tests. In both instances, we did not see any effects. So there was no evidence from these studies that the animals were particularly more anxious. The idea of post-traumatic stress disorder relates vaguely to hyper fear responses or abnormal fear responses. There was no evidence in the studies that were conducted by the company to indicate that there's any baseline changes as a result of tafenoquine administration.

We did one study after single doses, which were up to pretty high doses, and also the [indiscernible] study, interestingly, we dosed, and

then after a delay to see if there were any delayed effects the drug and in neither case, was there any evidence of a problem.

Now, these tests aren't perfectly sensitive. So for example, I think there's a publication with mefloquine that shows that it also did not show any adverse findings in the functional observational battery test.

However, I think there was evidence in that published paper that there were histological changes in the brain after mefloquine. So in that respect, it is different. For the studies that were submitted to this NDA, there were no histological changes in the brain of animals after single doses or multiple doses of tafenoquine and, of course, this is a single dose regimen.

So I think we concluded that there was no evidence that there were adverse brain effects from the proposed regimen.

DR. BADEN: Thank you. Follow-on? Thank you very much. Dr. Orza?

DR. ORZA: Can you speak to the issue that

was raised by one of the public speakers about rats being an inadequate model in which to look at this? And then I have a related question, but probably not for him.

DR. McMASTER: So at this point, we have a question. I don't say we have a signal. I say we have a question. And so perhaps the best use of animals at this point -- we're the most important species at this point -- would be to consider a close evaluation of the human data that we have.

So to answer your question, it's not clear that the rat or the monkey is better, but at this point, it's possible to ask the question in humans. And I think that would give us the best answer.

DR. BADEN: When you say close evaluation of the human data, what do you mean, future study or data already collected?

DR. McMASTER: I'm not a clinician. I have to defer to the clinicians on this, but there may have already been evaluations of neuropsychiatric effects in this study. Certainly, as we've talked over the months, as we've been reading this, there

have been no signals in the patients. If perhaps we need to, once a drug is approved, obviously, vastly greater numbers will be exposed to the product. And that will increase our power to be able to tease out any subtle issues that we may have missed. So it's possible. I'm not suggesting a post-marketing study, but I suspect at this point that a human evaluation would be more useful than a monkey study, for example.

DR. BADEN: Thank you. Is there another? Sorry, Dr. Orza?

DR. ORZA: I had a related question about a couple of times when we've been discussing the cases, who experienced adverse events of one type or another. It was said that, that they kind of disobeyed the instructions to not engage in strenuous activity.

So I'm just wondering how, when we think globally, the populations that are going to be potentially getting this drug if they're going to be going back to lives or situations where they really can't avoid that.

DR. BADEN: If I understand you correctly, the clinical study is a rarified environment and use in general is much more complex, which is always a challenge. And I'm not sure they'll be able to speak to the use in general, but obviously that has to be weighed and considered.

DR. ORZA: Yes. But specifically on that point, how significant, how important is it to take it easy once you've taken this drug?

DR. BADEN: So I guess the question to the applicant is, is there anything about taking this drug that should restrict activity versus the study had certain rules to follow?

DR. WEBSTER: Yes. I think the point you're raising relates to the elevated CPK that we saw in a healthy volunteer study. Normally, in healthy volunteer studies, particularly we're aware of carefully evaluating such things as effect on the QT interval, which relates to heart rate, et cetera.

We request that subjects are resting and recumbent for most of the time. Elevations in CPK

are related to increases in physical activity and therefore can be detected in our laboratory evaluations, but they're not of clinical concern. They just relate to heavy muscular exercise.

So we don't believe that, that has any implications for any safety concerns when used in the real world.

DR. BADEN: Thank you. Dr. Follmann?

DR. FOLLMANN: I have a question for the FDA. So we're going to be voting on whether this drug should be acceptable for the U.S. and primaquine is already licensed, I guess, in the U.S. And we've had a pretty extensive safety and efficacy evaluation of tafenoquine.

So I can imagine the label for tafenoquine reflecting the studies that have been done and our impression of what signals there are, but I wondered what happened with primaquine. So did that have a similarly extensive database for safety? Was it grandfathered in from the 1960s to something else? And how did the label particularly regarding safety for primaquine -- what is the

evidence based on that?

I would imagine a physician looking at these two labels would implicitly think they're based on similar amounts of safety data. And is that the case or not?

