ARAKODA™ (TAFENOQUINE SUCCINATE) TABLETS FOR THE PREVENTION OF MALARIA IN ADULTS

NDA 210607

Briefing Document for the Antimicrobial Drugs Advisory Committee

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ADVISORY COMMITTEE BRIEFING MATERIALS AVAILABLE FOR PUBLIC RELEASE

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1. Executive Summary

1.1. Proposed Indication

ARAKODA™ (tafenoquine) tablets are indicated for the prevention of malaria in adults for up to 6 months of continuous dosing.

The proposed indication includes all species of *Plasmodia* (the genus of parasites that cause malaria) and includes prophylaxis both in the endemic region ("in-country prophylaxis") and post-exposure ("post-exposure prophylaxis").

1.2. Dosage Form, Route of Administration, and Dosing Regimen

ARAKODA™ is an oral tablet containing 100 mg of tafenoquine base. The proposed prophylaxis regimen is a loading dose of 2 x 100 mg tablets once daily for 3 days before travel to a malaria area, followed by weekly 2 x 100 mg maintenance doses while in the malaria area, followed by one dose of 2 x 100 mg in the week following exit from the malaria area. Tafenoquine oral 100 mg tablets can be taken with or without food, although tafenoquine taken with food may be associated with better gastrointestinal tolerance.

1.3. Introduction

Malaria is a potentially fatal illness caused by protozoal infection of red blood cells (RBCs) with parasites belonging to the genus *Plasmodium*, transmitted to humans by the bite of an infected mosquito. Five species of *Plasmodium* infect humans, namely, *P. falciparum* (*Pf*), *P. vivax* (*Pv*), *P. ovale* (*Po*), *P. malariae* (*Pm*), and *P. knowlesi* (*Pk*) (WHO-2015).

The life cycle of malaria parasites is illustrated in Section 2.1. Briefly, when they bite, *Plasmodium*-infected mosquitoes inject malaria parasites into the human host, where they multiply first in the liver, and then inside RBCs. Within RBCs, malaria parasites produce toxic substances that are ultimately released into the blood, triggering fever and other malaria symptoms.

Malaria disease can be categorized as uncomplicated or severe. Uncomplicated malaria produces fever, chills, sweats, headaches, nausea, vomiting, body aches, malaise, jaundice, and enlarged liver and spleen. Severe malaria occurs when malaria infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. The manifestations of severe malaria can include potentially fatal "cerebral malaria" (malaria in the brain), severe anemia; acute respiratory distress syndrome; cardiovascular collapse; kidney failure; and other serious medical problems (CDC-2015). Currently in the US, about 1 in every 6 reported cases of malaria is severe (Cullen-2016).

In *Pv* and *Po* infections, patients who have recovered from the first episode of illness may suffer additional attacks ("relapses") that can occur after months or years without symptoms. Relapses occur because *Pv* and *Po* have dormant liver stage parasites ("hypnozoites") that may reactivate over time. Treatment to reduce the chance of these relapses should follow treatment of the first attack.

Approximately 216 million cases of malaria occurred worldwide in 2016, with an estimated 445,000 deaths (WHO-2017). Ninety percent of the cases were due to *Pf*, while *Pv* was the predominant parasite in the Americas and accounted for 30%-40% of cases in South-East Asia and the Eastern Mediterranean region. In the United States (US), the Centers for Disease Control and Prevention (CDC) received 1,727 reports of malaria in 2013, representing a 2% increase compared to 2012 (Cullen-2016). Among all reported US cases of malaria in 2013, approximately 270 (16%) were classified as severe illnesses, resulting in 10 deaths, the highest number since 2001 (Cullen-2016). *Pf* infections accounted for the majority of malaria-related hospitalizations in the US, with hospital stays typically lasting 4-5 days and costing ~$26,000 (Khuu et al-2017).

1.4. Unmet Need

Malaria hospitalizations and deaths are largely preventable through the use of personal protective measures, adherence to correct chemoprophylactic regimens, and medical care that ensures rapid and correct diagnosis and treatment (Khuu et al-2017). Although the trend of malaria cases has been increasing in the US since 1973, the use of appropriate prevention measures by travelers remains inadequate (Cullen-2016). According to recent CDC data, only 4% of US patients with malaria used the malaria prophylaxis drug regimen that was recommended for the regions to which they had traveled (Cullen-2016).

CDC current recommendations for malaria chemoprophylactic regimens in regions where chloroquine-resistant *Pf* exists are atovaquone-proguanil, doxycycline, mefloquine, and primaquine (CDC-2018). Of these, primaquine, atovaquone proguanil and doxycycline require daily dosing that can lead to poor compliance (see Section 2.4.1). Although mefloquine can be dosed weekly, the drug has been associated with serious adverse reactions, including neuropsychiatric side effects at prophylactic doses. In addition, mefloquine resistance has been reported that will diminish the drug's efficacy rate. Thus, there is an unmet medical need while in the endemic region for an effective drug with a potential for improved compliance and safety profile. In addition, post-exposure prophylaxis is complex and cumbersome, so there is an additional unmet medical need for a simple effective post-exposure drug regimen.

1.4.1. Military Perspective

Military personnel comprise one of the largest traveling populations in the US, and malaria remains the number one infectious disease threat to deployed US service members. As no malaria vaccine is on the horizon, the focus of military malaria prevention will remain chemoprophylaxis for the foreseeable future. Problems with currently available prophylactic anti-malarial drugs include not only their contraindications, potential side effects, and the issue of increasing drug resistance, but also poor compliance among soldiers following daily dosing in theater and during post-deployment administration. To address the many drawbacks of currently available malaria chemoprophylactic agents, the Department of the Army has been working on the development of tafenoquine as a prophylactic drug against malaria for nearly 3 decades.

1.5. Tafenoquine Product History

Tafenoquine has been developed as a government-private partnership with the United States Army Medical Material Development Activity (USAMMDA), the Walter Reed Army Institute of

Research (WRAIR), and GlaxoSmithKline (GSK). In 2009, USAMMDA and GSK agreed to separate the responsibilities for filing the prevention and treatment dossiers respectively. USAMMDA has subsequently licensed the prevention indications for tafenoquine to 60 Degrees Pharmaceuticals LLC (60P) with a subsidiary in Australia (60 Degrees Pharmaceuticals Australia Pty Ltd) while GSK retains the treatment indication for *Plasmodium vivax* (*Pv*) malaria.

Tafenoquine has been the subject of more than 25 clinical trials in over 4,000 healthy volunteers, including Phase 1 pharmacokinetics (PK) and safety studies; Phase 1 drug-drug interaction studies; malaria challenge studies; and Phase 2 and 3 studies for malaria prophylaxis. In addition, Phase 2 studies have been conducted for the treatment of *Pv* malaria.

60P filed a 505(b)(1) new drug application (NDA) for tafenoquine for the prevention of malaria in 2017.

1.6. Chemical Structure

Tafenoquine succinate is a new chemical entity belonging to the 8-aminoquinoline group of medicines and is a synthetic analogue of primaquine.

The chemical name of tafenoquine succinate is: 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy] quinoline succinate.

The structural formula is provided in Section 3, Figure 3.

1.6.1. Tafenoquine Mechanism of Action and Overview of Anti-Malarial Activity

The precise mechanism of action of tafenoquine is not known.

In nonclinical studies, the following types of anti-malarial activities have been observed for tafenoquine: 1) causal prophylactic activity against developing liver stages; 2) suppressive, blood schizonticidal activity against asexual blood stages; and 3) anti-relapse, anti-hyponozoite activity against dormant liver stages (i.e., “radical cure”). In addition, with respect to forestalling malaria transmission, tafenoquine has shown activity against gametocytes (malaria sexual stage parasites ingested by mosquitoes) and sporozoites (the stage injected by the mosquito into the human host).

In vitro, tefenoquine was effective against multiple *Pf* clones and isolates (Vennerstrom-1999), including those from Africa (Pradines-2006, Quashie-2013), Honduras (Gorka-2013), and Indochina (Gorka-2013). Tafenoquine was also active against highly drug-resistant forms of *Pf* (i.e., isolates resistant to chloroquine and antifolates and with reduced sensitivity to mefloquine and quinine) (Ramharter-2002).

In vivo studies (Section 6.2.2) demonstrated that tafenoquine is able to clear liver stage infection (causal prophylactic action) and blood stage infections (schizonticidal or suppressive action) in mice (*P. berghei*, *P. yoelli*) and monkeys (*P. cynomolgi*, *Pv* and *Pf* strains). In the monkey, tafenoquine cleared *Pv* infection with no evidence of relapse, achieving “radical cure”.

1.7. Nonclinical Toxicology

The principle findings seen in repeat-dose toxicology studies (see Section 7) performed with tafenoquine for up to 3 months in mice, 6 months in rats, and 1 year in dogs included the following: an increase in methemoglobin, mild anemia; bone marrow hyperplasia; splenic hyperplasia and increased spleen weight; an increase in liver enzymes and liver inflammation (dog); increased adrenal weight; kidney tubular nephropathy and pigment deposits (rats and mice); and phospholipidosis-related changes in the lungs of mice, rats and dogs. These effects were dose-related in incidence and severity.

Effects in animals were generally seen at doses which are subclinical, relative to the tafenoquine clinical dose on a mg/kg basis, as animals appear sensitive to the effects of tafenoquine. However, the majority of changes were reversible or partially reversible following off-dose periods of 2 or 13 weeks.

1.7.1. Nonclinical Assessment of Neurotoxicity

When a Functional Observational Battery (FOB) was conducted in rats to assess tafenoquine's potential for neurobehavioral toxicity, there were no abnormalities observed at doses equivalent to 6-times human exposure (Dow-2017). Furthermore, there were no drug-related findings in the brain sections of rats dosed with 500 mg/kg tafenoquine compared to controls. In contrast, functional and histopathologic abnormalities were reported when a rat FOB was performed with mefloquine (Dow-2006), and brain histopathology showed degenerating fibers in the nucleus gracilis and to a lesser extent in the nucleus cuneatus and solitary tract.

In rhesus monkeys, even at the highest dose administered (which was lethal to 50% of the animals tested), no specific neurologic signs were observed and no abnormal postmortem findings were identified in the brain (see Section 7.2).

1.8. Overview of Tafenoquine Clinical Development Program

The US Army filed the tafenoquine Investigational New Drug (IND) application in 1991. Since that time, tafenoquine has undergone clinical evaluation under a variety of development programs, including malaria chemoprophylaxis, post-exposure prophylaxis, malaria treatment, and malaria relapse prevention. The drug has been the subject of more than 25 clinical trials, including:

- Eight Phase 1 PK and safety studies in healthy volunteers: Study 050; Study 052; Study 003; Study 022; Study TQ-2016-01; Study 051; Study 014; and Study 057
- Two Phase 1 drug-drug interaction studies (Study 015 and Study 040) in healthy volunteers.
- Three Phase 1 malaria challenge studies: Study 053; Study 054, and Study TQ-2016-02
- Seven Phase 2-3 studies for malaria prophylaxis: Study 006; Study 030; Study 033; Study 043; Study 044; Study 045; and Study 049 (Post-exposure Prophylaxis);
- Two Phase 2 studies (Study 047 and Study 058) for the treatment of *Pv* malaria.

- Two 2 trials (Study 001 and Study 036) that were initiated but terminated early due to recruitment or administrative issues; and
- One study (Study 046) that was an open-label, named patient, compassionate use study.

In 1995, SmithKline Beecham (now GSK) became the licensee for all tafenoquine indications. In 2013, GSK formally discontinued its work on tafenoquine use for malaria prophylaxis, but this indication continued to be co-developed by the US Army in partnership with 60P.

