**FOOD AND DRUG ADMINISTRATION**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

# ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

**Thursday, July 26, 2018**

**8:30 a.m. to 3:52 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**

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**(Chairperson)**

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C O N T E N T S

**P R O C E E D I N G S**

**(8:30 a.m.)**

**Call to Order**

**Introduction of Committee**

**DR. BADEN: It is now 8:30. Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices that go bleep, if you've not already done so. I would also like to identify the FDA press contact, Theresa Eisenman. She's waving in the back.**

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

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

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

DR. YASINSKAYA: Good morning. Yuliya Yaskinskaya, clinical team leader, Division of Anti-Infective Products, CDER, FDA.

DR. PATEL: Good morning. Sheral Patel, clinical reviewer, Division of Anti-Infective Products.

DR. LI: Good morning. Xianbin Li, statistical reviewer from FDA.

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

DR. OFOTOKUN: Ighor Ofotokun, a member of the committee from Emory University, infectious diseases.

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

MS. BHATT: Dr. Gripshover, could you please introduce yourself?

DR. GRIPSHOVER: [Inaudible - audio gap] -- infectious disease, Case Western Reserve

University. And unfortunately, my flight was canceled, so I'm on the phone.

MS. BHATT: Thank you.

Kalyani Bhatt. I am the designated federal officer for this advisory committee.

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

DR. WEINA: Peter Weina, infectious disease, Walter Reed National Military and Medical Center.

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

DR. ORZA: Michele Orza, the Patient-Centered Outcomes Research Institute in Washington, D.C.

MR. MAILMAN: Josh Mailman, FDA patient representative.

DR. MOORE: Dr. Tom Moore, infectious disease physician in Wichita, Kansas, University of

Kansas.

DR. TAN: Kathrine Tan, chief of the domestic response unit, malaria branch, CDC.

DR. BILKER: Warren Bilker, biostatistician, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania.

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

DR. ATTILASOY: Good morning. Ercem Atillasoy. I'm vice president at Merck research labs for vaccines and infectious disease, regulatory affairs.

DR. BADEN: I would like to thank the committee and all presenting for being able to make it here despite the weather. And, Dr. Gripshover, we feel your pain, as the weather in Washington yesterday made travel for all extremely difficult. But I appreciate everyone's effort to be here to be able to have this meeting.

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 topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'll now pass it on to Kalyani Bhatt, who will read the Conflict 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, or FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special

government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not substantial as to be deemed likely to affect the integrity of the service which the government may expect from the employee.

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

Today's agenda involves the discussion of new drug application NDA 210607, tafenoquine

tablets, 100 milligrams, sponsored by 60 Degrees Pharmaceuticals, for the proposed indication of prevention of malaria in adults for up to 6 months of continuous dosing. This is a particular matters meeting during which specific matters related to 60 Degrees Pharmaceuticals' NDA will be discussed

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Atillasoy is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Atillasoy's role at this meeting is to represent industry in general and not any particular company. Dr. Atillasoy's

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, the 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 that they may have with the firm at issue. Thank you.

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

FDA Opening Remarks - Yuliya Yasinskaya

DR. YASINSKAYA: Good morning. My name is Yuliya Yasinskaya. I'm a medical team leader in the Division of Anti-Infectives, and I will provide you with an overview of the submission as well as the outline for the day.

The topic of today's advisory committee discussion is NDA 210607, tafenoquine for the

prevention of malaria. NDA 210607 is for tafenoquine tablet, 100 milligram. The applicant for this application is 60 Degrees Pharmaceuticals. The NDA was granted a priority review, and if approved, tafenoquine will be added to the armamentarium of drugs for malaria prophylaxis listed here.

The indications being sought is prevention of malaria in adult for up to 6 months of continuous dosing. Anticipated clinical regimen -- the presentation will refer to this as tafenoquine ACR -- includes two 100-milligram tablets taken daily for 3 days prior to travel to a malarious area, as loading dose, followed by a 200-milligram dose weekly while in the malarious area. And once the travel had been concluded, a single 200-milligram dose is taken within a week upon return from the malarious area.

The development program for tafenoquine ACR included 5 randomized, double-blind efficacy safety trials. Three of them compared tafenoquine ACR regimen to placebo in semi-immune population in

Ghana and Kenya and included studies 43, 45 and 30. A single trial compared tafenoquine ACR to mefloquine in non-immune military deployed to East Timor, study 33, and a single challenge study in healthy volunteers. The program also included the ophthalmic and renal safety study, study 57.

On this slide, efficacy results are of summarized. In two trials, 43 and 45, where tafenoquine was compared to placebo in the semi-immune population, Kenya and Ghana, for the protective efficacy endpoint in all randomized subjects, it was found superior to placebo. In study 43, parasitemia was observed in 92 percent of the placebo subjects at week 15 compared to tafenoquine ACR of 24.6 percent, whereby protective efficacy was calculated to be 73.3 percent with a 95 percent confidence interval of 54 to 84.5 percent, defining it as highly statistically significant.

In study 45, parasitemia in the placebo arm was observed in 93.6 percent of subjects at week 12 compared to 26.9 percent of subjects on the

tafenoquine ACR arm. This finding was also highly statistically statistically significant. I would like to note, the source data for studies 43 and 45 were not available for FDA audit.

In study 33, tafenoquine ACR was compared to mefloquine for the prophylactic success assessed at 26 weeks. tafenoquine ACR attained prophylactic success in 96.1 percent subjects compared to mefloquine of 96.9 percent, with a difference of 0.76 and a 95 percent confidence interval of minus 3.71 to 3.57. As the malaria attack rate in the study population was unknown, noninferiority margin in the study cannot be justified. Therefore, this study provides supportive data for the NDA.

In trial 30, tafenoquine ACR was also compared to placebo. In addition, a mefloquine arm served as a benchmark. However, there was an erroneous reading of the parasitemia slides in this study, requiring centralized blinded re-read. We consider this study is not concerning for efficacy.

An additional study of erythrocytic

Plasmodium falciparum phase challenge compared tafenoquine ACR to placebo and found that tafenoquine ACR provided 100 percent protection against the erythrocytic Plasmodium falciparum phase challenge compared to no protection in the placebo arm. The finding was highly statistically significant.

With regard to safety, for the indication of prophylaxis for the dose and duration proposed, we consider the safety database relatively small. 825 healthy subjects had been exposed to tafenoquine ACR in the development program and 529 of them had received tafenoquine ACR at the proposed duration of 6 months. The safety findings included hemolysis and methemoglobinemia, and the risk for hemolysis and methemoglobinemia is the highest in the patients with G6PD deficiency.

Upon review of the EKG data submitted, our QT multidisciplinary team had identified that the QT prolongation potential of greater than 20 milliseconds could be excluded.

Psychiatric adverse reactions were rare,

mainly limited to sleep disturbances. However, a few serious psychiatric adverse reactions primarily in subjects with underlying psychiatric illnesses had been observed, both in tafenoquine ACR as well as the extended safety database that included other dosing regimens. Ocular safety findings were primarily limited to vortex keratopathy.

For today, my presentation will be followed by the presentations by the applicant. Presentations by FDA will include efficacy presented by Dr. Xianbin Li; nonclinical findings will be presented by Dr. Owen McMaster; and safety findings will be presented by Dr. Sheral Patel. Both applicants and FDA presentations will be followed by clarifying questions. And after lunch, we'll have open public hearing followed by questions to the committee.

We have two questions to the committee today. Has the applicant provided substantial evidence of effectiveness of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing? If yes, we ask you to

provide any recommendations concerning labeling. If no, we want you to discuss any additional studies or analyses that are needed.

The second question deals with safety. Has the applicant provided adequate evidence of safety of tafenoquine for the prevention of malaria in adults up to 6 months of continuous dosing? If yes, provide any recommendations concerning labeling, and if no, we want you to discuss any additional studies or analysis that are needed. Thank you.

DR. BADEN: Thank you, 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 nonemployee presenters, to advise the committee of any financial relationships they have with the applicant such as consulting fees, travel

expenses, honoraria, and interest in a sponsor, including equity interests and those based on the outcome of the meeting.

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

We will now proceed with 60 Degrees Pharmaceuticals' presentations. Dr. Dow?

Applicant Presentation - Geoffrey Dow

DR. DOW: While we're getting the slides going, I'll just make a few introductory comments.

My name is Geoff Dow. I'm the CEO and chief scientific officer of 60 Degrees Pharmaceuticals. I have the privilege today of being the custodian of ARAKODA for malaria prevention, which we as the sponsor think will be a significant step forward for both travel medicine and for malaria eradication in the event that it's approved.

This product represents the product of 40 years of joint development with the U.S. and Australian militaries, and the presentation we'll make today wouldn't have been possible without the contributions of generations of researchers, the efforts of patients, and significant taxpayer contributions, as well as private investment. We're grateful for all of those contributions. We'd like to thank the FDA and the committee for the opportunity to present our data today.

Our objective will be to address the two questions posed by the FDA, but we're also going to take some time to address directly the concerns of the advocacy community in relation to neuropsychiatric safety.

Two weeks ago, we convened in this room to review the data for GSK's application for a single dose of 300 milligrams for Plasmodium vivax. In public statements, representing the sponsor, I supported this novel addition to the malaria armamentarium. But it's not ambitious enough because the reality is that Plasmodium vivax has a

much smaller global impact than Plasmodium falciparum. And if we want to really eradicate malaria eradication, we're going to really have to think differently about what products we use and how we use them.

The data in this table, and specifically highlighting the green numbers, show the case incidence of Plasmodium falciparum globally. Currently, the malaria community's approach to eliminating malaria is to focus on bed nets and the treatment of symptomatic disease. This worked for a period of time with malaria case rates declining from 2010 through 2013, but since then, those efforts have stalled.

So if we're really serious about global malaria eradication, we're going to have to think differently about what types of products we use and how we use them. Specifically, we may need new therapeutics with different kinds of labels that allow multiple dosing, longer durations of dosing, and dosing in asymptomatic subjects and in non-immune subjects, because, of course, the

malaria parasite reservoir is vastly greater than just those who have symptomatic malaria.

I also want to note that 17 years ago, I contracted falciparum malaria in a clinical trial in the context of easy diagnosis and access to effective treatments. If you're an African kid or traveler returning from holiday and you have malaria, that's simply not the case, and we have an obligation to do better.

This is the rate of U.S. malaria. It's increasing. And all of this is preventable if folks take their chemoprophylactic drugs. Ninety-six percent of malaria in the U.S., according to the CDC, is because travelers don't take their medications.

This lady is Shelley Hill who went to Thailand to look after elephants, contracted malaria, and ended up in the ICU in a Queensland Hospital. These photos are taken from the media coverage associated with that event. She had to have partial limb amputations because of the sepsis associated with falciparum malaria. This is

entirely preventable.

As a sponsor, we think ARAKODA, because of its long half-life ability to dose it for 6 months and its broad coverage against all the stages of malaria, is the only drug in the next 20 years, in the absence of an effective vaccine, that's going to allow us to make substantial progress towards these aspirational goals.

This slide represents the summary of the label claims, which we've asked the FDA to consider. Essentially, ARAKODA is presented as 100-milligram tafenoquine succinate tablets for prevention of malaria in adults throughout the 6 months of dosing, with a simple 3-day load followed by once-a-week dosing and a single dose upon return from travel.

Dr. Berman will present our efficacy data, which we think fairly convincingly shows a similar rate of efficacy for both prevention of malaria during travel and for post-exposure prophylaxis, and Dr. Smith will review the safety data that we think shows a safety profile similar to primaquine.

In the event that tafenoquine is approved, we think it will offer a number of benefits relative to the other medications that are currently available. Those that are FDA approved include doxycycline; Lariam, or mefloquine is the generic version; Malarone, or atovaquone proguanil is the generic version. ARAKODA affords the opportunity for weekly dosing, which doxycycline and Malarone don't have.

It's the only product that can kill all the mammalian stages of Plasmodium falciparum and Plasmodium vivax. It's appropriate for global use because there's no evidence of any drug resistance, and it's the only product that would allow a single post-exposure dose to prevent malaria and relapses post-travel. This is significantly improved pill burden, and we think our data show that the drug does not have a neurologic liability.

I just briefly want to summarize the life cycle of malaria and highlight the parts of it that ARAKODA targets. So as you know, mosquitoes inject sporozoites into the bloodstream, which immediately

travel into the liver. These form a process of amplification of asexual merozoites, leading to the release of erythrocytic merozoites into the bloodstream, which are amplified in red blood cells to cause the symptomatic disease we know as malaria. Some of these parasites turn into gametocytes, which are ingested by the mosquito to continue the cycle.

Two weeks ago, we heard about GSK's application, which targets 1 latent liver stage parasite, the hypnozoite. But ARAKODA, applied weekly and for a duration of period of time at the doses proposed, targets all the parasites. And this is a key aspect of why it may be useful for malaria elimination efforts.

In the next few slides, I just want to spend a little bit of time going over what we view to be the rationale for tafenoquine's development, understanding that this is a retrospective view. Primaquine of course is a useful drug. We know that it's the only drug that kills both the latent hypnozoite and the developing hepatic stage of

malaria. Data from the 1990's show that it's possible to administer primaquine daily with food for up to 12 months with no difference in tolerability from placebo and with quite an effective outcome. But in practice, the effectiveness of primaquine is less because it requires daily administration Because of the short half-life.

The major review published by the CDC in 2006 does not mention any specific warnings for neuropsychiatric events in the context of prophylaxis. ARAKODA is a primaquine analog, and you can see that from the structure. The core structure of primaquine is on the left, and ARAKODA represents that same structure with three functional groups substituted to blood metabolism. That results in an extension of the half-life from 6 hours to 14 days, and that's what facilitates the weekly dosing.

The activity against hepatic stages is retained, and as a consequence of the persistent pressure of drug in the blood, the activity against

the blood stages is improved. And again, despite the long half-life and the high dose for prophylaxis, we don't think there's any evidence of any neurologic risk either primaquine in the clinical literature or for tafenoquine in the sponsor's database.

We may hear a lot today about the similarity of different quinolones, but it's simply inaccurate to equate them as all being the same. There are structural differences that are important and need to be considered. Primaquine is an 8-aminoquinoline. You can see the boxed side chain in green hash on the left. That's what gives primaquine its structure and mode of action. It's activated to oxidative intermediates that kill primarily the hepatic stages of the disease.

In contrast, the defining feature of the amino alcohols is the amino alcohol side chain, and that's characterized in the mefloquine structure, which means that drug acts directly only on blood stages and increases the frequency of common neuropsychiatric events relative to the standard of

care

This table briefly summarizes some important particulars of the clinical trials that will be reviewed by Dr. Berman and Dr. Smith, subsequently. The three studies on the left, 030, 043, and 045, represent placebo-controlled studies that were conducted in areas of high P. falciparum malaria endemicity in Africa. Mefloquine was included as an efficacy comparator in two of these studies.

033 was conducted in a large cohort of Australian military personnel deploying under war-like conditions to Timor. In this study, because of the practicalities of ethical considerations of a deployment, it was not possible to include a placebo. There will be more commentary from our team on that issue later on.

Because of the ineffectiveness of daily prophylactic drugs, a weekly standard of care was required in order to have an active comparator in that study, and the only one available, of course, was mefloquine, which was why that was used. 033 had 2 safety signals with the vortex keratopathy

and changes in serum creatinine, which were followed up in the healthy volunteer study 057 to resolve those safety signals.

As the most recent sponsor for this indication, we've conducted two studies that are irrelevant for today's conversation. One is a challenge study in non-immune volunteers to confirm the efficacy of the intended dose against P. falciparum, and then we're also currently conducting a long-term safety study in healthy volunteers to document the health and safety and tolerability of ARAKODA versus placebo for a 12-month exposure period with the intent to change the label down the road. And it's important to remember that in these studies, the exposure to ARAKODA was up to six 6 months.

In the sponsor's presentation of the safety data, you'll see a slightly different format from the way that our colleagues at the FDA have presented the data, and we focused it on separating out the adverse events based on deployment versus non deployment. And the reason for that is that

deployment is well documented in the literature as a major risk factor for neuropsychiatric events. S we feel as the sponsor that you can't really understand the impact and context of those psychiatric events without making that separation between deployment and non-deployment.

It's also important to remember that the Australian government considered the Timor deployment to be war-like. A number of specific traumatic exposures to which soldiers were subjected have been documented, together with a high rate of PTSD PTSD associated with that conflict. Soldiers are exposed to a higher rate of both physical and psychiatric injury, and that will be evident when we discuss the safety data later on.

It's also important to remember that the impact of deployment dwarfs any subtleties about adverse event profiles of the drug that you use to prevent malaria. In this table, we show that the rate of increase in neuropsychiatric event burden is similar between mefloquine and Malarone even

though Malarone is not perceived to have a neurologic liability.

Our FDA colleagues are going to review, in a significant amount of detail, the nonclinical toxicology associated with ARAKODA, so we'll leave that job for them. We will be commenting specifically on the neurotoxicity of the product, or rather the lack of it, later in our presentation.

We've made a number of postmarketing commitments to the agency, the most important of which is the long-term safety study. This will evaluate the safety and tolerability of ARAKODA versus placebo for 12 months with an allocation of 300 placebo subjects and 300 ARAKODA subjects, with a primary endpoint focused on ophthalmic safety. However, we have also included some psychiatric and hematology assessments as secondary endpoints, and this study has been enrolling subjects since October 2017, more or less a coincidence with the submission of the application.

The inclusion criteria for this study also

allowed the enrollment of individuals with a prior psychiatric history. We've proposed a health database outcome study to monitor rare events post-approval and have agreed on a timeline and program for doing age and weight de-escalation studies to determine whether this product would be appropriate for a pediatric indication.

Finally, before we go into the detailed data presentations, I just want to throw out an idea of how we can think about risk in a different way. Malaria itself is a neurotoxin. These are data from Ric Price that show preexisting neurologic conditions and result in a substantial increased risk of seeing neurologic events post-malaria.

We're used to thinking about risk in terms of dose, and there's obviously a natural concern and question about whether the increased dose associated with prophylaxis may be associated with increased risk, and therefore there should be some comparison of labels. A helpful way of thinking about our dose compared to the dose that's already been approved is that the 300-milligram dose of

GSK's label is for treatment of symptomatic vivax malaria.

In contrast, ours is a 600-milligram dose in asymptomatic individuals, which is effectively a 600-milligram dose maintained at steady state for 6 months, and you'll see that borne out in some of the PK curves that Dr. Berman will talk about later in the presentation.

We don't have any co-medication. We don't have symptomatic malaria. We weren't privy to the discussions between the agency and GSK about why there was warning language required for psychiatric AEs. Perhaps malaria was part of that conversation. These two indications have very different risk profiles, and we would argue should have labels independently derived.

With that said, I'll just briefly outline the presentations that follow. Dr. Stephen Toovey and Mark Reid will address the military and civilian unmet medical need for new prophylactic drugs. Dr. Jonathan Berman will present the efficacy data. Dr. Bryan Smith will focus on the

safety. You'll hear from me again later with respect to neuropsychiatric safety, and then Dr. Stephen Toovey will summarize the risk-benefit profile of this product.

At this point, I'd like to hand over to Dr. Stephen Toovey to talk about the civilian unmet medical need. Thank you.

Applicant Presentation - Stephen Toovey

DR. TOOVEY: Members of the committee, ladies and gentlemen, I am Stephen Toovey. I'm a tropical and travel medicine physician. I have also spent a number of years actively managing and treating malaria, principally in Africa, and have been involved in antimalarial drug development. My PhD was actually examined by the Neurologic Safety of Antimalarials.

I'm going to talk about the unmet medical needs that we see for the civilian traveler. I just want to talk about this concept of the non-immune. Essentially, a non-immune person to malaria is an individual who did not grow up in and who is not continued to be resident in a malarious

area, and that is obviously the overwhelming majority of the United States population.

In non-immune individuals, falciparum malaria is a medical emergency. It's a progressive and often a fatal disease. And I think as we saw, the lady who visited Thailand to see the elephants, even if you survive, you can have permanent long-term complications. Vivax malaria, although not usually fatal, can in fact be fatal. It is still a very unpleasant disease, and importantly, it's a recurring disease.

I think a particular group that we also need to be aware of are what are called the VFR travelers in the travel medicine trade. These are folks who are visiting friends and relatives back home, so this typically is a recent immigrant, a recent arrival in the United States, who was semi-immune, who possessed some immunity, but whose immunity begins to wane. These are people who will also need protection when they go back home.

The final bullet points on this slide, actually at the risk of sounding dogmatic, the

benefit-risk ratio for malaria chemoprophylaxis for a non-immune person traveling to a malaria-endemic country, the question is settled. The benefit-risk ratio is clearly in favor of chemoprophylaxis.

So let's just fast forward a little bit, and what does it look like inside a travel medicine clinic or indeed a primary care physician's consulting room when a civilian traveler faces you? What do you put into the mix when you decide what you need to do or what advice you need to offer?

You need to understand the malaria risk at the destination or destinations. You need to understand -- and this is a very important point -- what the efficacy of these drugs is, or was, in clinical studies. And you need to translate that in your mind into what the effectiveness will be in clinical use.

So the effectiveness, in a clinical study, everything is controlled. So you have a very carefully scientific measured estimation, or measurement, of the drug's efficacy. Out there in the real world, outside of a clinical trial, all

sorts of things can happen, and you really have no control once you have prescribed the drug. So that is the effectiveness.

The travel medicine practitioner, the primary care physician, needs to have that picture in his mind. He needs to have confidence that this drug will be effective in use, because if it isn't, you're going to end up with the sort of picture we saw earlier of the lady who visited Thailand.

You then need to understand your patient, and you're taking a very holistic view and what will the patient -- patient or the traveler. You want to avoid them becoming a patient. What will the traveler be doing at the destination? Are they pregnant? What other illnesses do they have? What are the co-medications that they're taking?

Then you have this picture, and then you try and fit what we have in our current toolbox of malaria chemoprophylactic agents. You try and fit that together with the patient, and inevitably they're going to be a couple of compromises there. But you try and choose the best drug for that

traveler.

Probably once you have dispensed with all of the hard science, one of the most important things is this question of adherence or compliance. Will my traveler take this drug in a way that will be effective? And there you need to understand the safety and tolerability, bearing in mind most travelers are probably well when they leave home. You don't want to give them a drug that's going to make them ill. They'll be likely to stop it and then be at risk of malaria.

How often do they have to take it? Is it daily? Is it weekly? How much of a burden is this? When they get home and they're forgotten about the wonderful time in Thailand, or wherever else they have gone, how long are we asking them to take the drug for? Do we want them to take the drug for a month after they get back? And how many pills all together? It can be quite intimidating walking out of a clinic with a big box of pills. Psychologically, the fewer, the greater the adherence you're going to have.

The last bullet point really relates to the pharmacokinetics of the drug. If it has a long half-life, it's going to be a little bit forgiving with your civilian traveler who's late with a dose. So you have a bit of a safety margin built in.

The chart on the left. Dr. Dow has shown you. And this really is an almost unforgivable situation. In a first-world wealthy country, a disease that is quite preventable is increasing. Why is this burden increasing? It would seem -- and I think we know from the CDC data -- that the main problem is poor use of chemoprophylaxis, poor adherence to the drugs that we have. So we need to be doing something better. We need to have more options to offer our travelers.

This burden is civilian dominated as well, so we really need to be doing something for the individual traveler, whether that's the holiday-maker, whether it's somebody traveling on business, NGO worker or a missionary, and we need to be helping them in a new way. I think the curve

actually supports the need for drugs that will make adherence easier because I think that is really the key to this.

So what do we have already available? Casting your mind back to Dr. Dow's slides, essentially we have 4 agents available. If you look at the notable side effects column -- and I'm not going to go through this in any detail -- the point about it is that the notable side effects are actually quite different, so each drug has its own profile. And that actually helps you a lot when you are trying to fit the patient and the drug and the destination and the itinerary altogether. But it would be great to have another drug with a different profile. That would help us a lot.

The same thing applies to the final column on the right, the contraindications. If we had another choice, another drug, it would make our life easier to protect travelers.

The continued dosing after travel, a column more or less in the middle, if you're a frequent business traveler and you come home, and we're

asking you to take tablets again for another 4 weeks, in 2 weeks, you're probably gone again to another destination. So you might well end up being on continuous chemoprophylaxis. If we had a drug with a much briefer duration of post-exposure, that would be helpful.

Then the question of daily versus weekly dosing, I'll show you shortly, generally travelers prefer weekly dosing, but it would just be nice to have another option. Currently, the only one we have available that does that is mefloquine, and that, as we know, is a drug that has quite a notable side effect profile. Then the question of resistance, can we use this drug everywhere? Short answer would be -- that's an important consideration. The short answer for tafenoquine would be yes.

So weekly versus daily, this is not a meta-analysis of the literature. That would actually be quite a difficult thing to do. But if you do look in the literature, you really don't see anything supporting daily over weekly dosing.

These publications favoring weekly, we see it in civilians and in the military as well. The Tan publication of 2011 was actually a CDC expert committee report on the use of doxycycline, and this publication does make the point that the longer half-life drugs have a more forgiving PK, the point we made earlier.

Our current chemoprophylactic armamentarium, our current toolbox, is it good enough? Well, it's nice to have, but there are really issues with all of the drugs, all of the regimens that we have, and there's no ideal one size fits all. And all of us as travelers these days and as participants in the healthcare system, what would help us? New options. Regimens with reduced dosing frequency and pill burden that are easier to use. Reduced post-exposure duration; again, easier to use, improving adherence. And a drug with a different safety profile to that of the existing agents?

This is really just a formal restatement of the unmet medical need. What we're really looking for is simplicity both for the traveler, for the

clinician, and to try and improve adherence, and to start making that curve that we saw look a little different.

I would now like to hand over to my colleague, Mark Reid.

Applicant Presentation - Mark Reid

MR. REID: Thank you, Doctor Toovey, and thank you to the committee, ladies and gentlemen, and members of the FDA. I appreciate the opportunity of being able to speak today all the way from Australia, and please forgive my accent.

I was an infantry platoon commander for 12 years in the Australian defense force. My corps transferred the medical corps. I was actually responsible for being -- one of my assignments was to be the study coordinator of the study 033 during my first deployment to East Timor. We as a defense force struggled in East Timor with malaria.

We had an attack in our Second Battalion Royal Australian Regiment approaching 13 and a half percent in a 4-month wet season period on unobserved doxycycline. The reasons for that were

multiple, but a lot of them were due to the intensity of warfare today, the night operations with night-vision goggles and the intensity of what we are doing, and the fact that we had limited preventative medical asset with us at the time, and the reliance on daily medication.

Also, our platoon positions were extremely close to the refugees we were trying to protect. And these poor people were getting up in the middle of the night. They were moving out of their homes with their children, and they are taking their malaria with them. Then what we did as an international community is put many thousands of non-immune soldiers next to these people, and we fanned the flames of an epidemic. You can see here this young teenager with his mom had falciparum malaria in Balibo, in the fought town of Balibo on the East Timorese border, and I'm just thankful that our combat medics got to this young boy in time.

The problem we have when we're soldiering in the field is that we can't follow best practice

with malaria and other vector-borne disease prevention. When our soldiers expect to be in contact with the enemy, they will not put up a bed net. They will lie next to their shell scrapes, so when the contact comes in the middle of the night, they can roll into that shell scrape and take cover. You'll see in our safety data set a number of scorpion stings. The scorpions like to get into those shell scrapes as well.