DR. COX: Folks are helping me here, and I guessed 1952. Did I get that right?

DR. BADEN: Predated your tenure.

(Laughter.)

DR. COX: Predated my birth, I think.

(Laughter.)

DR. COX: So I guess the way to describe it is that the medical sciences have advanced significantly over the last several decades. So the quality of the evidence that we have for drug applications now, compared to, say, 40 years ago, we're more sophisticated in the way we look at things. And that's not just true of us. That's true of the medical literature.

So the amount of information that we have in the label is dated, to some extent, to the types of data that were available at the time the

application was approved. So like other drugs, like other therapeutic areas, what we have available now to evaluate the drug is probably more extensive than what we had back in the 1950s when it was originally approved, and the label reflects that. I mean, just looking at the primaquine label, it is an older-format label that looks consistent with something that was approved many, many years ago.

DR. FOLLMANN: To me, it would be a potential concern to the FDA that they're based on different amounts of data and information. They're the same kind of molecule and, yet, the way they're described in terms of safety and evidence is different. I don't know how you can reflect those nuances with the labeling for this or somehow that, that applies to how you label primaquine or maybe our remit here is just to look at tafenoquine by itself.

DR. COX: Yes, we would always like to have an ongoing collection of data that updates older information and incorporate that into the label,

but sometimes it is difficult. We do within this application have some information that allows us to look at primaquine and how primaquine performed. And that may really be the best information relevant to the adverse effects associated with primaquine from these studies, where it was in fact included in the comparator arm of some of the trials.

DR. BADEN: Thank you. Dr. Moore?

DR. MOORE: Thank you. So I think that's an important point. I mean, when you think about it, gentamicin probably would not have been approved if we had the tools then that we have now. The other thing, I think, conversely to look at, is the safety of primaquine. I mean, look at primaquine. It was approved back in 1952 with relatively less evaluation tools at their disposal.

If you look at the consequences of the drug since then, the chief consequence or side effect of the drug is hemolysis, as is true for all these. But in terms of neuropsychiatric effects, which is really more what we're discussing, primaquine has a

very long safety track record as far as we can tell based on 60-some years of use.

I think that's really the benchmark we have to look at.

DR. BADEN: Dr. Tan?

DR. TAN: To add to that, CDC did do an extensive review of the data that was available on primaquine for its use in prophylaxis in part and so on and again reiterating that we do have decades of use, of safety of use of primaquine since it has been approved.

Questions to the Committee and Discussion

DR. BADEN: Thank you. We will now proceed with the questions 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.

One of the things that I would like to do -- we on the committee are faced with decades of research, hundreds of pages of background reading,

hours of extensive presentations on a substantial amount of data.

I would like to take a little bit of time for us to discuss amongst ourselves what we consider the key questions in the data that we're struggling with. Please do not indicate how you are going to vote on either of the questions, but I would like us to have a chance to digest some of the information and to leverage the committee's expertise and, in the process, the agency will overhear our thinking of how to weigh the issues.

I'll start the discussion in that issues that have struck me in the information that has been shared -- and I think it is a comic conundrum of a new application -- has to do with the amount of safety data, whether it's 4,000 exposed, whether it's 500 exposed depending upon how one defines exposure.

So we're always left with the issue of the adequacy of the safety data. However, are the safety data shared reasonable given the disease, given what's being treated and the signals that we

see. And so I struggle with that because it's always an issue of, we can see a 1 in 300 chance of a serious side effect, so Stevens-Johnsons or TEN as mentioned may well occur at 1 in a million. And we'll never see that.

There are other concerns that have been raised that will not be seen at this rate of exposure. However, is that a reason to say we should wait? Is that too grave a concern or is that part of the process of considering a new entity for a disease, where the data we have, not necessarily the data we want, for a condition that has a significant disease footprint in real time.

So I struggle with that always and here is yet another time. However, the amount of data shared to me doesn't seem unreasonable in terms of the amount of safety signal. I am concerned about the 2 hypersensitivity cases, but I don't know how to weigh that. It's 2. And then perhaps placebo had hypersensitivity and we all see hypersensitivity in practice.

So it's hard to tease it out from

background, but with a drug that has a 15-day half-life or 10 weeks of exposure that's measurable, that concerns me. On the other hand, that's part of the advantage given the difficulty of taking a drug every day for 2 weeks. I don't know how others weigh the hypersensitivity concern in a drug of such half-life. Dr. Zito?