1.9. Clinical Pharmacology

1.9.1. Pharmacokinetics

The mean terminal half-life of tafenoquine ranges from 13 to 19 days. PK Parameters AUC and Cmax are directly proportional to dose, and tafenoquine exposure is essentially identical on a mg drug per kg body weight basis for males and females. Tafenoquine accumulates with repeated dosing, with weekly dosing resulting in an accumulation ratio of 4. Tafenoquine absorption increases with food.

Tafenoquine has no significant effects on the metabolism of cytochrome P450 substrates including CYP2D6, CYP2C9, CYP3A4 and CYP1A2 in drug interaction studies.

1.9.2. Minimum Plasma Trough Levels needed for Efficacy

Studies conducted in non-immune persons showed that symptomatic breakthrough of malaria occurred when tafenoquine plasma concentrations were generally < 50 ng/mL. Measured trough concentrations were never < 55 ng/mL amongst a sample of 96 individuals who completed a 6 month course of tafenoquine and who did not contract malaria despite the placebo attack rate of 30% (Edstein 2003; Walsh-2004a). Consequently, a precautionary plasma tafenoquine concentration of 80 ng/mL was selected as the minimum target trough value for prevention of symptomatic malaria development in non-immune individuals (Edstein-2003).

1.10. Summary of Clinical Data

1.10.1. Efficacy

The primary efficacy endpoint in all tafenoquine clinical trials was confirmed parasitemia. “Confirmed parasitemia” meant that the presence of malaria parasites in subjects’ blood smears was confirmed by two independent microscopists.

In efficacy trials, the tafenoquine anticipated clinical regimen (ACR) consisted of a loading dose of 200 mg per day x 3 days followed by a maintenance dose of 200 mg weekly. In addition to utilizing the highest well-tolerated daily dose of tafenoquine (Section 12.3), the ACR was found to generate appropriate anti-malarial plasma tafenoquine concentrations (target of >80 ng/mL trough level) in 95% of individuals.

Designation of which trials would be considered as key/pivotal for efficacy was based on FDA 2007 general Malaria Guidance and on FDA tafenoquine-specific recommendations of 2004 (Type B Meeting) and 2017 (pre-NDA Meeting). Briefly, the comparator-controlled Study 033

in non-immune subjects was to be considered pivotal, with support from 1 or more studies that included the following designs: a placebo-controlled prophylactic study in semi-immune subjects (e.g., Studies 043 and 045, conducted in Africa); a placebo-controlled prophylactic study in non-immune subjects in a human challenge model (Study TQ-2016-02); and a treatment study (Study 058, treatment of Pv malaria). Therefore, for "Prevention of Malaria while in the endemic region", the Applicant's pivotal/key efficacy trials consist of 5 studies: 033, 043, 045, TQ-2016-02, and 058. These studies addressed efficacy against both *Pf* and *Pv*.

In Study 043, Study 045, Study 033, and study TQ-2016-02, tafenoquine-treated subjects received the tafenoquine ACR. In Study 058, subjects received 400 mg per day for 3 days and were followed for cure. [Note: The 1200 mg-total-dose regimen in Study 058 results in the same cumulative dose as the ACR being administered for the 28-day period during which the primary efficacy endpoint (cure) was assessed.]

Phase 2/supporting studies that preceded and supported the key trials listed above consisted of the following: Study 053 (prophylactic efficacy of a single tafenoquine dose); Study 054 (multiple dose tafenoquine in a *Pf* human challenge model); Study 006 (various tafenoquine loading doses for prophylaxis in semi-immune African subjects); and Study 044 (a higher dose than the ACR for non-immune subjects in Southeast Asia).

In the prophylactic field studies, populations were uniformly healthy upon entrance into each study, without clinically significant abnormalities in entrance laboratory values and without clinically significant concomitant disease. Male subjects predominated. Mean age was 29 years (range 12-70 years), mean weight was 69 kg, and mean body mass index (BMI) was 23 kg/m^2.

1.10.1.1. Results of Key/Pivotal Efficacy Trials

Results from the 5 pivotal/key efficacy studies confirmed that the Tafenoquine ACR (200 mg per day x 3 days followed by 200 mg weekly) provided effective prophylaxis against malaria for subjects exposed to *Plasmodia* (Table 1 and Table 2) and supported the proposed prophylactic regimen in the tafenoquine prescribing instructions.

When compared to placebo: In Study 043 in semi-immune subjects exposed to *Pf* (Table 1), the 92% rate of prophylactic failure in the Placebo group was 81% higher than in the Tafenoquine ACR group (11%). Similarly, in Study 045 in semi-immune subjects exposed to *Pf*, the Placebo failure rate (92%) was 79% higher than with the Tafenoquine ACR (13%).

When compared to mefloquine: In Study 045 (Table 1), the Tafenoquine ACR was statistically non-inferior to the standard regimen of Mefloquine (250 mg x 3 days, then 250 mg weekly). Similarly in Study 033 in non-immune subjects (primarily for *Pv* but also with some calculated incidence of *Pf*, the Tafenoquine ACR showed efficacy identical to that of the standard Mefloquine comparator, as evidenced by the fact that no subject developed parasitemia in either group over 6 months of prophylaxis. Historic control data indicated that 11.79% of subjects would have become infected (6.88% with *Pv*, 4.91% with *Pf*) under the study's conditions. Therefore, in Study 033 as in Study 045, Tafenoquine was statistically non-inferior to Mefloquine.

Table 1: Summary of Efficacy Data from Pivotal/Key Studies (Prophylaxis)

Study	Type of Population	Treatment	N	No. of Prophylactic Failures	% Failures
033	Non-Immunes	Tafenoquine 200 mg	462	0	0
		Mefloquine 250 mg	153	0	0
043	Semi-immunes (Africa)	Placebo	59	54	92%
		Tafenoquine 200 mg	53	6	11%
045	Semi-immunes (Africa)	Placebo	94	86	92%
		Tafenoquine 200 mg	91	12	13%
		Mefloquine 250 mg	46	6	13%

Efficacy data for the malaria challenge and treatment studies are summarized in Table 2.

Table 2: Summary of Efficacy Data– Pivotal/Key Studies (Challenge and Treatment)

Study	Type of Study	Treatments	N	No. of Failures	% Failures (95% CI)	Adequate Clinical Response
TQ-2016-2	Challenge in Healthy Non-immune	TQ[a] 200 mg x 3 days, then 200 mg at Day 10	12	0	0%	
		Placebo	4	4	100%	
058	*Pv* Treatment	TQ 400 x 3 days	46	5 (Early) 1 (Late)	10.9% (Early) 2.2% (Late)	87%
		CQ[b] + PQ[c]	24	0 (Early) 2 (Late)	0 % (Early) 8.3% (Late)	91.7%

[a] TQ = Tafenoquine
[b] CQ = Chloroquine
[c] PQ = Primaquine

In the Challenge Study (TQ-2016-02), tafenoquine steady state drug concentrations were **100% effective** against approximately 2,800 *Pf* blood stage parasites inoculated into non-immune volunteers (i.e., protective efficacy = 100%). This suggested that after challenge in the field by *Plasmodium* sporozoites, any parasites that escaped being killed by tafenoquine in the liver would be killed by tafenoquine in the blood.

In Treatment Study 058, an adequate clinical response was seen in 87.0% of the Tafenoquine group vs 91.7% of CQ+PQ group (treatment difference -4.7%)

- Relapse Efficacy: With respect to relapse at Day 120. Tafenoquine was highly effective (100%) in relapse prevention vs CQ+PQ (95%),
- Implications for Prophylaxis: In Study 058, initial parasitemia was 8000 parasites/μL and tafenoquine at 400 mg/day x 3 days eliminated all blood stages of *Pv* by Day 8. Tafenoquine exposure at 400 mg/day x 3 days is similar to tafenoquine exposure with the 200 mg ACR. Hence, results of Study 058 suggest that the Tafenoquine ACR regimen would work against the relatively low *Pv* parasite burden (< 1 parasite/μL blood) present during prophylaxis,

1.10.1.2. Efficacy: Prophylaxis while in the Endemic Region and Post-Exposure

For prophylaxis against all malaria, there are 2 sequential phases: prophylaxis while in the endemic region and post-exposure prophylaxis.

For prophylaxis while in the endemic region, the pivotal trial is study 033, for which the ACR was as effective as standard mefloquine prophylaxis in non-immune Caucasians on military patrol: no subject in either group failed prophylaxis. In historic controls, we calculated that 6.88% of subjects would have been infected with *Pv* and 4.91% of subjects would have been infected with *Pf*. This trial was particularly supported by study 045, in which the tafenoquine ACR was compared to mefloquine and also placebo in semi-immune subjects resident in a *Pf* region in Africa. The Protective Efficacy compared to placebo for tafenoquine was 86%, identical to the value for mefloquine. By these trials, tafenoquine was comparable (non-inferior) to mefloquine against both *Pf* and *Pv*, in 2 racial types (Caucasians and Blacks), and in 2 endemic regions (Oceania and Africa). It is useful to also mention study 044 in which Thais, of whom approximately half were non-immune, were randomized between a low total dose of tafenoquine (400 mg per day x 3 days as loading dose, then 400 mg monthly for months 2-5) and placebo. There was 1 prophylactic failure in the tafenoquine group vs. 30 failures (21 *Pv*, 8 *Pf*, 1 mixed species) in the placebo group. This study reinforces the efficacy of even a low total dose of tafenoquine against both *Pf* and *Pv*, in this instance in Asian subjects.

For post-exposure prophylaxis, again the pivotal study is study 033. In this study, tafenoquine-treated subjects did not receive further drug after leaving the endemic region, whereas mefloquine-treated subjects received standard primaquine prophylaxis. There were 4 *Pv* relapses in tafenoquine subjects vs. 1 relapse in mefloquine/primaquine subjects, which given the 3:1 randomization, was not statistically different. This study showed that tafenoquine administered only up to the time of leaving the endemic region is as effective as primaquine in preventing *Pv* relapse. The other need in post-exposure prophylaxis (if sporozoite challenge occurs in the days before the subject exits the endemic region) is to kill initial liver and blood stages in the week following that challenge. With tafenoquine's long half life, we consider that merely 1 final dose of tafenoquine in the week after leaving the endemic region will continue effective prophylaxis during this time period.

1.10.2. Safety

The Sponsor's safety database includes data from 3,184 subjects who were exposed to tafenoquine across more than 20 studies. For purposes of the Integrated Summary of Safety, these studies were grouped by their dose and duration of tafenoquine administration into 3 analysis datasets: Short-Term studies, Clinical Use studies, and the Extended Dosing Dataset (Section 12.1). Analysis of the Short-Term studies (administration of 3-day loading doses, Section 12.3) showed that subjects who received the 3-day tafenoquine 200 mg once daily loading dose experienced fewer adverse events (AEs) and fewer gastrointestinal AEs, than did those who received higher daily doses of tafenoquine. For gastrointestinal AEs, dose-dependence was observed for nausea, abdominal pain, diarrhea, gastrointestinal reflux disease (GERD), and flatulence.

Because malaria prophylaxis must continue for the duration of an individual's stay in a malaria endemic region, prolonged tafenoquine dosing was evaluated in the Clinical Use studies (Section 12.4), where 988 subjects across 6 studies received Tafenoquine regimens that called for either weekly or monthly dosing for as long as 6 months. These subjects showed good compliance with their prolonged dosing regimens, with 83.6% -90.4% completing their prophylactic dosing as planned.

The Extended Dosing Dataset (Section 12.5) evaluated the Tafenoquine ACR in 825 subjects across 5 studies (Studies 030, 033, 043, 045, and 057). Three of these studies (030, 043, and 045) were conducted in resident African populations who were healthy except for the possibility of asymptomatic parasitemia (which was cleared prior to initial receipt of study drugs). Study 033 was conducted in healthy Australian soldiers who were deployed in a combat zone during study participation, and Study 057 was conducted in healthy volunteers in the United States. As comparators to the Tafenoquine ACR, the Extended Dosing Dataset also included subjects who received an active comparator (Mefloquine, n=309) or Placebo (n=396). The majority of subjects in the overall dataset were male (72.0 - 83.9%) and between the ages of 20 and 49 (75.6% to 82.1%).