We don't know when we're going to eat or sleep next, and then the Army says to us, "You have to take your drug at 12 hours 16 minutes after the last time you took it." Often our pills were in the bottom of our rucksacks, they're broken apart, and we're trying to manage dosing while we're trying to dodge a bullet and dodge an improvised explosive device.

Now, we have 5 evacuations from the East Timor campaign to the intensive care unit of the roll-down hospital. Most of them survived. One of the Malaysian soldiers died from cerebral malaria. But from the 3 ADF soldiers, 18 to 21 years of age,

one evacuated on a ventilator, any reason they survived is because the roll-down hospital was prepared and they had a good armamentarium ready, including non-approved drugs such as IV artesunate.

You can see from this slide, this is our experience with our paratroop battalion in the middle in the Oecusse province, a mechanized armored Battalion 57 Royal Australian Regiment down there in the far right-hand corner and our second battalion there on the left. When we arrived and we we're able to see use weekly medication, it was the first time in our living history that we had achieved no malaria cases in the ADF infantry units since Vietnam at least. And we had 8 cases of relapsing vivax malaria when we got back to Australia. We were certainly exposed, but whilst we there, we had no clinical cases.

We had an Indonesian battalion opposite our positions obviously keeping an eye on their side of the border. Their soldiers were dying from falciparum. They were using Fansidar, sulfadoxine and pryirmethamine, intermittently to suppress.

Their medical officer came across the border in a meeting to meet with our medical officers. They knew that were on an experimental drug, and they needed and asked for our help.

So from an ex-soldier's perspective, what I'd like to say is what we need in the toolbox is something that was really simple, something that's safe and effective. We need a long half-life in the drugs available to as soldiers because if we miss a dose because of our operation, we need that protection. If we can take it with or without food, that's really handy. We don't know when we're always going to eat our next meal. And fewer pills is better from a military perspective.

Certainly, for post-exposure prophylaxis, when the soldiers get harm, we really don't want to issue them another 14 days of primaquine and say, "Off you go, boys. You need to take these every day while you're on leave." Because frankly, the average young soldier just wants to drink beer and take as little drug as he has to take once he gets home to his loved ones.

I'm going to hand it over to Dr. Berman. Thank you for your attention.

Applicant Presentation - Jonathan Berman

DR. BERMAN: I'm Josh Berman, fast-track drugs. I've been given a new clicker, so let's see how it goes.

My part of this presentation is to discuss efficacy and to remind the recommended regimen is 200 milligrams based starting with loading dose for days prior to entering the endemic region, then 200 milligrams weekly while in the endemic region, and once in the week thereafter.

Summarizing this way reminds us that we're talking about two periods of prophylaxis: in the endemic region and also post-exposure prophylaxis. People generally talk about in the endemic region, but it's been emphasized already today, post-exposure prophylaxis is also an important consideration, and we'll get to that at the end of this talk.

It may be of interest of how our 200-milligram based regimen was derived. It was

done in a PK/PD type of analysis. Early on, we had some failures in non-immunes and mixed immunes, and they all had drug concentrations at the time of failure that were less than 50 nanograms per mL.

In this mixed-immune study, there were no failures in persons with concentrations greater than 55 nanograms per mL, and this suggested that a cut-off point of 50 nanograms per mL would be the right one. But to be precautionary in a margin of error, we set the cut-off at 80 nanograms per mL, which means that trough concentration should be higher than 80 nanograms per mL.

At about the same time, we had a dose-ranging study in which a 200-milligram dose compared to the 400-milligram dose really showed a plateau of efficacy, just about. The 400-milligram dose was not as well tolerated as the 200-milligram dose, so the 200-milligram based regimen was chosen since it was the highest well-tolerated regimen, and also had Mac essentially a maximum plateau of efficacy.

Turning now to the use -- sorry. One

further consideration, however, was how the dose we chose conformed with our previous pharmacokinetic requirements. And to investigate that, we performed a population PK study of about 10 trials and more than 800 subjects. And you can see the results here on this slide of predicted concentrations versus time and months on the horizontal axis.

I guess an average person would be 75 kilograms, which would be this blue line. And you see that after the loading dose, we get greater than 200 nanograms per mL. And even one week after that, at a trough, the levels are much higher than 80 nanograms per mL after about 6 further dosages steady state is reached with about a Cmax of 300 nanograms per mL and the trough far in excess of 200 nanograms per mL.

This graph also shows the predicted concentrations for a large person, 150 kilograms. And you see even for that high weight, concentrations are in excess of 80 nanograms per mL at all stages of the recommended dosing cycle.

So now we can turn to the efficacy dossier. The first problem we face in malaria prophylaxis is that we cannot carry out the ideal experiment. This is a disease for which there are positive comparators and which occurs in persons non-immune to malaria.

So the ideal study is a new drug, ARAKODA in this case, versus a positive comparator in a non-immune population. But you do need to have a placebo group to show that there's actually malaria in the place where the study was occurring. In other words, if you compared ARAKODA to comparator in Washington, D.C., you'd get a zero percent failure in both cases, but that would be a meaningless result.

The problem is the placebo because for a rapidly mortal disease in the patient population of non-immunes, randomizing to placebo in a field trial is ethically questionable. The malaria drug guidance of 2007 mentions that other types of study designs have been employed. And the implication of this is that putting them all together, you will

get a good inference of the ability of the new drug to provide successful malaria prophylaxis.

One design that's used is the comparator controlled study in non-immunes. You do have to estimate the historic placebo rate, not from internal data. Another design is a placebo-controlled study in malaria-endemic communities. These semi-immunes do not get sick when they're parasitemic, so you can randomize to placebo. But the contribution, the comparison of efficacy in this semi-immune population to that in the non-immune population is unknown.

A third type of study is a challenge study. In non-immunes, you can randomize to placebo because subjects are so carefully followed, but interpretation is difficult here because of an unknown relationship between one parasite used in the study to the multiplicity of parasites used in the field. The guidance also suggests that treatment studies would be useful.

When we put together our total dossier, we were pleased to find that we did in fact have at

least one study with each of these characteristics: study 033, the comparator study in non-immunes; 2 studies in semi-immunes; a PV treatment study; and then also a Pf treatment study done in a challenge model to complete the package.

Instead of going through all these, I think it's simplest just to quote from agency's briefing documents and start with their summary. They consider that studies 043 and 045 demonstrate statistically significant protection against parasitemia. This means in Pf.

They also look at study 033 and say that FDA analysis showed no observed cases of malaria in the prophylactic phase of this trial and that FDA agrees with the assessment that there's a high likelihood that subjects in this study were exposed to both Pf, Pv. And basically, you put all these statements together, and they give confidence in the efficacy of ARAKODA against both Pf and Pv. And we are pleased and acknowledge the support of the efficacy from the agency.

With that understood, the agency is a

conservative institution, really, and sponsor is supposed to be perhaps more expansive. And we'd like to go further into someplace that the agency did not choose to go, which is a frank comparison of ARAKODA to standard of care. And the reason to go in this direction is that there are standards of care. We suspect that prospective subjects, and their doctors, and this advisory committee may well ask how ARAKODA compares to standard of care. So for that, we will now get into a noninferiority comparison between ARAKODA and standard of care, which happened to be mefloquine in studies 045 and 033.

Study 045 is the simple one to analyze, so we'll do it first because all the data we need is contained within the study. This study was done in semi-immunes in northern Ghana. After treating existing parasitemia, subjects were randomized to a large number of regimens, including ARAKODA, mefloquine, and placebo. The subjects were followed for 12 weeks. The primary analytic population, you see here, the rates were not large.

Women averaged 45 kilograms and men average 54 kilograms.

The data is shown in the next slide for placebo. Most of the subjects failed, 92 percent, for ARAKODA. Some failed, 13 percent, from mefloquine. Some failed really the same amount, 13 percent. And protective efficacies with a primary analytic population that we used were the same.

But this is all a comparison to placebo, and what we want here is the comparison of everything to standard of care, and we can do it in this way. The ARAKODA failure rate was actually 13.1 percent; mefloquine was 13 percent. The difference is 0.1 percent with a relatively small number of subjects in these groups and a 95 percent confidence interval for this difference.

ARAKODA could be as much as 14 percent worse than mefloquine. And the question with noninferiority trials is always, well, is this a low number that's good or a high number that's bad? And the general way in which this is evaluated is

by comparing that difference to the difference between placebo and standard of care on the grounds that the difference between new drug and standard of care should be much less than the difference between placebo and standard of care.

The difference between placebo and standard of care, mefloquine in this case, is 79 percent. In sponsor's view 14 percent is a small fraction of 79 percent. So we conclude that ARAKODA was noninferior to mefloquine in this study.

Study 033 is much more complicated, but in our minds, much more important because it contained the population non-immunes that will take this product in the future. And if you look at the bottom bullet, the weight, which is perhaps another determining factor in prophylactic efficacy, a mean of 81 kilograms is pretty close to at least some of the heavy Americans that ultimately will take this product if approved.

In this study, there were two phases; first, a prophylactic phase in which during deployments, subjects were randomized to ARAKODA or mefloquine,

and that was 26 weeks. When they left the endemic region and returned to Australia, which is a non-endemic place -- well, at least the barracks -- the mefloquine subjects received 14 days of primaquine, a good dose, 30 milligrams a day, while ARAKODA received just placebo. Then relapse was followed in this post-exposure phase, and the ability of primaquine, or ARAKODA, respectively, up to the time of leaving the endemic region in the latter case was assessed.

We do have to say a few words about the primary analytic population. The per-protocol population was defined in the protocol as the primary analytic population. Some might choose to use an ITT population for analysis, but an ITT population really says that persons who are not followed, discontinued, or lost, are assumed to be a failure, and thus included in the total list of failures.

This definition might actually be reasonable for, say, study 045, where a semi-immune who gets parasitemic will not know it and will not come to

medical attention. But this definition is not consistent with the clinical situation in non-immunes. A non-immune who becomes parasitemic will be very sick, will certainly seek out medical attention, and will not be lost to follow-up.

So use of the per-protocol population as the primary analytic population is both what was in the protocol and also makes clinical sense in opposition to using the ITT population for this purpose.

We can see the results on the next slide here. The per-protocol population is given. There was a 3 to 1 randomization for the two products. During deployment, in the endemic region for 26 weeks, there were no failures, no incidence of parasitemia in either group. Upon return in the post-exposure phase of this study, there were 5 relapses, that is P. vivax relapses for the 24 weeks specified by the protocol, and then beyond protocol, another 3 failures were found for a total of 8 failures.

We need to calculate the approximate placebo

incidence during deployment to do a noninferiority analysis, and we can start with these relapses, which were 8, eight relapses of P. vivax. That tells us that we can be 100 percent certain that there was P. vivax during deployment. These 8 cases did not come from Australia.

But we'd like to be more precise about how many cases of P. vivax there were during deployment, and the way to do this -- a one way to do it -- is to recognize that those 8 cases come after primaquine or ARAKODA, respectively, relapse prevention. If these products were 80 percent effective in preventing relapse, there would be 40 cases in the total population during deployment of which 8 then got relapse. If these products were 70 percent effective in preventing relapse, there would have been about 25 cases of P. vivax during deployment.

So the 70 percent number is a conservative number, which comes from the recent presentation from GSK in which there was about 70 percent efficacy for these two products combined when

re-infections are included as relapses. So that's why this is a conservative number. We use those numbers, say 25 divided by about 600, and you get 4-plus percent of P. vivax during deployment.

It is very hard to challenge this estimate of the amount of P. vivax during deployment, very hard. It starts with internal data, the relapse rate afterwards, and uses a conservative estimate of the protection against relapse by these two products.

We now have to estimate Pf exposure during deployment, and this is a little looser, and it's done by simply taking the ratio of Pf to Pv in similar circumstances and multiplying by the rate of Pv exposure that we already have. In prior exposures, the absolute amount of Pf and Pv doesn't matter. That can vary between these other examples. What matters is the ratio of Pf to Pv. If we take prior deployments of the ADF in this region, the ratio was 0.15. The protocol actually specified a community survey done at the time of this present deployment within 1 kilometer of the

deployed troops. The ratio of Pf to Pv was 0.74.

For a region in which Pv is both Pf and PV and which Pv dominates, it's hard to think that the ratio of Pf to Pv will be less than 0.15 or greater than 0.74. Anyway, if we use those numbers and multiply by Pv, we get a total exposure rate of about 4.6 percent to 12 percent, with only the last number of the Pf number being challengeable. And even that, it's pretty hard to challenge, as I've indicated.

Now we can go into our noninferiority analysis. For the per-protocol population, the failure rate for ARAKODA was zero. The failure rate for mefloquine was zero. The difference between these is zero. But with a large number of subjects in this trial, tafenoquine could be as much as one 1 percent worse than mefloquine.

It doesn't matter, as you can see here, really what the historic failure rate is -- if it's 4.6 percent, 8 percent, 12 percent -- 1 percent is a small fraction of that. It literally wouldn't matter, we think, if the historic control rate was

4 percent or 3 percent; 1 percent would still be a small fraction of that. So sponsor concludes that ARAKODA was noninferior to comparator, which happened to be mefloquine in this study as well.

To summarize in-country prophylaxis -- and the first two bullets really are just what FDA has said, that there were no subjects who had parasitemia for ARAKODA in 033, and there is a high likelihood that there would have been at least some exposure to both Pv and Pf in this study in non-immunes. And in study 045, ARAKODA for Pf was statistically superior to placebo.

That's really what the FDA is saying, and we would go, as you see, a little further here. And the FDA may not want to go that far, but we would go a little further to say that in both these studies, ARAKODA was noninferior to comparator.

Whether you accept the first two conclusions or all three conclusions, it's important to point out that these conclusions hold for two different racial groups, African nationals and Caucasians. They hold for two different endemic regions, Africa

and Oceania. They hold for two different degrees of immunity, semi-immune and very importantly non-immune. And they hold for both Pf and Pv.

We can finish this talk with one side on post-exposure prophylaxis. Bottom line up front, we propose 1 dose of ARAKODA in the week following exposure to be sufficient for post-exposure prophylaxis.

Why do we need post-exposure prophylaxis? There are two reasons. One is to kill hypnozoites of Pv if you're in a Pv area to prevent their relapse and to get relapsing malaria. This is really the subject of the GSK indication, at least in their case in a treatment mode, in our case in a prophylaxis mode, in which 1 dose was approved. So 1 dose will work for us as well.

The second need is to deal with late-arriving parasites. It takes about 7 days for parasites to mature in the liver before exiting liver and infecting the blood. And if you are challenged with parasites in the day prior to leaving the endemic region, most of these

pathophysiological processes will occur after you leave the endemic region, so you have to continue a prophylaxis for at least 7 days.

For an 8-amino-quinoline such as primaquine, which have very high and anti-liver activity, prophylaxis only has to be continued for 1 week after leaving the endemic region, and this is true for Malarone as well, which is an excellent anti-liver agent for initial liver forms.

So since tafenoquine is an analog of mefloquine, an 8-amino-quinoline, and in animal studies has excellent anti-liver activity, we propose only extending prophylaxis for 1 week for tafenoquine as well. But for this long half-life drug, extending prophylaxis for 1 week means merely 1 dose, 1 dose only in the week after leaving the endemic region.

In our view, 1 dose of ARAKODA, especially with respect to compliance, compares favorably to the complicated regimens which still have to be used. If you're on mefloquine prophylaxis in the endemic region, mefloquine for 4 weeks plus

anti-hypnozoite therapy and 14 days of primaquine, and you're on Malarone prophylaxis in the endemic region, Malarone daily for 1 week, plus your anti-hypnozoite therapy, which is primaquine for 14 days.

With that summary of efficacy, let's turn now to safety done by Dr. Bryan Smith.

Applicant Presentation - Bryan Smith

DR. SMITH: Committee members, colleagues at the FDA, ladies and gentlemen, my name is Bryan Smith. I'm the chief medical officer for 60 Degrees Pharmaceuticals. I'm pleased to be able to present an overview of the safety data associated with ARAKODA.

Dr. Berman has just given you an overview of the dose justification for the 200 milligrams per day for 3 days load and then 200 milligrams weekly based upon PK/PD. I wanted to throw this slide up so that we could also look and evaluate it from a tolerability standpoint.

So I draw your attention to the green bars that you see before you. That is the tafenoquine

200-milligram, once-a-day dose. You see a side effect profile similar to what one would have anticipated with the GI symptoms predominating. And on the far right, then, you see, again, 200 tolerated about as well as a primaquine regimen. But at doses above that, we began to see increasing amounts of GI adverse events.

The total safety database for tafenoquine is 3,184 subjects of various doses and various durations. Included within this is 825 subjects that have received the anticipated clinical dose. Importantly, as displayed here and through the rest of my talk, you're going to note that of the 825, 492 of those subjects, which we're calling deployed military, were from study 033, recalling war-like conditions and unique exposures that these individuals had, which were highlighted by Dr. Dow and Mark Reid earlier in the talk. The 333, then, of the anticipated clinical regimen were in resident populations not exposed to those unique. And then for comparator purposes, we have 309 for mefloquine and 396 for placebo to be able to

evaluate those adverse events.

Overall, the mean duration of exposure in the anticipated clinical regimen was 21.2 weeks and more than half of them receiving the full 6 months. Maximum duration of exposure was just under 30 weeks, and the total number of study doses just at about 24.

There were no treatment related deaths in the program. There was one death in study 045, which was considered unrelated to study drug. A 53-year-old black male presented with abdominal pain and was hospitalized. Seventy-five days after his first ARAKODA dose, it was revealed at that time that he had had prior episodes of abdominal pain. The medication was stopped, and the patient died at day 131 with a presumptive diagnosis of suspected hepatocellular carcinoma that was listed as an SAE; however, no autopsy was performed.

Treatment related adverse events that have led to discontinuation, there were 34. Of those, if we look at those that were considered possibly, probably, or definitely related to ARAKODA because,

again, of some of the uniqueness of study 033, that leaves us with 16 or about 1.9. None were definitively related to ARAKODA. And of those 19, there was a unique procedure in study 045 that required discontinuation of subjects if their laboratory evaluations went outside of the normal range.

So you'll see there 6 subjects were actually withdrawn from the study because of ALT increases over the upper limit of normal of 41, with what were fairly modest ALT elevations between 47 and 145 that likely would not have required withdrawal by usual criteria. If we subtract these 6 subjects, we're left with 10 or about 1.2 percent. For comparison purposes, there were 4 in the placebo group, or 1 percent, that were also considered possibly, probably, or definitely related to study drug.

Here is a overview of all of the AEs in the ARAKODA versus placebo. What we can see here is that the vast majority of the adverse events are mild and moderate in nature across all of the

groups. Similarly, while rare, at about 1 percent, severe adverse events are similar across all of those groups. In subjects with SAEs, treatment related SAEs, similar at about between 2.2 and 3.3 percent in the non-deployed residents.

The listing of adverse events occurring in greater than or equal to 1 percent of the subjects with an incidence numerically greater than placebo, we see the first 4 are quite common adverse events: gastroenteritis, back pain, nasal pharyngitis, and diarrhea. I'd like to particularly draw your attention to those to demonstrate the difference between the overall ARAKODA population and the non-deployed subjects.

You certainly see, quite clearly, in the gastroenteritis, the nasopharyngitis, and the diarrhea, the effects of study 033 and soldiers living in the conditions, which have been described to you; whereas one looks at the incident rates of the non-deployed resident subjects and the placebo groups, you actually see quite similar results.

Moving down through the list then, we do see

keratopathy overall at 8.2 percent of subjects in this database, and we're going to talk about the ophthalmologic adverse events a little bit more later. Then continuing on down the list, again, for those of used to, what I'll say, normal clinical trials, you see quite an interesting list of adverse events; again, in some cases largely driven by 033 and in some cases exclusively; so soft tissue injury; arthralgia; heat rash, exclusively 033; viral infections; lacerations; vomiting; again, tinea pedis; motion sickness exclusively associated with soldier activities, and transport in a jungle area.

Then completing the list down through the end of 1 percent, we see, again, low levels of GI upset, insomnia, which is a particular interest to some overall at 1.2 percent. Again, removing confounders of reasons why soldiers may not sleep very well, we see actually very similar rates at 2 cases at 0.6 percent non-deployed and 3 are 0.8 in the placebo group.

Some have postulated that the

gastrointestinal adverse events associated with 8-amino-quinolines are centrally mediated, and therefore may be prodromal to CNS effects. Available evidence to our interpretation reveal that GI adverse events are locally mediated. We know that for primaquine, despite increasing the overall exposure about 40 percent and taking primaquine with food, this actually ameliorates the GI intolerability. And as Dr. Dow has shown, has adverse event rates very similar to placebo with continuous dosing even up to a year.

We know that similarly, the GI effects of ARAKODA are less frequent when given with food at doses even greater than the 200-milligram recommended dose. In 2 rhesus monkeys that died during nonclinical testing after being given doses of 12 milligrams per kilogram, which is noted to be 45 times the dose required for radical cure in the Rhesus model, autopsy of those animals revealed GI inflammation and hemorrhage from the stomach all the way through to the colon, indicating local GI effects. CNS and brain sections in those studies

did not reveal any CNS lesions.

One also cannot really determine that these GI side effects have any link prodromally to the psychiatric AEs that we're seeing in the data as well. Only 4 of 32 subjects that had various psychiatric AEs also had nausea and vomiting. And of those, only 1 subject in 057 had the nausea and vomiting, which actually was predating their psychiatric AE.

As we've mentioned, we do see a kind of unique or unusual ophthalmologic profile with ARAKODA. Initially, before this was known to occur and described, 5 cases of the benign corneal deposits, the vortex keratopathy were reported as SAEs. Once this was identified as a known effect of the study drug, they ceased to be classified as SAEs, but extensive evaluation has been done to look at that.

As Mark Reid had intimated, in study 033, then, a special 100 began to look with detailed eye exams to evaluate the vortex keratopathy but also to look at the retina in greater detail. During

that follow-up, 2 cases of retinal disorders were described, mild granularity and pigmentation of the retinal pigment epithelium; 1 case with hard drusen. Neither of the cases was there any effect on vision.

The concerns over this and the fact that it was occurring towards the end of the 6 months of deployment led to study 057, which was specifically designed to look at ophthalmologic and renal safety. The primary endpoint on this study was to assess night vision effects with the forward light scatter.

This study confirmed the onset of new onset corneal deposits in 21.4 percent of the ARAKODA subjects as compared to 12.5 of the placebo. Importantly, there were forward light scatter test failures in either treatment group. There were no vision changes in either group. The keratopathy itself resolved in 95 percent of the cases by 12 weeks, and in all of the cases by 48 weeks.

Tafenoquine is an oxidative drug and puts increased oxidative pressure on the hematologic

system. Therefore, we do see slight decreases in the hemoglobin and a large percentage of patients receiving continuous dosing for up to 6 months as seen here. So 60.1 percent of subjects would have very small, 0.66 grams per deciliter, decrements in the hemoglobin. These are clinically non-significant and asymptomatic.

As was seen with primaquine with continued dosing, however, you begin to see the response of the bone marrow, a slight [indiscernible] parasitemia, and returns towards baseline. Also consistent with the oxidative pressure of tafenoquine itself, we do see asymptomatic clinically non-significant elevations in hemoglobinemia in 13.9 percent of the patients greater than 1 percent. None were greater than 10 percent in our safety database.

With primaquine, we know that as a class that 8-amino-quinolines have the G6PD deficiency liability, and when given to individuals with G6PD deficiency, it can cause hemolytic anemia. For mild hemolysis, the class 3 or moderate

deficiencies, as was shown by Alan [ph] in the '50s, will have a hemolysis after 1 or 2 doses of primaquine. But interestingly, if continued dosing occurs, you actually will see a response from the bone marrow, again, and returned towards normal blood levels. Only with the very severe deficiencies, the class 2 Mediterraneans, the hemolysis continues as long as drug pressure is applied. Because of the concerns for this, we interrogated our database to say were there individuals contained within the 3,184 subjects who received tafenoquine.

There were 13 individuals in our database that had received tafenoquine. The top line is 6 subjects that were variant class 3 or moderately deficient, which were given low doses of tafenoquine early in development. These were all asymptomatic with no hemolysis. The other subjects, which you see below there, then were given doses greater than the 200 milligrams that has been proposed for the anticipated clinical regimen, that for various reasons, clerical errors

or clinical trials, mistakes, were given tafenoquine.

Only 1 subject, the one at the very bottom receiving 400 milligrams per day for 3 days, required hospitalization and transfusion. She recovered thereafter. All of the others were picked up only in laboratory screening.

Quite interestingly, and I think somewhat counter-intuitively and surprisingly, 2 of the most severe deficient that are listed in red here, had asymptomatic hemoglobin decreases of 2.1 grams per deciliter and 2.8, relatively modest from what maybe we would have anticipated.

This is the final overview slide in the safety section, where we have pulled some of the adverse events, again, to highlight the importance of being able to evaluate the unique stressors of deployed military from study 033 from the overall study database. So again, on the top row, we've pulled subjects with injuries, poisonings, procedure complications that have been highlighted; things like the scorpion stings that have been

highlighted before.

You'll see overall, it appears that up to 28 percent of those subjects may have had adverse events in this classification. However, almost all of those are being driven, 39.8 percent of those, all coming from that single study. Similarly, if one looks at subjects with psychiatric adverse events, in the overall population, 3.9 compared to the placebo at 0.8, it appears that there is this elevation. However, when one looks at the deployed military subjects, you see 5.1 of them just from that one study alone; the non-deployed at 7 or 2.1, compared to the placebos at 3 and 0.8.

So with that, I will conclude the basic safety overview. I will turn back over to Dr. Dow, who will continue with a safety presentation.

Applicant Presentation - Geoffrey Dow

DR. DOW: In the next series of slides, we're going to directly address the concerns expressed by the advocacy community about neuropsychiatric safety. The Quinism Foundation

have put this quite succinctly on their website, stating a belief that tafenoquine, a new quinoline drug, is even more neurotoxic than mefloquine.

Based on data, these concerns appear to be centered around four key issues, which I'm summarizing here before we'll address them systematically. The first point that is made is that mefloquine is neurotoxic in rats; that tafenoquine has a lower EC50 in vitro against rat neurons. And as a consequence of that, tafenoquine must be more neurotoxic than mefloquine.

The other point that is made is that in the 1940's and '50s, some 8-amino-quinolines were found to be neurotoxic in humans and Rhesus monkeys as evidenced by these publications listed below.

The third issue is that there have been a number of adverse event reports made to the TGA by veterans groups 16 years after the completion of clinical trials, in which they attribute their neuropsychiatric experiences to the exposure to tafenoquine in those same clinical trials.

Then finally, as Dr. Smith addressed in the

earlier presentation, there's a hypothesis that GI distress may be centrally mediated, and we hope that we've discharged that suggestion with data. In fact, the GI events are locally mediated.

In a former life, I was a research scientist at Walter Reed Army Institute of Research, and I spent my time looking at the neurotoxicity of mefloquine and trying to find drugs that would be an improvement. As a consequence of that work, we did some neurotoxicity assessments in rats and showed that a single dose of mefloquine cause permanent histopathological changes and some behavioral effects. I personally don't know whether these data underlie the neurologic events that are associated with mefloquine clinically, but this paper is often cited by the advocacy community in support of that suggestion.

This table summarizes the sponsor's view of what's known about the neurotoxicity of some 8-amino-quinolines. You could see in order of progression from plasmocid to primaquine, there's a degradation in the therapeutic index both in

monkeys and in humans. And in fact, the rhesus monkeys predict the therapeutic outcome in humans pretty well.