DR. ZITO: Well, I would think that, given the need, we could proceed to see that it is not delayed in being made available, but that we would assure, try to assure that the very best methods in epidemiologic methods in doing a post-marketing surveillance study to address the concerns would balance the benefit and risk.

DR. BADEN: Dr. Orza?

DR. ORZA: My follow-up on your point was going to be similar, that we're always in this situation and it can be somewhat ameliorated by assurances that there will be very robust post-marketing both continued testing as well as surveillance. And I think the difficulty is that, in reality, that frequently doesn't happen to the

extent that we hoped for when we kind of made the trade-off.

DR. BADEN: Dr. Beyrer?

DR. BEYRER: Just an additional point that, in the HIV model, which I'm most familiar with, we have learned that one of the real benefits of treatment is the huge impact it has on reducing onward transmission.

So that of course is a very big part of the global goal here with eradicating this liver phase with this new agent. And so I would just add that I think part of that post-marketing surveillance ought to be also, if at all possible, surveillance epidemiologic measures of the impact that this is having on malaria control, where it's being used, because I think that, that certainly is a part of the benefit side, the public health benefit of dealing with this relapsing malaria variant.

DR. BADEN: So it's the issue of how much data can be generated as part of a prospective study, which will always be limited, and then how much will be after the fact when there's broader

use, and enabling that kind of data acquisition.

DR. BEYRER: Yes, but specifically saying that there's another kind of data that's important, which is not just safety of the individual, but the public health.

DR. BADEN: The community.

DR. BEYRER: Yes, absolutely.

DR. BADEN: The community as well.

DR. BEYRER: The impact on onward transmission.

DR. BADEN: And the same issue with the psychiatric data, which are equally as hard to interpret when you have two cases. Other issues that were raised were around generalizability. And I'm not sure I'm convinced that the activity of this agent and the hypnozoites in one part of the world is different than the activity and hypnozoites in another part of the world. But that issue was raised, and I don't know if others have concerns with that generalizability. We should think more deeply about that. Or is that less of a concern in this setting. It seems like, Dr. Tan,

you had a reaction.

DR. TAN: With the exception of the Chesson strain that was brought up in Papua, in Indonesia, I would think that this could be generalizable to vivax hypnozoites in other regions.

DR. BADEN: Dr. Moore?

DR. MOORE: Just to echo what Dr. Tan was saying, I mean, really, when you look at the recommendations for treatment, we use primaquine regardless of where the vivax was acquired globally. Based on these data and although we weren't asked to consider the other data specifically, as I mentioned, this drug has been used in Australia for quite some time in the Australian Defense Ministry.

There is little if any reason to believe that there is any reason that this drug would not work for the hypnozoites of vivax, regardless of where they're acquired on the globe.

DR. BADEN: Do members of the committee have any other issues they would like to discuss amongst the committee? Dr. Beyrer?

DR. BEYRER: Not an additional issue, but just a carry-on to that point, which is I think that we heard from various different speakers today that, of course, the innovation here is the single dose and that, that benefit both likely has bearing in a number of international settings, but also in the U.S. So in that sense, there's also a generalizability to the ease of dosing and the single dose approach that I think that's generalizability to.

DR. BADEN: Thank you. Dr. Weina?

DR. WEINA: When you brought up the idea of having this discussion among ourselves, I thought that was a great idea from the standpoint that sitting on enough of these committees now, I'm struck by two things.

One of the things is that, after the vote and people bring up their points as to why they voted the way they voted, sometimes you see other members go, "Geez, I wish I had thought of that," number 1.

But the other thing I'm struck by is,

sitting in enough of these committee meetings, bringing up and raising the issues that we're bringing doesn't necessarily mean that we object to the product going forward or bringing up a point about a safety issue. That it sure seems safe doesn't necessarily mean that we want to necessarily approve it, but it's that discussion that becomes necessary, for example, when we're talking about HIV drugs.

I know that I use primaquine very different than a lot of my colleagues that treat malaria just because of my experience with it and my comfort with primaquine, just like many of my colleagues feel much more comfortable with using HIV drugs than I feel when I go to them and ask them for advice as to how to do it. So having these discussion is really important to inform the FDA, I think, about the labeling aspects, and things to think about for the labeling, and how much weight actually to put on things, so those were the things that I'm struck by.