No deaths occurred among subjects who received the Tafenoquine ACR. The most common treatment-related adverse reactions leading to treatment discontinuation (Section 12.5.4) in Tafenoquine ACR-treated subjects were increased alanine aminotransferase (ALT) (6 subjects), decreased hemoglobin (3 subjects), and decreased glomerular filtration rate (GFR) (2 subjects). Only 1 or 2 subjects were discontinued due to AEs in other body systems. A total of 49 SAEs were reported in the Tafenoquine ACR group (Section 12.5.5), but only 23 SAEs were considered treatment-related, affecting 22 (2.7%) subjects. Of the 23 SAEs: 7 were an eye disorder, 5 were decreased glomerular filtration rate, 4 were an infection or infestation, 4 were gastrointestinal disorders, 2 were a nervous system disorder, and 1 was a blood/lymphatic system disorder. No SAE was considered to be related to tafenoquine in the following categories: psychiatric disorders; skin and subcutaneous tissue disorders, or general disorders and administration site conditions. Overall, the 22 (2.7%) subjects with treatment-related SAEs in the Tafenoquine ACR group was comparable to the 9 (2.3%) of Placebo subjects with treatment-related SAEs.

Adverse reactions occurring in ≥1% of subjects in the Tafenoquine ACR group and at a greater incidence than in the Placebo group (Section 12.5.6) were the following: diarrhea, GERD,

vomiting, chest pain, seasonal allergy, body tinea, motion sickness, keratopathy, gastroenteritis, impetigo, nasopharyngitis, otitis externa, sinusitis, tinea infection, tinea pedis, tonsillitis, viral infection, arthropod bite, heat illness, joint injury, laceration, ligament sprain, muscle strain, soft tissue injury, thermal burn, arthralgia, back pain, neck pain, lethargy, insomnia, oropharyngeal pain, heat rash, in-growing nail, and rash. Among the Tafenoquine ACR-treated subjects, subjects in study 033 (n=492) were deployed military personnel who were exposed to unique deployment-related extrinsic factors, whereas subjects in studies 030, 043, 045, and 057 were non-deployed (n=333) and not exposed to these external stressors. The incidence of AEs in non-deployed tafenoquine-treated subjects was lower than in deployed soldiers, and in some cases was lower than the Placebo group (Table 36).

1.10.2.1. Gastrointestinal Effects

As an analogue of primaquine, tafenoquine shares some aspects of primaquine's adverse effect profile, which includes gastrointestinal side effects (Sanofi-Aventis-2016). Gastrointestinal AEs that were reported at incidences ≥1% in Tafenoquine ACR-treated subjects included: abdominal pain, constipation, diarrhea, dyspepsia, gastritis, GERD, nausea, and vomiting. However, among these AEs, only diarrhea, GERD, and vomiting occurred at a higher incidence than in the Placebo group. Overall, discontinuations due to gastrointestinal AEs were rare, affecting only 0.2% to 0.4% of subjects who received the tafenoquine ACR. Gastrointestinal AEs that occur with tafenoquine may be ameliorated by taking tafenoquine with food.

1.10.2.2. Hematological Effects

Tafenoquine shares primaquine's profile for hematological AEs, including anemia, methemoglobinemia, leukopenia, and hemolytic anemia in individuals with G6PD deficiency (Sanofi-Aventis-2016). With tafenoquine, hemoglobin frequently decreases by 0.66 g/dL (Section 12.6.2). However, only 3(0.4%) of ACR-treated subjects discontinued prophylaxis due to decreased hemoglobin, a percentage that was similar to the Placebo group (0.3%). Among subjects who received the Tafenoquine ACR, methemoglobin levels ≥1% were observed in 13.9% of subjects, indicating that methemoglobin levels may have mildly exceeded the physiological norm (Section 12.6.2). However, no subject developed methemoglobin levels ≥ 10%, a level associated with hypoxia. Hemolytic anemia occurred only rarely in the Tafenoquine ACR group, affecting 2 (0.2%) of subjects.

1.10.2.3. Cardiac Effects

Although primaquine can cause cardiac arrhythmia and prolongation of the QT interval on ECG (Sanofi-Aventis-2016), ECG data in the Sponsors database showed no similar effects for tafenoquine (Section 12.7.1.1). In subjects who received the Tafenoquine ACR for 26 weeks, the mean QTcF interval decreased (-4.5 msec), arguing against any QTc prolongation effect. These findings are consistent with the results of a published non-Sponsor thorough QT/QTc study (Green-2014).

1.10.2.4. Eye Disorders

Among eye disorders that occurred at incidences ≥1% in the Tafenoquine ACR group (Section 12.7.3), only keratopathy was reported at a higher incidence (8.2%) than in the Placebo

population (0%). Vortex keratopathy (manifesting as benign corneal deposits) has been noted in some subjects treated with the tafenoquine ACR. However, these corneal changes did not impact vision, and they resolved within 1 year in all cases (Section 12.7.3.1). Administration of the Tafenoquine ACR for up to 6 months did not cause retinal toxicity (Section 12.7.3.2).

1.10.2.5. Nervous System Disorders

Nervous system AEs leading to study discontinuation in the Tafenoquine ACR group (Section 12.7.4) were hyperesthesia and visual field defect, each of which affected only 1 (0.1%) subject. Neither of these AEs was considered severe. Hyperesthesia followed a period of heavy ethanol use and post-ethanol malaise. It was treated with non-prescription modalities and resolved without sequelae. Visual field defect resolved spontaneously within 6 weeks.

The overall percentages of treatment-related nervous system AEs (Table 46) were comparable for the Tafenoquine ACR and Placebo groups (3.8% vs. 3.5%, respectively). Percentages of subjects with headache (1.9%) and dizziness (0.8%) in the Tafenoquine ACR group were lower than in the Placebo (2.5% and 1.0%) and Mefloquine (2.6% and 2.3%) comparator groups. Although lethargy occurred more frequently in the Tafenoquine ACR population (1.1%) compared to Placebo (0%), all cases of lethargy in Tafenoquine ACR subjects occurred in deployed military subjects in Study 033. These soldiers had limited opportunities for sleep and participated in patrols and combat during the night. No cases of lethargy were reported among non-deployed resident populations who received the Tafenoquine ACR.

1.10.2.6. Psychiatric Disorders

Psychiatric AEs reported during clinical trials of the Tafenoquine ACR are summarized in Section 12.7.6. Psychiatric AEs leading to study discontinuation in the Tafenoquine ACR group included depression and a suicide attempt, each of which occurred in 1 (0.1%) subject. The suicide attempt occurred when the subject was acutely intoxicated with ethanol and had reportedly been prompted by the subject's marital problems. The event resolved within 2 days and was considered unrelated to tafenoquine. The subject who was withdrawn due to depression had a history of intracranial injury. Depression resolved after approximately 3 months of treatment with paroxetine.

Only one psychiatric AE occurred at an incidence ≥1% in the Tafenoquine ACR group. This was insomnia, which affected 1.2% of subjects.

A review of psychiatric data from Study 033 revealed that the military subjects in that study had a unique psychiatric AE profile compared to subjects in other Tafenoquine ACR studies due to the combat environment to which these soldiers were exposed (Section 12.7.6.1). Compounding this psychologically hostile environment were the many physical insults and injuries which the soldiers experienced as a result of their warlike deployment (Table 48). However, in spite of the stressful environment to which the Tafenoquine ACR Deployed subjects were exposed, the incidence of psychiatric AEs in the Deployed ACR population was only 5.1%, with the majority of psychiatric AEs assessed as mild (84.4%) and considered not related or unlikely related to the study drug (52.0%).

Among the non-deployed resident population that received the Tafenoquine ACR Table 47 , psychiatric AEs that were considered possibly or probably related to tafenoquine were insomnia,

sleep disorder, neurosis, and depression. Incidence of insomnia in non-deployed ACR subjects (0.6%) was lower than in the Placebo group (0.8%), while sleep disorder, neurosis, and insomnia each affected only 1 non-deployed ACR subject.

No psychiatric AE was considered definitely related to tafenoquine.

1.11. Conclusion

Tafenoquine fulfills the unmet medical need for an efficacious and safe prophylactic antimalarial with a convenient (weekly) dosing regimen for in-country use. Tafenoquine offers advantages over atovaquone proguanil and doxycycline on the basis of compliance, and over mefloquine on the basis of tolerance. In addition, the proposed 1-dose post-exposure tafenoquine regimen offers considerable potential compliance advantages to all present post-exposure regimens.

2. Introduction

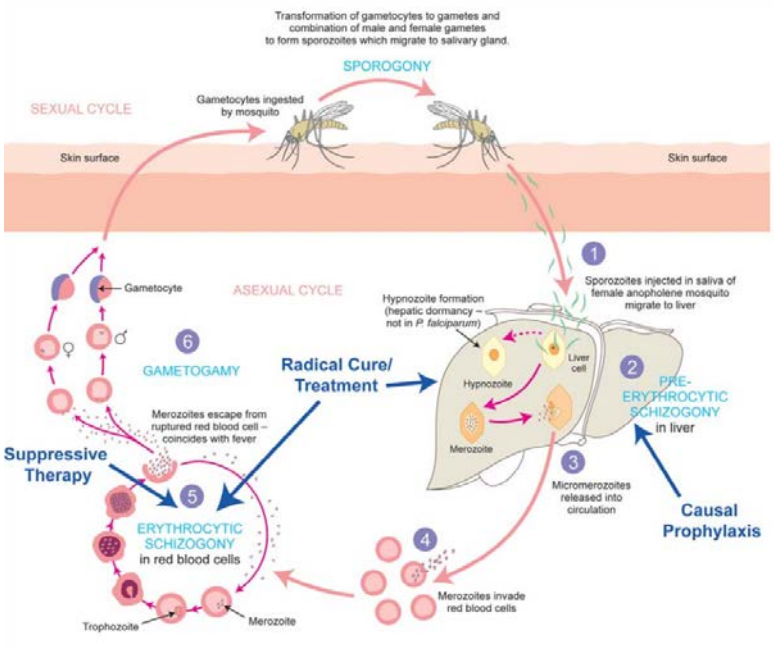
Malaria is a potentially fatal illness caused by protozoal infection of RBC with parasites belonging to the genus *Plasmodium*, transmitted to humans by the bite of a *Plasmodium*-infected mosquito. Five species of *Plasmodium* infect humans, namely, *P. falciparum* (*Pf*), *P. vivax* (*Pv*), *P. ovale* (*Po*), *P. malariae* (*Pm*), and *P. knowlesi* (*Pk*) (WHO-2015).

2.1. Malaria Parasite Life Cycle

The life cycle of malarial parasites is shown in Figure 1 (for *Pv*) and in Figure 2 for *Pf*. When they bite, female *Anopheles* mosquitoes inject malaria parasites (sporozoite forms) into the human host, and within an hour the sporozoites have infected liver cells. Once inside the liver cells, malaria parasites multiply (asymptomatically) until the cells eventually burst, releasing malaria parasites into the blood. In the bloodstream, the parasites (now asexual forms called schizonts) infect red blood cells, where they multiply, ultimately causing the red cells to burst. This triggers fever and other malaria symptoms (Berman-2001). Also within red cells, some malaria parasites become gameotocytes, the parasite's sexual stage. Gameotocyte can be ingested by a mosquito during a future mosquito bite, setting the stage for malaria to be transmitted to a new human victim.