Plasmocid was the archetypal neurotoxic 8-amino-quinoline, and then two others, pentaquine and pamaquine, had neurotoxicity at higher doses than we use therapeutically for malaria. In Rhesus monkeys, you only get your neurotoxicity at very high repeat doses that are systematically toxic. And in fact, in those animals, hepatotoxicity is the major toxicological event of concern.

Similarly with primaquine in humans, there's no evidence after 60 years of use of any neurologic events that are observed with the earlier 8-amino-quinolines at the intended dose, and in clinical trials at doses up to 16-fold higher than the labeled dose, you don't see any of these events either.

Some of these neurological events are quite striking. They include motor coordination and equilibrium, death, persistent hypertension, paralyzed palate, and they all occur with fairly

rapid onset relative to the day of dosing. So in clinical trials and animals studies, they're going to be noticeable.

Another concern that's been expressed is that the rat study, which we'll get to in a minute, wasn't in an appropriate spaces. And this is based on the idea that rats are less susceptible to plasmocid toxicity than other species. But an actual fact, neurotoxicity due to plasmocid in all the laboratory animals species is progressive and terminal. It just depends on what dose you give and for how long. This slide here shows that they're all susceptible.

It's important to realize that before we actually look at the data, is there any reason based on a medicinal chemistry platform to suggest that tafenoquine even be neurotoxic at all? Dr. Schmidt, who did all the Rhesus monkey studies, later in life published several reviews looking at the structure activity relationships for 8-amino-quinoline, including up to about 7[00] or 800 of them.

He made an interesting observation that the installation of a 4-methyl group on the 8-amino-quinoline ring basically resulted in the abolition of neurotoxicity relative to matched pairs of 8-amino-quinolines that did not have that structural feature. Tafenoquine has such a 4-methyl substitution. And if you are neutrally observing the data, you would hypothesize that perhaps the drug would not be neurotoxic at all.

In 2017, we published a GLP neurotoxicity study in rats and showed that at 9 times therapeutic exposures, there was no evidence of any brain lesions on neurobehavioral changes. Thus, as a sponsor, we feel we've done an appropriate job of discharging any plasmocid or mefloquine-like neurotoxicity in the appropriate model.

We do also have some Rhesus data in the literature and in the sponsor's database, and I'd like to take the opportunity just to cover some of this. First, to draw your attention to the first row, with that 1.8-milligram dose asterisk in the top left-hand corner, this represents the

cumulative dose over 3 days of ARAKODA that cures 95 percent of P. cynomolgi infections in Rhesus monkeys. The Cmax is 50 nanograms per mL. That was determined in 35 animals. These data are published.

Now, I draw your attention to the bottom row with a cumulative dose of 7 to 22 milligrams over 3 to 7 days. These are, again, published studies. And while they weren't formal neurotoxicity studies, two of them were conducted by board certified veterinarians, at preference, in Thailand. These people cared deeply for their monkeys and are unlikely to have missed the striking neurologic symptoms described earlier with the other neurotoxic 8-amino-quinolines.

In a toxicokinetic where doses higher than the therapeutic dose were given for up to 4 days, you begin to see GI events in methemoglobinemia come in as you increase the dose. No evidence of any neurologic events, despite close clinical observation of the monkeys, after each dose for up to 4 hours.

In the 2 monkeys for which this dose of 48 milligrams per kilogram were lethal, and in which the ratio of the Cmax to the therapeutic dose was 11 times exposure, there was no clinical neurologic signs. There was no evidence of any histopathological changes consistent with neurotoxicity at necropsy. And in fact, the cause of toxicity and death was hepatotoxicity and other events.

Then, of course, we've also dosed in the nonclinical program for up to 2 years in rats and mice and 2 year in dogs at cumulative doses, and in the case of dogs, daily doses, that exceed the cumulative exposure that you saw with neurotoxicity with plasmocid. The CNS is not a target organ, and lungs, spleen, kidney, and various other organs at very high doses are the target organ in those species.

Now, we'll turn our attention to some of the clinical data. I listed some of the neurologic symptoms as a cluster that are observed in the monkey studies and human studies with pentaquine,

plasmocid, and pamaquine. We've turned those into MedDRA codings and searched our safety database to see if there was anything there.

At the first column, you have phase 1 studies 4 to 600 milligrams, then the 200-milligram times 3 loading dose, a high loading dose of 400 milligrams times 3, and then the recommended dose with placebo on the right. And you can see that for the phase 1 and phase 2 programs, there's no signal.

There's a single case out of 713 of hypertension at 400 milligrams times 3. At the recommended dose, there were 2 cases of abnormal coordination which presented at study entry with that adverse event and 2 cases of mild syncope that were considered unrelated to study medication. The numbers for erectile dysfunction are similar in the recommended dose versus placebo. In short, there's nothing really to see here.

I believe there will be some discussion in the FDA presentation about serious events in folks who have a prior psychiatric history, so we'd just

like to address this up front.

There have been 3,184 exposures to tafenoquine. These are the 5 cases of psychiatric SAEs, discontinuations, and severe adverse events in the whole exposure database. The first event was a case of a suicide attempt, which was considered to be unrelated to study medication, and there were other things going on in that patient's life.

There were 3 cases of psychosis all considered unlikely or due to concomitant illness. And it's important to remember that these folks, because of their unstable condition and the likelihood of recurrence of their existing illness, would not actually have been allowed to be entered or enrolled into formal psychiatric trials to evaluate psychiatric drugs, for example. In this list, there's really only one case of depression that could perhaps be considered related to study drug.

It's also important to point out that although some of the pivotal studies excluded folks

with a prior psychiatric history because mefloquine was used as a comparator, there are actually 15 studies in the total safety database in which there were not specific psychiatric exclusions by presenting total exposures of 1,985 subjects.

In that population, there were 8 psychiatric events that could possibly have some relationship with study drug. Four of these were mild insomnia, which Bryan referred to earlier as having an incidence rate overall of 1.2 percent compared to placebo of 0.8 percent. Two were in the context of a drug cocktail study where one of the co-medications administered was midazolam. One case, someone was anxious about drawing blood. And there's only one case which was also referred to in a prior slide where there was an incidence of severe event likely related to concomitant illness.

We also have a number of subjects with a known psychiatric history based on concomitant medications who did well on tafenoquine, and I've listed these three cases here for your information. And finally, because we're dosing for a long period

of time, we wanted to look and see whether there was any dose and schedule relationships in the psychiatric events observed.

In this analysis, we've excluded the 033 study population, as we've already shown you that population had an increased incidence of psychiatric illness relative to non-deployed residents who also took ARAKODA. We've also considered events that have some reasonable relationship possibly with study medication.

In the left-hand column, we have the 200-milligram intended dose with exposure for 3 days or less compared to greater than 3 days of exposure. So with 3 days of dosing or 6 months of dosing, there's basically no difference in psychiatric events. And if I can direct your attention to the second column from the right at the bottom, it's basically similar to the placebo rate.

If we increase the dose to a 400- to 600-milligram load over 3 days -- so that's the third data column from the right -- the total

increase of psychiatric events increases a little bit but not much. If we increase the dose to 400 milligrams and give it either for 3 days -- sorry, weekly or monthly, in a small population, there was only 1 incidence of insomnia. So overall with this picture, there aren't any dose or schedule related increases in psychiatric events.

At this point, I have to take a step back and just say a few words that aren't data related. I work with veterans on my team every day. I've spent 15 years working with or around military folks, and I deeply respect the service that Australian and U.S. veterans who may be viewing these proceedings today have made to their country.

I understand that the adverse events that have been reported to the TGA are sincerely expressed and real as they're experienced, and that folks who are in that position are deeply impacted as are their families. But we're trying as a sponsor to move a drug forward that we believe will make a huge difference to the impact of malaria in

the world, so we have to view these adverse events critically and from a data perspective to do our best effort to assess causality. So what I'm going to say in the next few slides I understand will sound insensitive.

Seventeen-year psychiatric event reports have been reported to the TGA in February 2017. This was at the time that we submitted out dossier. We understand that these reports were made by or on behalf of ADF veterans who believe exposure to tafenoquine in clinical trials 16 years earlier may have caused their neuropsychiatric events.

We've been provided some of the details of these cases by the ultimate sponsor for radical cure at GSK. They wrote for these cases up as an IN safety report, and we were able to link 4 of these 4 cases two the 049 and 033 studies based on some of the information provided. With the remaining 13 cases, for which there was sufficient data to do cross-matching, we were able to find 8 in our study records for study 033.

In these two slides, I'm going to summarize

what the sponsor's findings were in relation to our own clinical trial database. In 3 of the 4 GSK IND safety report cases, we were unable to find any evidence of adverse events, specifically neuropsychiatric nature in our database. In one case, we found a case of insomnia, which is obviously milder and qualitatively different than what was reported to the TGA in the adverse event report and was also associated with a preexisting injury that was actively being treated.

For the 8 cases where we could find information in our database, 7 had no neuropsychiatric events, and the single case had a neuropsychiatric event that was reported after returning from the deployment, having previously successfully taken 27 days ARAKODA. From the sponsor perspective, we don't think there's any causal relationship between these events that have been reported and tafenoquine based on the data available to us. For the record, we know that the FDA has audited both 049 and 033.

At this point, I'm going to hand over to

Dr. Stephen Toovey, who will convey the risk-benefit for tafenoquine overall for travel and make a few concluding remarks for how we see the drug being used.

Applicant Presentation - Stephen Toovey

DR. TOOVEY: Ladies and gentlemen, members of the committee, should this drug be approved, what would it look like? Well, earlier I was talking about the benefit-risk of chemoprophylaxis, which is a settled issue. If we look at the benefit-risk of this drug, what does it look like?

Overall on the right-hand side, you can see the risks. I think as you've seen from the fairly exhaustive presentation on safety today that you've received, these are actually quite well understood, also given the history that we have of the whole drug class.

One of the principle risks is obviously drug-induced hemolysis. This is well understood. This risk can be managed obviously with a G6PD test before prescription of the drug. Other adverse reactions I think you have seen in great

detail, and these are generally not disabling and are reversible. So on the risk side, I think we have a fairly clear picture, and there don't appear to be major risks.

On the benefits side, obviously that stacks up. And if you have a look, that kind of list works through from preclinical to the actual effectiveness considerations. So the drug is not teratogenic, not mutagenic. I think we saw a fairly convincing presentation about the absence of neurotoxicity. The drug is a causal prophylactic. In other words, it actually gets at the parasite in the liver before it gets out into the blood and causes mischief. And that actually translates into dosing and to adherence benefits.

Importantly, it's active against all species, so we don't have to split our treatments the way that was explained earlier with different drugs. We have one drug here that's doing everything we would like. I think we also saw that fairly disturbing picture of the lady who ended up having amputations. Malaria is not a disease to

trifle with or to play with. As I said earlier, falciparum malaria is a medical emergency in a non-immune. Vivax malaria will make your life very unpleasant, and there is a distinct morbidity and occasional mortality with it. So these are diseases we really need to prevent.

I'll make a point here, prevent malaria sequelae. What do we mean by that? These are long-term complications. Again, I come back to the picture of the lady who visited Thailand. She, for the rest of her life, will have to live with these amputations.

Adherence. Do we think that the weekly dosing, the reduced pill burden, the good safety and tolerability, and the reduced post exposure duration of therapy would be a benefit and would improve adherence? I think the short answer to that is it would seem that they would.

The forgiving PK for late doses is another benefit, another advantage. And today, we have a lot of travelers. We have all travelers, travelers with chronic diseases who at one time, these would

have been stay-at-home folks. These people are now out traveling the world. The typical picture you get is of the silver foxes, as they're called, traveling the world on their pensions.

These people often are taking other medications, and tafenoquine has a low potential for drug-drug interactions, which actually simplifies the prescribing both in the travel clinic and in the primary care setting where physicians and other healthcare providers may not be that familiar with the antimalarial armamentarium. So we're making life easier for the traveler and the prescriber here.

I think we have also seen there is an absence of QT concern, of cardiac liability. And the absence of a neuropsychiatric liability actually is a huge benefit not only to travelers but to the prescriber as well. In the clinical setting, particularly, this these drug, if it is approved, will be prescribed not only in travel clinics but across the country in primary care practices. And if we have a safer drug without

neuropsychiatric liability, it's going to make life easier for the prescriber, too.

So overall, we have a drug with an acceptable safety and tolerability profile. We balance the risks against the benefits, and the drug starts to look positive. So having said that, we've got a good benefit-risk ratio. Should the drug be approved, what would it look like in practice? Would it be a drug that would be used? I believe this would enter frontline practice actually very quickly and would be well received by prescribers and travelers.

I've broken out the different categories of traveler there. I think it's pretty clear what they are. I think the only group there who would not gain immediate benefit would be the individual traveler traveling on short-term notice, where you don't actually have time to do the G6PD testing. Once you've got that out of the way, this drug should be available to all, all classes of travelers.

I think it will be a particular

benefit -- well, the military has been discussed in detail. From my perspective as a civilian practitioner, I can see the military benefits. For the long term traveler and the expatriate who is away for 6 months or even longer in country, a drug that's well tolerated, easier to use with a forgiving regimen, that's a benefit. Something that one sees a lot of are the frequent travelers. The person I mentioned, this week he's in Brazil. He's home for 10 days; 2 weeks later, he's in southeast Asia. Give the guy a break. Don't ask him to take 4 weeks of tablets after he gets back.

I think the other thing, if you look at the bottom bullet point, we have here a drug with global efficacy working around the world. Currently, we don't have a concern about resistance. And it's working against all species. This is going to, again, make life easier for the prescriber and obviously for the traveler, too.

This famous curve that we have shown you, I think this is your third viewing of this. We actually have to do something to bend that curve

down. It can't be right that in our current state of knowledge, in the developed world, in an affluent society, that we actually have a curve that looks like this. We should be, and we must be able to be doing something better.

New Drugs with a different safety profile, different side effect profile, with improved adherence are the keys to this, I think. I've summarized here the benefits for the traveler. It's going to make his life easier with improved adherence. It's a simple forgiving regimen. Even the military would prefer, we understand, a simpler regimen. I think you've heard that quite clearly. And this will be a benefit to the frequent traveler.

For the prescriber -- and I think, again, let's bear in mind that not everybody who's going to prescribe this drug will be a travel or tropical medicine expert. This will be used in a primary care setting, quite a lot I believe. This will make those practitioners lives much simpler. They will have a safer drug without the neuropsychiatric

liability. It works everywhere. It's a forgiving regimen, and it's a weekly dosing.

So I think at this point, we've come to the end of our presentation, and I'd like to thank everybody. And just to I think reiterate the message, we have a potential here for a drug that works against all species of the parasite across the globe. Thank you.

Clarifying Questions

DR. BADEN: I would like to thank the applicant for covering a lot of data in a very short amount of time, and the committee very much appreciates that. We now have 9 minutes for some clarifying questions. We will, if we don't cover all of the clarifying questions, have opportunity later in the morning to ask further questions.

So let me start with Dr. Orza. And for our committee members, we'll have the same practice. Let myself or Ms. Bhatt know if you have a question. If with a question you have a follow-on question, please indicate that to me, so we can try to be as thematic as possible and hopefully improve

efficiency of getting the concepts clarified.

Dr. Orza?

DR. ORZA: Michele Orza. I think we're looking at really distinct populations potentially using this, so I wanted to focus first on the U.S. travelers and just ask a couple of clarifying questions.

The CDC data that you showed a couple of times about poor adherence, is that because people are not getting prophylaxis in the first place; they're not thinking to get it, and/or they get it, and they just don't adhere to it? They don't take it properly.

Then related to the adherence question, you showed kind of a rough meta-analysis, but is there really any data about the simplicity -- if you're a traveler and you're out of your daily or weekly routine, that it really is not much easier to remember to take a pill once a week versus once a day.

The last time, we heard a lot about because of the long half-life of the drug, delayed

sensitivity reactions. So I was thinking about a traveler who would take this for 3 days and then hit the road, and then maybe a week or two later, they would experience the delayed sensitivity reaction, and then be who knows where.

So I'm just wondering if you had any data about those three issues.

DR. DOW: So, I'll ask Dr. Toovey to address the first two questions, what's the reason for the lack of adherence. And then maybe, Sally [ph], if you could get the hypersensitivity backup slides prepped for Bryan to address that question once Dr. Toovey has finished.

DR. TOOVEY: Thank you for the questions. I think it's a very good question. I think the short answer is it's -- and we've seen this in other countries as well. It's a combination of factors. Obviously, if don't start with prophylaxis in the first place -- well, you can't really fail prophylaxis, but you're at risk of malaria.

So we see that. But we also see people not completing their regimens. They often start out

with good intentions. We used to see it actually quite a lot. At one time, we were using chloroquine with proguanil, which one was weekly, then one was daily. It was a very cumbersome regimen. And people would get that all wrong and would end up with toxicities and all sorts of things.

So I think the short answer is it is people failing to take the drug in the prescribed manner. And there have been studies -- there are some I can think of from France, for example, where blood levels show that despite what people are saying, clearly something's gone wrong. And the only way you can really explain it is they haven't taken the drug. So anything that makes it easier for them to take the drug has got to be helpful.

Now, your second question is a little more difficult to answer. It was, is there really a water-tight clinical trial in a way that would compare weekly against daily studies or daily use of the drug? I'm not sure how you'd do that, because you would have to be giving placebos and

you couldn't blind it. So everybody would end up on a daily dose.

You can only, I think, rely on experience from what one hears in travel clinics and travel medicine practice, and in surveys that are taken in the literature, which is what I showed you. And I think you were right. I think it was a rough view of it, but I think that's as good as it gets, to be honest.

So I think it turns out to be a common sense answer. Personally, I should know better. But if I'm taking something, I prefer it weekly. There will be definitely people who would prefer it daily; I accept that. But I think that comes back to the point we need more choices. At the moment, we only have one drug that's available for weekly use, mefloquine, with all the problems that are associated with that. So I think it comes down to choice and just having more options available in the end.

DR. TOOVEY: Thank you, Dr. Orza, for the questions. We took note of the same concern two

weeks ago from the advisory committee, and we thought it was an astute and appropriate question. So obviously, we had two weeks to prepare for this, so we went back and interrogated our database to see if we could get some answers.

One thing I would say before we start is, remember that this is quite different because we've got the 3-day load before you're leaving home station and heading into a malarious area. So we're at very close to steady-state concentration before you've jumped on the plane, or the boat, or whatever and left. So whatever side effects, we would have anticipated that you would see them initially right there.

Hypersensitivity reactions have been reported 3 times within our safety database, and you see those reflected here. On day 165, there was conjunctivitis, sinusitis, and rhinitis treated with antihistamine, and the symptoms resolved in a day. On day 183, an allergic reaction, body as a whole, again, treated with antihistamine and resolved the next day. And then at doses

substantially higher than the anticipated clinical dose, again on day 112, allergic dermatitis and some eye edema, unspecified treatment therapy and resolution of the symptoms in 5 days.

So over a 6-month protracted period of dosing, these look like allergic reactions that many of us might have to ragweed, or grasses, or flowering plants, life.

I just want to show you, then, the two cases that were reported by GSK with Krintafel that caused the concern from 2 weeks ago, you can see on day 17, the lip swelling, difficulty breathing; the second case, day 18, again, difficulty swallowing. This was much more clinically concerning, so treated with antihistamines and the corticosteroids. The descriptions for us clinicians of these two events are quite distinct from the three more benign.

I would point out, again, which was made a earlier, this is within the context of co-administration with chloroquine, and these are in malaria patients. So it's a quite different

population, as well, than what we have for prophylaxis.

DR. BADEN: Thank you.

It is 10:40. We have a list of questions from almost every member of the panel that we will need to get to. But I think we need to take our 10-minute break, give the agency the opportunity present their view of the data, and then we will have as much time as possible for further clarification. I'll ask all of the committee members, as well as all of the respondents, to be as pointed as possible so that we can cover as much ground as possible because there are many, many important issues that we need to clarify.

I'd like to thank, again, the applicant for covering a lot of ground. We'll have a 9-minute break and resume at 10:50, promptly. Thank you.

(Whereupon, at 10:40 a.m., a recess was taken.)

DR. BADEN: We will now resume and proceed with the FDA presentations. I think Dr. Li will present on the clinical efficacy.

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 the efficacy of tafenoquine in the prophylaxis of malaria.

The proposed indication of this NDA is prophylaxis for malaria in adults for a period of up to 6 months. I will skip the dosage, as you have seen this before, several times.

There were 5 prophylaxis efficacy studies at the proposed dose. Three of the studies provided substantial evidence of efficacy of TQ for this indication. They were randomized, double-blind controlled studies. Studies 043 and 045 were similarly designed, placebo-controlled studies in semi-immune subjects.

There were two additional studies that I will discuss. The first is study 033, which was an active control trial in non-immune treated soldiers. Due the difficulty of determining the extent of malaria exposure for this study

population, we consider this study informative but difficult in determining conclusively if it shows the effect of TQ. Observing no case of malaria in an active-controlled study can mean proposed drugs work or that no one was exposed to malaria.

The other study is study 030. This was a placebo-controlled trial in semi-immune subjects that failed to show a treatment effect. When there is a failed study, we need to make sure that it does not point to evidence against the efficacy of the drug.

The applicant determined that the failure to detect the treatment effect was likely a problem with the smear slide reading. Additionally, the positive control failed to show a effect. Therefore, we do not believe this study points to a problem. I will only briefly discuss this study later.

Study 043 was a phase 2B placebo-controlled, single-center study in Kenya, an area of P. falciparum malaria infection. Healthy subjects received a 3-day presumptive course of halofantrine

to eliminate any existing plasmodium parasitemia.

Subjects were then randomized equally to 1 of the 4 groups. TQ load only 400 milligram for 3 days, TQ low-dose 200 milligram for 3 days, and weekly for 10 to 15 weeks. TQ high dose 400 milligrams for 3 days, and weekly for 10 to 15 weeks, and then placebo. Of the folks on the TQ low-dose group, study visits included day 1 of loading dose, then weekly including 4 weeks of follow-up.

The key inclusion criteria included healthy subjects of 18 to 55 years. The key exclusion criteria included any cardiovascular, liver, neurologic, or renal functional abnormality, which could place subjects at an increased risk of an adverse event, AE, or confuse the results; and also use of antimalarial drugs not prescribed by study physician within 2 weeks of study drug initiation and a G6PD deficiency.

The primary endpoint or confirmed parasitemia by week 15 was defined as having 2 consecutive weekly blood smears positive for

plasmodia, read independently by two microscopists blinded to one another's diagnosis.

Regarding the analysis population, the applicant defined the ITT efficacy population, intention-to-treat population, that included subjects who completed clearance treatment and loading dose and at least 1 weekly dose. They also defined the efficacy populations, which included subjects in the ITT efficacy population who had at least 1 on-therapy smear.

Most of these populations included subjects based on post-treatment information, which could lead to differences across randomized treatment arms. For this reason, we used an all randomized population, which included all randomized subjects for our efficacy assessment. Note, use of this different population did not impact the overall conclusions.

The protective efficacy, PE of a TQ regimen, relative to placebo was calculated where PE was derived from the proportion of subjects who had parasitemia at any time during the prophylactic

phase. In the formula, I is the instance of parasitemia and RR is relative risk. PE could be understood as reduced instance of parasitemia with zero indicating no protection and the one indicated 100 protection.

Although there were 3 TQ groups, there was no planned adjustment for the confidence level due to multiple comparisons. We used Bonferroni method for multiple comparisons with a type 1 error adjusted to 0.05 divided by 3 equals 0.17. Chi-square test was used for comparing proportions of parasitemia using a type 1 error rate just mentioned. 98.3 percent confidence intervals for the difference between TQ and the placebo were calculated.

Only limited baseline characteristics were available. Approximately 60 subjects were randomized per arm. There was a higher proportion of males in the TQ low-dose group. The distribution of age was comparable.

The proportion of parasitemia was lower in the TQ group compared to placebo. In this analysis

of all randomized subjects, subjects with missing outcome were considered a failure. Missing values were due to AE, loss to follow-up, and protocol deviation. The percent of missing data was lower in the placebo arm.

In the TQ low-dose group, a higher proportion of subjects had protocol deviations. Three subjects not starting clearance medication or taking enough doses of it, 3 having no further details. Five of these 6 subjects were not included in the applicant's defined ITT population.

The estimated PE for the TQ low-dose group was 73.3 percent. For the three TQ groups, all the lower limits of CI's were greater than 35 percent and the chi-square p-values were highly significant.

The majority of the subjects with observed parasitemia, 99 percent were infected with P. falciparum. P. malariae parasites were only detected in 1 subject in the TQ low-dose only group. The treatment effect was consistent between males and females in the TQ low-dose group. In conclusion, this study

demonstrated the efficacy of TQ 200-milligram compared with the placebo group.

The second trial in a semi-immune population was study 045. This was a placebo-controlled trial with multiple TQ doses in Ghana. Prior to study drug administration, subjects received 18-day antimalarial radical cure treatment.

Subjects were randomized to one of the 6 groups, including 4 TQ groups, a placebo group, and the mefloquine MQ group. Treatment included loading dose for 3 days and weekly doses, including 12-week prophylactic phase. Study visits included day 1 of loading dose and 12 weekly visits during the prophylactic phase and 4 additional weekly follow-up visits, including blood smear.

The inclusion criteria included subjects in good general health; males aged 18 to 60 years and females aged 50 to 60 years, excluding women in reproductive ages. The exclusion criteria were very similar to those in study 043. The primary endpoint for parasitemia by week 12 was defined as the first occurrence of malaria infection as

documented by a single positive blood smear from both field microscopists.

Full data set was the analysis population used by the applicant. The definition contained exclusions that could have been affected by randomized treatment. Because that might lead to differences in treatment groups, we used the safety data set for the primary analysis, which included all randomized subjects who completed the radical cure phase successfully and started the loading dose of medication.

Since this study was blinded, whether or not a subject started randomized treatment should not be impacted by treatment. Using different analysis calculations did not impact the overall conclusions of the study.

The analysis included calculations of CI for PE. The confidence level was not specified in the protocol. We used Bonferroni adjustment for the 4 TQ versus placebo comparisons. Type 1 error was 0.05 divided by 4 equals 0.0125, and the confidence level was 98.75 percent.

This table only contains placebo, TQ 200 milligram, and MQ group. The safety population contained 94 placebo subjects and 93 TQ subjects. Baseline characteristics were comparable. Note that the mean age for females was higher than for males because women younger than 50 years old were not eligible for the trial, so they excluded women of child-bearing ages.

Using FDA's efficacy analysis, where missing outcome was considered as a failure, parasitemia was about 94 percent in the placebo group; 27 in the TQ group, and 17 in the MQ group. The difference between TQ and MQ were due to different proportions of missing data, mainly due to a high proportion of discontinuation from AEs in the TQ group. Of 8 subjects with AEs in this TQ group, 3 had hemoglobin reduced and 5 had an ALT increase.

The PE for TQ was 71 percent. The lower limit of CI for PE was greater than zero at 55.8 percent, indicating a significant protective effect. The other three TQ groups also achieved a significant PE. In

conclusion, this study demonstrated that TQ was statistically significant.

Of the majority of subjects with observed parasitemia, 98 percent were infected with P. falciparum. P. malariae parasites were only detected in 4 subjects in the placebo group. Subgroup analysis indicates consistent treatment effect among sex, age, and weight groups. Note that the sample sizes were small in some groups. Analysis by study site did not show any concerning differences.