DR. BADEN: Before we move to formally

voting on the questions, are there any other issues members of the committee would like to discuss and have input on how to weigh or aspects of the presentation or data that warrants some discussion? Dr. Orza?

DR. ORZA: Maybe some thinking on, globally, this will be used in places where it's endemic and where people are looking at multiple infections and having this treatment multiple times potentially and just what is the thinking about that, because all we have is information on one time in 6 months, 6 months out.

DR. BADEN: I've struggled with that point as well, that the data we're given are tafenoquine, chloroquine, given together, times 1. We're not presented tafenoquine given on its own as radical cure. We're not given repeated dosings for radical cure.

So from my perspective, there's a lot of data missing. On the other hand, from my perspective, is this a reasonable study to establish the initial efficacy and side effect that

isn't so complicated to interpret?

So there are many more questions in my mind, and that's why at least in part of the earlier discussion with the applicant and the agency, I was trying to understand if there's a reason to believe that there's a uniqueness of how it was deployed that should restrict how it's used versus the uniqueness of how it was deployed and was a series of pragmatic decisions to generate a reasonable dataset.

So I share your concern, but I'm still struck, at least for me, this is not an unreasonable dataset to make an initial assessment with many more questions. Dr. Mailman?

MR. MAILMAN: We're given clearance at 6 months. It's not like we're giving clearance only two months or three months in. So we're at least through some cycles of the life cycle of malaria, so I don't think it's quite one time. It's a decent period of time.

DR. BADEN: Dr. Weina?

DR. WEINA: I just want to add the one

caveat, though, and that is that I've brought this up at virtually every meeting we've had on every drug. And that is that, when a new drug gets approved and it's approved, here in the United States, we can use it off-label. They can't market it that way, but it sure as hell can be used off label.

So if we say let's approve it for single radical-use treatment in 16-year-olds, well, if somebody decides that they want to use it in a 15-year-old for prophylaxis. It's just not approved for that purpose.

DR. BADEN: Dr. Moore?

DR. MOORE: So these are the concerns that we always have, have had on this panel for years. And there's no way to reconcile that. I mean, we can't protect patients from bad decisions by physicians.

UNIDENTIFIED SPEAKER: There should be a shirt that says that.

(Laughter.)

DR. MOORE: Right. And I'm not saying that

one particular thing that he raised is a bad decision. What I'm saying in general is that -- and this is from personal experience -- anecdotally, I can tell you there are lots of physicians -- well, thankfully not lots, but there are some physicians that use drugs off label with disastrous consequences and based on limited or no data.

Unfortunately, that's not the reach of this panel. Strictly, that's something that's beyond the reach of the panel. With regard to the tafenoquine data, all I would say is that the pragmatic decisions that led to the generation of the data we were asked to review and discuss also has an ethical basis as well because you can't do the clinical studies in a different way to generate specific data ethically, looking at tafenoquine by itself.

That's a serious problem with regard to recruitment. I mean, scientifically and ideally, you'd like to have just tafenoquine by itself, but it can't be done and I think we'll have to look at

that if we have a post-marketing study.

I take that back. There have been some data which were not presented at this meeting, but will be presented in two weeks regarding the use of tafenoquine, multiple doses, for prophylaxis, which we'll discuss another time.

DR. BADEN: But even if data can be generated, we still are left with, are the data before us reasonable for the questions before us.

(Crosstalk.)

DR. BADEN: Yes. Dr. Orza?

DR. ORZA: I agree with the dilemma of, after approval, it can be used however it wants and, ultimately, we can't protect patients from bad decisions. But I don't think we should totally throw up our hands in hopelessness at that because I think that there are things that can be done in the labeling, in the med guide, in the instructions to patients, in the guidelines that the Infectious Disease Society develops that can help both clinicians and patients weigh these options because, hopefully, it will be an option. Right?

Globally, I'm not too sure about that, but at least in the U.S., hopefully it will be an option that physicians and patients talk through together and make the decision that's best for that patient.

DR. BADEN: Yes, Dr. Mailman?

MR. MAILMAN: I'll bring up what I brought up before. We might do something where we do a label that says we require GP6D testing, which is easy to get in the U.S. Or now we're waiting on something else to be developed that might not show up in the time that the drug's available, so it's hard to keep those not decoupled.