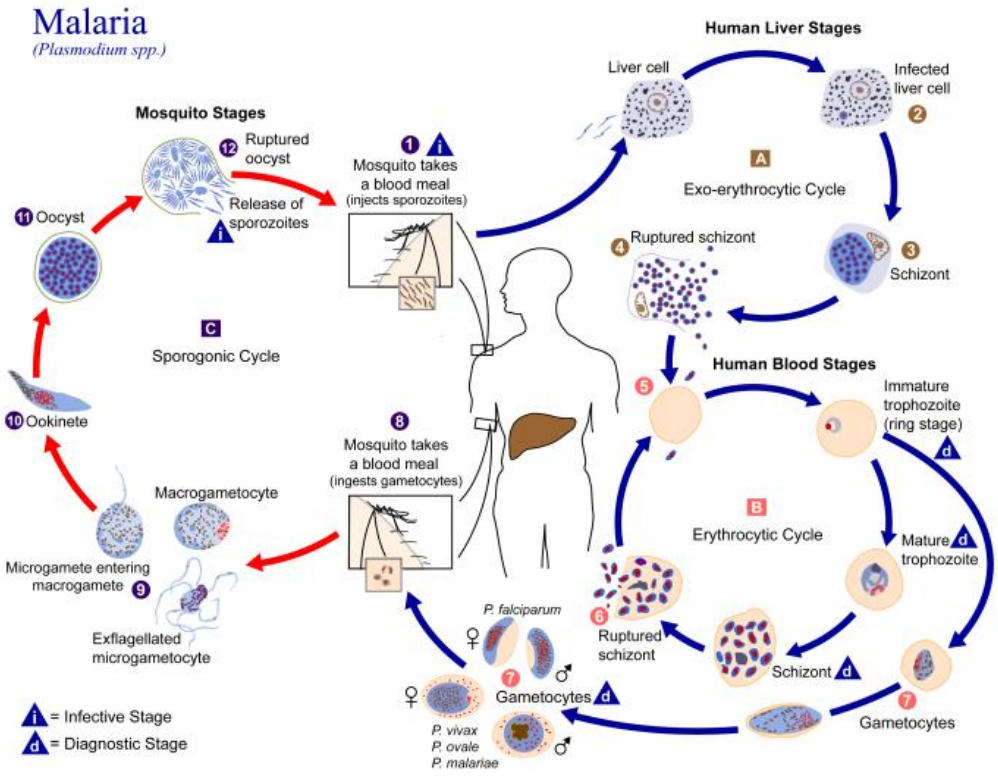
In terms of life cycle, *Pf* differs from that of *Pv* in not having a hypnozoite stage. Hypnozoites are forms of the malaria parasite that lie dormant in the liver, eventually awakening to cause malaria symptoms in the future (i.e., a malaria "relapse").

Figure 1: Malarial Parasite Life Cycle (*P vivax*)



Source: FDA-2007

Figure 2: Malarial Parasite Life Cycle (*P. falciparum*)



Source: CDC-2017a

2.2. Malaria: The Clinical Picture

Malaria's clinical symptoms are caused by the parasite's asexual blood stage parasites (CDC-2015). As the parasite develops inside RBC, waste products are produced, and these are dumped into the bloodstream when the infected red cells burst. This triggers fever, shaking chills, and other symptoms of malaria. Infected red cells can also stick to the walls of blood vessel in a process known as "sequestration", causing localized damage in the brain, kidneys, and other organs.

Malaria disease can be categorized as uncomplicated or severe (CDC-2015). Uncomplicated malaria produces symptoms such as fever, chills, sweats, headaches, nausea, vomiting, body aches, malaise, jaundice, and enlarged liver and spleen. Severe malaria (typically caused by *Pf)* occurs when malaria infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. The manifestations of severe malaria include "cerebral malaria" (malaria in the brain), that can produce abnormal behavior, impairment of consciousness, seizures, coma, and death. Survivors of cerebral malaria may have persistent neurologic problems such as trouble with movements (ataxia), palsies, speech difficulties, deafness, and blindness.

Severe malaria can also cause severe anemia; acute respiratory distress syndrome; extremely low blood pressure and cardiovascular collapse; kidney failure; metabolic acidosis (excessive acidity in the blood and tissue fluids); and hypoglycemia (low blood glucose) (CDC-2015).

Currently in the US, about 1 in every 6 reported cases of malaria is severe (Cullen-2016).

Malaria Relapses (CDC-2015): In *Pv* and *Po* infections, patients who have recovered from the first episode of illness may suffer several additional attacks ("relapses") that can occur after months or even years without symptoms. Relapses occur because *Pv* and *Po* have dormant liver stage parasites ("hypnozoites") that may reactivate over time. Treatment to reduce the chance of these relapses should follow treatment of the first attack.

2.3. Malaria Epidemiology

In 2015, nearly half of the world's population was at risk of malaria (WHO-2017). Most malaria cases and deaths occur in sub-Saharan Africa; however, South-East Asia, Latin America and the Middle East are also at risk. In 2015, there were 91 countries with ongoing malaria transmission.

According to the World Health Organization (2017), approximately 216 million cases of malaria occurred worldwide in 2016, with an estimated 445,000 deaths. Ninety percent of the cases were due to infection with *Pf*. In sub-Saharan Africa, *Pf* was the most prevalent malaria parasite, accounting for 99% of malaria cases in 2016. *Pv* was responsible for about 4% of cases globally but about 36% outside of Africa. *Pv* is the predominant parasite in the WHO Region of the Americas, representing 64% of malaria cases, and *Pv* accounts for more than 30% of cases in the WHO South-East Asia and 40% in the Eastern Mediterranean regions.

In US residents, malaria is the cause of considerable morbidity and mortality. During 2013, the Centers for Disease Control and Prevention (CDC) received 1,727 reports of an onset of symptoms of malaria in the United States (US) (Cullen-2016). This total number of cases represented a 2% increase compared to the 1,687 cases reported for 2012. *Pf*, *Pv*, *Pm*, and *Po* were identified in 61%, 14%, 3%, and 4% of cases, respectively. *Pf* infections, which accounted for the majority of malaria-related hospitalizations in the US, typically resulted in a hospital stay lasting 4.36 days and costing $25,789 (Khuu et al-2017).

Among all reported US cases of malaria in 2013, approximately 270 (16%) were classified as severe illnesses, resulting in 10 deaths, the highest number since 2001 (Cullen-2016)

2.4. Unmet Medical Need for Malaria Prophylaxis in the Endemic Region

Malaria hospitalizations and deaths are largely preventable through the use of personal protective measures, adherence to correct chemoprophylactic regimens, and medical care that ensures rapid and correct diagnosis and treatment (Khuu et al-2017). With respect to the use of chemoprophylaxis, CDC data show that only 4% of US patients used the malaria prophylaxis drug regimen that was recommended by the CDC for the regions to which they had traveled (Cullen-2016). The CDC concluded that although the trend of malaria cases has been increasing in the US since 1973, the use of appropriate prevention measures by travelers remains inadequate.

2.4.1. Current CDC-Recommended Drugs for Malaria Chemoprophylaxis (in-County Use)

CDC (2018) malaria chemoprophylactic recommendations for regions where chloroquine-resistant *Pf* exists are atovaquone-proguanil, doxycycline, mefloquine, and primaquine. The dosing schedules, estimated efficacy rates, and adverse effects for these drugs are described

below. The recommended duration of dosing after leaving the endemic region is based on whether the agent kills the liver stage of the parasite (a causal agent) in which case the duration is 7 days, or kills the subsequent blood stage of the parasite (a blood schizonticidal agent) in which case the duration is 28 days. These time periods respectively approximate the time of solely liver infection, and the latest time over which parasites are reasonably expected to exit the liver and to infect the blood.

2.4.1.1. Atovaquone/Proguanil (Malarone)

Atovaquone/proguanil prophylaxis should begin 1-2 days before travel to malarious areas and should be taken daily, at the same time each day, while in the malaria endemic area and (since this agent is causally-active) daily for 7 days after leaving the area (CDC-2018). The CDC website does not provide efficacy figures, but information in the Malarone® (atovaquone/proguanil) label (GSK-2016) suggests that per-protocol Malarone prophylactic efficacy is approximately 98%. Atovaquone resistance, where present, will diminish that efficacy rate. Common adverse effects reported in persons using atovaquone/proguanil for prophylaxis or treatment are abdominal pain, nausea, vomiting, and headache.

2.4.1.2. Doxycycline

Doxycycline prophylaxis should begin 1-2 days before travel to malarious areas. It should be continued once a day, at the same time each day, during travel in malarious areas and daily for 4 weeks after the traveler leaves such areas. Efficacy is thought to be between 92-96%. Doxycycline frequently causes mild-moderate nausea, vomiting, abdominal pain, photosensitivity, and vaginitis; and uncommonly can cause the severe reactions of esophagitis and esophageal ulcerations (Tan-2011).

2.4.1.3. Mefloquine

Mefloquine prophylaxis should begin 1-2 weeks before travel to malaria areas. It should be continued once a week, on the same day of the week, during travel in malaria areas and for 4 weeks after a traveler leaves such areas. Information in the Lariam® (mefloquine hydrochloride) summary of product characteristics (Roche-2018, UK) suggests mefloquine prophylactic efficacy to be approximately the same as that of Malarone, i.e., approximately 98%. Mefloquine resistance, where present, will diminish that efficacy rate.

Mefloquine has been associated with rare serious adverse reactions (e.g., psychoses or seizures) at prophylactic doses; these reactions are more frequent with the higher doses used for treatment (CDC Yellow Book-2017b). Other side effects that have occurred in chemoprophylaxis studies include gastrointestinal disturbance, headache, insomnia, abnormal dreams, visual disturbances, depression, anxiety disorder, and dizziness. Other more severe neuropsychiatric disorders occasionally reported during post marketing surveillance include sensory and motor neuropathies (including paresthesia, tremor, and ataxia), agitation or restlessness, mood changes, panic attacks, forgetfulness, confusion, hallucinations, aggression, paranoia, and encephalopathy. On occasion, psychiatric symptoms have been reported to continue long after mefloquine has been stopped. Mefloquine is contraindicated for use by travelers with a known hypersensitivity to mefloquine or related compounds (e.g., quinine and quinidine) and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis,

schizophrenia, other major psychiatric disorders, or seizures. It should be used with caution in persons with psychiatric disturbances or a previous history of depression. Although mefloquine has the important advantage of being taken weekly, the association of mefloquine with adverse neuropsychiatric effects has prompted the Food and Drug Administration (FDA)-mandated addition of a "black box warning" to the product (FDA-2013) and has curtailed its use by the US and other allied militaries.

In the US, mefloquine drug label information (TEVA Pharmaceuticals USA-2017) advises: "During prophylactic use, the occurrence of psychiatric symptoms such as acute anxiety, depression, restlessness or confusion suggest a risk for more serious psychiatric disturbances or neurologic adverse reactions. In these cases, the drug should be discontinued and an alternative medication should be substituted." When mefloquine prescribing and patient safety guidance were compared for the US, UK, Ireland, Australia, New Zealand, and Canada (Nevin-2016), there was agreement among all 6 countries to discontinue mefloquine or call the prescriber for roughly the same 4 categories of symptoms: anxiety disorders and symptoms; changes in physical activity; depressed mood disorders and disturbances; and deliria (including confusion). In a 2017 Cochrane meta-analysis (Tickell-Painter-2017), when mefloquine's effects were assessed across studies and compared to those of other antimalarials, best estimates of absolute effect sizes for mefloquine versus atovaquone-proguanil were 13% versus 3% for insomnia, 14% versus 7% for abnormal dreams, 6% versus 1% for anxiety, and 6% versus 1% for depressed mood. Best estimates of absolute effect for mefloquine versus doxycyline were: 12% versus 3% for insomnia, 31% versus 3% for abnormal dreams, 18% versus 1% for anxiety, and 11% versus 1% for depressed mood.