Study TQ-2016-02 was a phase 1B placebo-controlled challenge study conducted in Australia in healthy, non-immune adults to determine the efficacy of TQ after blood stage P. falciparum challenge. Subjects received TQ of placebo on days 1 to 3. On day 13, subjects received asexual blood stage parasites by intravenous inoculation. Subjects were followed until day 34, the end of the study.

Sixteen subjects were randomized 3 to 1 to the TQ or placebo group. The efficacy endpoint was malaria by the end of the study based on

parasitemia and the clinical symptoms. The analysis population was ITT, which included all randomized subjects. No subjects were removed from any analysis. The proportion of malaria by the end of the study was compared using Fisher's exact test. Four subjects were randomized to placebo and 12 to TQ. This imbalance in demographic factors is expected given the very small sample size.

The study results showed that all 4 placebo subjects had asexual positive counts from day 17, 4 days after the challenge and developed malaria from days 20 or 21. No TQ subjects had malaria. The difference in malaria incidence rates was highly significant based on the p-value from the Fisher's exact test.

Placebo subjects received antimalaria rescue treatment from days 21 to 25. No TQ subjects met the criteria for early initiation of rescue therapy, and as planned, received it from day 30 to 33, as mandated in the protocol to make sure there was parasite clearance prior to the end of the study.

Now I will move to the active control study in non-immune subjects. Study 033 was a phase 3 active-controlled, double-dummy study for prevention of P. falciparum and P. vivax malaria conducted in East Timor in non-immune Australian soldiers. Subject were randomized 3 to 1 to the TQ or MQ group. There were 2 phases in the study, a 26-week prophylactic phase and a 24-week relapse follow-up phase after the soldiers returned to Australia.

During the prophylaxis phase a loading dose and maintenance doses were given. During the relapse phase, subjects in the TQ group received placebo, while subjects in the MQ group received primaquine PQ 15 milligrams twice daily for 14 days. Note that the final dose in the proposed regimen given in the week following exit from the malaria area was not included in this study.

Inclusion criteria included healthy male or female subject between ages 18 and 55 years. Exclusion criteria included demonstrated G6PD.

History of allergy or intolerance to MQ, PQ, or another 8-amino-quinoline and clinically significant abnormalities. The primary efficacy endpoint was a prophylactic success, no clinical malaria during the prophylactic phase.

Clinical malaria was defined as having a single positive smear with concurrent clinical signs and symptoms consistent with malaria infection. Blood smears were taken at baseline and at each visit during the prophylactic phase at weeks 4, 8, 16, and 26.

Analysis populations included the ITT population, which included all randomized subjects who took at least 1 dose of prophylactic study medication. We used this as the analysis population for the primary analysis. The per-protocol population was used by the applicant for the primary analysis.

The difference in prophylactic failure proportions was calculated along with 95 percent CI. As there was an active control group in the study, the applicant attempted to

establish noninferiority of TQ to MQ. As we discussed, we do not believe this is possible.

Baseline demographic characteristics on the medical conditions were comparable. During the 26-week prophylaxis phase, TQ had 96.1 percent success rate and MQ 96.9 percent success rate. All failures were due to missing outcomes. The difference in success proportions was minus 0.8, and the lower limits of 95 CI was negative 3.7 percent, indicating that TQ could have as much as a 3.7 percent lower rate of success compared with TQ.

The study continued once subjects returned from the malaria area for an additional 24-week follow-up. There were 5 failures during this time period, 4 in the TQ group and 1 in the MQ group, less than 1 percent per arm. All were due to P. vivax. There were 25 subjects with missing data during the follow-up phase. These subjects were considered as failure in the FDA's analysis.

The proportion of success for TQ and MQ was

95 percent and 96 percent, with a difference of about negative 1.2 percent. The lower limit of CI was about negative 4.7 percent, indicating that TQ could be as much as 4.7 percent lower in success proportion than MQ.

In order to establish noninferiority, it is important to know the placebo attack rate at the time and place where a study was conducted. Seeing no case of malaria in a study could mean that both treatment were effective or that subjects were not exposed to malaria. The applicant provided the information on a community-based survey of local subjects and on reports of malaria from previous years. We believe it was likely that the subjects exposed to malaria pathogen. We cannot know this conclusively, however, we believe this study provided reassuring evidence of efficacy in non-immune subjects.

Now, I will briefly discuss study 030, a study that failed to show the efficacy of TQ. This study was a placebo and active-controlled study in semi-immune subjects from Western Kenya. Subjects

received 3-days of halofantrine to clear any existing parasitemia. Malaria-free subjects were equally randomized to one of the groups: placebo, TQ, and MQ. Efficacy assessment was prophylactic outcome at week 25.

The original analysis of this study did not show any efficacy of TQ or the active control MQ. Where the study was still ongoing, it became clear that there was a problem with the slide reading. Unplanned , blinded slide re-reading was conducted at the end of the study. 766 slides were provided to the Navy medical research unit for blinded re-reading. Of those that were originally read as positive, only 31 was re-read as positive. Based on this information, as well as the lack of significant effect of the active control MQ, the lack of effect seen in study 030 did not appear to be a cause of concern.

In conclusion, three studies, 043, 045, and TQ-2016-02, provided evidence for TQ's efficacy in prophylaxis of malaria. Study 033 provided reassuring evidence in non-immune subjects.

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

DR. BADEN: Thank you.

Dr. McMaster?

FDA Presentation - Owen McMaster

DR. McMASTER: Good morning and welcome. My name is Owen McMaster. I'm a pharmacology and toxicology reviewer in the Division of Anti-Infective Products, and this morning I'm going to give a brief overview of the nonclinical pharmacology and toxicology data submitted to support this NDA.

Tafenoquine is an 8-amino-quinoline, as synthetic analog of primaquine and also a cationic amphiphilic compound. This is a group of compounds known to be associated with phosopholipidosis, and we'll discuss this a bit more later on.

The package was comprehensive and evaluated pharmacology, toxicology, and the pharmacokinetics of tafenoquine. It was complete as consistent with the guidelines put out by ICH and evaluated genotoxicity, reproductive toxicity, juvenile

toxicity, carcinogenicity, in addition to single- and repeat-dose studies. The pharmacology studies evaluated cardiovascular function, pulmonary function, and neurobehavioral function. None of the findings from these studies indicated any risk to patients taking tafenoquine.

As a result of the particular interest in the neurotoxic potential of the drug, what I'll do is go into a little bit more detail on two studies, which focused on the potential neurobehavioral effects of tafenoquine. The first was a single dose neurobehavioral assessment in adult rats, and the second was a multiple dose juvenile toxicity study in rats.

The first study evaluated doses up to a 500 milligrams per kilogram in adult rats, which were subjected to neurofunctional assessments, particularly functional observational battery and motor activity. The locomotor activity was evaluated pre-dosing as well as 6, 24, and 48 hours post-dose. The functional observational battery evaluations were conducted pre-dose as well as 30

minutes and 3 hours post-dose.

As you can see by this slide, the functional observational battery was very involved but involved a couple of particular functions which might address the issue of perhaps whether or not the animals were more anxious than usual. In particular, the ease of removal, responds to visual approach, reactivity to handling, arousal, auditory assessments, in addition to all the other ones listed on this slide.

Motor activity was evaluated in 60-minute sessions, which were divided into 12 5-minute sessions because the motor activity of rats, as time goes on, changes very drastically. Total horizontal and vertical movements were recorded, and there were no drug related adverse findings from these studies at doses and exposures, which were multiple times compared to the human dose.

The second study was an oral juvenile toxicity study where animals were dosed from day 7 postnatally into adulthood. The doses went up to 25 milligrams per kilogram and animals were dosed

every 5 days. At the end of the dosing on day 62, animals were allowed a 2-week drug-free period after which motor activity and auditory startle response and learning and memory were evaluated. This was to allow the sponsor to demonstrate whether or not there were any latent effects from the drug, given the particular pharmacokinetic properties of the drug. Again, there were no drug related effects on neurobehavioral function at several-fold, what would be expected from the human exposures.

The toxicology studies evaluated genotoxicity, carcinogenicity, and reproductive function, in addition to single- and repeat-dose studies, which went as long as 6 months for the typical tox study in rats and one year in dogs, in addition to the 2-year studies in rats and dogs which were specifically designed differently to evaluate carcinogenicity. Adverse events that were of special interest to us affected blood, kidneys, lungs, liver, and reproductive function, and were consistent in general with what we saw in the

clinic.

So for example, in the blood, methemoglobinemia, mile anemia, and reticulocytosis were observed. Kidney nephrosis could possibly reflect sequelae from the methemoglobinemia, and as I'll discuss in a bit more detail later on, there were increased renal tumors in male rights only. In the lung, we saw evidence of phospholipidosis and increased lung weight. And in the liver, there was increased weight, again, phospholipidosis, increases in certain enzyme markers, as well as hemosiderin deposition, which was not considered adverse.

All of these findings were reversible except for two, the cytoplasmic vacuoles, which is indicative of phospholipidosis and which did reverse over time, but they did not completely disappear, and the hemosiderin deposition, both of which are not considered adverse.

In reproductive studies, we found that there were abortions in the rats. Consistent with ICH S1 recommends carcinogenicity studies in rats and

mice. These studies were conducted over the lifetime of the animals, and renal tumors were identified in male rats only. This slide shows the increase in adenomas and carcinomas in the two highest doses in the rat carcinogenicity studies.

We detected renal tumors in male rats, but there were no tumors any of the mice or in the female rats. The genotoxicity evaluations show that this compound was non-genotoxic, and given the above considerations, it's not clear if the positive findings in male rats indicates a risk to humans taking tafenoquine for prophylaxis.

Reproductive toxicology studies were conducted in rats and mice, and while there were no abortions in rats, pregnant rabbits dose of tafenoquine during organogenesis showed abortions. At the highest dose, abortions seen in the presence of maternal toxicity decreased food consumption and bodyweight, which would have confounded the result if that was the only finding. But at the lower dose, in the absence of these confounders, in other words, where there were no decreases in food

consumption and no decreases in bodyweight, we did also see abortions.

Questions have been raised, as we've heard discussed previously, regarding the adequacy of the nonclinical neurotoxicity assessments, and these are based largely on published data that indicate that 8-amino-quinoline are associated with neurotoxicity. Questions also have been raised regarding whether or not rats and dogs are sensitive to the neurotoxicity of the 8-amino-quinoline.

We in fact have data, including published data, that show that monkeys, rats, and dogs are in fact sensitive to 8-amino-quinoline toxicities, and I'll discuss these data from Richter and Schmidt, admittedly very old papers, which outline the findings after these other 8-amino-quinolines.

I'm going to take plasmocid as an example. In his 1949 paper, N. Schmidt described hyperesthesia, incoordination, loss of equilibrium after plasmocid in dogs, while the Schmidt paper didn't show a lot of neurobehavioral effects,

although they did show some GI findings and paralysis of the nictitating membrane, abdominal cramping. The Richter paper showed tumors, increased muscle weakness, ataxia, and loss of deep reflexes. So there's a difference as you go across investigators. Rats showed paralysis of the lower jaw and tongue and mice showed ataxia and paralysis of the hind limbs, as well as tongue and lower jaw.

Just to be clear, these are plasmocid effects.

Histopathology findings after plasmocid administration include severe degenerative lesions in the spinal cord and brain and cerebellum, and monkeys and dogs showed some lesions in the dorsal motor nucleus of the vagus and moderate lesions in the dorsal root ganglia. Rats showed moderate to severe lesions in the mesencephalic nucleus.

Overall, our neurotoxicity conclusions are as follows. Clearly, the findings that we've just described in the Schmidt paper were described as being at fatal intoxication. Lethal doses of plasmocid do produce a variety of effects, which

vary across species and vary across studies.

Given the fact that we've demonstrated that rats and dogs, which were closely evaluated for the tafenoquine NDA, are in fact sensitive to the neurotoxicity of plasmocid. And given that brain lesions by themselves do not always predict neurobehavioral effects, and vice versa, neurobehavioral effects do not always predict brain lesions, we consider that additional nonclinical studies would be difficult to interpret and are not warranted.

Tafenoquine was appropriately evaluated according to ICH guidelines and was not shown to be associated with neurobehavioral or histological effects in rats, mice, or dogs at clinically relevant doses despite findings, which have been published, with other 8-amino-quinolines at very high doses.

The principal nonclinical findings were hematologic, pulmonary, hepatic, renal, and reproductive. These were generally reversible. And when they were not reversible were not

considered adverse. Tafenoquine was not associated with neurobehavioral or histopathological findings. Thank you.

DR. BADEN: Thank you. Dr. Patel will review the safety data.

FDA Presentation - Sheral Patel

DR. PATEL: Thank you, and welcome. My name is Dr. Sheral Patel, and I'll be presenting the safety data for NDA 210607.

Tafenoquine has been studied in the fed state. The median Tmax is 14 hours with a range of 6.1 to 72 hours. It is highly protein bound. It has slow and negligible in vitro CYP450 metabolism in human liver microsomes and hepatocytes. The mean half-life is 16.5 days with a range of 10.8 to 27.3 days. There is no significant effect of TQ on the PK of substrates CYP2D6, 3A4, 2C9, and 1A2. There are no significant transporter interactions.

This slide summarizes the overview of the presentation today. First, I'll go through our approach to the safety review, then I'll review exposure, adverse event summary, discontinuations

and study withdrawal, serious adverse events, treatment-emergent adverse events, and submission-specific safety issues of which there are six. We'll be spending quite a bit of time on that final section.

More than 20 clinical trials were included by the applicant. Most of these were conducted from 1992 to 2006. Pooled analyses were conducted to detect potential low frequency events. All the subjects receiving the tafenoquine anticipated clinical regimen, or TQ ACR, regardless of exposure duration, were included in this extended dosing safety set.

We acknowledge inherent weaknesses in combining data from heterogeneous studies, and we avoided drawing safety conclusions across treatment groups from the pooled analyses. For submission-specific safety issues, individual study data as well as pooled data from select studies were reviewed. Several agency disciplines contributed to the safety review.

In addition to the Division of

Anti-Infective Products, we had consultants from cardiovascular, renal, neurology, psychiatry, and ophthalmology. In addition, the ear, nose, and throat devices branch provided input.

There were five main studies that we used for our safety review, and these studies comprised the extended dosing safety set. This was study 033, 057, 030, 043, and 045. Study 033 was a phase 3 study conducted from 2000 to 2001. This was a randomized, double-blinded, active comparator study in non-immune subjects where deployed military personnel were enrolled.

These subjects received the TQ ACR, the tafenoquine anticipated clinical regimen, 200 milligrams daily for 3 days, then 200 milligrams weekly. The TQ ACR was compared to mefloquine or MQ, and study 033 had the most number of subjects with a planned TQ dosing of greater than 23 weeks.

Study 057 was a phase 1 study conducted from 2003 to 2006. This was a randomized, double-blinded, placebo-controlled study in healthy volunteers to evaluate renal and ocular safety.

The TQ ACR was compared to placebo, and the planned TQ dosing was greater than 23 weeks.

Finally, study 030, 043, and 045 were phase 2/3 studies conducted in 2000, 1997, and 19908. All were randomized, double-blinded, placebo-controlled studies. Study 030 and 045 also had an active comparator. These studies enrolled semi-immune subjects from Kenya and Ghana. The TQ ACR was compared to other TQ doses, mefloquine, and/or placebo, and the planned TQ dosing was from 12 to 15 weeks.

More than 3,000 subjects were exposed to tafenoquine in clinical trials and received multiple TQ doses. 825 subjects received the tafenoquine ACR for any duration. Remember, the ACR is the anticipated clinical regimen, tafenoquine 200 milligrams daily for 3 days, then 200 milligrams weekly. The mean exposure in this group was 21.l2 weeks with a range of 10 to 29 weeks.

529 subjects were exposed to the ACR for greater than or equal to 23 weeks, and the majority

of these subjects were non-immune. These 825 subjects who received the ACR for any duration comprised the extended dosing safety set. These subjects were enrolled in those five studies discussed previously.

This table summarizes the adverse events in the extended dosing safety set. Remember, this is a pooled analysis of heterogeneous studies, so we're really looking at that one treatment group. In the TQ ACR group, there were zero deaths. There was one subject who received tafenoquine 50 milligrams weekly who died due to suspected hepatocellular carcinoma. 5.7 percent of the subjects in the TQ ACR group had at least one serious adverse event or SAE. 1.3 percent of the subjects had an SAE leading to study withdrawal. 83.9 percent of the subjects in the TQ ACR group had at least one treatment-emergent adverse event or TEAE, and 4.1 percent of these subjects had a TEAE leading to study withdrawal.

The most common TEAEs leading to study discontinuation in the TQ ACR group included

increased ALT, decreased hemoglobin, and decreased GFR. SAEs leading to study discontinuation in the TQ ACR group included visual field defect, hemolytic anemia, suicide attempt, and glomerular filtration rate decreased. In the placebo group, the SAE was metamorphopsia, which is a visual distortion where straight lines appear curved. In the mefloquine group, SAEs leading to study discontinuation included anxiety and rash. We'll discuss more about these TEAEs and SAEs later on in the presentation.

This table summarizes selected serious adverse events in the extended dosing safety set. This is a pooled analysis of heterogeneous studies, so we're looking for those low-incidence adverse events within a treatment group. In the TQ ACR group, selected SAEs included keratopathy, glomerular filtration rate decreased, gastroenteritis, retinal disorder, hemolytic anemia, visual field defect, and suicide attempt. Selected TEAEs occurring at greater than or equal to 2 percent in the extended dosing safety set

included vertigo, abdominal pain, diarrhea, nausea, vomiting, musculoskeletal pain, arthralgia, myalgia, headache, dizziness, and lethargy.

Next, we'll move on to the discussion of submission-specific safety issues. There are six which I'll focus on in the presentation today. This includes ophthalmic, cardiac, hematologic, neurologic, psychiatric, hepatic biliary, and gastrointestinal. When discussing these specific safety issues, I'll first review known safety issues and labels for quinoline drugs approved for malaria prophylaxis or treatment, and then I'll move on to a discussion of the specific safety analyses.

Tafenoquine, as you know, is an 8-amino-quinoline. Primaquine is also an 8-amino-quinoline. Chloroquine and hydroxychloroquine are 4-amino-quinolines, and mefloquine is a quinoline methanol.

Ophthalmic issues are noted in the labeling for chloroquine, hydroxychloroquine, as well as mefloquine. Ocular effects include effects on the

ciliary body, cornea, and retina. Visual field defects have also been described. The label notes irreversible retinal damage with long-term use or high dosages for chloroquine and hydroxychloroquine, and the mefloquine label has warnings for optic neuropathy and retinal disorders.

This table summarizes the ophthalmic adverse events in the extended dosing safety set. Remember, this is a pooled analysis of heterogeneous studies, and we're looking for those low-incidence adverse events within a treatment group. Ophthalmic TEAEs leading to discontinuation in the TQ ACR group included night blindness and visual acuity reduced in the same patient. Ophthalmic SAEs included keratopathy and retinal disorder, and ophthalmic TEAEs occurring in greater than or equal to 1 percent of the study subjects included conjunctivitis.

I wanted to take a moment to just describe keratopathy. Vortex keratopathy can occur with drugs with cationic amphiphilic structures such as

tafenoquine, chloroquine, and hydroxychloroquine. These drugs can cause corneal epithelial deposits. There typically is no effect on visual acuity and few ocular symptoms, and the deposits usually resolve with cessation of therapy. All the subjects with keratopathy were enrolled in study 033, which was 1 of 3 studies conducting ophthalmic assessments.

As was noted, detailed ophthalmic assessments were conducted in three studies. TQ is associated with reversible keratopathy. Effects on the retina were difficult to ascertain. There was a potential problem with the quality of the fundoscopic examinations and/or their interpretation. The applicant has an ongoing healthy volunteer study to characterize the TQ ophthalmic effects over one year.

The table summarizes keratopathy observed in studies conducting detailed ophthalmic assessments. In study 033, in the TQ ACR group, 69 of the 74 subjects experienced keratopathy at 6 months. This resolved in 42 of the 69 subjects at 3 months

post-treatment and all resolved by 1 year. In comparison in the mefloquine group, zero subjects had keratopathy.

In study 057, 15 of the 70 subjects in the TQ ACR group experienced keratopathy during treatment. This resolved in 14 subjects by 14 weeks of onset and by 48 weeks in the final remaining subject. In the placebo group, 4 of the 32 subjects experienced keratopathy and all resolved by 6 weeks of onset. And finally, in study 058, which was a P. vivax treatment study, 12 of the 46 subjects had keratopathy at day 28, and by day 90, this resolved in 6 subjects, was ongoing in 4 subjects, and 2 subjects were lost to follow-up. In comparison in the primaquine and chloroquine group, zero subjects had keratopathy at day 28.

Cardiac issues are noted in the label for primaquine, chloroquine and hydroxychloroquine, as well as mefloquine. This includes potential QT prolongation, cardiac arrhythmias, cardiomyopathy, and other cardiac effects. No thorough QT study

data were submitted. However, ECG data from study 14 were reviewed. Fifty-eight healthy subjects receive 1 of 3 TQ 200-milligram formulations at a dose of 400 milligrams each day for 3 days. There was no significant relationship between TQ concentration and QTc interval changes. There was no large mean increase greater than 20 milliseconds in the QTc interval for TQ 400 milligrams, and preclinical studies did not reveal a QT liability.

Hematologic issues are noted in the label for primaquine, chloroquine, hydroxychloroquine, and mefloquine. This includes the association of hemolytic anemia and G6PD deficiency. Other hematologic issues include anemia, methemoglobinemia, leukopenia, and other blood dyscrasias.

This table summarizes the hematologic adverse reactions in the extended dosing safety set. Remember, this is a pooled analysis of heterogeneous studies, and we're looking for those low-incidence adverse events. Hematologic TEAEs leading to discontinuation in the TQ ACR group

included hemoglobin decreased and hemolytic anemia. Hemolytic SAEs included that one case of hemolytic anemia. And hematologic TEAEs occurring at greater than or equal to 1 percent of the study subjects included anemia, leukocytosis, and thrombocytopenia.

All three subjects with hemoglobin decreased were enrolled in study 045 where study criteria had subjects discontinued for minor changes in laboratory parameters. For all three cases, no treatment was required, and the TEAE resolved in 28 to 50 days.

Both subjects with hemolytic anemia were G6PD negative. One subject experienced a hemoglobin drop of 14.4 to 9 grams per deciliter at day 3, and the other subject experienced the hemoglobin drop from 13.1 to 10.9 grams per deciliter at day 23. One subject was treated with multivitamins and ferrous sulfate, while the other received no treatment, and the anemia resolved in both subjects.

We looked at hemoglobin decrease in the

extended dosing safety set, and it appeared that TQ may be associated with decreases in hemoglobin levels. Two percent of the subjects in the TQ ACR group experienced a hemoglobin decrease from baseline of greater than or equal to 3 grams per deciliter.

We had laboratory results for methemoglobin for study 033 and study 043, and it appears that TQ is associated with increases in methemoglobin levels. Fifteen percent of the subjects in study 033 and 74.6 percent of the subjects in study 043 had a methemoglobin level of greater than or equal to 1 percent. In comparison, there were zero subjects in the mefloquine group and 4.9 percent of the subjects in the placebo group had methemoglobin levels of greater than or equal to 1 percent.

1.8 percent of the subjects in study 033 and 12.7 percent of the subjects in study 043 had a methemoglobin level of greater than or equal to 3 percent to less than 5 percent. In comparison, there were zero in the placebo group and the

mefloquine groups. There was one subject in study 033 and 9 in study 043 that had methemoglobin levels of greater than or equal to 5 percent. It's important to note that there was no subject who had a methemoglobin level of greater than or equal to 10 percent, a level where cyanosis typically may appear.

Neurologic issues are noted in the labeling for primaquine, chloroquine, hydroxychloroquine, and mefloquine. The primaquine label notes adverse reactions of dizziness. The chloroquine, hydroxychloroquine label notes issues such as muscular weakness or skeletal muscle myopathy, auditory effects, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia, and polyneuritis. The mefloquine label has a boxed warning, contraindications, warnings, precautions, and adverse reactions for neurologic issues in the label.

This table summarizes the neurologic adverse events and extended dosing safety set. Once again, this is a pooled analysis of heterogeneous studies,

and we're looking for those low-incidence adverse events in a particular treatment group. Neurologic TEAEs leading to discontinuation in the TQ ACR group included hyperesthesia and visual field defect. Neurologic SAEs in the TQ ACR group included headache and the one case of visual field defect. Neurologic TEAEs occurring at greater than or equal to 1 percent of the study subjects included headache, dizziness, and lethargy.

It should be noted that systematic monitoring for neurologic symptoms was not performed, and we may be underestimating the true incidence of these neurologic TEAEs. In addition, neurologic TEAEs after TQ discontinuation was difficult to assess.

The one case of hyperesthesia leading to discontinuation occurred in a 26-year-old white male who has hepatitis B carrier positive. He reported moderate hyperesthesia on study day 12. Prior to the TEAEs, study personnel documented at least one episode of heavy alcohol use in the subject together with alcohol associated malaise

while on study. Hyperesthesia was treated using unspecified non-medicinal modalities and resolved after 130 days.

Visual field defect occurred in a 45-year-old female who developed mild reduction in visual field approximately 3 weeks after starting treatment. This was confirmed in both eyes by a visual field analyzer. No retinopathy was observed. The subject received no treatment, and the event resolved approximately 6 weeks after onset.

In study 033, it appeared that the TQ ACR may be associated with neurologic TEAEs. These TEAEs were numerically lower or similar to mefloquine. These TEAEs included headache, fatigue, and lethargy, vertigo and tinnitus, dizziness, and myalgia. It's important to note that there was one case of deafness in the mefloquine group.

In study 057, the TQ ACR may be associated with myalgia. There were 6 cases in the TQ ACR group versus the zero in the placebo group. This

is a small study, so it's difficult to make definitive safety conclusions. However, there is one case of tinnitus in the TQ ACR group, which should be noted.

Study 030, 043 and 045 were pooled together, and it appeared that TQ ACR may be associated with headache, myalgia and, dizziness. In general, these TEAEs were higher or similar to placebo and lower than mefloquine.

Psychiatric issues are noted in the labeling for chloroquine, hydroxychloroquine, as well as mefloquine. This includes irritability, nervousness, emotional changes, nightmares, psychosis, and suicidal behavior. The mefloquine label has a boxed warning, contraindications, warnings, precautions and adverse reactions for psychiatric issues.

This table summarizes the psychiatric adverse events in this extended dosing safety set. Once again, this is a pooled analysis of heterogeneous studies, and we're looking for low-incidence adverse events within a treatment

group. In TQ ACR group, psychiatric TEAEs leading to discontinuation included depression and suicide attempt. The one case of suicide attempt was considered an SAE. 3.9 percent of the subjects in the TQ ACR group experienced a TEAE within the psychiatric disorders system organ class, and specifically 2.5 percent of the subjects experienced a TEAEs considered a sleep symptom.

Similar to neurologic issues, systematic monitoring for psychiatric symptoms was not performed, and we may be underestimating the true incidence of these adverse events, and psychiatric TEAEs after TQ discontinuation were difficult to assess.

The one case of depression leading to discontinuation occurred in a 28-year-old white male with a history of intercranial head injury who reported moderate depression beginning on study day 24. He was withdrawn from the study and treated with paroxetine. His depression resolved after 87 days [indiscernible].

The other case was a case of suicide attempt

in a 24-year-old male who was found to be acutely intoxicated with ethanol 8 days after TQ exposure. The family reported the subject had marital problems and had taken poison for suicide. He had ethanol on his breath, was combative, and disoriented on presentation to the drug center. The subject was hospitalized, and the event resolved 2 days later.