DR. BADEN: Yes. There will be aspects that'll have to be coupled. We shall move forward now with the voting. So we'll 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're unsure of your vote and 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. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll 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'll continue in the same manner until all questions have been answered or discussed. So the question before us is, has the applicant provided substantial evidence of the effectiveness of tafenoquine for the radical cure, prevention of relapse, of plasmodium vivax malaria in patients 16 years of age and older?

If yes, please provide any recommendations concerning labeling. If no, what additional studies, analysis are needed? Are there any questions about the wording of the question?

(No response.)

DR. BADEN: If no questions, then we shall

proceed to the vote. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds and then we're done.

(Voting.)

MS. BHATT: Voting results, yes 13, no zero, abstain zero, no voting zero.

DR. BADEN: So we will start with Dr. Follmann, if you wish to explain any aspects of your vote or advice to the agency.

DR. FOLLMANN: Thanks. Yes. I'm Dean Follmann. I voted yes. I thought the efficacy data was very strong. They showed in the dose-ranging study and in the definitive study a substantial benefit compared to placebo.

When we do a pooled analysis to compare it to the primaquine regimen, we see they're very similar with confidence interval less than a margin of 10 percent. So this wasn't very hard.

Just a couple comments, I don't think we really have any data on reuse of this drug for someone who's infected over several occasions and

it seems, within the studies, they could have looked at that. What they did do is, once infection recurred, they were given primaquine. In principle, you could have randomized to primaquine and tafenoquine.

Yes. You could have randomized to the two drugs and then you would have gotten some information on repeat use. The other comment I would have about labeling specifically is, primaquine has a label. And I don't know what study it was based on. The studies we saw today were based on excluding severe malaria.

So if you're a strict constructionist, maybe that would be in the label. But is that fair in a way? Because maybe primaquine should have the same issue, so I don't really know about that. It seems like there's a potential for labeling disparity given the difference in information the two drugs have had.

If one says can't use in severe, the other is agnostic about it, would that fairly tip it to the drug that's agnostic about it? I don't know.

So the FDA can wrestle with that.

DR. BADEN: Thank you. Dr. Honegger?

DR. HONEGGER: Jonathan Honegger. I also voted yes. I felt that the evidence for efficacy was robust. I'm grateful that the investigator sponsored and patients participated with a placebo arm to show that. And I'm grateful that there was a primaquine arm as well for a benchmark comparison.

I echo the comments that future analysis of this drug in the setting of when chloroquine is not used will be important.

DR. BADEN: Dr. Clark?

DR. CLARK: Nina Clark, I voted yes. I thought that the studies were well designed and conducted. And there were no significant discrepancies in analysis noted by the FDA. I also thought the pooled analysis was helpful to look at. And the fact that tafenoquine is a single-dose therapy, to me, represents a really important advantage.

Regarding labeling, I agree with

contraindicating its use in those with less than 70 percent of normal G6PD activity. And I think hematologic tests should be monitored after treatment given the potentially or presumed wider use than the patient types that were included in these studies.

DR. BADEN: Thank you. Dr. Gripshover?

DR. GRIPSHOVER: Hi. I'm Barb Gripshover and I voted yes as well for the same reasons. I thought that all three studies showed that it was efficacious and that I did appreciate having both the comparator, primaquine, as well as the placebo arm and the pooled analysis was great.

I think that I also am worried about repeat infections and I think that's something going forward we want to know if it's going to remain efficacious, especially when it's in areas where people will be repeat infected. And also it's going forward to know if we can use it by itself after either treatment of an acute severe infection; can they again get that rather than primaquine?

DR. BADEN: Lindsey Baden. I voted yes. I think the consistency of the efficacy data across the three studies were highly consistent and effective.

DR. WEINA: Pete Weina. I voted yes. I think the data was very strong, good, robust data. I think it's critical for us to have options, especially as previously stated because of the possibility of repeat infections and, just to get on my soap box quickly, HIV, tuberculosis, we treat with multiple drugs all the time and we have tons of different options to go with and, for malaria, we have so much disrespect for it that we still treat it with a single drug and hope that it's going to stick around for 50, 60 years. And I don't think we're going to have that luxury in the future, so I think this is critical to have.

DR. BADEN: Dr. Green?