As a result of these regulatory and literature warnings, mefloquine prescriptions in the US military fell from approximately 50% of all malaria chemoprophylactic scripts in 2007 pre-black box warning to approximately 5% in 2010-2011 post black-box warning (Kersgard-2013).

Notably, because of these warnings, the public is aware that mefloquine has been linked to neurotoxicity, which complicates the interpretation of any study involving mefloquine. As a result, in blinded placebo-controlled studies of mefloquine, even placebo "treatment" has been associated with an increased incidence of neuropsychiatric AEs (Overbosch-2001).

2.4.1.4. Primaquine

With primaquine, prophylactic dosing begins 1-2 days before travel to malarious areas, continues daily (at the same time each day) while in malaria area, and then extends, for this causal agent, for an additional 7 days after leaving the areas (CDC-2018). Efficacy is thought to be approximately 85% (Hill-2006). Primaquine cannot be used in patients who have not been tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency or who are found to have G6PD deficiency. Furthermore, primaquine cannot be used for malaria prophylaxis in US military populations as this is an off-label use (CDC-2017c). The most common adverse event (AE) in people with normal G6PD levels is gastrointestinal upset if primaquine is taken on an empty stomach. This problem is minimized or eliminated if primaquine is taken with food (CDC-2017b).

2.4.2. Existing Therapies and the Risk of Poor Compliance

Among existing CDC-recommended therapies, 3 of the prophylactic antimalarials need to be administered daily: atovaquone/proguanil (Malarone), doxycycline, and primaquine. Adherence to any one of these daily antimalarials appears to be inferior to adherence to a weekly prophylactic mefloquine regimen. For example, in a recent report of Tolerability and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan (Saunders-2015), "compliance with daily doxycycline was poor (60%) compared with 80% with weekly mefloquine," although the effect of AEs on compliance was reasonably controlled (i.e., about 30% of soldiers reported AEs for either mefloquine or doxycycline). This study enlarges upon findings from 2 prior studies: 1) Phillips (1996) showed 10% better compliance for mefloquine compared to doxycycline, in spite of a similar incidence (6%) of adverse effects; and 2) Hoebe (1997) showed 13% better compliance for mefloquine (78%) compared to proguanil (65%).

For primaquine, a 2017 review of antimalarial "target product profiles" states that "compliance is poor, given the 14-day therapy course in asymptomatic individuals" (Burrows-2017). This statement is supported by work such as by that by Takeuchi (2010), who found that the relapse rate in *Pv* patients who received directly observed therapy with primaquine was only 3%, whereas the relapse rate in patients who self-administered primaquine was 11%. Although these statements refer to the use of primaquine to treat hypnozoites, they also suggest that daily therapy in asymptomatic subjects taking primaquine prophylaxis will be poor. Diminished compliance correlates well with increased incidence of clinical disease, since as mentioned above, 96% of malaria cases, thus probably every mortal case, in US personnel reported to the CDC in the latest (2013) data summary occurred in persons who were not compliant (Cullen-2016). This conclusion is supported by the CDC statement that "In comparison with drugs with short half-lives, which are taken daily, drugs with longer half-lives, which are taken weekly, offer the advantage of a wider margin of error if the traveler is late with a dose. For example, if a traveler is 1–2 days late with a weekly drug, prophylactic blood levels can remain adequate; if the traveler is 1–2 days late with a daily drug, protective blood levels are less likely to be maintained" (CDC Yellow Book-2017b).

2.4.3. Summary of Deficiencies in Current CDC-Recommended Drugs for Malaria Prophylaxis

CDC current recommendations for malaria chemoprophylactic regimens for regions where chloroquine-resistant *Pf* exists (Table 3) are atovaquone-proguanil, doxycycline, mefloquine, and primaquine. Of these, primaquine, atovaquone proguanil and doxycycline require daily dosing that can lead to poor compliance. Although mefloquine can be dosed weekly, the drug has been associated with rare serious adverse reactions, including neuropsychiatric side effects at prophylactic doses. In addition, mefloquine resistance has been reported that will diminish its efficacy rate. Thus, for chemoprophylaxis while in a malaria-endemic region, there is an unmet medical need for an effective weekly drug that is considered safe. The addition of another agent to the armamentarium with a differentiated safety and tolerability would be welcomed. This would extend the options available to travelers possessing differing relative and absolute contraindications, promoting greater chemoprophylactic adherence. This would have both individual and public health benefits.

Table 3: Summary of Considerations for Choosing a Drug for Malaria Prophylaxis (CDC) in Regions where Chloroquine-resistant *P. falciparum* Exists

Drug	Prophylactic Efficacy	Resistance May Diminish Efficacy	Requires Daily Dosing	Continued dosing after travel	Notable side effects	Contraindications or issues with pre-existing illnesses
Atovaquone/ Proguanil	98%	Yes	**Yes**	7 days	GI effects, Headache	Renal impairment
Doxycycline	92-96%		**Yes**	**4 weeks**	GI effects, Exaggerated sunburn, Vaginal candidiasis Esophagitis and esophageal ulcerations (uncommon)	Sun sensitivity
Mefloquine	98%	Yes	No	**4 weeks**	GI effects, headache, insomnia, abnormal dreams, visual disturbances, depression, anxiety disorder, dizziness, psychosis (rare), seizures (rare) Post-marketing: Neuropsychiatric disorders, including sensory and motor neuropathies (paresthesia, tremor, ataxia), agitation, restlessness, mood changes, panic attacks, forgetfulness, confusion, hallucinations, aggression, paranoia, encephalopathy. **(FDA Black Box Warning for Neuropsychiatric side effects).**	Known hypersensitivity to mefloquine or related compounds (quinine and quinidine); Cardiac conduction abnormalities; Seizure disorder; Psychiatric illness (active depression, recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders
Primaquine	85%	**Yes**	**Yes**	7 days	GI side effects	G6PD deficiency

2.5. Unmet Medical Need for Post Exposure Prophylaxis

Prophylaxis after the last day of contact with an infected mosquito requires protection against 2 forms of *Plasmodium*: 1) initial liver forms of *Pf* and *Pv* that have not yet exited the liver to infect the blood; and, 2) dormant liver forms ("hypnozoites") of *Pv* and *Po* that can later exit the liver and infect the blood.

Post-exposure prophylaxis to eliminate initial liver forms of *Pf* and *Pv* that have yet to leave the liver requires 4 weeks of drugs if the drug only kills blood parasites ("schizonticidal drug" such as mefloquine) but only 7 days for drugs that kill initial liver forms in situ ("causal drug" such as Malarone or primaquine). Post-exposure prophylaxis to kill *Pv* dormant forms, thus preventing relapse, requires an 8-aminoquinoline, the only category of antimalarial agents known to have clinical anti-hypnozoite activity. For this purpose, primaquine dosing (30 mg per day for an adult) is given for 14 days after leaving the endemic region (CDC-2017b). If the endemic region has both *Pf* and *Pv*, as is generally true for malaria-endemic regions other than sub-Saharan Africa, protection is needed against both initial liver forms that have yet to leave and hypnozoites.

The unmet medical need for post exposure prophylaxis is for a short, ideally 1-dose, regimen to replace 7 daily doses of Malarone or 4 weekly doses of mefloquine, especially when either of those regimens is combined with 14 daily doses of primaquine.

2.6. Unmet Need: The Military Perspective

As in many other industrialized countries, military personnel comprise one of the largest traveling populations in the US. In 2016, approximately 1.3 million US military members were on active duty, and approximately 800,000 were in the reserve forces (CDC-2017c). Malaria remains the number one infectious disease threat to deployed US service members, and the number two vector-borne disease overall (Table 4).

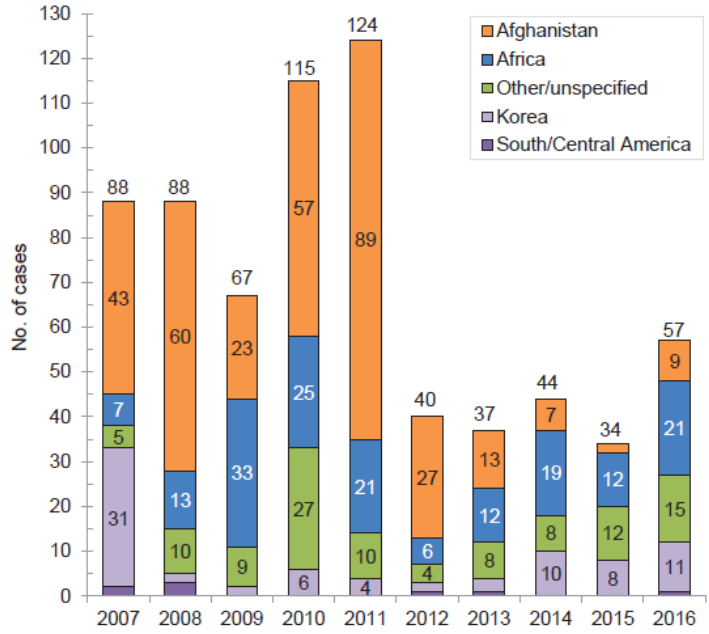
Table 4: Top Five Vector-Borne Diseases: Numbers of Confirmed, Possible, and Suspected Cases, active and reserve components , US Armed Forces, 2010-2016

	Confirmed Cases		Possible Cases		Suspected Cases	
	Active	Active + Reserve	Active	Active + Reserve	Active	Active + Reserve
Lyme Disease	629	721	76	129	1904	3268
Malaria	306	346	96	122	339	475
Dengue	68	86	52	79	110	175
Chikungunya	32	78	-	-	8	18
Rocky Mountain Spotted Fever	55	64	42	54	282	449

Source: Armed Forces Health Surveillance Branch-2018

Between 2007 and 2016, the majority of malaria cases in the US Armed Forces (Figure 3) were acquired in either Afghanistan or Africa (Armed Forces Health Surveillance Branch-2017).

Figure 3: Annual Number of Cases of Malaria Associated with Specific Locations of Acquisition. U.S. Armed Forces 2007-2016



As no malaria vaccine is on the horizon, the focus of military malaria prevention will remain chemoprophylaxis for the foreseeable future. Problems with currently available prophylactic anti-malarial drugs include not only their contraindications, potential side effects, and the issue of increasing drug resistance, but also poor compliance among soldiers following daily dosing in theater and during post-deployment administration (see Section 2.4.2). Although military personnel are required to take their malaria chemoprophylaxis agents as prescribed to maintain mission readiness, there is great variability in the extent that individual commanders enforce these policies, and continued outbreaks of malaria occur in military populations because of poor compliance (CDC-2017c).

Malaria Relapse in Military Populations (CDC-2017c) - As a matter of policy, the US military routinely uses primaquine for presumptive antirelapse treatment (PART) in returning military populations to prevent the late relapse of *Pv* malaria or *Po* malaria. In 2003, CDC recommended 30 mg (base) of primaquine daily for 14 days for PART based on available evidence, but the FDA-approved regimen remains at a lower dose of 15 mg. Adherence to the daily 14-day regimen is poor unless primaquine is given under directly observed therapy, which is rarely done. As a result of noncompliance and subtherapeutic dosing with the 15 mg (base) for 14 days regimen, periodic outbreaks of relapsed *Pv* malaria continue to occur in returning military personnel. Use of the higher-dose primaquine regimen for PART is now recommended for military personnel.

To address the many drawbacks of currently available malaria chemoprophylactic agents, as detailed above, the Department of the Army has been working on the development of tafenoquine as a prophylactic drug against malaria for nearly 3 decades.