I study 033, psychiatric TEAEs were numerically higher in the TQ versus MQ group, 5.1 percent versus 4.3 percent. Sleep symptoms were similar in the TQ and MQ groups, 3.5 percent versus 3.7 percent. In study 57, the incidence of psychiatric adverse events were similar in the TQ and placebo groups, 4.9 percent versus 5.1 percent. However, a TQ may be associated with depression, and here were 2 cases in the TQ ACR group versus zero in the placebo group. Again, study 057 is a small study, so it may be difficult to draw definitive safety conclusions.

In study 030, 043 and 045, the incidence of any psychiatric TEAE in the TQ group was

numerically lower than the mefloquine group but higher than placebo. In the TQ ACR group, the incidence was 1.2 percent compared to 0.4 percent in placebo and 2 percent in mefloquine. You should note the 1 case of suicide attempt in the TQ group discussed previously.

This table summarizes TEAEs in subjects with an underlying psychiatric illness exposed to tafenoquine. These subjects did not receive a TQ ACR, the tafenoquine anticipated clinical regimen, 200 milligrams daily for 3 days, then 200 milligrams weekly. However, it's important to note the time of onset of these TEAEs relative to the half life of tafenoquine.

There was a 23-year-old male who received 400 milligrams per day for 3 days of tafenoquine who experienced paranoid ideation and hallucinations 25 days into the study. This subject had a history of psychosis undisclosed at enrollment. There was a 22-year-old male who received a single dose of tafenoquine 350 milligrams who experienced psychosis 3 weeks

into the study, and this subject had a history of two psychiatric hospitalizations.

There was a 30-year-old male who was administered a single dose of tafenoquine 500 milligrams who also experienced psychosis 1 week into the study, and he had an underlying illness of schizophrenia not disclosed at enrollment. And finally, there was a 44-yea- old female who received a single 8-milligram dose of tafenoquine who experienced nervousness 3 weeks later. It was found that she was self-medicating with diazepam, promethazine, and tramadol.

Gastrointestinal and hepatobiliary issues are noted in the labeling for primaquine, chloroquine, hydroxychloroquine, and mefloquine. Adverse reactions include nausea, vomiting, epigastric distress, and abdominal cramps. In the chloroquine hydroxychloroquine label, there are precautions for use in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs, and the mefloquine label recommends periodic evaluation of hepatic function

with long-term use.

There were no major gastrointestinal or hepatobiliary toxicity observed with the TQ ACR. In the extended dosing safety set, 2 subjects withdrew due to abdominal pain and irritable bowel syndrome. Both were considered SAEs. Six subjects withdrew due to increased ALT. All of these subjects were enrolled in study 045. So similar to the subjects that withdrew for decreased hemoglobin, these subjects were excluded due to minor variations in laboratory parameters.

In addition to the SAEs of abdominal pain and irritable bowel syndrome, there was an additional SAE of diarrhea. No subjects met Hy's law criteria. TEAEs occurring at greater than or equal to 1 percent in the extended dosing safety set in the TQ group included diarrhea, nausea, vomiting, and abdominal pain. These TEAEs in study 033 were numerically lower, but similar to the mefloquine group. It is difficult to assess the TQ ACR safety when administered without food.

This table summarizes our key safety

findings associated with TQ ACR, the tafenoquine anticipated clinical regimen, tafenoquine 200 milligrams daily for 3 days, then 200 milligrams weekly. The TQ ACR is associated with reversible vortex keratopathy. An ongoing study may help clarify the effects of the TQ ACR on the vision and the retina. There is no large mean increase in the QTc interval anticipated at TQ 400 milligrams, a dose higher than the ACR.

TQ ACR exposure was associated with a decrease in hemoglobin , hemolytic anemia, and methemoglobinemia. In addition, TQ ACR was associated with headache, lethargy, dizziness, vertigo, tinnitus, and myalgia. It's important to note that systematic monitoring for neurologic issues was not conducted, so we may be underestimating the true incidence of these adverse events.

Psychiatric adverse reactions, particularly sleep disturbances, were associated with TQ ACR exposure, and adverse reactions leading to study discontinuation included suicide attempt and

depression. Similar to neurologic adverse events, systematic monitoring for psychiatric adverse events was not conducted, so we may be underestimating the true incidence of these adverse reactions. There were no major gastrointestinal or hepatobiliary toxicity observed with the TQ ACR, and diarrhea, nausea, and vomiting were all common TEAEs.

This concludes my safety presentation. I want to take a moment to acknowledge the entire FDA review team who contributed to the safety review. Thank you for your attention.

Clarifying Questions

DR. BADEN: Thank you very much, Dr. Patel. And I would like to commend the agency for covering a lot of ground and conveying it very efficiently.

I will open discussion for clarifying questions to the agency, and then we will turn back to clarifying questions for the applicant and more discussion. Please get our attention to get you on the list of questions. I will start with the first question for Dr. Patel.

In looking at the data, if I understand, much of the data is collected 26 to 13 years ago. And you alluded in your comments that you were bringing together data from disparate studies. How comfortable are you that the data had been collected in a similar way, the toxicity tables are similar, the scoring, the assays, like the methemoglobin assays were similar? Because I noticed some significant differences between studies, and that just for me raises questions to make sure data consistency and interpretability are substantial. I'm interested in your thoughts.

DR. PATEL: These were heterogeneous studies conducted over a large time span. When we pooled the data together, we were really concentrating and looking for those low frequency adverse events, acknowledging the differences in study designs, the differences in monitoring that were taking place for each different study.

DR. BADEN: They used the same tox tables? Was that homogeneous or not, or a lot of this is you're left with what was done, of course?

DR. PATEL: Yes. So we worked with what we had. As you know, the ways of coding adverse events changed throughout the course of when those trials were conducted.

DR. PATEL: Thank you. Dr. Bilker?

DR. BILKER: I realize my questions are for the sponsor. Should I wait?

DR. BADEN: Yes, please.

DR. BILKER: Okay.

DR. BADEN: For comments to the agency that builds on a theme, please get our attention. We will go back to the sponsor, and obviously the question I asked will be relevant to both discussants. Dr. Lo Re?

DR. LO RE: This is a question for Dr. Patel. The sponsors this morning showed a slide, number 39, in their material where they looked at the pharmacokinetics of tafenoquine according to different body weights. And they looked at the different predicted concentrations of tafenoquine according to time by the different body weights. And they particularly showed an

interesting figure that for the people who were underweight, particularly at 50 kilos, the concentration above the 80 nanogram per mL threshold was actually quite high.

So I'm wondering if you had looked at in the agency adverse events according to specifically subgroups of BMI to see if toxicities in particularly underweight individuals, given that the serum concentrations are so high, were magnified in those BMI subgroups.

DR. PATEL: We're going to have our pharmacometrics respond to that question.

DR. BADEN: Thank you. And if the reviewer can just state your name and perspective.

DR. LIU: It's Chao Liu. I'm the pharmacometrics team leader for this submission. In terms of addressing the question whether or not the safety adverse reactions are related, we quantitatively assessed the relationship between tafenoquine exposure to diarrhea and the hemoglobin changed from baseline based on the data from study 033 And based on available data, we didn't

see a significant trend in terms of correlation between tafenoquine exposure to diarrhea and hemoglobin change.

For psychiatric disorder, we tried to do this assessment, but due to the low-incidence rate, it wasn't quite conclusive in terms of quantitative analysis.

DR. BADEN: Dr. Ofotokun? Thank you.

DR. OFOTOKUN: This question is for Dr. Patel. I just wanted additional clarity on the hematologic side effects of the product. Given what we know about G6PD deficiency in primaquine, with these hematologic side effects, how severe were they? Were they reversible, and what happened to those few individuals with hematologic side effects, hemolytic anemia, methemoglobinemia? What happened to them? Were they followed long enough to know what happened afterwards?

DR. PATEL: The cases of the subjects who were discontinued due to decreases in hemoglobin, those cases I think were -- we typically probably wouldn't know them, provided treatment or such.

They were excluded due to minor variations in laboratory parameters. They were asymptomatic and did not require any treatment.

There were the two cases with hemolytic anemia. Both of those subjects were asymptomatic, and one received some treatment with multivitamins and I believe iron sulfate, and the other one received no treatment, and both of those resolved. The applicant may be able to describe. There are some cases of subjects who received other doses that were G6PD positive and exposed to tafenoquine who experienced hemolytic anemia.

DR. BADEN: If I may build on that comment, and it's on your slide 25, the methemoglobin anemia appears to be, between 033 and 043, a 60 percent delta. I'm having trouble understanding that observation, and I'm interested in your thoughts.

DR. PATEL: Yes, I agree. So these studies were conducted at different times and in different places, and we can ask the applicant if there is differences in how the laboratories were obtained.

DR. BADEN: Along those lines, I'll ask the

applicant if you can make a running list of issues that get raised, and then we will re-address this after we finished clarifying from the agency. And along those lines as well, the applicant mentioned 8 individuals enrolled who had G6PD deficiency. Did you have a chance to review those cases, and do you have any insight?

DR. PATEL: Yes, we reviewed those cases, and our findings were consistent with what the applicant had discussed.

DR. BADEN: Dr. Ofotokun, did you have follow-on questions?

DR. OFOTOKUN: Probably, I would need some additional clarity from the applicant later on.

DR. BADEN: Okay. Dr. Follmann?

DR. FOLLMANN: Thank you. This is Dean Follmann. I had a question for Dr. Li. I was interested in study 033, which was in the soldiers who went to East Timor. And I assumed this would be designed as a noninferiority study because they're just two arms and you would expect similar outcomes for it. So with a noninferiority study, I

would have expected there to be sort of a margin prespecified in the protocol along with some rules or discussion about how you would ascertain whether the attack rate in the area, the military end was sufficient.

So my question is, really, was there a protocol that the FDA looked at and contributed on or was it sort of an after the fact kind of study you had to analyze? That's one question.

The other is, you were hesitant to extrapolate to concluding noninferiority from the study, and I'd like to hear a little more about your thinking about your hesitancy.

DR. LI: It's a very good question. I took a review in the middle, at the very beginning of NDA review. I believe we did not review the protocol. We received the study report at the pre-NDA stage. So I think at the very beginning in the protocol, they proposed a 10 percent margin if my memory is correct. Then after the NDA submission, they proposed a different margin. This margin is not pre-approved by the FDA based on my

understanding.

DR. FOLLMANN: Thank you. Maybe I'll have a follow-up for the sponsor then. That's all I have

DR. LI: Regarding the noninferiority conclusion for this study, the sponsor derived at an attach rate for the untreated subject from the current study and assuming the efficacy rate for the treated group, for example, 75 percent or 80 percent effective. They derived the prevalence in untreated subjects. It's based on very strong assumptions. We really don't know the effect of the active control.

Also, in justification of the noninferiority margin, they used a number not considering the variability in estimates. So that's why I hesitated to make a strong conclusion from this study.

DR. FOLLMANN: Thank you.

DR. LI: Thank you.

DR. BADEN: Thank you. Dr. Orza?

DR. ORZA: I have four short clarifying questions for the FDA. The first is how unusual is

it for the excretion pathway to be unknown? That was an interesting note I thought.

Two, how unusual or troubling is it for you to not have access to the data for two of the supporting studies?

Three, with regard to the labeling for mefloquine, it was my understanding that the black box warning got added later. So I was wondering what was the threshold for adding that, and how many person-years of use did we have before we met that threshold and discovered the need for the black box?

Then fourth, I didn't know whether FDA had any requirements related to considering the potential for resistance, either existing or for it to develop, with the introduction of a new drug like this.

DR. COLANGELO: Hi. I'm Phil Colangelo, clinical pharmacology team leader with the Office of Clinical Pharmacology. With respect to your question about the excretion pathways for tafenoquine, tafenoquine is a very long half-life,

16 or so days. So it's not ethical to conduct a radio labeled ADME study to determine the absorption, distribution, metabolism, and excretion of the drug. So therefore, we didn't ask for it because we know this, and therefore it was not done.

DR. NAMBIAR: Sumathi Nambiar. I can take questions 2 and 3. I think question 2 was about the lack of source data, and question mefloquine labeling. Do I have the questions right? Okay.

In terms of source data, ideally, we do like to have access to the source data because we would like to verify the authenticity of the data that we're reviewing, and we like to make sure that the data that are captured in the data sets can actually be traced back to the source data. So the traceability is very important.

Whether or not we necessarily inspect the source data for every single study in the NDA really depends upon the application. But in general, for the key efficacy studies and key studies that are supporting an application, we

would like to be able to review the source data and have the confidence that the data we're reviewing and interpreting are in fact valid.

In terms of mefloquine, mefloquine was approved in 1989, and over time, there were periodic updates to the labeling with regard to the different adverse events as they emerged in the postmarketing setting. If I remember correctly, I think it's 2013 is when the labeling was updated to include the boxed warning. And I don't think there was a specific number or threshold that it met. But with the accumulating safety data when it reaches a point where we think it rises to the level of a boxed warning, we do update the labeling. So I don't know if there is a particular number of person-years that was achieved.

So did that answer your questions?

DR. ORZA: Yes. Just roughly, if you had any sense of how much data had accumulated or how many people had used it for how long, before we understood that that was there and added it to the label.

DR. NAMBIAR: All that I can say is it was 1989 and 2013. So many years have lapsed since approval, but I think it's also important to note that even if a box warning wasn't added, labeling updates did happen periodically. With postmarketing safety data, we are limited in really quantifying how many exposures were there and how many reports because it's really based on what reports we get. But at some point, when we realized that we not only had a critical mass, but then the severity of some of these reports and the chronicity of some of these reports, persistence I think led us to escalate it up to a boxed warning.

Your fourth question about resistance, Dr. Bala, who's a microbiologist, will address.

DR. BALA: Hi. I'm Shukal Bala, the clinical microbiologist for this application. Resistance is a little challenging to measure. For indications such as prophylaxis, there is no baseline pathogen, so whatever breakthrough infections occurred, that's the parasite one can have.

I would like to mention again the tools which are there to measure resistance are not nearly as well advanced as for some of the antibacterial and antifungal drugs.

DR. BADEN: Just to build on Dr. Orza's question, the efficacy is reported at about 70 percent. So presumably that means 30 percent failure. Were there any parasites obtained in that context and were they evaluated? Are you aware of any?

DR. BALA: No. No testing was -- the only results we had was for blood smears, which of course you cannot process for any molecular testing or in vitro sensitivity.

DR. BADEN: Thank you.

Follow on? No. Then we'll add Dr. Green.

DR. GREEN: Thank you. My question is for Dr. McMaster. I think it's pretty short and sweet.

Your data in rats and the association with renal tumors look like there was one at 1 milligram per kilogram and two at 2 milligrams per kilogram. Can you clarify what that dosing is relative to

what the planned dose is for the use of this drug as prophylaxis?

DR. McMASTER: These were doses that were lower than clinical doses.

DR. GREEN: Lower than clinical doses?

DR. McMASTER: Yes.

DR. GREEN: Thank you.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Just another question for Dr. Patel for clarification of the study design. There was one phase 3 study that was conducted in a non-immune population in Timor, and then there was another group of studies which you described as phase 2/phase 3 that were conducted in semi-immune population.

Can you clarify why that was labeled phase 2/3 instead of phase 3?

DR. PATEL: The three studies that you're referring to, study 030, 043, and 045, some of those studies were comparing different doses in addition to the tafenoquine anticipated clinical regimen, as well as placebo and mefloquine. So

that's why we labeled it phase 2/3.

DR. OFOTOKUN: So can we then conclude that there was no true phase 3 study in semi-immune population?

DR. PATEL: Well, in that phase 2/3 study, there is a comparison of the anticipated clinical regimen versus placebo and/or mefloquine within those studies, which would be considered what we would look at for a phase 3 study.

DR. BADEN: Dr. Nambiar?

DR. NAMBIAR: If I can just add to that, I think from our standpoint, we worry less about the nomenclature, whether it's phase 2 or phase 3. It's more if it's an adequate and well-controlled trial that we can interpret.

DR. OFOTOKUN: So the assessment, those were adequate enough to be considered phase 3?

DR. NAMBIAR: Again, we don't worry -- less whether it's phase 2 or phase 3; whether it was an adequate and well-controlled trial. And the two studies 043 and 045, in our assessment are adequate and well-controlled trials that we can interpret.

DR. OFOTOKUN: Okay.

DR. BADEN: And then the question, the strength of the data taken in toto.

I think those are the clarified -- do you have for the agency, Dr. Mailman?

MR. MAILMAN: Not Dr. Mailman but Mr. Mailman, which is fine. Just following up, looking at the sponsor's -- I can't remember -- page 54, which gives a safety database. And it basically said we had 825 people who had the dose that we're talking about here. And if we throw out the 492, it leaves us with the 333 that actually are in the safety database, and here are the numbers.

Given that we're talking about putting this to what might be millions of people, do we have a large enough number to look at the adverse effects from a trial design, and have we seen enough patients who could possibly have these adverse effects? We're kind of looking at a needle in a haystack with only 333 if we take the non-deployed residents. Is this a big enough number? I'm not

the biostatistician in the room, but it seems small.

DR. NAMBIAR: Thank you for your question. You're right. When we're looking at drugs being developed for prophylactic indications, where obviously the use is in a much larger population, we like a larger safety database. For treatment indications, for more serious diseases where there's an unmet need, we do accept smaller numbers, at least the 300.

So is this database on the smaller side? Yes, and I think Dr. Yasinskaya noted that in her presentation as well. But this is what we have, so we will look at the data. We look at the overall risk-benefit considerations, and if the overall risk-benefit is favorable, there might be ways to supplement safety data post-approval. So we take all that into consideration.

But again, that's what we're seeking, input from the committee as to what might be your thoughts on the size of the safety database, the safety signals, and how we might evaluate this

further if there is a need.

DR. BADEN: And just building on that, Dr. Nambiar, there are 3,000 exposed at different doses for different duration, and the 333 is in the non-deployed at the ACR for the 6 months, but then there's the 12 months, and then there -- there are many other permutations that we have to consider that's unknown, the adequacy of the overall database.

DR. NAMBIAR: That's correct, and 825 is the ACR. That's the number we have for the ACR.

DR. BADEN: With and without the deployed, depending on how one --

DR. NAMBIAR: Yes --

DR. BADEN: -- and this just speaks to the complexity of looking at the safety data because all of these competing factors, including duration, which may not be 6 months.

DR. NAMBIAR: Yes. And I think the number's 529, which got the longest duration, which is 6. The longer duration is up to 6 months.

DR. BADEN: Thank you. Dr. Orza?

DR. ORZA: I thought that the total number of people exposed in any way to tafenoquine was 4,000 and something.

DR. PATEL: In our review, it was 3,184.

DR. ORZA: At the last meeting, there were -- I thought there were over 4,000.

DR. BADEN: But there it may be different applications with -- I don't know if they're all combined.

DR. ORZA: No. I was just thinking in terms of the total safety database, anyone ever exposed to tafenoquine at any dose, because we are looking for a drop in the ocean.

DR. NAMBIAR: But for purposes of our review, we are focusing on this application.

DR. BADEN: If no other clarifying questions for the agency, then we will turn back to the applicant for the next 15 minutes before we break for lunch. And I think Dr. Bilker was first up from the earlier session.

DR. BILKER: Okay. Thank you.

Dr. Toovey mentioned that older people are

traveling more than in the past. That's a good thing. But in the sponsor presentation, there was no mention of potential age differences in efficacy or differences in types or rates of adverse events observed across the age groups. The FDA presentation included subgroup analysis specifically just for study 045, but it was broken down by age group. But there was only 1 subject over age 65.

What information do you currently have on the effect on this and adverse events panel in subjects over age 65? And then a follow-up to that, is there a potential for different optimal dosing for subjects over age 65?

DR. BADEN: I'll have Dr. Dow coordinate the response.

DR. DOW: So I'll just add a couple of comments, and then Dr. Toovey can elaborate if he would like to. We have very little data in subjects older than 65. And I think the overall comment was related to the low propensity for drug-drug interactions in subpopulations who may be

taking con meds for other purposes.

Do you have a follow-up question?

DR. BILKER: You just mentioned optimal dosing. That was my other question, was about the optimal dosing.

DR. DOW: I'm sorry.

DR. BILKER: Are there any potential differences? I know you don't have the data yet, but are there potential differences in what the optimal dosing may be in those over 65?

DR. DOW: I don't think we know the answer to that yet.

DR. BADEN: Dr. Green?

DR. GREEN: I have two questions. I'll ask my second question first. I'm looking at the summary slide you gave us of all the different studies that you have done in support of this indication. I note that with the exception of a study of 16 patients, you've not done any new studies in 11 years, and we've just talked about the limited safety database available to us.

I wonder if you could offer us the rationale

for why we should consider this at this time with no data, really, in 11 years, a small safety database, and yet such a high index of unmet need and clearly lots of people going to malaria areas, including deployed troops, which could get you the numbers and repeat a study like the one that was perhaps done in Timor but maybe with less stress. Thank you.

DR. DOW: Sally, could you please -- yes. Thank you.

So the two studies that we have done as a sponsor since we acquired the licensing rights in 2013 are the two studies listed on the right. 60PH02 was a challenge study in non-immune volunteers to confirm the efficacy of falciparum against blood stages of that parasite in non-immune volunteers. And then we've made a commitment to the agency to complete an ongoing safety study with 300 folks on ARAKODA and 300 folks on placebo for up to a year. That's the study on the right.

Sally, if we could go to the postmarketing requirements slide, please.

(Pause.)

DR. DOW: So while that slide's getting prepped, this postmarketing commitment slide will enroll 300 placebo subjects, 300 ARAKODA subjects. We'll follow them for up to a year with a 6-month follow-up. The primary endpoint is focused on the ophthalmologic safety to try and understand the issues that the FDA highlighted in the earlier presentation.

We know that at least with keratopathy, it's a progressive process where you see more of it over time, and then it resolves. So the original genesis of the study was around trying to confirm that over a 12-month exposure period, we don't see anything different from what we saw with 6 months.

So we're looking here at the 4 bullets at the top of this slide. We've also incorporated a mini psychiatric assessment, which is designed as an initial tool to assess active psychiatric illness in a very detailed questionnaire. We've also followed up on two of the events that were seen at low frequency, albeit a little bit higher

than the placebo Group, specifically in the sleep disorders. So that's what the LESQ assessment is.

Although the numerical rate of dizziness was lower than both mefloquine and placebo in the aggregate assessment of the safety population, we've put in a dizziness handicap inventory assessment because we know that's of particular interest to some folks. And then the Columbia Suicide Rating Scale will also be incorporated, and that will address the more serious issues related to that. We've also incorporated detailed hematology assessments to better understand the impact of tafenoquine on those small hemoglobin drops and the elevated but asymptomatic methemoglobin levels.

As a sponsor, when you -- this is a $20 million dollar study which involves the most complex set of eye exams and psychiatric assessments we think that any prophylactic antimalarial drug has been subjected to. And we did it more or less coincident with the submission of the dossier, and even though that's a risk to

the sponsor in terms of a parallel we review with a study that's ongoing, that underscores our commitment to trying to understand safety signals and follow up on them.

So we initiated enrollment in October of 2017. This will go on for a period of about two years. The other notable feature about this particular study is that it does not exclude folks with a prior psychiatric medical history. So as long as they're stable and can be enrolled in the study, we'll be following those folks for up to a year on tafenoquine as well.

It's obviously difficult to do a larger -- frankly, this study is going to occupy a lot of our resources over the next two years answering these important questions. And then the question you get to is how do you continue to monitor in a larger population, particularly for rarer neuropsychiatric events, understanding that it's not the sponsor's belief that there is a signal there? And the way to do this is through database outcomes where you actually get concrete

diagnosed neuropsychiatric events, and you have access to a denominator through prescriptions.

So our proposal to the agency is that we conduct a prospective health database outcome survey of this type, which has been used in the past to address advocacy consents in relation to the punitive neuropsychiatric events as some of the flu antivirals.

Then finally, we do have 200 and something adolescent subjects in our database with a loading dose that encompasses the 200 milligram times 3 load. We feel that for simplicity at this point, we need more data in pediatric subjects before the indication gets expanded. So we've committed to the agency to do a pediatric safety study for up to 6 months exposure in a malaria endemic country in the coming years.

We're a small company. Where there's resources available. We will also commit to following up on other safety signals if there's a reasonable hypothesis and there's an ability for us to execute the study with other partners.

So that's what we've committed to so far.

DR. BADEN: Dr. Green, do have a follow-on or your second part question?

DR. GREEN: I think my second part question will be much easier for you to understand. I just wanted to confirm that when we looked at the variation -- this came from either Dr. Smith or you in looking at the neuropsychiatric effects. And you had this slide where you looked at in the deployed study versus the non-deployed study, but in the non-deployed study, it was still 2.1 percent incidence of psychiatric effects.

I just want to make sure that we heard about that 2.1 percent when you reviewed the data for us because I just want to -- so that we weren't just talking but we talked specifically about in the non-deployed setting. I understand the confounder of looking in the deployed setting.

DR. DOW: So Sally, could you please load the slide at the end of Bryan's presentation? The rationale for putting this slide together is that deployed folks are at risk of a high level of both

physical and psychiatric injury, and we wanted to get a sense for how those two populations differed.

You have 4 columns here, placebo on the left, all tafenoquine subjects at the anticipated regimen in the 2nd data column, then the deployed subjects, and then the non-deployed subjects. Under the hypothesis, you would see a higher rate and physical and psychiatric injury in a deployed population. We tried to break it out that way.

The first line is the number of injuries and poisonings and procedural complications, which cover the scorpion stings that Mark mentioned, and lacerations, and thermal burns and all of that sort of stuff. And you can see that there's a higher risk in the deployed group versus the non-deployed group.

If you jump down to the second data row, similarly, although there's in the overall population a higher rate of psychiatric events in ARAKODA versus placebo, when you break that out to reflect the difference between deployed and non-deployed settings, the risk is quite a bit

higher in the deployed situation. And numerically the difference between placebo and non-deployed subjects is 1.3 percent.

If you further break that down to things that we might reasonably consider related to study drug -- so excluding the definitely unrelated events as categorized by the investigators who did the study -- the rate goes down, and the difference between the placebo and the non-deployed arm is 1 percent.

Then to address the question that you put specifically about psychiatric disorders affecting sleep, there's a numerically similar right between placebo and non-deployed in this example. And you can see, again, the increased risk in the military population for that adverse event.

DR. GREEN: Actually, I'm not interested in the sleep. How about the other 3 that are not sleep? So you have 6 that are non-deployed, 3 that are sleep. What were the other 3?

DR. DOW: Could we pull up -- I'm just trying to figure out which is the best backup slide

to address this question. Thanks.

Oh. We'll talk about that after lunch.

DR. BADEN: I have a follow-up.

DR. FOLLMANN: I have a follow-up.

Slide 69, I thought it would have been nice if you would have broken that down and have a column for 033, the tafenoquine arm and the comparator arm as the FDA had done. I think the FDA as a slide similar to those, which I thought was very helpful. It showed similarity of rates with the tafenoquine and mefloquine arms. But you have a couple of categories here that they didn't have, so it might be helpful to show those broken down by the two arms in 033.

DR. DOW: We'll get something to you over the lunch break so we can have a quick look at that afterwards.

DR. BADEN: Thank you. Question for the agency, Dr. Dow presented the three follow-on studies they're committed to. How assured are we that they will occur? Just trying to understand, once approval occurs, let's say it occurs, then

what confidence do we have that the follow-on data will be collected as suggested or we trust?