DR. GREEN: Michael Green. I voted yes. I think that, while formally powered comparisons for noninferiority between primaquine and chloroquine to TQ plus chloroquine was not carried out. The

results of the three studies presented convinced me that, in this optimized study circumstance of higher compliance probably with the PQ plus CQ than would be in practice.

We saw what I think is probably equivalence and I would presume that, then, in the real-world practice, it would be superior. Having said that, this study was specifically not carried out in patients with severe malaria and, accordingly, I would be concerned with the labeling language that did not account for a lack of evidence in such patients. I would presume that, for at least now, the label would be stating the use would be in combination with chloroquine and not with other agents besides chloroquine for P. vivax at this time until there's additional data.

People may do it, but I think that this is what the data is based on. This is what my recommendation is voting for and in not knowing how it would combine with other agents, I don't know that there could be unsuspected drug interaction or something that could lead to an untoward outcome

that wasn't expected.

DR. BADEN: Dr. Orza?

DR. ORZA: Michele Orza. I voted yes and I agree with the comments previously made and would just reiterate the suggestion that there be, as I always would like to see, when there are options, that there is help for both the clinician and the patient to weigh those options and make a choice.

DR. BADEN: Mr. Mailman?

MR. MAILMAN: Josh Mailman, I voted yes. I concur with the statements that were made before, but also voting for patient convenience and patient compliance because I think those are things that will help in this area.

DR. BADEN: Thank you. Dr. Moore?

DR. MOORE: For me, this is a bit of a slam dunk. I mean, the efficacy data were to me very compelling and the kind of compelling data we don't often see in clinical trials. I think what's been said has been said. I think this would make an excellent addition to the armamentarium of fighting malaria and it's nice to be able to bring the

treatment of malaria into the 21st century.

DR. BADEN: Thank you. Dr. Tan?

DR. TAN: I'm Katherine Tan. I voted yes. I concur with the statements already made about the consistency of the efficacy data and the potential for improved adherence with single dosing. And the clinical advantages aside, I think that this will be a very important tool in the control of global malaria.

All of our malaria in the U.S., most of it, is imported from travelers traveling abroad. And so control abroad is really key to controlling imported malaria in the U.S. And so that's another added reason for it.

DR. BADEN: Thank you. Dr. Beyrer?

DR. BEYRER: Chris Beyrer. I voted yes. I also found the efficacy data and the consistency of it across the three studies very compelling and I also was compelled by the global health malaria control effort. And I found that aspect of this really very important for the global effort against malaria.

DR. BADEN: Thank you. Dr. Zito?

DR. ZITO: I voted yes and I have two points in terms of recommendations. I'm not an expert in the field of infectious disease, but I would like to suggest that a strong, creative approach to post-marketing surveillance could be putting in place -- today we have electronic medical records and all sorts of good opportunities to do really essentially protocols in community-based individuals, which would add greatly to generalizability.

Also, this was a 6-month endpoint and I'd like to know about one year or after at a minimum. And then my second recommendation is again as a non-expert in the labeling. I was quite astonished at the use of the term radical cure, which is really not an operational definition of what has taken place in this study.

I don't really understand the merits of using that. And so I would recommend that you just stick with what you actually measured operationally, which is whatever the words are, but

I think you all know it better than me.

DR. BADEN: Thank you.

So just to briefly summarize for the agency, it was unanimous on efficacy. There was one panel member who said a slam dunk. As many panel members said data highly consistent regarding efficacy. However, there are many lingering questions that will have to be worked out on efficacy, including the repeat dose issue, how the label reflects primaquine, not to confuse the community, although those are different questions, how to use in severe vivax, where it may not be usable up front, but perhaps in the tail.

The options for treatment is really important. The global health benefit is important. We need to provide some guidance to the patient provider so they understand how this new agent fits in. The convenience compliance is a very important factor. The issue of efficacy; we'll need to dissect out reinfection versus relapse and durability at a year when tools become available that can help dissect that out.

Then the generalizability seemed reasonable. So that is on the efficacy side. Question 2, has the applicant provided adequate evidence of the safety of tafenoquine for the radical cure, prevention of relapse of plasmodium vivax malaria in patients 16 years of age and older. If yes, please provide any recommendations concerning the labeling. If no, what additional studies and analyses are needed?

We'll now go to the vote with the same process.