3. Tafenoquine Product Information

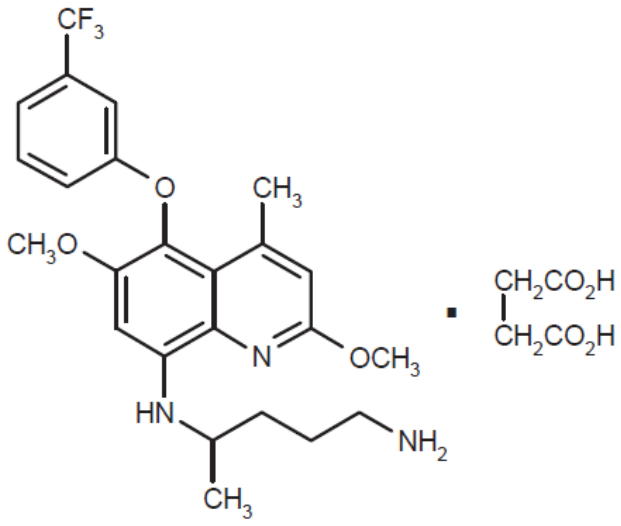
The antimalarial tafenoquine succinate is a new chemical entity belonging to the 8-aminoquinoline group of medicines and is a synthetic analogue of primaquine. Tafenoquine is a primaquine congener synthesized by adding a methoxy group at the 2 position, a methyl group at the 4 position, and a 3-trifluoromethylphenoxy substitution at the 5 position of the quinoline ring (Figure 4). Addition of these moieties to the quinoline nucleus imparts marked physicochemical differences that improve the in vitro antimicrobial and PK profiles over those of primaquine, and lead to attractive in vivo pharmacodynamic, toxicological, and safety profiles.

The chemical name of tafenoquine succinate is:

(±)- 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy] quinoline succinate

The structural formula is provided in Figure 4.

Figure 4: Structure of Tafenoquine Succinate



Molecular weight: 581.58 (succinate salt); 463.50 (free base anhydrous)

CAS registry number: 106635-80-7

Molecular Formula: $C_{24}H_{28}F_3N_3O_3.C_4H_6O_4$

The active ingredient in ARAKODA, tafenoquine succinate, is an almost white to orange solid. ARAKODA tablets each contain 100 mg of tafenoquine free base in the form of tafenoquine succinate (125.5 mg).

ARAKODA™ also contains the following excipients: Microcrystalline Cellulose; Mannitol; Magnesium Stearate. The tablet film coating inactive ingredients include: hypromellose, titanium dioxide, iron oxide red, and macrogol/polyethylene glycol 400.

4. Tafenoquine Clinical Development and Regulatory History

4.1. Tafenoquine Clinical Development

In 1991, the US Army filed the tafenoquine IND application, and SmithKline Beecham (now GSK) became the licensee for all tafenoquine indications in 1995. In 2013, GSK formally discontinued its work on the use of tafenoquine for malaria prophylaxis, but this indication continued to be co-developed by the US Army in partnership with 60P.

In 2017, 60P filed a 505(b)(1) new drug application (NDA) for tafenoquine for the prevention of malaria, and the company has engaged a contract manufacture in India to manufacture and package both the drug substance and drug product for the marketed product. The recently manufactured drug product has undergone clinical investigation in a malaria challenge model (Study TQ-2016-02) to support product efficacy in accordance with End of Phase 2 recommendations from FDA and also in a PK study (Protocol-TQ-2016-01) to show bioequivalence to prior capsule formulations used during clinical development.

4.2. Overview of Tafenoquine Clinical Development Program

Since the US Army filed the tafenoquine IND application in 1991, tafenoquine has undergone clinical evaluation under a variety of development programs, including malaria chemoprophylaxis, post-exposure prophylaxis, malaria treatment, and malaria relapse prevention. The drug has been the subject of more than 25 clinical trials involving more than 4000 subjects, including:

- Eight Phase 1 PK and safety studies in healthy volunteers (Table 5), including Study 050; Study 052; Study 003; Study 022; Study TQ-2016-01; Study 051; Study 014; and Study 057
- Two Phase 1 drug-drug interaction studies (Study 015 and Study 040) in healthy volunteers (Table 6)
- Three Phase 1 malaria challenge studies (Table 7), including Study 053; Study 054, and Study TQ-2016-02
- Seven Phase 2-3 studies for malaria prophylaxis (Table 8): Study 006; Study 030; Study 033; Study 043; Study 044; Study 045; and Study 049 (Post-exposure Prophylaxis);
- Two Phase 2 studies (Study 047 and Study 058) for the treatment of *P vivax* malaria (Table 9).
- Two 2 trials (Study 001 and Study 036) that were initiated but terminated early due to recruitment or administrative issues; and
- One study (Study 046) that was an open-label, named patient, compassionate use study.

Table 5: Phase 1 Studies in Healthy Volunteers

Study No. (Publication)	Study Design[a]	Study Objectives	Tafenoquine Doses Administered	Population
Single-Dose Studies				
050 (Brueckner et al-1998a)	R, DB, PC	PK and Safety in fasted state	4 -600mg	N=75; 75M/0F
052 (Karle et al-1995)	R, PG	PK and Safety in fasted state	100, 200, or 400 mg	N=18; 18M/0F
003	R, O, PG	PK and Safety in fed vs. fasted state. Gender effects.	400 mg	N=32;16M/16F
022	R, PG	PK and Safety in fed vs. fasted state. Gender effects.	200 mg	N=40; 20M/20F
TQ-2016-01	O	Compare PK parameters of the new TQ clinical formulation (100 mg tablets) to PK of the 200 mg capsule used in previous TQ trials (specifically Study 022).	200mg (dosed as two 100 mg tablets)	N=70; 35M/35F
Multiple Dose Studies				
051	R, DB, PC	PK and Safety in fasted state	200, 400, or 600 mg weekly x 10 weeks	N=36; 30M/6F
014	R,O,PG	Relative bioavailability of 3 different oral formulations.	400 mg daily x 3 days	N=58; 43M/15F
057[b] (Leary et al-2009)	R, PC	Renal and ocular Safety.	200 mg daily x 3 days, then weekly x 23 weeks	N=120; 73M/47F

[a]R=Randomized; DB=Double-blind; P=Placebo-controlled trial; PG=Parallel-group; O=Open-label; PK=pharmacokinetics.
[b]Study 057 was a Phase 1 renal-ocular safety study in healthy volunteers. Because it was primarily a safety study and because it utilized the anticipated clinical regimen (ACR) of tafenoquine for malaria prophylaxis, it is also grouped with the prophylaxis studies for the purposes of the safety evaluation.

Table 6: Phase 1 Drug-Drug Interaction Studies in Healthy Volunteers

Study No.	Study Design[a]	Study Objectives	TQ Doses Administered	Population
015	O, SS	Study PK and DDI of tafenoquine +desipramine	400 mg daily x 3 days	34; 20M/14F
040	O, TP, NR, C	Study PK and DDI of tafenoquine +midazolam, flurbiprofen, caffeine	400 mg daily x 3 days	28; 18M/10F

[a]O=Open-label; SS=Single sequence; TP=Two-period; NR=Nonrandomized; C=Crossover; DDI = Drug-drug interaction; PK=pharmacokinetics; M=male; F=female.

Table 7: Phase 1 Malaria Challenge Studies in Healthy Volunteers

Study No.	Study Design[a]	Study Objectives	TQ Doses Administered	Population
Single-Dose Studies				
053 (Brueckner-1998b)	R, DB, PC	Determine prophylactic efficacy of TQ against *P falciparum* malaria in non-immune fasted subjects when given prior to mosquito inoculation	600 mg	N=6; 4M/2F
Multiple-Dose Studies				
054	R, DB, PC	Determine whether TQ was prophylactic against *P falciparum* malaria Gather PK (TQ co-administered with food) and safety data.	600 mg daily x 2 days, then 300 mg weekly x 4 weeks or 600 mg daily x 2 days, then 300 mg one week later	N=10; 10M/0F
TQ-2016-02	R, DB, PC	Evaluate the prophylactic activity of TQ against challenge with *P falciparum* asexual blood stage parasites in non-immune participants; characterize the exposure-response relationship for TQ; and provide safety and tolerability data for TQ in a controlled disease-like setting.	200 mg daily x 3 days, then 200 mg one week later	N=16; 6M/10F

[a]RCT=Randomized; DB=Double-blind; PC=Placebo-controlled; TQ=tafenoquine; M=male; F=female.

Table 8: Malaria Prophylaxis Studies (Phase 2 and 3)

Study No.	Study Design[a]	Study Objectives	TQ Doses Administered	Population
006 (Lell-2000)	R, DB, PC	Malaria prevention in semi-immune subjects of Lamaréné, Gabon (highly endemic *Pf)*	25, 50, 100 or 200mg daily x 3 days	N=415; 194M/221F
030	R, DB, PC, AC (mefloquine)	Prevention of malaria in semi-immune subjects of Nyanza Province, Kenya (area holoendemic for *Pf*)	200 daily x 3 days then 200 mg weekly for 24 weeks	N=300; 195M/105F
033 (Charles-2007, Nasveld-2002a, Nasveld-2010)	R, DB, AC (mefloquine)	Prevention of malaria in non-immune members of the Australian Defense Force (ADF) deployed to Bobanaro District, Timor Leste (area mesoendemic for *Pf* and *Pv*)	200 mg daily x 3 days, then 200 mg weekly throughout deployment	N=654; 632M/22F
043 (Shanks-2001)	R, DB, PC, PG	Determine the chemosuppressive effectiveness of weekly regimens of TQ in preventing *falciparum* parasitemia compared with placebo in semi-immune Kenyan subjects	400 mg daily x 3days or 200 mg daily x 3days, then 200mg weekly for 10-15 weeks or 400 mg daily x 3days, then 400 mg weekly for 10-25 weeks	TQ groups 174; 109M/65F
044 (Kocisko-2000, Edstein-2001, Edstein-2003, Walsh-2004a)	R, DB, PC	Determine the efficacy of monthly doses of TQ vs. placebo in the chemoprophylaxis of multi-drug resistant *Pf* and *Pv* in Thailand	400 mg daily x 3d, then 400 mg monthly	TQ n=104 Placebo n=101
045 (Hale-2003)	R, DB, PC, AC (mefloquine)	Determine the chemosuppressive efficacy of weekly TQ (25 to 200 mg) in preventing *falciparum* parasitemia compared to placebo and to mefloquine in semi-immune adults living in the Kassena-Nankana district of Northern Ghana. Establish the minimum effective prophylactic dose of weekly TQ. Assess TQ tolerability.	25 mg daily x 3days, then 25 mg weekly for 12 weeks; or 50 mg daily x 3days, then 50 mg weekly for 12 weeks; or 100 mg daily x 3days, then 100 mg weekly for 12 weeks; or 200 mg daily x 3days, then 200 mg weekly for 12 weeks	All Groups n=509: TQ Groups n=369; 238M/131F

Table 8: Malaria Prophylaxis Studies (Phase 2 and 3) (Continued)

Study No.	Study Design[a]	Study Objectives	TQ Doses Administered	Population
049 Post-exposure Prophylaxis (Nasveld-2002b, Nasveld-2005, Edstein-2007, Elmes-2008)	O, R, PG, AC (primaquine)	Compare the effectiveness and tolerability of TQ with PQ in preventing *Pv* malaria in non-immune ADF after leaving malarious areas of Papua New Guinea and East Timor.	200 mg daily x 3 days or 200 mg twice daily x 3 days or 400 mg daily x 3 days	N=1512; 1431M/81F

[a]R=Randomized; DB=Double-blind; PC=Placebo Controlled; AC=Active Comparator; PG=Parallel Group; O=Open label; TQ=tafenoquine; M=male; F=female.