DR. NAMBIAR: Just to clarify, these are the applicant's proposals for postmarketing studies.

DR. BADEN: No, I know. I understand that.

DR. NAMBIAR: So they don't necessarily reflect agreements. I just want to make sure that that's clear.

DR. BADEN: No, reflect agreements, but if they were to choose not to do them, they could.

DR. NAMBIAR: So postmarketing requirements -- and maybe Ed will correct me -- under the authority that we got with the Food, Drugs, and Cosmetics Amendments Act, FDAAA, we do have certain authorities if it's a postmarketing requirement versus a postmarketing commitment. And whenever there is a study that is needed for a safety related concern, then it ends up being a postmarketing requirement.

DR. BADEN: And that postmarketing requirement occurs at the time of the approval or can occur after approval?

DR. NAMBIAR: No, so -- in general. I'm not talking about the specific examples here.

DR. BADEN: Of course.

DR. NAMBIAR: Postmarketing requirements are established typically at the time of approval. Certainly, if there are safety signals that arise post-approval, we have the authority to establish postmarketing requirements. And for every postmarketing requirement, we have dates that are set. So there are dates for protocol submission. There are dates for when the study report should be submitted and the study should be completed.

So there are a set of milestone dates that are required, and the applicants have to agree to those. And those are included as part of the approval.

DR. BADEN: That clarification is very helpful. Thank you.

Follow on? Dr. Lo Re?

DR. LO RE: Vincent Lo Re. In your slide before the other slide where you talked about the postmarketing requirements that Dr. Green had asked

about, can you just clarify which of the tests are based on symptomatic monitoring for neurologic symptoms? One of the things that Dr. Patel the agency had said was that there was a potential underestimation of neurological symptoms because those tests weren't systematically done.

So I wanted to just get a sense of which of the tests here were specifically focused on neurologic. You talk about in the health databases that you're going to look at a neuropsychiatric events, but I just wanted to know if in the long-term safety study you specifically had neurological monitoring included.

Then secondly, you've pulled out in the bottom group of bullets specifically focused on pediatric participants. But in follow up to Dr. Bilker's comments about patients over 65 years and given the comments about potentially this is going to be used in or older patients who are going to be traveling certainly after their retirement years, are there certain fixed numbers where you're going to look at specifically individuals over 65

years as part of this postmarketing requirement?

DR. DOW: The neuropsychiatric assessments that we've prospectively planned, the 4 inventories that we've listed here, I might ask Dr. Ranson to comment on the MINI specifically in terms of the scope of events that that covers.

DR. RANSON: The MINI neuropsychiatric interview is a validated assessment that relies on diagnosis of Axis 1 disorders. That has been developed and is in general clinical practice. That is given at baseline to establish any psychiatric diagnoses, as well as it's given repeatedly throughout the study.

The Columbia Suicidality Rating Scale is an assessment of suicidality, and that's given on a monthly basis throughout the entire study. Because insomnia is the highest psychiatric disorder that has been found in the studies, we have a specific Sleep Severity Assessment Questionnaire.

The neurologic specific disorders, however, that we see most frequently are headaches and dizziness. And these are, of course,

self-reported. If anyone reports an assessment of dizziness or disorientation, we do have the Dizziness Handicap Inventory to further explore that. Patients are given a diary to record their symptoms throughout the study. Compliance has been very good. We have reminders, medication reminders, that are frequent to ensure compliance.

If I could maybe address one additional question with regards to methemoglobinemia, we are assessing methemoglobinemia throughout this study compared to questions of older methodologies versus current methodologies. We're carefully monitoring this throughout the course of the study with modern methods, and to date we are seeing cases of methemoglobinemia. They have all been under the 10 percent clinically significant level. The highest that we've seen is one subject with 6 percent at hemoglobin concentration.

DR. BADEN: Thank you.

There are many more questions, including follow-ons, however, the hour is late. It's 12:45. I think we need to break for lunch. We will resume

at 1:35 with the open public hearing session, and then we will resume with the questions that are left hanging currently.

So we will reconvene at 1:35. Please take your personal belongings. Committee members, remember that there should be no discussion of the meeting during the lunch amongst yourselves, with the press, or any members of the audience. Thank you. We'll resume at 1:35.

(Whereupon, at 12:45 p.m., a lunch recess was taken.)

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

(1:39 p.m.)

Open Public Hearing

DR. BADEN: We will resume, and we will resume with the open public hearing part of the agenda, and then we will return to more clarification and discussion of the data, particularly with the applicant

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 that 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 have any financial relationship that you may have with the sponsor, its product, and if known its direct competitors.

For example, this financial information may include the sponsor's payment of your travel,

lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue or financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and in this committee place great importance on 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, there'll be 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 one 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're representing for the record.

DR. NEVIN: Good afternoon. I'm Dr. Nevin, the executive director of the Quinism Foundation. I have no financial [mic fade] to disclose. I'm joined in the audience today by several individuals who are suffering the chronic and disabling effects of mefloquine poisoning.

Our foundation is disappointed at the FDA's decision to approve NDA 210795. We believe that the approved drug will pose a danger to the public's health and that FDA has failed to adequately consider the critical safety concerns that we raised at the July 12th open meeting.

As we discussed two weeks, tafenoquine is a member of a drug class with demonstrated CNS neurotoxicity described as striking and identified not just in some but in all of the nearly 140 members of the 8-amino-quinoline class tested in World War era studies. The sponsors would have this committee believe that tafenoquine alone,

among all drugs of this class, lacks this property despite there being no evidence the drug was ever rationally designed to avoid this property.

When tested in Rhesus monkeys, these drugs cause highly focal lesions affecting diverse areas of the CNS, including the brain stem and the limbic system. The localization of these lesions reflects the signs and symptoms observed clinically with use not only of the 8-amino-quinolines, but with use of more broadly structurally related quinoline drugs, including chloroquine and mefloquine.

We believe FDA erred in uncritically concluding the CNS of tafenoquine on the basis of the very limited ad hoc animal model data submitted by the sponsors. We also disagree with the conclusions of FDA that additional animal model testing is not indicated and would cause confusion. If ever such testing was needed, it is now.

The FDA has also seemingly overlooked in vitro tafenoquine neurotoxicity data. These data were provided by the Walter Reed Army Institute of Research, clearly showing a lower IC50 in cultured

rat embryonic neurons for tafenoquine than mefloquine, a quinoline drug with accepted CNS neurotoxicity.

Both today's sponsor and the U.S. military very clearly acknowledge that mefloquine is neurotoxic and that this property limits the drug use, and have suggested that tafenoquine lacks this property, in part, on the presumed benign pharmacovigilance experience with primaquine, which the committee should consider is almost always co-administered with either chloroquine or mefloquine to which these adverse effects may be misattributed.

We are concerned about the sponsor and FDA are overlooking clear evidence of the inadequacy of the submitted clinical safety data. Here are the adverse event data from study 033 conducted among members of the Australian military. We note in comparison to data from the most recent Cochrane review of mefloquine, shown in the right most column, there is clear evidence of underreporting of neuropsychiatric adverse effects in these

sponsor's data. Assuming equal underreporting in each arm of the sponsor study, there is every indication tafenoquine shares the same liability to CNS adverse effects as mefloquine.

The committee is also urged to consider that several subjects in this trial are likely to provide evidence to a pending Australian Senate inquiry later this summer investigating serious allegations related to the use of tafenoquine in the Australian military. This evidence may provide context to the underreporting seen here and should be considered by this committee prior to being asked to vote on the safety of tafenoquine on the basis of what is obviously incomplete data.

Today, this committee is being asked to consider an indication for tafenoquine essentially identical to that sought for mefloquine 30 years ago. When mefloquine was being evaluated for safety at the time, common neuropsychiatric adverse effects such as anxiety, depression, abnormal dreams, and insomnia were not even identified in the stud submitted for FDA review. There's every

reason to believe the committee today is being asked to consider similarly incomplete data for tafenoquine.

International drug regulators now recognize that insomnia and abnormal dreams that occur with mefloquine use must be considered prodromal to more serious adverse effects and the drug immediately discontinued. These warnings were tragically not in place at the time of mefloquine's licensing 30 years ago. However, at the time mefloquine was licensed it was known that, like the tafenoquine today, its use was associated with episodes of psychosis. And particularly in military settings, episodes of psychosis are not benign events.

This is Master Corporal Clayton Matchee photographed here in the act of a deadly assault on Somali captive Shidane Arone during the ill-fated Canadian mission to Somalia in 1993. It is now known, years after the fact, that Matchee was suffering from visual hallucinations at the time of this event, which were likely caused by mefloquine. His psychosis was preceded by prodromal symptoms,

including insomnia, abnormal dreams, and anxiety. But absent current warnings, he was not instructed to discontinue the drug. Following this event, Matchee attempted suicide, and he was left with a permanent and disabling brain injury.

So as with NDA 210795, our foundation is recommending non-approval of this NDA. Publicly available data do not support the safety of tafenoquine at any dose, and particularly not at the high-end continuous doses, which are proposed for this indication. But should the drug nonetheless be approved, we make the following additional recommendations informed by our experiences with mefloquine.

First, we are recommending a boxed warning, advising of CNS neurotoxicities as a class effect of the 8-amino-quinoline and warning of the potential for permanent adverse effects. Psychiatric and neurologic symptoms, including insomnia and abnormal dreams should also be listed as prodromal as in the currently approved European mefloquine labeling and a contraindication to

further use of the drug.

In place of the proposed loading dose, we also recommend an initial safety assessment period with a modified dosing regimen of 100 milligrams biweekly for 3 to 4 weeks to permit a more gradual introduction of the drug so that these prodromal symptoms can be better identified. We also recommend restricting distribution of the drug to clinicians certified to comply with the box warning and to limit initial dispensing of the drug to no more than the initial safety assessment period prior to issuing a full prescription for up to 6 months of planned travel.

Lastly, we recommend the sponsor be required to conduct at a minimum, neurotoxicity testing using comparable methods for the extensive testing done on other 8-amino-quinoline using those as positive controls.

Thank you very much, committee, for your attention.

DR. BADEN: Thank you. Will speak number 2 step up to the podium and introduce yourself.

Please state your name and any organization you're representing for the record.

MR. ZOTTIG: Good afternoon, ladies and gentlemen. Thank you for allowing me to present the unmet medical military need for new weekly chemoprophylactic malaria drug at today's advisory committee meeting. I'm Major Victor Zottig, and I'm a product manager of antimalarial drugs for the United States Army Medical Material Development Activity, or USAMMDA.

I would like to make the following disclaimers. The views expressed in this presentation are my own and do not necessarily represent the views of the United States Army or Department of Defense. I have no financial conflicts of interest. Discussion of specific pharmaceutical products does not reflect an endorsement of those products. USAMMDA has several agreements through U.S. Statutory Code 15 USC 3710-alpha, which encourage a collaboration with 60 Degrees Pharmaceuticals for the development of tafenoquine for malaria prophylaxis.

The Department of Defense has had a long and proud history of developing antimalarial drugs. The military's focus on antimalarial research is for the health, wellbeing, and protection of service members deployed to malaria endemic areas. Malaria is the top military infectious disease threat to deployed service members, and the Army has over 100,000 soldiers in over 150 countries around the world where a significant number of troops are exposed to malaria.

Malaria is a devastating disease, especially to non-immune individuals who represent the majority of our military forces. For example, during World War II, over 695,000 service members contract malaria. Think about that number. 695,000 is more than the current and strength of the total U.S. Army, including active duty, reserve, and National Guard soldiers. Despite the current armamentarium of protective measures available to service members, such as permethrine treated uniforms, insecticides, bed nets, and prophylactic medications, service members still

fall ill to malaria.

You can see by the chart, roughly 30 to 60 service members contract malaria annually. Even with these small numbers, malaria can still influence military operations because each one of these service members are hospitalized and has significant recovery periods prior to returning to duty.

These infections were all preventable and each case results in damaging a service member's health and welfare, sometimes permanently. These low numbers provide a false sense of security due to the fairly stringent measures taken to enforce malaria prevention and compliance.

In the Army's 243 year history, every deployment of a large number of soldiers to malarious areas has resulted in malaria cases. The only exception is Operation United Assistance to Liberia for the 2015 Ebola response, where soldiers' health was of paramount concern. Command discipline resulted in strict prophylactic adherence.

Malaria prevention measures by the military can and do fail mainly due to poor prophylaxis compliance and malaria drug resistance, which is spreading across many of the antimalarial drug classes. Compliance failure is not only the service members for getting or unwilling to take their daily medication, but the lack of time or access due to combat environment. New prophylactic drugs for malaria are critically needed, especially ones that have longer half-lives to provide flexible dosing options during challenging operational conditions and provide compliance forgiveness.

Currently, the FDA-approved chemoprophylactic drugs used in the military have critical vulnerabilities. The military's policy on prophylactic medication identifies doxycycline and atovaquone and proguanil, or Malarone, as its first-line therapy for malaria prevention. Chloroquine is generally not used due to widespread resistance, and primaquine not used as a prophylactic for the military.

After a boxed warning was placed on mefloquine, it is generally no longer prescribed. However, it is the last option for those individuals who cannot take the primary therapies due to intolerance or contraindication. Regarding the primary therapies, doxycycline is a daily medication which can be difficult to take on a regular schedule for service members. From my own personal experience using doxycycline in my deployment to Iraq in 2003, it was impossible to take the medication the same time every day, essentially making the drug useless for malaria prevention.

In addition, photosensitivity and other side effects can prevent a certain portion of the service members from receiving the drug. Although Malarone resistance is not widespread, it is found in certain malaria regions. There is no other option for service members that cannot take the three approved medications.

The current status of available antimalarial chemoprophylactic drug options for the military is

not ideal, and the requirement for a weekly antimalarial prophylactic drug represents an unmet military need. The DoD and nongovernmental organizations are still conducting research on new antimalarial drugs, however, these drugs are not expected to be available in the near future.

Malaria is a debilitating and potentially fatal disease. I cannot emphasize enough the severe impact it can have on the military's ability to complete its mission and the detrimental effects it has on service members' health. Thank you for your attention and consideration.

DR. BADEN: Thank you for your comments.

My understanding is speaker number 3 was unable to make it, and seeing nobody to the contrary, we will move to -- will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. KAUFMAN: Yes. My name is Lois Kaufman, and I am speaking today on behalf of Dr. Kevin Baird.

"My name is Dr. Kevin Baird. I hold no financial interest in the applicant company, and they have provided no financial compensation to me in any form and any time. I speak freely as an objective subject matter expert.

"I am professor of malariology in Nuffield Department of Medicine, University of Oxford, United Kingdom. Twelve years ago, I retired from 22 years of active duty in the United States Navy Medical Service Corps with the rank of captain. Prior to that, I worked in the Division of Experimental Therapeutics, Walter Reed Army Institute of Research. In all of this time, 37 years and counting, I have labored to improve the prevention and treatment of malaria, Plasmodium vivax in particular.

"During the 1990's and early 2000's, I headed efforts by the U.S. Navy to validate the use of primaquine as primary causal prophylaxis against malaria infection. We recognize the great advantage of chemoprophylaxis that prevents the formation of latent hypnozoites in travelers,

stages unaffected by suppressive chemoprophylaxis using blood schizonticides, the strategy that has dominated travel medicine practice for more than 70 years.

"We labored to demonstrate the safety and efficacy of daily primaquine dosing and preventing primary and latent attacks, and actually did so in a series of clinical trials in Southeast Asia and Eastern Africa. Others did so in South America.

"When we later approached the U.S. FDA in order to change the primaquine label to include this indication, no stakeholder, U.S. DoD and Sanofi Pharmaceuticals, the IND holder, was willing to put up the substantial funding required for success in that application. The effort was abandoned by 2005.

"So today, primaquine, primarily chemoprophylaxis, remains a validated but off-label use for this indication, thus placing providers at risk in prescribing this option despite it being rationally preferred and superior to labeled suppressive chemoprophylaxis options.

"Today, the U.s. FDA weighs the application of stakeholders willing to invest the resources and energies needed to see a labeled indication for tafenoquine as primary causal prophylaxis against malaria. Over the years, I have written and spoken publicly of the inferiority of the dominant suppressive chemoprophylactic options against malaria and of the great advantages of causal prophylaxis for travelers, principally in preventing late post-travel attacks by Plasmodium vivax.

"This parasite occurs whenever there is endemic malaria, excepting only Haiti. Almost no traveler at risk of malaria is free of risk of latent hypnozoites. Those attacks if not treated promptly and effectively very often progressed to life threatening severe disease syndromes, especially similar to those of falciparum malaria in clinical character and quantified risk of death as an outcome.

"Allowing such attacks with chemoprophylaxis regimens that do not prevent them would be

considered inappropriate and reckless if not the only available labeled options. This status quo must change by introducing superior options, having regulatory legitimacy.

"Tafenoquine as primary causal prophylaxis would indeed offer travel medicine providers and their patients a clearly superior and labeled option if the applicant succeeds in their efforts with the U.S. FDA. It is my sincere hope that they do succeed so that we may at last see travel medicine to disfavor the demonstrably inferior practice of suppressive chemoprophylaxis against all of the malarias. Thank you."

Clarifying Questions (continued)

DR. BADEN: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. We will now resume our discussion with the applicant and clarifying questions. We'll start with -- I think the applicant may have prepared some comments from earlier discussion and clarifications.

DR. DOW: So I think I'll just go systematically through some of the highlights that came out of the initial round of questions, and then we may a slide or two to address some of the questions in relation to psychiatric events that were posed.

Starting from the top, there was a question raised about the applicant's, assertion of noninferiority and why the FDA, although generally supportive of the idea that efficacy was observed in that study, didn't come to the same conclusion about noninferiority. So I was hoping Dr. Berman could address those methodologic differences.

DR. BERMAN: I'll try to keep this down to less than 20 minutes. In the broad sense, if we take the agency's efficacy slide number 2, we are in a consensus agreement with that. And that was a summary of the placebo-controlled trials. Also, now we can turn to the non placebo-controlled trials, which is study 033, and we can take their slide 43, and we can look at the last bullet which says, "This study provides important, reassuring

evidence in non-immune subjects," and also we're in consensus with that.

In other words, in engaging in this colloquy at this point, we're going to be discussing one part of only one study out of the total dosing. I don't want people to think that we're in disagreement with the agency on most or even all broad subjects of efficacy, which we're pleased to acknowledge and accept.

If we can go to my slide that I previously presented, the study 033 slide, what I tried to do in my talk is give a high level view of an extremely complex subject. And to answer this question, I'm going to have to get into the weeds, and I regret spending so much time on it. But if we can get to --

DR. BADEN: We are under time constraints, so if you can --

DR. BERMAN: Well, maybe we should put this one towards the end instead of at the front.

DR. BADEN: Or if you can focus in on the key point --

DR. BERMAN: Well, there's two -- I know what you're saying, sir, but I deliberately -- if we can come up with my slide, there are two aspects to a noninferiority.

Well, first of all, the question was asked, what does the protocol for? The protocol calls for 10 percent difference? That's what the protocol calls for. And either our analysis with the per-protocol population being analyzed, which is a 1 percent difference, or the agency's analysis using lost patients as failures, which gives a 3 and a half percent difference, is clearly less than 10 percent.

So if that's the simple criteria, then we're both actually in agreement that tafenoquine is non-inferior to mefloquine. The problem is that standard, which is used for a lot of antibiotic trials of 10 percent, I think is probably based on treatment trials where you should be able to clear virtually all the subjects, the patients in that case. If you have a noninferiority margin of 10 percent, but the placebo rate let us say is

8 percent, then you have a fundamental problem, which is that the drug can be worse than placebo and still be considered noninferior.

So that's why we used not an absolute level of 10 percent, which is normally called for it, and I think one of the questions was directly asking about, but a relative level between the degree of inferiority of tafenoquine to mefloquine compared to the inferiority of placebo to mefloquine.

Now, there's a second problem, which is the lack of an internal placebo group, which is normal for noninferiority trials. If we take the agency's ITT approach and enlarge the number of failures, based on that, of the tafenoquine versus mefloquine difference, we enlarge fat but because the placebo failure rate is simply a number, it's not these failed over those attempted. It's simply a number. The placebo failure rate cannot increase commensurably because of using an ITT analysis. So the reason I have to insist on using a per-protocol analysis is because our placebo rate cannot adjust as the tafenoquine and mefloquine rates would

adjust with an ITT analysis. So that's the first point.

The second point, which I guess I will not get into -- thank you for the interest of time -- is to say that I do not think that our analysis of the placebo rate can be seriously challenged. I very much respect to the FDA reviewer who gave an excellent presentation, as I've said to start with, and 94 percent of what he said we're fully in consensus. But his comments about the imprecision of our placebo calculation were general and not specific. And I'm just going to, especially with the interest of the time, just sit here and say, I do not think that one can seriously challenge our assertion that there was at least 4 percent incidence of exposure to the troops at the time of deployment.

Now, the final step, 4 percent in our minds is a large number compared to 1 percent. And therefore, we do consider that we've shown noninferiority, and thank you for your time and attention.

DR. BADEN: No, very helpful. To follow on, on that, the data in the 043 and the 045 study, which are placebo controlled do not have this challenge. Is that correct?

DR. BERMAN: That's right. And in my comment, I in fact said that, actually, the ITT analysis for 045 is much more supportable than the analysis sponsor did because everything can get adjusted. You actually have placebo patients.

The real importance of study 033 is that it is in the population which very closely mirrors the population who will take this product at least to the United States. That is to say by weight, and by especially non-immunity, which is the primary patient determinant of disease severity, not in terms of race necessarily -- they were all Caucasians -- not in terms of gender because they were almost all male, but in terms of the two major predictors, especially non immunity.

So we focus our noninferiority analysis on that study, and that's the one which I'm particularly interested in maintaining. Let's put

it that way.

DR. BADEN: Thank you. Dr. Orza, you have a follow-on? And I'll ask all of us to be as pointed as possible because I am worried about timing, and I know there are many questions we have as a group.

DR. ORZA: This is a follow-up question about the historical controls, and it's not by way of a challenge, it's by way of a question. But those were based on level in the community, the level in the community. And I was wondering if one difference might be that in addition to taking the prophylaxis, the troops would have also had repellent impregnated clothing and be using repellent, and perhaps the base and the camps had insecticide. So would that have made it not quite comparable?

DR. BERMAN: So thank you, ma'am. That's a good question. Actually, the original analysis was done by Dr. Dow in an academic sense, so I'll ask him to deal with that part. But there are two parts of the calculated placebo rate. The first part is the calculation of the P. vivax rate, and

as mentioned, you start with internal data, 8 subjects who actually had vivax by virtue of their relapse.

Then the question is how many were exposed to vivax. And also was mentioned, if we take the GSK data, which shows basically a 70 percent ability to prevent vivax, those 8 cases represent 30 percent of the original cases and that multiplies, divides out to 25 cases during deployment.

I think that -- especially because the GSK data is known to be conservative, that is to say the vivax prevention rate is added to by the re-infection rates, so it's artifactually low, I think that data is extremely strong.

What you're really addressing now is the Pf to Pv ratio either in the previous deployments or in the concomitant deployments because we use that, multiplying that by the vivax rate to get to the calculated Pf rates. For that, let me turn to Dr. Dow who did the original analysis of this and to address that question.

DR. DOW: So there are two ways of getting to the Pf to Pv ratio. One of them is to look at the local population, which you referenced, and that's on the higher end of the scale, 0.75 Pf to Pv; and the other which was the more conservative way we used in our original publication, which was to look at the ratio in Australian troops in the same area deployed the previous year. So that's how we derived the Pf value.

The overall estimate of the attack rate that we got between 4.6 and 12, which Dr. Berman articulated, is very similar to the levels observed the year before with Australian troops when they first deployed, between 6 and 12 percent. And then as Mark Reid alluded to earlier, because of the operational environment, soldiers don't always comply with the pestilent protective measures even though they were available.

I'd like to get back on to the safety questions that were posed prior to the break. Sally, if you could please project the slide that we just made for psychiatric events in the

non-deployed population for tafenoquine.

There were 4 events and 3 subjects. Two of them were considered unlikely in relatedness and 1 of them was considered possibly related. And as a broader point, we've published all this safety data in a publication last year, so it's all out there in the literature.

Then there was a second slide, and I think the request was to look at 033 specifically, the comparison of psychiatric events, excluding events considered by study investigators to be unrelated. These are the events here. And, Janet, remind me, were these individual subjects or individual events?

DR. RANSON: Subjects.

DR. DOW: Individual subjects. And we haven't categorized here the severity or relatedness, but we do note that the two mefloquine cases of anxiety were severe.

If the chair will indulge me, would we be able to respond to a number of the comments that Dr. Nevin made, or would you like to focus this

time on other issues?

DR. BADEN: No, continue to clarify, and let's keep things as pointed as possible in responding. Thank you.

DR. DOW: Okay. Sally, could you bring up the slide that relates to the TGA event reporting, please?

As Dr. Nevin alluded to, there's been a lot of activity on the efficacy front in Australia, and there have been two broad issues that are raised and then two inquiries called to investigate them.

The first is that there was some sort of inappropriateness in the way that studies 033 and 049 were conducted. That was investigated by the Australian military, Office of Inspector General, and basically found that those allegations were essentially baseless. We've provided the link to that here.

The second issue is this continued reiteration despite what our colleagues at the FDA has said about some sort of brain injury associated with tafenoquine, both the FDA and an independent

group with the Australian Veterans Administration have determined that there's no basis to this.

I used to think that in vitro assays were predictive. If you do an IC50 in one drug versus the other drug and it's lower, maybe it has some predictive value. And maybe that was reasonable 10 years ago before we did the rat study showing it was no neurotoxicity with tafenoquine. But now that that study's been done, we need to move on from using in vitro data to base safety decisions upon.

Sally, could you bring up the slides related to the prodromal effects of mefloquine, please?

DR. BADEN: Dr. Orza has a question.

DR. ORZA: Sorry. A quick question about the study 033 where it says that they consented to participate.

DR. DOW: Yes?

DR. ORZA: If they didn't want to take either drug, what did they do? Because it was done on a troop-by-troop basis, right?

DR. DOW: I'm going to ask Mark Reid to

address that question because he was actually involved in the study.

DR. ORZA: I mean unit by unit.

MR. REID: It's a good question because defense, vulnerable populations. So we're at pains to have a very robust consenting prices. And I think a mistake we made is we didn't video the process in a blinded way so that we could share that publicly. We were very careful to brief our soldiers and clarify that if you deploy to a malarious area, you must take an antimalarial. You have the option of participating in our study or you take a licensed drug.

Now, our director general at the time of health services was worried that the option of taking a weekly unregistered drug compared to a registered daily medication would unfairly put soldiers in a predicament where they were choosing experimental participation over registered drug. So he made it clear under a health policy directive that those soldiers could participate free of participation in the study and take

open-label registered mefloquine provided they are under the direct supervision of the study team, because we were subjecting soldiers to a war-like condition, and mefloquine was our third line therapy. It was only to be used under policy if the soldiers could not tolerate doxycycline or Malarone.

Now, at the time and still today, the only comparator drug on a weekly basis that we can ethically offer our soldiers to participate in and still deploy was mefloquine.

DR. BADEN: Thank you.

DR. DOW: So a comment was made about prodromal effects of mefloquine. This is the label. "Take folks off mefloquine if you get one of these events."

Next slide, please. These are the comparable rates in the review that Dr. Nevin referenced, comparing mefloquine to doxycycline and mefloquine to atovaquone proguanil. You will see that the incidence of events for the mefloquine arms are quite different in these two analyses, and

remember that these are meta-analyses of lots of input studies, but the rates of events in arms that don't have a neuropsychiatric limitation are much lower.