(Voting.)

DR. BHATT: Voting results, yes 12, no 1, abstain 0, no voting 0.

DR. BADEN: We will now start with Dr. Zito. And state your vote for the record and any comments regarding the FDA's labeling issue.

DR. ZITO: Well, except the safety information and the consistency of the safety information, there certainly are a lot of debatable points that came up here that relate to the importance of the neuropsychiatric adverse events,

for one, and the hemoglobin decrease for another.

So I'm imagining that these would be areas for post-marketing surveillance to settle those questions.

DR. BADEN: Thank you. Dr. Beyrer?

DR. BEYRER: Chris Beyrer. I voted yes as well on the safety issues. I thought that safety looked quite consistent with primaquine. And as we discussed as a group, the labeling issues around G6PD is an important aspect of the safety.

We know that and we know that, that is already part of further discussions and pre-existing psychiatric conditions warning on the labeling. But I was otherwise quite comfortable with the safety.

DR. BADEN: Thank you. Dr. Tan?

DR. TAN: Katherine Tan. I voted yes. Just to echo what Dr. Beyrer has said, I thought the safety profile was similar to primaquine. We have already discussed G6PD testing.

DR. BADEN: Thank you. Dr. Moore?

DR. MOORE: Not much to add. There remain

some safety concerns, which I think with a single dose of treatment, based on the data provided, are very reassuring that, if they are present there, they appear to be minimal or no greater than primaquine.

Whether that is true for repeated dosing is another story in which we'll presumably be addressed with the meeting in two weeks.

DR. BADEN: Dr. Mailman?

MR. MAILMAN: Josh Mailman. I voted yes. I echo what the previous speakers have said. I thought that both the sponsor and the FDA responded to all the questions about additional safety concerns and also what we've already addressed with the G6PD.

DR. BADEN: Dr. Orza?

DR. ORZA: Michele Orza. I voted no. I'm a little nervous about being a minority of one in this august group. I was reacting largely to the word adequate and the discussion that we had about how fundamentally it's never really adequate. I mean, I am reassured that it's broadly similar to

the profile for the PQ. I have some remaining concerns about the long half-life and especially concerns about, when it gets out there globally in settings that are very much less controlled and supported than the U.S. setting, that there be a lot more attention paid to post-marketing and studies and surveillance.

So the no vote was really to encourage that to happen.

DR. BADEN: Dr. Green?

DR. GREEN: I voted yes. In sitting through the presentations and especially the concern for the potential for neuropsychiatric adverse events, it became clear to me why this was brought to the committee. The data shared with us today appears to include as many as 3,000 plus treated individuals, including those receiving a higher and/or lower dose than what is being proposed as the indicated dose.

To my mind, the data as presented do not confirm a risk for this potential neuropsychiatric side effect, though it does not rule it out and

does support a need for ongoing vigilance.

Further, I think the studies in lab animals looking for potential neuropsychiatric effects are encouraging. Thank you for sharing it. I would have encouraged you just to include that in the plan presentation and not wait for one of us to potentially ask to see those data because it was really very reassuring.

Having said that, the need for ongoing vigilance does not warrant a specific contraindication through labeling, advising consideration to potential risks and benefits in the individuals with a prior history of neuropsychiatric disease.

However, potentially considering using it with caution might be reasonable, so you can consider that and then individualize your decision.

In terms of other side effects discussed, I agree within support the plan for post-marketing surveillance in both the United States and elsewhere in the world for the side effects with anemia, nausea, et cetera.

DR. BADEN: Dr. Weina?

DR. WEINA: Pete Weina. I voted yes. And I have to basically echo an awful lot of what Dr. Green just brought up. I understand why a presentation that seemed like a total slam dunk, they wanted to bring to the committee. And that was probably because of the side effect issues.

I have to agree with Dr. Green that I don't think the data supports an overt concern at that. Of course, you can never truly rule it out, so having post-marketing surveillances is always critically important and prudent, but specific labeling regarding it, I don't think is warranted.

DR. BADEN: Lindsey Baden. I also voted yes. Safety is forever a difficult area to assess given efficacy is geared to a specific finding and one can power a study for that. Safety often appears random early on until a pattern emerges and maybe at a 1-in-100 rate, or 1-in-1,000 rate, or 1-in-1,000,000 rate.