Table 9: *P vivax* Treatment Studies (Phase 2)

Study No.	Study Design[a]	Study Objectives	TQ Doses Administered	Population
047 (Walsh-1999, Walsh-2004b)	R, O, NC (CQ)	Determine efficacy of various dosing regimens of TQ when combined with CQ in preventing relapse of *P vivax* malaria in Thailand. Safety and PK of TQ in normal and infected subjects.	500 mg once or 500 mg x 3d, repeated 1 week later or 300 mg daily x 7d	Part 1: N=79; 38M/41F Part 2: N= 135; 76M/59F
058	R, DB, AC,	Assess whether treatment with TQ alone could radically cure *P vivax* malaria in adults.	400 mg daily x 3 days	N= 70; 57M/13F

[a]R=Randomized; O=Open label; DB=Double blind; NC=Negative control; CQ=Chloroquine; AC=Active control; TQ=tafenoquine; M=male; F=female.

Aside from the studies listed in the tables above, 3 additional studies were conducted but were not included in the larger safety analyses. These were Study 046 (an open label compassionate use treatment study) and 2 studies with small enrollments that were terminated early (Studies 001 and 036).

Also, 5 additional clinical trials were conducted by GSK utilizing tafenoquine. No safety data is available for these 5 trials in the Sponsor's database; however, limited safety information has been provided in the various literature publications based on these trials (Table 10).

Table 10: Safety Information Available from Publications of GSK Clinical Trials of Tafenoquine

Study No. and Study Design	Doses Administered	Study Population	Study Findings (Publication)
TAF 106491 Phase 1, double-blind, randomized, parallel-group study	Chloroquine (CQ) alone 600 mg on Days 1–2, and 300 mg on Day 3 Tafenoquine (TQ) alone 450 mg on Days 2 and 3 CQ + TQ CQ 600 mg on Day1; CQ 600 mg + TQ 450 mg on Day 2; CQ 300 mg + TQ 450 mg on Day 3	Healthy subjects, 18–55 years old, without documented G6PD deficiency N=70, 37M/33 F	Blood samples for PK and PD analyses were collected for 56 days. There was no clinically significant PK interaction with concomitant administration of TQ and CQ. Safety data, including electrocardiograms, were collected for 56 days. Co-administration of TQ and CQ was generally well tolerated, with GI events being the most common drug-related event. (Miller-2010, Miller-2013)
TAF115051 (Follow-on study of TAF106491) Blinded pharmacogenetic analysis (DNA sequencing of the G6PD gene)	None	2 healthy females who experienced hemoglobin decreases > 2.5 g/dL after TQ dosing in Study TAF106491 and who were not detected by the assay used to exclude G6PD-deficient subjects from that study	G6PD sequencing in the two subjects identified known functional G6PD variants which had previously been associated with G6PD deficiency. Therefore, G6PD deficiency was a plausible explanation for the observed hemoglobin decreases. (GSK-2012)
TAF110027 Phase 1, Open-label, randomized, dose escalation study	Single dose of TQ 100 mg, 200 mg, or 300 mg	51 healthy females with moderate G6PD deficiency + normal controls	A dose response for hemolysis was noted for G6PD deficient females, precluding 600 mg as a dose for further development. (Rueangweerayut-2012)
TAF114582 Phase 1, single-blind, randomized, parallel-group, placebo- and positive-controlled, multiple-dose study	5 study Groups: TQ 300 mg single dose, TQ 600mg single dose, TQ 400 mg OD for 3 days, Moxifloxacin 400 mg single dose (positive control), Placebo	260; 181M/79 F (18-63 y)	There was no effect on QTcF prolongation after a single TQ dose of 300 mg or 600 mg. However, a mean 6.6 msec prolongation of QTcF compared to Placebo was seen at 72 hours post final dose in the group that received a total TQ dose of 1200 mg over 3 days (i.e., TQ 400 mg x 3 days). (Green-2014)

Table 10: Safety Information Available from Publications of GSK Clinical Trials of Tafenoquine (Continued)

Study No. and Study Design	Doses Administered	Study Population	Study Findings (Publication)
TAF112582 Phase 2b, randomized, placebo controlled, parallel group, double-blind, double dummy dose ranging study	All subjects pre-treated with CQ X 3 days. Investigational products Single dose TQ 50 mg; Single dose TQ 100 mg; Single dose TQ 300 mg; Single dose TQ 600 mg; PQ 15 mg x 14 days: CQ alone (placebo)	329 243M/86F age≥16	All doses were well tolerated. The 300 mg dose was selected for Phase 3 based on hemolytic potential of 600 mg in G6PD-deficient subjects. (Llanos-Cuentas-2014, Tenero-2015, St.Jean-2016)

4.3. Tafenoquine Regulatory History

60P filed a 505(b)(1) new drug application (NDA) for tafenoquine for the prevention of malaria in 2017. Selected correspondence relevant to the regulatory history of ARAKODA™ (tafenoquine) tablets (NDA 210607) is outlined in Table 11.

Table 11: Tafenoquine Regulatory History: Information Addressing FDA's Agreements/Recommendations

Type of Correspondence	Sponsor (at the time)	Agency Agreements/Recommendations
Type B Meeting Minutes 17Dec2004	USAMMDA	FDA recommendations regarding acceptable study designs for trials to support registration
Pre-NDA Meeting Comments 10July2017	60P	Issues discussed included the proposed structure and content of the NDA.
ARAKODA receives Fast-Track Designation	60P	Priority review is granted.

In Type B Meeting Minutes, 17Dec2004, FDA indicated that it would accept data from Study 033 to support registration of tafenoquine. Also, FDA suggested "conducting either a treatment study to examine asymptomatic parasitemia in an endemic area or a malaria challenge study."

5. Clinical Pharmacology

5.1. Minimum Trough Plasma Tafenoquine Concentrations Needed for Efficacy

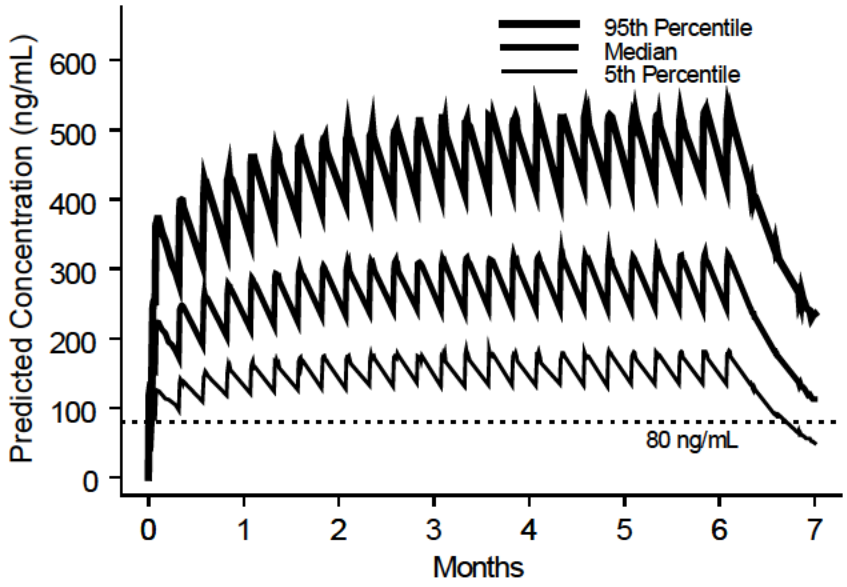
Studies conducted in non-immune persons, which is a population similar to the population for which prophylaxis is intended, showed that symptomatic breakthrough of malaria occurred when tafenoquine plasma concentrations were < 50 ng/mL. In Study 053, one subject became parasitemic on Study Day 31 with onset of clinical symptoms beginning on Study Day 28. The subject had a peak tafenoquine concentration of 182 ng/mL which declined to 48 and 18 ng/mL at 763 and 1075 hours (31 and 44 days post drug administration). In Study 044, three symptomatic breakthroughs occurred 6 to 12 weeks following prophylaxis. Two participants had *Pv* relapse with tafenoquine plasma concentrations between 20 and 21 ng/mL, and one participant had *Pf* relapse with tafenoquine concentration 38 ng/mL (Edstein-2003). Furthermore, one participant had *Pv* relapse during the prophylaxis phase, with tafenoquine concentration of 40 ng/mL (the participant was found to have been non-compliant with investigational product). This level was one-third of the mean trough level of soldiers who were compliant with investigational product and did not contract malaria during the same period of the study. Measured trough concentrations exceeded 55 ng/mL amongst a sample of the 96 individuals who completed a 6 month course of investigational product and who did not contract malaria despite the placebo attack rate of 30% (Edstein-2003; Walsh-2004a). Consequently, a precautionary plasma concentration of 80 ng/mL was selected as the minimum target trough value for prevention of symptomatic malaria development in non-immune individuals (Edstein-2003). This plasma level is achieved when individuals are dosed according to the recommended regimen of 200 mg per day x 3 days followed by 200 mg weekly.

5.2. Biopharmaceutics Studies Summary

Single dose, dose ranging, and multiple dose PK studies, as well as population PK studies, have been performed for tafenoquine and provide a well characterized PK profile.

The population PK analysis was conducted consolidating clinical PK data from Studies 001, 002, 003, 004, 005, 014, 015, 033, 044 and 058. Of particular interest is the plasma concentration-time profile for the ACR (Figure 5). The population PK model predicts that for the anticipated clinical regimen of 200 mg per day x 3 days followed by 200 mg weekly, trough levels are >80 ng/mL in 95% of individuals.

Figure 5: Plasma Concentration-Time Profile Following Tafenoquine 200 mg Loading and Weekly Administration



Conclusions from the individual and population-PK studies are:

1. The mean terminal half-life of tafenoquine ranges from 13 to 19 days.
2. PK Parameters AUC and C_{max} are directly proportional to dose.
3. Tafenoquine exposure is essentially identical on a mg drug per kg body weight basis for males and females.
4. Extent of absorption increases an average of 41% and 31% based on AUC_{∞} and C_{max}, respectively, when administered with food. However, PK modeling of the ACR revealed similar exposure versus time curves after multiple doses.
5. Tafenoquine accumulates with repeated dosing: weekly dosing results in an accumulation ratio of 4.
6. Minimum trough concentrations $\geq$ 80 ng/mL correlate with efficacy (see Section 5.1).
7. There are no significant effects on the metabolism of cytochrome P450 substrates including CYP2D6, CYP2C9, CYP3A4 and CYP1A2 in drug interaction studies.

6. Microbiology

6.1. Postulated Mechanism of Action of Tafenoquine

The precise mechanism of action of tafenoquine is not known.

6.2. Antimalarial Activities of Tafenoquine

For tafenoquine, primary pharmacology refers to the efficacy against any stage of any *Plasmodium* species. The following types of antimalarial activities have been observed for tafenoquine:

- causal prophylactic (activity against developing liver stages);
- blood schizonticidal (activity against asexual blood stages);
- anti-hypnozoite (activity against dormant liver stages);
- anti-gametocyte (activity against blood sexual stages); and
- anti-sporozoite (activity against the stage injected by the mosquito into the human host).

Non-clinical testing of tafenoquine has focused on evaluating activity against *Pf* and *Pv*, examining the drug's causal and suppressive prophylactic activity *in vivo* and its ability to achieve radial cure. In nonclinical studies, tafenoquine has demonstrated both causal and suppressive prophylactic effects in mice and monkeys, as well as radical curative effects in monkeys.

6.2.1. In vitro Pharmacology

In vitro data supporting the anti-malarial efficacy of tafenoquine against asexual blood stages of *Pf* include the following findings:

- When tafenoquine and 12 other 8-aminoquinolines were screened against seven *Pf* clones and isolates (NIG59, NIG9171, D6, W2, TM91C235, WR75-235 and TM91C40), tafenoquine was more effective than primaquine against all isolates with an average IC_{50} approximately 3-fold lower than primaquine (Vennerstrom-1999).
- In studies by Pradines (2006), tafenoquine was up to 2-fold more potent than primaquine but less potent than chloroquine and mefloquine against *Pf* isolates from Djibouti (East Africa), Gabon (Central Africa) and Senegal (West Africa).
- In studies by Gorka (2013), the IC_{50} of tafenoquine and primaquine were comparable (2189.9 nM and 1990 nM, respectively) against the *Pf* clone HB3 (Honduras, chloroquine-sensitive). Against the *Pf* clone 2Dd2 (Indochina, chloroquine-resistant), the IC_{50} of tafenoquine (2092 nM) was lower than the IC_{50} of primaquine (4695 nM).
- Susceptibility testing of 160 Ghanaian *Pf* clinical isolates showed a pooled national IC_{50} value of 93.6 nM for tafenoquine, suggesting high sensitivity to the drug (Quashie-2013).