Next slide, please. So we've looked at treatment related prodromal psychiatric events at the recommended dose of ARAKODA, and you cans see here, we've got the ARAKODA deployed versus the ARAKODA resident, versus placebo. And you can see that the rate of these prodromal events in ARAKODA resident folks isn't much different from placebo. We've already talked about the increased rate in soldiers in the setting of combat stress.

Next slide, please. No. I think we're done with those slides. The only other comment I wanted to make was how long-term safety study is powered to assess differences in these prodromal endpoints if they occur. So we have a follow-on study in the population without psychiatric exclusions, based on prior medical history that will shed light on these events and confirm what we believe to be the case, which is there is no signal in a non-resident

population.

Moving on to some of the other points that were made, resistance, very difficult to assess for an 8-amino-quinoline because you're basically looking at a combination of how the parasites react to the action against the developing liver stages, and most or all of the parasites are killed there. Any that make it through and go to gametocytes, there's also a killing action of the drug on the transmission stages.

We know right from the approval data of primaquine, that there was an inherent difference of about to twofold between specific strains of vivax. This is the regular temperate variety, which is why you need 30 milligrams a day to treat the Chesson strain and 15 milligrams to treat ordinary vivax.

Despite 60 years of years, there's basically been very little shift in the susceptibility of P. vivax to primaquine. So for that reason, we think because the mechanism of action is similar, it's unlikely that there'll be resistance development to

tafenoquine.

I think that covers all the points that I remember there being questions about. I'm sure I probably missed some, so I'd be happy to take further questions.

DR. BADEN: I think we have many more questions, so we'll go back --

DR. DOW: Okay. Let's do it.

DR. BADEN: -- to the committee resuming our questioning, and we can resume with I think Dr. Moore --

DR. MOORE: My question's been answered. Thank you.

DR. BADEN: Great. Dr. Follmann?

DR. FOLLMAN: Yes. Thanks. I'm was interested in the 10,000-person study you briefly alluded to as sort of a follow-on safety study that you were intending to do or so on. You mentioned it might be in TRICARE, which I guess is military health system, so this would be mostly soldiers deploying and some would get tafenoquine and others might get other things, just some more details

about that.

Also I guess, when do you think you'd have 10,000 tafenoquine subjects in this study? Ten years? Five years? Something like that?

DR. DOW: TRICARE was our initial proposal to FDA, and we haven't finalized an agreement with them about exactly how that study will look. And we look forward to further discussions over the next week or two with our colleagues at the agency to settle that.

We had suggested TRICARE because it contains both military folks but also their families, including pediatric subjects. So you do get a mixture of families and deployed folks in that database. It doesn't have to be limited to that one. That was the one we selected based on similar studies done in the past with the flu antivirals that seem to be a logical place to start. And it does not have to be 10,000. That's something that we're going to discuss with the agency further.

But the reason for that number was because in the large database survey conducted by Ikotel,

10,000 seemed to be the number you needed to get to, to begin to show some differences in individual neuropsychiatric endpoints, remembering that for the rare ones that are the most concerning, they're obviously very few of them in and we need as many higher end as possible.

In terms of duration, it depends how many prescriptions we get out there quickly. The total peak prescriptions a year might be up to 250,000 once we hit peak sales in a few years. So I would say that the time frame would be probably two years before we're in a position to retrospectively look at that data.

DR. FOLLMANN: And you would have comparative prophylactic drugs as well to compare I trust.

DR. DOW: Yes. And we would most likely be looking at Malarone as the comparator since it's the daily standard of care.

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

DR. ZITO: Just picking up on the TRICARE data source, currently, you could be conducting a

retrospective analysis because to see the extent to which any of the comparators are being used currently and over what period of time, and you want to identify new users; correct?

DR. DOW: Correct.

DR. ZITO: Because when you say prescriptions, we get confused. So we're talking about new users of --

DR. DOW: But by definition, tafenoquine would be new prescriptions in the U.S. context.

DR. ZITO: Right.

DR. DOW: And you would bracket it so that the time at which you recorded prescriptions of the other drugs was in the same time window.

DR. ZITO: Yes. So a lot can be learned about how long it's going to take for any postmarketing study. And some of that could be done now with comparators.

The second point I have on this is to what extent could the FDA be a part of or the approval process for the postmarketing study that you will conduct so that there is, in advance, good

agreement about what are the critical measures that should be attended to.?

DR. DOW: We welcome that input from our colleagues with FDA.

DR. COX: We can review that protocol and provide comments and get appropriate folks involved to look at a larger study of such a design. So yes, we look forward to that.

DR. BADEN: Dr. Zito, if you have other questions.

DR. ZITO: The other question was on where the number 300 comes from in your, I guess, your cohort. You talked about 300 on the active drug and 300 placebo. And where does the number 300 come from, and why is there not a comparator group in this case?

DR. DOW: I'm going to ask Dr. Ranson to address the question about the sample size, and I'm going to think about the answer to the second question while she's providing that information.

DR. RANSON: So the current study was principally designed to be an ophthalmic safety

study. A primary efficacy endpoint is changes in essentially retinal disorders that are examined by very precise instruments over time, and we're expecting a very low-incidence rate of a few percent.

So we have 300 active subjects and 300 placebo-controlled subjects. These are not malarious areas so we can conduct a placebo-controlled trial.

I think, Chuck, you did a further analysis looking at the -- oh he's looking at me strangely. In terms of -- Mark, do you --

MR. REID: If you power off your study for a primary endpoint of ophthalmic safety, it becomes extremely difficult. And we age match the population to an ADF by 33 study. And in younger eyes, the background rate of retinal disorders is quite low. So essentially it comes down to a rule of 3 on our best guest looking at publications principally around the Blue Eye Mountain Eye study and the Beaver Dam study, where we estimated what would be the highest rate of retinal eye changes

naturally in a background population at the age group of around 55. And that's where all the soldiers were in terms of the ADF 033 study.

DR. BADEN: Dr. Tan?

DR. TAN: I have two questions. Most of the endpoints that we're talking about is while on the study drug. I'm really interested in let's say the traveler who comes back and may develop malaria after they're off of the drug. In the semi-immune population studies, they were followed -- and please correct me if I'm wrong -- for 4 weeks. And it's difficult when they're still in that endemic area to know if that infection is failure or just re-infection or new infection.

Then in the non-immune population, I believe they were followed afterwards. But I'd like a clarification. They were given no post-trip course, is that correct? No post-trip drug. And then what's the time to parasitemia after they were off the tafenoquine?

DR. DOW: With the semi-immune subjects, the follow-up was 4 weeks. For the non-immune

subjects, there was basically 6 months where they were monitoring P. vivax relapses. So in effect, it's a 6-month follow up. And then in 033, the tafenoquine and mefloquine were given right up to the end of deployment. And then the tafenoquine subjects were given primaquine placebo, and then the mefloquine subjects were given primaquine for 2 weeks.

DR. TAN: What was the time to parasitemia in those that were given tafenoquine?

DR. DOW: It's in slide number 48 of the sponsor's slides, please, Sally.

There's your answer right there in the right-hand column.

DR. TAN: All right. Thank you very much. But I have a second question.

DR. BADEN: Please.

DR. TAN: First to clarify CDC recommendations for primaquine, we do not recommend primaquine in places with falciparum. We actually recommend primaquine prophylaxis in places that have primarily vivax because of its efficacy for

causal prophylaxis, so just to clarify that.

The reason for that is because we are concerned about its efficacy, its schizonticidal efficacy in the blood stage for falciparum. So the fear is that if there's incomplete causal prophylaxis at the liver, that it's not going to get that blood staged in falciparum, especially, primarily.

Now, going to tafenoquine, which is similar to primaquine, it sounds like there is some data to show its schizonticidal activity, but if you can please reassure me. I believe there's the challenge study with 12 individuals, but I imagine the confidence intervals are quite wide on that. And in the non-immunes, if you can just please review the efficacy for that falciparum piece, schizonticidal.

DR. DOW: Sure. Could we go to the backup slides that have the challenge study? There are three or four challenge study slides. Perhaps I'll just comment on the rationale for doing that study. We know from the animal studies that tafenoquine is

overwhelmingly causal, kills most of the liver stage parasites. And we recognize that primaquine, if you skip a dose, you're at higher risk of getting falciparum. That's the consensus.

We hypothesized that based on mouse data where we see a very strong blood stage effect against berghei with tafenoquine, but we should see a similarly strong effect against falciparum against the blood stages only. So this was designed as a test of the hypothesis that we would see the expected activity against blood stages, hypothesizing that in a few patients, there might be some escapes.

This is the study design briefly. This is the design, the loading dose and then a dose a week later. Then there was the IV inoculation of blood-stage parasites. And then for the controls that got malaria, a rescue treatment at the end -- sorry, a rescue treatment at the end to be absolutely sure everything was eradicated. And that same rescue treatment was given to placebo subjects earlier if there was symptomatic malaria

or observed.

Next slide please. So these studies are necessarily small just because of the logistics of doing them safely. We had 12 in ARAKODA, 4 placebos, 100 percent efficacy, and you can see the confidence intervals here.

DR. BADEN: Any other questions, Dr. Tan?

(Dr. Tan gestures no.)

DR. BADEN: Dr. Weina?

DR. WEINA: This question is probably for Dr. Berman first. A really good discussion on the reasoning for selecting the 80 nanograms per mL for the cut-off for successful prophylaxis, and a discussion regarding the 200 versus the 400 because of the tolerability. And then there was the discussion later on about the tolerability, and it showed that obviously 200 was better tolerated than 400, but 200 BID was pretty much exactly the same by tolerability to the 200 once a day, and much, much better than the 400.

That kind of led me to looking back at some of the original data sets and wondering had you

tried 100 milligrams. And when we look at study 045, the data for the 100 milligrams looks as good as the 200 milligrams. And I'm kind of wondering why 200 became the choice instead of 100.

DR. DOW: You're right. In one of the African studies in a semi-immune population, there was similar efficacy between the 100 and 200-milligram doses. But of course, in any malaria drug development campaign, you don't know whether there's going to be a difference in susceptibility with non-immune versus semi-immunes. Although the decision to pick 200 was made as a combination of susceptibility and other considerations, this also would need to be cautious and make sure that you've got adequate blood levels to address known and documented failures in non-immunes, and in particular those 5 cases with concentrations that we showed were all symptomatic cases; whereas in the African studies, parasitemia is the end point, not a clinical malaria endpoint.

DR. WEINA: So toward that end, do you have PK data for 100 milligrams?

DR. DOW: Yes, we do. That will be in one of the backup slides, slide 64 in the backup slides. What you're seeing here is three curves. These are simulated concentrations based on the PoP-PK analysis of 800 subjects, and any 80 nanogram threshold is what we're trying to beat, and 3 curves are presented in each graph: the 95th percentile, the median, and the 5th percentile.

In the fasted and fed, you can see that even in the lowest 5th percentile, we get above the 80 nanogram per mL threshold, but we're below that for the lower 5 percent confidence interval at a 100-milligram dose. So this pharmacokinetic simulation combined with the fact that we have symptomatic breakthroughs with 9 concentrations means that there's some question as to whether we would get the same level of efficacy in a non-immune population relative to the dose that's been selected.

DR. WEINA: It's hard to see on that particular graph, but the 5th percentile for the 100 milligrams, does that exceed the 55 nanograms

per mL or not?

DR. DOW: It would be right on the cut-off.

DR. WEINA: Okay. Thank you.

DR. BADEN: Dr. Moore, you had a follow-on?

DR. MOORE: I do, of the sponsor. So the 5th percentile, I'm going to assume that those individuals in that group were not extraordinarily heavy but rather older. Is this correct?

DR. DOW: In this population PK model, the two things that correlate with the PK parameters, the major one was body weight. But we don't have the graph here today. We've broken it out separately based on body weight. And even though that's a covariate, we're still above the 80 nanograms per mL in the higher body weight individuals. And I believe those simulations were provided in the clinical pharmacology section of the dossier.

DR. BADEN: No further follow-ons, then Dr. Gripshover on the phone, do you have questions?

DR. GRIPSHOVER: Yes. One's been answered. I noticed the mefloquine side effect profile in

your trials is pretty comparable to the tafenoquine but much lower than what you presented from the Cochrane database. Did they capture all of the AEs carefully? There was a striking difference, especially if you looked at the ones that were in a non-deployed study, like in Africa.

DR. DOW: With respect to --

DR. GRIPSHOVER: I'm sorry. The neuropsych differences, the incidence of neuropsych compensations in both tafenoquine and mefloquine in your studies is much lower than that what you showed in the Cochrane database. If we think that -- it's hard to say that this one is safer if it looks the same in your studies, but the incidence is clearly lower than the trials. And I guess I wondered if you can postulate why or do you feel that the data was -- it wasn't [indiscernible]; is that true, narrow side effects?

DR. DOW: Just briefly reviewing where we are, the FDA showed a slide, and we showed a slide using a different comparison of relatedness that showed the adverse events in mefloquine versus

tafenoquine in a deployed population. And we need to remember that that's against the backdrop of a war-like engagement with a significant major confounding variable in terms of the psychological stress of warfare, that we interpret those data as being a consequence of the operating environment.

DR. GRIPSHOVER: But [indiscernible] --

DR. DOW: Hang on. We also showed a slide earlier in the presentation that in that deployed environment, Malarone looks the same as mefloquine even though Malarone is not considered to be a neuropsychiatric drug. Then with respect to the non-deployed situation, the rate of related AEs is a percent higher than the placebo. And then in terms of the Cochrane database system, the absolute right is not comparable to a clinical trial setting because that's a meta-analysis of lots of different controlled studies, database studies that have all been mixed together to come up with an answer. So it's the treatment difference relative to placebo that's the important thing to consider.

I guess the other thing that we also have to

remember is that the clinical literature show that mefloquine is actually a nocebo, so this data from the travel medicine literature comparing Malarone to mefloquine, where if you tell folks they're taking mefloquine, there's actually a neuropsychiatric adverse event related to mefloquine placebo. So some of the attributable similarities may be due to a nocebo effect telling folks that they're getting a neuropsychoactive drug.

DR. BADEN: Thank you. I want to go back to the question I asked the agency just before the lunch break. My understanding is 60 Degree Pharmaceutical took over the lead in the development around 2009, if I understand the briefing document correctly. But that's not completely germane to my question.

My question is, how confident are you in the data generated 25 years ago to 12 years ago? And how can you reassure us that those data are high quality? Or how have you reassured yourselves and how can you reassure us that those data are high

quality?

DR. DOW: Clarifying the comment, we became the licensee as of 2013. With a legacy data set, the data are what they are, and we have done the best job we can putting together the safety information that we have, coding it old so comparisons can be made across studies. We're confident that the safety profile based on the data we've submitted is benign. We've committed to doing longer term safety studies to provide more data for our stakeholders in the agency to continue to evaluate the drug over time. And that will be our commitment going forward, is to follow up on and signals as they appear, if they appear.

DR. BADEN: But you must have done -- I'm just trying to get a sentence of some [indiscernible] --

(Crosstalk.)

DR. DOW: Actually, I would like Bryan Smith, who used to be the project leader at Musonda prior to my involvement, to make some additional comments about the studies.

DR. BADEN: Thank you.

DR. SMITH: So thank you very much for bringing up the question because I think it's germane not only to the veracity of the data that we presented directly, but to developing drugs in this space in general. So as Dr. Dow had mentioned, I'm also one of the retired military people and spent six years as the product manager for tafenoquine during this phase from 2010 to 2016.

So to begin to start to answer your question, honestly, I was directed to take a look at the dusty box and figure out whether we were going to try to save this drug or whether we were going to kill it. And my assumption going into it is I was going to kill it. So we started the process of going through the legacy data sets with a large CRO. And in looking at the status of that data, it was what tafenoquine could do, what it would do, how would we use it militarily, what it was going to fix for us, and what are other options were.

The further we went along that process, it became clear that in fact the original drug designers and developers had given us a really good drug. Maybe we hadn't done such a good job in product management to get it through quickly, but the drug was doing what it was. So the next step was could we support the data. So we went back and looked at monitoring reports, ensuring the GCP compliance of each of those studies, and then bringing the data sets themselves into a modern context where we could do the integrated analysis, because I couldn't make sense of what to do with the 3,000 subjects until I got there.

During that same timeframe -- well, let me also say, those trials were sponsored either by our colleagues in the Army, so either U.S. Army sponsored or they were some version of SmithKline Beecham that then became GSK through the iterations of that, so a collaboration between industry and the U.S. government that were really done at a very high standard. So we felt more comfortable that the studies were actually holding up.

So the intent really, honestly, up until the time frame you had mentioned, when I took the program over, was that because there is no profit motive to do this work, it's extremely difficult to do, as you've all wrestled with here this afternoon. Comparing to a small treatment prophylaxis is difficult, and there is no body that generates forward; how do you get the resources; how do you get the time; how do you get the subjects to be able to move forward to be able to bend the curve, which we've tried to express.

So the intent was, really, that the Army would do all of that development and hand it over to GSK once they got their approval that they got two weeks ago, and then say would you just file an ANDA? The cold hard reality of that is, no one will take it. So after putting it out broadly in the Federal Registry, looking for co-development partners, it was 60 Degree Pharmaceuticals that came up and was willing to go ahead and do the heavy lifting.

DR. BADEN: And along those lines, the

re-review of the slides, was that triggered in part by this review?

DR. SMITH: If you're speaking to study 030 directly, no. That was done actually before the database re-analysis. That was identified early on. And again, because the positive comparator was also failing, they went back and looked at the actual study design. Unfortunately, colleagues that predate us had made a decision to go with a single slide reader, not the ABC rule, which all of our other trials were always done.

DR. BADEN: Sure.

DR. SMITH: So the false positives, which were in both groups, is what ultimately led to --

DR. BADEN: And that speaks to reevaluation to try and prove the quality of the data over time as people became aware of certain weaknesses.

DR. SMITH: Absolutely right. But the trial designs themselves and how the slide-reading paradigm then was used, the Army learned a lot from that. Obviously, there still was very valuable information contained within 030, particularly on a

safety standpoint. So we still wanted to salvage the parts of that.

DR. BADEN: Along those lines, the methemoglobinemia I pointed out, the 60 percent difference in two studies, any explanation for that? Is that aspects of data collection?

DR. SMITH: Mark, I don't know if you want to address that. The agency had asked the same question, so we gave some data, what we could, because again, there is substantial periods of time difference between those as well.

DR. REIG: It is a good question. I was curious why the agency brought in their device team as part of the review, and it's very clear to me now. And actually the agency had thought about this problem of pre-NDA because as part of the submission, they asked us to specify all the methemoglobinemia methods that had been used in all historic studies and actually specify the method that was used was being used, in our prospective long-term safety study that Janet had already spoken to earlier this evening, where we had one

case at 6 percent methemoglobinemia.

The standard of the assay has been quite variable for a number of years, so we've been at pains. And I think the database reflects that over time. These are legacy studies, and we've been very careful prospectively moving forward now, particularly with a long-term safety study, to have most precise and accurate laboratory assay method available to us on a centralized basis.

The other concern with methemoglobinemia, as you well know, is a time restraint on actually analyzing the blood. And these are field studies, so we've got to get the hematology blood to a laboratory where we can analyze blood parameters, including the methemoglobinemia before that value shifts. That can't be done at a centralize laboratory.

Indeed, for 033, we measured our hematology in the field and methemoglobinemia in the field by a radiographic method. And we froze out on liquid nitrogen vapor and we took our biochemistry samples out and we analyzed them at a central laboratory.

So we were very aware of the risks of laboratory variability and managing that in our safety database.

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

DR. ORZA: Yes, I had a follow-on about the Army's development of this drug and its apparent interest in having it approved so that they can use it, and whether there was any thought or opportunity to actually test it in our military. We don't have any data from our military. And if not, if there's a thought about doing that going forward, if it's approved, at least under intense postmarketing kinds of surveillance conditions.

DR. DOW: I would love to do a study in active duty military once or if we have approval, and I think there's all kinds of questions that our colleagues would like to answer with respect to comparators to standard of care, specialty studies for folks doing high intensity tasks of various types.

We don't have specific plans yet because

there's a policy landscape to navigate before it's appropriate to do those sort of studies, but I think both our colleagues at DoD and us are committed to generating more data as appropriate in the future.

DR. BADEN: Dr. Ofotokun, you had a follow-on.

DR. ORZA: Sorry. I just wanted to finish the --

DR. BADEN: I'm sorry.

DR. ORZA: -- because right now, it seems like we're saying that the high-stress conditions of deployed military are not the right circumstances for using this drug.

DR. DOW: No, that isn't what we're saying. We're saying that if you go to a high-stress combat zone and you give active soldiers Malarone or you give them mefloquine, you're not going to see a difference in the overall burden of neuropsychiatric events. So it's a deployment related phenomenon that's driving the neuropsychiatric profile.

So I think that any antimalarial drug would perform in that high-stress environment. You get a high rate of neuropsychiatric events. This is ordinary travelers or folks who aren't traveling.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Thank you very much. And thank you, Dr. Dow, for all of the clarity that you have provided so far. And I must say that I'm really intrigued by the breadth of spectrum of activity of this product, but I am still very concerned about this issue of hemolysis, methemoglobinemia, and G6PD deficiency, noting that I think in more than half of the studies, individuals with G6PD deficiency were excluded from the study. And in studies where they were included, we probably had about maybe 6 or 8 individuals that have a G6PD deficiency in that study.

We know that G6PD deficiency is a very -- perhaps the most common enzyme genetic deficiency. There are almost 400 million individuals that are affected. People of African

descent, about 14 to 15 percent of the population is affected by G6PD deficiency, and the level of G6PD deficiency varies. So it's not just a zero-sum game; you have it or you don't have it. And therefore, reference to drugs that can precipitate hemolysis in that setting mat differ from individuals to individuals.

So I need some more assurance about that aspect of the safety of the drug. And one question I want to ask you is, should this drug be approved, will it be on the condition that people with G6PD deficiency will be excluded, they will be trying to get that with individual with G6PD deficiency?

DR. DOW: Yes. So primaquine, as you know, is an approved 8-amino-quinoline that has a contraindication for g G6PD deficiency. There will be one in our label as well. So no one will be able to use this drug without having a G6PD test.

In terms of the overall safety database, there were 3,148 exposures, a dozen or less screening failures, remembering that particularly in the field studies, in that setting, it's not

always easy to get it right all the time. And of those dozen or so folks, there was only 1 case that was symptomatic; so 1 case out of 3000 and something folks in our trial database overall.

I think that in the context of a U.S. travel population where the G6PD screening is routinely available for insurance companies, it's standard blood screen that's ordered by a physician. The overall quality of the testing is going to be good and the failures few.

DR. BADEN: Dr. Zito?

DR. ZITO: In relation to G6PD deficiency, what is the probability of that screening occurring in Africa and other areas?

Zero. Thank you.

DR. DOW: So the issue of G6PD screening in malaria-endemic countries is an entirely different base because there's no standard laboratory infrastructure to do it. So the degree of ability to use any item in a quinolone in a malaria-endemic country is going to be dictated by the quality of the available testing.

We haven't been directly involved in this effort, but there are a number of NGOs who are working on hand-held G6PD screening devices, which are in the process of being approved for regulatory purposes, and I believe would form the backbone of the testing effort in a malaria-endemic country once they've been approved by regulators.

DR. ZITO: To finish the thought, are you marketing then basically to an American military population or tourist population more than you are addressing the global need?

DR. DOW: So our initial regulatory applications have been to the Australian TGA and to the U.S. FDA focused specifically on the travel medicine population. In the future, if it's appropriate, we may consider making our effort to the global eradication effort because we feel that the ability to give a drug for up to 6 months has a much higher probability of nailing the problem, particularly in an asymptomatic population, than just focusing on a single dose of P. vivax active cases.

That's probably five years in the future, and there's a series of safety studies that we need to do to operationalize the hopefully approved 6-month regimen to make sure it's appropriate for a more global population. And if we can find the funding and operational partners to do that, we would love to.

DR. BADEN: As time is short, we will have a few more questions, but again, as pointed as possible. Dr. Atillasoy, you're on.

DR. ATILLASOY: Yes, real quick. So besides the confidence you mentioned you have in the prior data, just to clarify, you have conducted those latter two studies, 2016-01 and 02, correct, with the final market image? And you conducted those, correct; the PK challenge studies in your image, correct?

DR. DOW: Yes. So 60P02, that challenge study we did using the tablet that's intended to be marketed, and then the long-term safety study 60PH04, 60P is the sponsor of that study as well, which has been enrolling subjects since October of

last year, again, using the tablet that's intended to be marketed.

DR. ATTILASOY: Very good. One other quick question just on the keratopathy, in terms of time, the eye findings in terms of the time to onset of seeing those findings, I think it was either -- you mentioned in slide I think 49 and 65 -- excuse me, 59 and 65. Is it a time event, meaning if someone is in the field for not that long, dosing the product, let's say, much shorter than 6 months, when would we expect to see those types of eye findings?

DR. DOW: So I'll ask Mark Reid to comment on the timing of onset of the keratopathy, and then I'll comment on the travel medicine consequences of that.

MR. REID: Thank you, Doctor. The short answer is it's variable. And our 057 study, we felt most presentation by 12 weeks after we'd reached the steady state.

DR. BADEN: Dr. Bilker?

DR. BILKER: Yes. I think this is a quick

question. I wanted to get clarification on what was the FDA's role in the design, implementation, and oversight of the legacy DoD studies?

DR. COX: The legacy studies were done a number of years ago. To be honest with you, I'm not actually sure.

Do others have comments on that?

DR. BILKER: So the FDA wasn't involved or you don't know?

DR. COX: It was a number of years ago when those studies were conducted. Do you all have any information about whether they came into the agency at that point in time? Again, you can see when things happened many, many years ago, it becomes less clear exactly what the interactions may have been at that point in time. But please?

DR. DOW: They were all done under IND except for one, and I can't comment on the back and forth between the DoD and the agency beyond that because I wasn't there.

DR. BADEN: Dr. Weina?

DR. WEINA: A real quick pragmatic question. Your 100-milligram tablets, how is that packaged? The whole issue here is to try and --

DR. DOW: Aluminum blisters, packs of 8.

DR. WEINA: Packs of 8. Okay.

DR. DOW: Two packs of 8 in a box. And again, that isn't approved yet, but that's what we proposed.

DR. WEINA: No. I'm just curious because the whole issue here is to try --

DR. DOW: We were trying to go for one month deployment in a box because almost all U.S. travel is less than a month.

DR. WEINA: Thank you.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Yes. I just wanted to confirm that all your studies were blinded, even the legacy studies. Is that correct?

DR. DOW: Janet, can you comment on that please?

DR. BADEN: Please use the microphone.

DR. DOW: Come up to the microphone.

DR. RANSON: There were some [inaudible - off mic], but otherwise, yes.

DR. FOLLMANN: I meant the major efficacy studies.

DR. RANSON: Yes. They were all double-blinded. We showed that on that one slide.

DR. DOW: The major efficacy studies were all double-blind and controlled.

DR. FOLLMANN: And one final question. 033, so that was blinded. Were the soldiers told what drug they were on after the study was over?

DR. DOW: Mark, can you address that please?

MR. REID: We write to every single soldier. We inform them of their treatment assignment because we had creatinine elevation, and we wanted to inform our soldiers of that finding as well as the vortex keratopathy because a number of special -- what we term the special 100, we amended the study to do a long-term follow-up because we wanted to see resolution of those benign corneal deposits and demonstrate their resolution out to 12 months; so, yes.