However, the fear of a safety concern is not a reason not to move forward with a therapy that

has efficacy for a disease with real consequence. And so the amount of safety data presented seemed reasonable and reasonably reassuring. However, the two hypersensitivity cases, the two psychosis causes are pause for concern and warrant very careful post-marketing monitoring to see if a pattern really emerges and then a mitigation strategy if necessary.

However, a concern for a possible safety concern in the future is not a reason not to have a therapy available today. And I think the totality of the safety data in the context of primaquine is quite reassuring and just warrants, as stated before, some way to enhance post-marketing studies. And I would commend that to the applicant to do their due diligence in post-marketing studies and to the agency to try and encourage such data to be generated, as it will serve all of us better to have those data. But overall, the safety data, I think, were reassuring. Dr. Gripshover?

DR. GRIPSHOVER: I'm Barb Gripshover and I voted yes. I thought the safety data did look

pretty comparable to primaquine. I think, in terms of the label, one thing that I think is important just to make a note, that people remember that drug does stay in you for 10 weeks. And people think that, they give it one dose and they may forget when someone comes with hypersensitivity two weeks later.

So I think that it should just be in there as a reminder and that maybe we should use with caution in persons with a history of psychosis. I wouldn't say don't, but until we know more, especially since we do have another option that isn't in you for 10 weeks, and then just to maybe note that we have seen some late hypersensitivity cases -- and then if we don't see them in the post-marketing studies later on, we could maybe always take that out.

DR. BADEN: Dr. Clark?

DR. CLARK: Nina Clark. I voted yes. And I had similar thoughts to others on the panel who voted yes. I thought that the safety data presented were reassuring. That being said, there

are limited data in older adults and some other populations. And I'm wondering if the labeling should reflect that such as people with renal or liver dysfunction, elderly, and those who are on drugs that may be substrates for the renal transporters.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: Jonathan Honegger. I voted yes for reasons that have already been mentioned. I just wanted to also echo or state that I'm glad to hear that pediatric studies are ongoing, I believe, and I hope that those are carried through to completion. Also, just to give some perspective that made me feel comfortable is that, in the U.S., at least examples I'm familiar with, people who treat malaria don't see it all the time, so we tend to go back and look at guidelines and look things up.

I'm often going to the CDC. So in addition to the agency and the sponsor, hopefully in the post-marketing protocols, can be aligned with the CDC, which is a website that people tend to turn to

when they're treating malaria.

DR. BADEN: Thank you. Dr. Follmann?

DR. FOLLMANN: I'm Dean Follmann. I voted yes for many of the reasons that have been articulated already. I thought the safety profile was similar to PQ. I think, for a U.S. post-marketing study, I think I'd be nice to look at both PQ and TQ so you can have a comparison group instead of just a one-arm post-marketing study. And that's all I have.

DR. BADEN: Thank you. So that concludes the voting and discussion for the agency. It was 12 yes, 1 no on the adequacy of the safety data. The overall sentiment was, it looked broadly similar to PQ. The safety data was largely reassuring. However, the series of events of specific note require careful monitoring in a post-marketing assessment.

The hemoglobin, the methemoglobinemia, the G6PD, should be easier to slate into a label. The issue of the PK data so that the practitioners are aware of the real tale in half-life, so that

they're able to incorporate that into their thinking is probably prudent, and that other populations such as elderly, pediatric, those with co-morbid illness need to be thought about in case there are any alterations in drug handling and if not, as those data are generated, to also be provided so the community is aware.

The 1 no vote was just overall concerned about the adequacy of the safety data, which is of course a lingering concern. So now that we are complete with the committee's activities, I would like to thank the applicant and the agency for tremendous presentations of a tremendous amount of data to allow the committee to have such a fruitful discussion.

Then if there are any final comments from the agency?

DR. NAMBIAR: Thank you, Dr. Baden. I'd like to thank the committee for taking the time to participate in today's discussion and for all the advice they have given us, very useful. We'd like to thank all the speakers at the open public

hearing for sharing their thoughts and also would like to thank the applicant for all the hard work that they've done with this application. And lastly, big thanks to the review team at our end for all the hard work as well.

I wish you all safe travels and we'll see some of you in two weeks.

Adjournment

DR. BADEN: The meeting is now adjourned and you have 25 minutes back.

(Whereupon, at 3:35 p.m., the meeting was adjourned.)