DR. BADEN: Thank you. Dr. Tan, did you have the last question?

DR. TAN: This is actually a quick question for FDA in terms of postmarketing surveillance. There is a comment about how it can be recommended or required. And if it is required, is it possible -- what sort of requirements can be added to that in terms of things to look for, how to measure certain outcomes?

DR. NAMBIAR: So it really depends on the design of the study. As was noted earlier, we do engage in discussions with the applicant in terms of design of the study. We have an opportunity to review the protocol and provide feedback. So depending on the design of the study and what are the questions we're asking of the study, we have the ability to provide feedback.

Questions to the Committee and Discussion

DR. BADEN: We will now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public

attendees may not participate except at the request of the panel. Before we get to the exact question, I want to see if there's any discussion amongst the panel about the challenges with the data and helping each other understand it.

Dr. Weina?

DR. WEINA: Just one quick comment that I think is important in consideration, and that is that I was sitting, reflecting on my often discussed concerns regarding off label use. And now that we know that tafenoquine has already been given the stamp of approval to go forward, I know that a lot of my tropical medicine colleagues like to use primaquine prophylactically, which is clearly off label, because it is not currently approved for prophylactic use.

The question then becomes, with tafenoquine approved, why wouldn't we just use it off label? Why come to the agency and get an approval for prophylaxis?

DR. BADEN: I think that's a different -- I mean, the data before us are for this particular

indication?

DR. WEINA: No, no. I understand.

DR. BADEN: There are plenty of other permutations.

DR. WEINA: I understand. But what -- I'll get to my point. And my point is, because of the intended population that it's to be used in -- and this is really clearly a potentially important new addition to our toolbox, especially for deployed military, but not only just deployed military, but, for example, frequent travelers to endemic areas like the
Secret Service. And these individuals now currently have to be practically on doxycycline or Malarone non-stop because they're constantly going in and out of these populations. And this gives us yet another option out there.

You cannot prescribe it as a force health protection policy unless it is FDA approved for that indication. And that's one of our biggest problems that we have. Although it is used, primaquine is used off label, it can never be used

for the military for that purpose even if it may be the most appropriate scientifically. And I think that's an important consideration about approving it or not approving it.

I think that it's important to understand that off-label use occurs and that the possibility of tafenoquine being used that way is a real risk. But if we don't potentially put restrictions on how it's going to be used, that's a missed opportunity for the agency.

DR. BADEN: I look at the same issue from the flip side, which is we can always think of other ways it might be used or weaknesses in the data. And I think these data have a lot of weaknesses that are concerning in terms of the legacy nature, the nature of the safety data at 6 months; older folks, pediatric folks. On the other hand, the perfect data will never arrive because there will always be one more group.

I share Mr. Mailman's concern about how many need to be treated before we have some comfort with safety. And it can be 300, it can be 3,000, it can

be 30,000, it can be 3 million, it can be 30 million.

DR. WEINA: Or it could be never.

DR. BADEN: Well, it depends on whatever the rate is. One in a million rate will require that much higher. So in struggling with these data, we have the data we have. And of the data we have informative enough to balance that safety, efficacy, without -- then we can always think that there will be other uses and requirements. And I think that Dr. Tan was getting at, if it were to be approved, then how do we encourage the collection of data to start filling in these many potholes?

DR. WEINA: Understood. I'm just thinking about that in the context of what a wise man said a couple of weeks ago about being afraid of a risk that we can't define.

DR. BADEN: Yes. Dr. Tan?

DR. TAN: Two comments. One regarding the efficacy data, I think a point was made that it is difficult to ethically do a placebo-controlled study in non-immunes. So there is a struggle

there, so we have to look at what we do have available to us. And given the challenges with trying to calculate the attack rate and show non-inferiority, we just have to realize that the data may not ever be available for that.

DR. BADEN: And along those lines because of your question about the challenge study, how convincing is the schizonticidal activity, based upon the challenge study, accepting the small numbers?

DR. TAN: Yes. I think that's a very good question. I think with the evidence in front of us, I think it's very encouraging. I don't quite understand the differences with primaquine, to be very honest. As they had mentioned, it's not well understood, the mechanism, but it's very encouraging.

Actually, the second point about the safety data, I wanted to also bring up that having been in the field of malaria prophylaxis for a while, and reading these studies on reported adverse events, and being familiar with this Cochrane review, we

have to remember that adverse events, one, are commonly reported even in those taking no prophylaxis or placebo; and two, it's true, mefloquine really does have a nocebo effect. So I just wanted to support that.

DR. BADEN: I want to remind the committee we should not be indicating how we're voting. My intent of this discussion is to air some of the expertise that different members of the committee have so that we're better informed and had away some of the information, because you are more familiar with the malaria challenge model than most of us.

Dr. Ofotokun?

DR. OFOTOKUN: I just wanted to say, I know we have asked a lot of questions for clarification. I also wanted on the flip, I'm familiar with malaria. I grew up in a malarious-endemic zone. Looking at the spectrum of activity of this products, again, I don't think we know of any drug out there that really has the spectrum of activity against the various stages of malaria as is

presented for this product. And I think the question I struggle with in my mind is whether the data is strong enough for me to believe this.

DR. BADEN: And don't answer that question.

DR. OFOTOKUN: I'm not going to answer that question, but I'm just saying that it's something -- while we talk about a lot of the negative side, we also have to remind ourselves of some of the positive data that was also presented by the sponsor.

DR. BADEN: Thank you. Dr. Follmann, you had a comment?

DR. FOLLMANN: Just a brief comment. You brought up the issue of what's our comfort with this legacy data that was so long ago. And I take comfort in the fact that there were blinded studies, so the two arms should be treated separately, and I judge the evidence accordingly.

DR. BADEN: And I have much discomfort with data that you don't have all the primary support, but I do take comfort in your comments, and I take comfort that data were reevaluated and examined as

markers to try and assure quality and continue to refine the findings in a consistent way.

Dr. Orza?

DR. ORZA: Mine is really a question that just relates to the last two comments; one about efficacy and one about safety.

So about efficacy, it is being proposed for all types of malaria, and we have seen very strong evidence, I think, P. falciparum. We saw a little bit of evidence about vivax, but that was about failures. We know it was vivax because it was failures. So does that mean the drug didn't work against that? And then there was one reference to P. malaria.

But how strong, really, is the evidence for all types of malaria? That's my efficacy question.

DR. BADEN: And I think that will have to be asked; not now, but that will be an ongoing question.

DR. ORZA: And the question about safety is, we've had a lot of focus on the neuropsychiatric side effects, but the FDA made reference to renal

cancer and also reproductive toxicity. So there hasn't been much discussion about the cancer, and how that would be reflected, and what the reproductive toxicity would suggest about labeling for women and use in women of reproductive age.

DR. BADEN: Dr. Zito had a comment.

DR. ZITO: I have a little bit of concern about why the phrasing of question 1 relates to prevention in adults up to 6 months of continuous dosing. It sort of implies that there's a really good picture here of both adherence, as well as safety. That is the way the question was worded.

DR. BADEN: And I presume the question is worded that way because those are the data.

DR. ZITO: Yes.

DR. BADEN: So the question is based on the data, not necessarily all the other things we would like in practice.

DR. ZITO: Although only half the population actually had 23 weeks or more.

DR. BADEN: Okay. If there is no other discussion, we should move to the voting.

We will use an electronic voting system for this meeting. Once we begin the vote, 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 or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'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 the questions have been answered or discussed.

So the first question, has the applicant provided substantial evidence of the effectiveness of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing? If

yes, please provide any recommendation concerning labeling? If no, what additional studies analyses are needed?

Before we go to the vote, any other questions on the question?

(No response.)

DR. BADEN: Then let's vote.

(Voting.)

DR. BADEN: This is a long vote.

Dr. Gripshover, please vote. We electronically are tracking you --

(Laughter.).

DR. BADEN: -- and cannot complete the process without your input.

If she is not able to electronically vote, perhaps she can email her vote in that count since it'll be secret, somehow have it on the record prior to closing the voting.

(Pause.)

DR. BADEN: Okay. Have her vote first, and then the rest of us can vote. Let's re-vote; same question.

(Voting.)

MS. BHATT: The voting results: yes, 11; no, 2; abstain, zero; no voting, zero.

DR. BADEN: So we will now go around the room and briefly state your vote and any key comments. We'll start with Dr. Follmann.

DR. FOLLMANN: Thanks. So I voted yes. This is Dean Follmann. I thought the efficacy was quite clear. There were three strong placebo-controlled studies showing strong efficacy. I like to challenge study to give additional information about what happens with immune -- or the non-immune population, which is of interest for this indication, and that was sort of 100 percent efficacy, actually.

I thought study 033 and 030 were strongly supportive of efficacy as well, so this was not difficult for me. Kind of curious about how it might be used in an eradication campaign, but I know that's down the road later, but interesting.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Very briefly, I voted yes for

the same reason. I was convinced about the efficacy data that was presented and also the need and the gaps that are unmet that this drug can potentially meet. So that was why I voted, and I also saw the potential for eradication down the road.

DR. BADEN: Dr. Lo Re?

DR. LO RE: Vincent Lo Re. I also vote yes. I thought the applicant showed the efficacy of tafenoquine anticipated clinical regimen demonstrating superior protective efficacy compared to placebo in double-blind studies 043, 045; a similar prophylactic success rate compared to mefloquine in study 033.

I would note that efficacy data in persons greater than 65 years of age and in the pediatric populations are lacking right now, so I would suggest that the product label indicate the lack of efficacy data in these age groups. And I certainly think it would be prudent for the sponsor to examine efficacy in these age groups.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hello?

DR. BADEN: Yes. We can hear you now.

DR. GRIPSHOVER: Oh, good, because I was afraid I wouldn't hear you. So I voted yes. And I, as other people, thought the studies in the semi-immune were convincing and that even though there weren't any other infections, and study 033 was very supportive because I think it was clear there was one area. And I do think, though, there's not a lot of data on the efficacy of that post-exposure prophylaxis, so that's one thing to look for down the line, too; as we did have some relapses in that group, and exactly when do they take that one dose, 1 week after they come back.

DR. BADEN: Thank you. Dr. Baden. I voted yes. I think, as stated, the efficacy data are largely consistent, and I think the placebo-controlled trials demonstrate substantial activity. I think that there are many missing pieces of data that will need to be looked for, some of which -- and I compliment the sponsor on proposing follow-on studies to the agency to ensure

that they're done as noted: does it work for ovale; does it work for malarious 2D6 metabolism; how resistance emerges; the G6PD; the duration of treatment.

I think there are many, many questions that need to be addressed, however, the core data presented are compelling for its activity against the target pathogen.

Dr. Weina?

DR. WEINA: Pete Weina. I voted yes. As I said earlier, I really believe that drugs are going to be used off label, and if we don't have some kind of control of them, especially with postmarketing surveillance in trials, I think that's a missed opportunity. So toward that end, I think it's really important that we look not only at what has been proposed. But also while it's very encouraging that you have a drug that has very few interactions with other drugs, based upon what we know about its metabolism. I think it's still important to look at it in the older population because it is going to be the older population of

travelers that's going to be utilizing this drug.

I've been involved in a lot of clinical trials with tropical medicine over the years, including malaria, and I think that the data was very convincing and very strong for the efficacy of this product.

DR. BADEN: Thank you. Dr. Green?

DR. GREEN: Michael Green. I voted yes. Basically, as has been stated, there's essentially complete consistency in results of all studies without any signals suggesting a treatment failure. Also, as noted, it would be important to confirm the potential differential efficacy in the elder population as is the intention in the pediatric population. And I just hope that in the pediatric studies, they're going down to young children because they return with their families to places endemic from malaria.

I heard the sponsor talk about data in the adolescents. I didn't hear anything in younger children and toddlers. And I would, as was previously mentioned, expect the labeling for this

product, if approved, to address these limitations for the current time.

DR. BADEN: Dr. Orza?

DR. ORZA: Michele Orza. I voted a very reluctant no, primarily in reaction to the word "substantial." I do think it's terribly important to have options for prophylaxis, and this would add to them. But I feel like all of the pieces of evidence that we have form a sort of a patchwork, an imperfect patchwork with a lot of holes in it. And there's something that we would like to be different about each piece that prevents it from adding up to what I would consider substantial. But I do think that the sponsor and the military have made heroic efforts to revive a potentially missed opportunity.

DR. BADEN: Thank you. Mr. Mailman?

MR. MAILMAN: This is Josh Mailman. I voted yes. Since this is an activity question, just like many others who have spoken before me, it showed substantial activity in the trials that were -- or the data that was shown. I imagine when we get to

question 2, we'll have other things to comment about. But as far as activity, I thought it showed to be an active drug. Thank you.

DR. BADEN: Dr. Moore?

DR. MOORE: I voted yes for a couple of reasons. Well, the main reason is that it clearly was shown to be efficacious. The concern I have regarding the labeling for the FDA would be that the BMI of an Australian or American soldier is significantly different than your average Midwesterner who's going to be going overseas to travel. So I'm concerned about or would be interested to find out the efficacy in the very large. Also the elderly, because people who were going to be traveling and going to malarious areas typically will -- among U.S. travelers anyway, will be older.

The other thing I would say about the -- I'm hoping the FDA will approve this drug for prophylaxis, take the panel's recommendation. However, I would caution that the graph that was shown three times earlier today showing the steady

rise in malaria cases in the United States, imported malaria, when you look at the data is really not necessarily due to lack of adherence to prophylaxis but rather the complete absence of prophylaxis because most of those individuals are people who grew up in malarious areas and didn't take anything to go back and visit. But hopefully that will change with a regimen that you can take less frequently.

DR. BADEN: Thank you. Dr. Tan?

DR. TAN: Kathrine Tan. I voted yes. The reasons for voting yes, I thought they showed good efficacy in the data they presented. I don't think that having the perfect data is really feasible or ethical in a non-immune population, but I think the preponderance of the data was very consistent and the consistent handling of the legacy data.

DR. BADEN: Thank you. Dr. Bilker?

DR. BILKER: Warren Bilker. Warren Bilker. I voted yes. I thought that the efficacy was shown across the various studies, as Dr. Follmann elaborated. And I also agree with Dr. Lo Re about

the need for future studies in pediatric in greater than 65 subgroups, and I'd like to see mandated postmarketing studies in those groups.

DR. BADEN: Dr. Zito? Microphone please. It's not on.

DR. ZITO: Okay. Now I have the microphone on. I reluctantly voted no. I have concerns that there is a need -- besides this patchwork, which was a good word to use -- patchwork of small studies with very, very small samples here and there, there is a need for a larger study that measures 6-month outcomes really regularly across that interval with observed adherence and opportunities to assess ocular hematologic and psychiatric adverse events along the way, because the history of this is a class problem, and this drug is in this class with a lot of known serious adverse events.

DR. BADEN: So question 1, 11 said yes; 2 said no. The yeses predominantly based their assessment on the consistency of the data across the efficacy trials and the challenge study, but

raised many issues, missing data that future studies should address, and encouraged the agency to strongly support and even mandate such studies, such as older/younger, thin or fatter, among other things, as has been noted.

The noes leaned towards no reluctantly, but the data were too patchwork, studies were too small, and some of the adverse events, which we'll get to next, need to be better followed, characterized, and assessed.

We should now move to question 2. Has the applicant provided adequate evidence of the safety of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing? If yes, please provide any recommendations concerning labeling. If no, what additional analyses/studies are needed?

MR. MAILMAN: Can we open this for questions before we vote?

DR. BADEN: Is there a question about the question?

MR. MAILMAN: Yes, there's a question about

the question. In the applicant's presentation, we were given additional studies that were part of their safety follow-up. And yet, if we vote yes on this, may we comment on additional studies as well, even though it's not in there?

DR. BADEN: The question, as I read it, is, is the package of data enough to establish safety? Not is the package of data enough to establish complete safety? And that the data we're considering are part of the application even though there are additional data out there but are not part of this IND, if that makes sense.

MR. MAILMAN: Yes, but the applicant has said there are additional studies that will go as part of the --

DR. BADEN: Oh, in the future.

MR. MAILMAN: Right.

DR. BADEN: Yes. So if there are things that we would want the agency to recommend or to mandate, I would interpret that as part of the comment --

DR. BADEN: MR. MAILMAN: The

recommendations.

DR. BADEN: The recommendations that the agency should make sure blank happens if we or you thought that was so important.

Any other questions?

(No response.)

DR. BADEN: Then let's vote on the question. While we're voting, Dr. Gripshover, please vote, early and often.

(Laughter.)

(Voting.)

MS. BHATT: Voting results: yes, 9; no, 4; abstain, zero; no voting, zero.

DR. BADEN: So we will now discuss our votes starting with Dr. Zito.

DR. ZITO: Well, I guess the main point would be that much more information is needed about the safety, particularly in terms of ocular effects, hematologic, psychiatric. And apparently a very large, much larger, postmarketing surveillance study would be essential. And in my mind, it would really need to have FDA input and

the use of existing large data sets, like you mentioned, from TRICARE so that you could know in advance, pretty much, how long it's going to take for you to acquire information from a community population.

DR. BADEN: Dr. Bilker, please state your vote and any comments.

DR. BILKER: Warren Bilker. I voted yes. Although, as in many cases, I would like to have seen more data, I thought there was sufficient data to show the safety of the drug. But as with the efficacy, I would like to see mandated postmarketing drug studies.

DR. BADEN: Dr. Tan?

DR. TAN: Kathrine Tan. I voted yes. I thought they presented sufficient data for safety for use now, but postmarketing surveillance will definitely be needed.

DR. BADEN: Dr. Moore?

DR. MOORE: Ditto, except for the evidence that was provided was sufficient to demonstrate safety; not perfect. And I think postmarketing

studies would be critical.

DR. BADEN: Mr. Mailman?

MR. MAILMAN: This is Josh Mailman. I voted yes. I think it was a challenging data set. I think given what they had, they presented all that they could. I do take a look at their label claims and I wonder if there will be some additions to either the adverse effects or some counter indications given some of the blood things that we saw. So I would ask to have that looked at. And then the postmarketing studies, whether there's some way to check blood levels or something because we have a lot of people who are traveling and coming back. So those are my comments.

DR. BADEN: Dr. Orza?

DR. ORZA: Michele Orza. I voted a somewhat perplexed no. I do think the safety database is small and spotty, and there are a lot of issues. But I'm perplexed by the comparison of this drug to already approved drugs, one of which the military has already backed away from. And sometimes it looks like this is comparable to those, and other

times it looks like we're changing our mind, actually, about those. So the side effects with Lariam aren't as bad as we thought and the side effects with Malarone are worse than we thought.

So I really couldn't quite figure out how to gauge this in comparison to others. But in and of itself, I would really like there to be more in the way of a postmarketing studies and postmarketing surveillance.

DR. BADEN: Dr. Green?

DR. GREEN: Michael Green. I voted no, although that does not necessarily mean I would have voted no if this was a single question. The latter combined question would be a very hard decision to make and one which I would be quite ambivalent about.

Primarily on safety concerns, as evidence of efficacy, I think has been established, but safety may be a different question. As has been discussed, the safety database for TQ on this proposed regimen was relatively small, under a

thousand patients. Established safety signals have been identified for anemia, keratopathy, or however one pronounces that, non-specific neurologic effects like headache, lethargy, dizziness, and GI side effects.

But none of these are necessarily significant enough, in my opinion, to have prevented approval. The concerns, however, of a potential risk of psychiatric side effects cannot be fully addressed, I think, with such a small exposure at this duration of use. The animal studies with TQ are quite reassuring related to these concerns. However, it's very difficult to address the question whether TQ will behave like PQ or MQ with such a small experience. On the one hand, the structure of the product seems more like PQ than MQ, but it's unclear if the hypothesis of the lack of the hydroxyl group on the compound eliminates this risk.

I am very troubled by the lack of completed studies in the last 10 years, though heartened by the current ongoing safety study and proposed

postmarketing studies. I don't completely understand why additional studies have not been undertaken or why the application needed to be considered before the completion of 60PH04, though this study is designed to look at eye side effects and not necessarily the full range of effects that we're being concerned with.

In the end, I recognize the need, but I'm uncertain of the urgency to approve. And yet given the lack of current alternative options and the possibility that postmarketing studies will define the current unknowns relating to safety, coupled with the concern that a valuable agent may be lost, I split my vote and express my ambivalence.

If the agency does approve the application, I urge them to require the proposed postmarketing studies, as well as specific studies in the over-65 year old population and to complete the pediatric studies. The label should clearly include issues relating to G6PD, and I am not sure what should be said with regards to patients with a history of psychiatric illness. Thank you.

DR. BADEN: Dr. Weina?

DR. WEINA: Pete Weina. I voted yes. I focused mostly on the, in quotations, "adequate evidence." It's impossible to prove many of these side effects without a doubt. It's just really tough to prove that negative. I think monitoring this drug under oversight with postmarketing surveillance is clearly better than ignoring the fact that this drug is going to get used off label if it isn't approved. When faced with a clear known risk, either clear known risk from malaria for the potential patients that we'll be using this or a clear known risk that the drug will be used off label, fear of an unknown risk should not be the reason to deny approval of it.

Clearly, neuropsychiatric precautions ought to be at least part of the labeling and G6PD deficiency requirements for testing should be clearly part of the label as well.

DR. BADEN: Dr. Baden. I voted yes. I am troubled by many aspects of the safety data, including the antiquity of it and the lack of

clarity of how systematically it was collected and scored. However, the data provided are fairly convincing of a reasonable safety profile in terms of major concerns. However, that doesn't mean that, therefore, it's safe, no concerns; effective, no concerns; and use it unbridled. That then comes to the agency and the need to suggest -- and I would strongly consider mandating -- follow-on study to clarify the safety in the real world and in real time with current methods to ensure that it's behaving the way we expect it to.

I share Dr. Weina's concern that uncommon safety events, it's impossible to exclude uncommon safety events with small data sets. So whatever data set we have, an event rate that is slightly smaller will not be detected. So one can forever be chasing that safety concern, and one needs to determine that the data available are adequate for a reasonable amount of safety given the disease that's being treated, and I think they have exceeded that threshold.

Dr. Gripshover?

DR. GRIPSHOVER: Hi. I voted yes for exactly the same reasons, actually. I think the data looks like there's adequate safety. I'm not convinced that it's that much better than mefloquine, though. In the comparator trials, the side effects were pretty much comparable. But I do think we definitely need the postmarketing studies to get a better handle, especially looking at neuropsych. And I actually think I would still put something in the label to at least consider cautioning it because we don't know for sure. But I think there was enough data to say that there's a reasonable amount of safety.

DR. BADEN: Thank you. Dr. Lo Re?

DR. LO RE: Vincent Lo Re. I voted yes. I thought that the sponsor presented sufficient data to highlight the safety. They had 3,184 persons from more than 20 studies. However, given that there were only 529 patients who were exposed to the tafenoquine anticipated clinical regimen for more than 23 weeks, I think that the label should

note limited safety data in longer term use. And I think that the ongoing study the sponsor has undertaken to examine the long-term safety will be valuable.

I would note that the safety data, again, in those greater than 65 and in those less than 18, is lacking. The key studies primarily enrolled people 18 to 55, and I think the product label should indicate the lack of safety data in these age groups.

Further, I think given the pharmacokinetic data demonstrating the tafenoquine trough concentrations, which were really far beyond the 80 nanogram per millimeter threshold for those with very low BMIs equal to 50, appearing to me potentially 4 times as higher, I think additional analyses in this BMI group would be valuable to determine if certain adverse events are more common in this group.

Then finally, I think there were certainly safety findings warranting additional evaluation and postmarketing studies; notedly, the ophthalmic,

hematologic, neurologic, and psychiatric AEs. I actually think it was very prudent of the sponsor for proposing those postmarketing studies to further determine the incidence in nature of those adverse effects, and I hope that the FDA will mandate and monitor these studies going forward.

DR. BADEN: Thank you. Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun. I voted no for the following reasons. While I am really persuaded and satisfied with the efficacy data that was provided, I thought the safety data fell slightly short. Having said that, I would like to see this product move forward.

One, I thought that for a prophylactic drug that is going to be used in a healthy population, the sample size that has been exposed to the drug so far is significantly -- I mean small, 3,000 in a population that is a worldwide population, over a billion people that are at risk for malaria. I thought the sample size was too small to make a definitive -- regardless of what it did not show,

the sample size was too small to make a definitive conclusion one way or the other.

I also taught that the duration of follow-up of the study is rather short. I would have loved to see longer follow-up beyond the 24 weeks. I'd like to see a year or more of follow-up because deployed personnel would probably be on the drug for a longer period of time. I was also concerned about the diversity of the population that was studied; mostly white in one of the studies; mostly black in the other study. The young, the old, women of childbearing age, people of Asian descent were not included in study population.

So those were some of the concerns that I have. But nevertheless, I am very encouraged by the fact that the sponsor is doing additional -- promises to do additional postmarketing studies, and I think those studies should be well designed. And I think the agency should be involved in the design of those studies to ensure that some of the deficiencies that have been noted by all of us on this panel are

incorporated into those designs in terms of the population, the diversity of the population, the duration of the study, and perhaps the size. I would like to see a really large sample size looked at and followed very closely to monitor the various side effects that have been discussed.

DR. BADEN: Dr. Follmann?

DR. FOLLMANN: Dean Follmann. I voted yes. I noted that the question here asked for adequate evidence of safety, and the earlier question was for substantial evidence of efficacy. I thought that was obviously by design by the FDA, and I felt comfortable we had adequate evidence for safety for licensure.

I think the proposed study of 10,000 seems like a nice, big study for me and I think it should be done, mandated, I suppose. I think it's important to get a better handle on the relative risk of psychiatric disorders. That's the theme that's been I guess most troubling or most concerning to me in terms of the safety analyses I've seen.

DR. BADEN: The vote was 9 to 4 regarding the safety. The themes for those agreeing with adequate safety data is that the question asked for adequate, sufficient safety data, and most of us thought that the data met that standard. However, the PK data might be useful in better understanding both efficacy and safety, and there might be opportunity there to refine how the product is used. The neuropsych is a particular concern for all of us, but will be difficult to get a handle on given the nature of that finding and its frequency.

The no contingent largely rested on data are small, small in number, small in time, small in number of groups studied. And that for a prophylactic indication, one would want substantially more data in many of those groups that would be in the real world.

Ultimately, I think all of the panel felt pretty strongly that follow-on studies would be needed, whether recommended or mandated. I think many of us thought that several of them should be mandated. The sponsor's proposal of studies was

very encouraging, and obviously the agency will have to work with them. But strongly encouraging if not mandating those follow-on studies I think was a theme that emerged as well.

So I thank all of the committee members for your time and effort and participation a weathering the weather. I would like to ask the agency if they have any last comments before we adjourn.

DR. NAMBIAR: Thank you, Dr. Baden. I really would like to thank the committee. We appreciate all your input today. I know many of you were here about two weeks ago, and many of you will be back again in two weeks. So we do apologize for making you work extremely hard but appreciate all the input. We're also sorry that some of you had travel woes yesterday, so appreciate you coming in today despite a few hours of sleep last night, and Dr. Gripshover for having joined us on the phone.

Our thanks also to the applicant for all the work on the NDA; speakers at the open public hearing; and a special thanks to the review team

and all our consultants that have really helped us in the review of this NDA. So thank you, safe travels, and see you in a couple of weeks.

Adjournment

DR. BADEN: Thank you, and we'll now adjourn the meeting.

(Whereupon, at 3:52 p.m., the meeting was adjourned.)