- Tafenoquine was active against highly drug-resistant forms of *Pf* (i.e., isolates resistant to chloroquine and antifolates and with reduced sensitivity to mefloquine and quinine) (Ramharter-2002).

6.2.2. In vivo Studies in Animal Models

In vivo studies demonstrate that tafenoquine is able to clear liver stage infection (causal prophylactic action) and blood stage infections (schizonticidal or suppressive action) in mice (*P. berghei, P. yoelli*) and monkeys (*P. cynomolgi, Pv* and *Pf* strains). A single dose of ≥16 mg/kg [human equivalent dose (HED) ≥1.3 mg/kg] cleared established murine *P. berghei* parasitemia, whereas a single oral or subcutaneous dose of at least 8 mg/kg tafenoquine to the mouse [HED 0.65 mg/kg] protected against liver infection with sporozoites of *P. berghei*. Similarly in the monkey, 3 doses of at least 0.8 mg/kg (total dose 2.4 mg/kg; HED of 0.77 mg/kg) in the rhesus monkey or 1.0 mg/kg for 3 days (total dose 3.0 mg/kg; HED 0.96 mg/kg) in the *Aotus trivirgatus* monkey cleared established *Pv* blood parasitemia. A slightly faster clearance of *Pv* was seen at 3.2 mg/kg given for 3 days (total 9.6 mg/kg; HED 3.1 mg/kg) and no monkey showed recrudescence. Three doses of tafenoquine at ≥ 0.3 mg/kg given 3 days (total dose ≥ 0.9 mg/kg; HED 0.3 mg/kg) prior to infection challenge, prophylactically protected the liver of rhesus monkeys from infection with *P. cynomolgi*.

7. Nonclinical Toxicology

The toxicity of tafenoquine was explored following oral administration to the mouse, rat and dog for up to 13, 26 or 52 weeks respectively. The principle findings seen in repeat dose toxicology studies performed in mice, rats and dogs with tafenoquine for up to 3 months in mice (0.1-3.0 mg/kg/day), 6 months in rats (0.5-9.0 mg/kg/day), and 1 year in dogs (0.1-4.0 mg/kg/day) included a significant increase in methemoglobin; the appearance of blue tongue or gums in the dog; blue skin/ears and pallor in rodents; a mild anemia followed by compensatory erythropoiesis; increased deposition of brown/hemosiderin pigment in a number of tissues; bone marrow hyperplasia in rats and dogs; increased spleen weight (all species) and splenic hyperplasia, as well as splenic congestion and pooling of red blood cells in rats and dogs; an increase in liver enzymes and pigment deposits (all species), and inflammation in the dog; increased adrenal weight, pigmentation and congestion in the rat; kidney changes in rats and mice namely tubular nephropathy and pigment deposits; and phospholipidosis-related changes in the lungs of mice, rats and dogs. These effects were dose-related in incidence and severity.

Changes in the kidney of rats and mice, namely proximal tubular necrosis and dilation, were considered a consequence of hemoglobin resorption. No significant renal toxicity was seen in the dog despite pigment deposition in renal tissue noted after 52-weeks' dosing.

Effects in animals were generally seen at doses which are subclinical, relative to the clinical dose on a mg/kg basis, as animals appear sensitive to the effects of tafenoquine. The majority of changes were reversible or partially reversible following off-dose periods of 2 or 13 weeks.

Histopathological examinations at necropsy in the above species incorporated the brain and spinal cord. The central nervous system was not found to be a target organ for tafenoquine toxicity.

Summary: The nonclinical toxicity data has demonstrated the sensitivity of all toxicology species to the effects of tafenoquine, although without the normal margin of exposure between plasma (or dose) levels causing toxicity in animals and those intended for prophylactic use in humans. All toxicities observed in animals have been shown to be dose- and duration-dependent and fully or partially reversible.

7.1. Assessment of Neurobehavioral Toxicity in Rats and Monkeys

To assess tafenoquine's potential for neurobehavioral toxicity in an animal model, a Functional Observational Battery (FOB) was conducted in rats ("Irwin Study") (Dow-2017).

Rats received either control solution or tafenoquine (125 mg/kg, 250 mg/kg, or 500 mg/kg) administered once orally (Dow-2017). An FOB was performed on neurobehavioral group animals at pre-dosing (Day -1) and at 0.5, 3, 6, 24 and 48 hours after dosing. Animals from the neurobehavioral groups were necropsied at 72 hours or 168 hours after dosing, and Hematoxylin & Eosin (H&E) and silver-stained sections from the brains of control and high-dose rats were evaluated. Also, blood samples for tafenoquine toxicokinetics were collected at 1, 3, 5, 8, 24, 48, 72 and 168 hours after dosing.

Findings:

- Based on C_{max} , tafenoquine exposure (mg/kg) showed rat:human ratio of 1:2
- At 6-times human exposure, there were no abnormalities in the FOB (24 or 48 hrs post-dose)
- There were no drug-related findings in the brain sections of rats dosed with 500 mg/kg tafenoquine compared to controls (i.e., no neurodegeneration, no effect on axon morphology, no effect on the nucleus gracilis).

In contrast, functional and histopathologic abnormalities were reported when a FOB was performed with mefloquine (Dow-2006). Brain histopathology showed degenerating fibers in the nucleus gracilis and to a lesser extent in the nucleus cuneatus and solitary tract after mefloquine exposure.

7.2. Assessment of Neurotoxicity in Rhesus Monkeys

Table 12 presents a summary of the clinical findings observed in rhesus monkeys when tafenoquine was administered at doses ranging from 1.8-48 mg/kg. Even at the highest dose administered (48 mg/kg), which was lethal to 50% of the animals tested, no specific neurologic signs were observed and no abnormal postmortem findings were identified in the brain. Limited exposure (Cmax) data are available for some doses from Dow (2011) and NDA 210607, and these are also presented in Table 12. Therapeutic indices, calculated relative to the minimum effective dose for radical cure in monkeys (1.8 mg/kg, Dow-2011) based on dose administered or exposure are also presented in Table 12. Given that no neurotoxicity was observed even at the lethal dose, we can say that the neurologic therapeutic indices of tafenoquine, whether calculated based on dose (>27) or exposure (>11) are comparable to or better than primaquine.

Table 12: Summary of Clinical Signs Observed at Increasing Tafenoquine Doses in Rhesus Monkeys

Cumulative Dose[a] (mg/kg)	Cmax (ng/mL)	TI (dose) [b]	TI (exposure)[c]	N	Source	Neurological Signs and Other Safety Observations
1.8[d]	~50	1	1	35	Dow-2011	No specific neurologic signs were noted in any of the academic studies. The Dow (2011) and Ditusa (2014) studies were supervised by a board-certified veterinarian and neurologic signs would have been recorded if observed. The study in the NDA was a toxicokinetic study in which clinical observations were made for 4h following each dose – no clinical (including specific neurologic signs) were noted. Methemoglobin increases of 5% reported at 18 mg/kg (from Dow-2011).
7	ND	3.9	NA	23	Puri and Dutta-2003	
12	124	6.7	2.5	11	Dow-2011; NDA 210607	
18	ND	10	NA	4	Dow-2011; Ditusa-2014	
22.1	ND	12	NA	10	Puri and Dutta-2003	
24	284	13	5.7	3	NDA 210607	One animal vomited. No neurologic signs reported. Methemoglobin elevated
48 (Non-Lethal)	333	27	6.7	2	NDA 210607	None. Methemoglobin elevated. No neurologic signs reported.
48 (Lethal)	551	27	11	24	NDA 210607	Clinical signs included listlessness, vomiting, depression and poor appetite in two animals. Two animals died. Methemoglobin elevated. No specific neurologic signs observed. Liver and kidney necrosis observed at necropsy. The brain of one animal was examined post mortem – No abnormal findings were reported.

[a] Cumulative dose over 1-7 days alone or in combination with other antimalarials.
[b] TI (dose) = Therapeutic Index (Dose) = Dose administered/curative dose of 1.8 mg/kg.
[c] TI (exposure) = Therapeutic Index (Exposure) = Cmax at dose administered/Cmax at curative dose.
[d] Dose curing 95% of *P. cynomolgi* infections in combination with blood schizonticidal drugs.

Tafenoquine is an 8-aminoquinoline, and older studies performed outside of the tafenoquine development program have shown that clinical signs of neurotoxicity can occur when the 8-aminoquinolines plasmocid, pentaquine, or pamaquine are administered to monkeys (Table 13). No such signs were observed with primaquine, the 8-aminoquinoline most closely related to tafenoquine.

Table 13: Neurotoxicity of Selected 8-Aminoquinolines in Monkeys and Humans

8-Aminoquinoline	TI Monkeys[a]	TI Humans[b]	Clinical Neurologic Signs in Humans or Monkeys Related to Brain Lesions	Onset of Clinical Signs Relative to Dosing (Days)	Dose-Limiting Toxicity in Humans
Plasmocid (Schmidt-1948, Schmidt-1949)	≤1	≤1	Nystagmus, loss of pupillary reflexes, motor coordination and equilibrium, death	≤2	Neurotoxicity
Pentaquine (Schmidt-1951, Craige-1948)	≤3.7	2	Syncope, persistent hypotension without other cause, erectile dysfunction, death	Humans <28 Monkeys <12	GI Distress
Pamaquine (Schmidt-1951, Loken-1949)	9	8	Paralyzed palate, death	≤7	GI Distress
Primaquine (Schmidt-1951)	14	>16	No PC, PT, or PM-like clinical signs reported in humans after 60 years use of therapeutic dose or in clinical trials at 16x labeled dose (Hill-2006; Clayman-1952; Recht-2014)	NA	GI Distress

[a] Calculated by dividing the highest cumulative dose not causing significant loss of neurons or clinical neurologic signs (related to brain lesions) by the minimum effective dose for radical cure of *P. cynomolgi* from Schmidt (1983).

[b] Calculated by dividing the dose associated with brain lesions or clinical neurologic signs related to brain lesions by the therapeutic dosed used for radical cure of *P. vivax* malaria.

The Sponsor's database was searched to identify tafenoquine-treated subjects who had reported AEs that were similar to the clinical signs of brain lesions that were seen in monkeys exposed to plasmocid, pentaquine, or pamaquine. Only rare cases (0.2% or less) of syncope, coordination problems, and erectile dysfunction were reported (Table 14).

In the Tafenoquine ACR group, 2 tafenoquine-treated subjects in Study 033 were found to have abnormal coordination (Table 14). In both cases, the abnormality was first documented at the very beginning of the study (Day 0), suggesting that this AE might have been influenced by pre-existing factors. In one subject, an important confounding factor was the subject's chronic use of loratadine to treat allergies, which began 7 years prior to study entry and continued throughout the study. Even at a typical 10 mg dose, loratadine can cause motor control side effects (Kavanagh-2012), and these effects can become even more apparent when the drug is taken on a chronic basis (Baumann-Birkbeck-2014). The second subject had a history of spinal surgery.

Also in the Tafenoquine ACR group, two single episodes of syncope were reported (Table 14), one in Study 033 and one in Study 057. Both were mild, isolated episodes that were considered unrelated to tafenoquine. One case was "treated" with acetaminophen.

Table 14: Clinical Signs Associated with Brain Lesions in Monkeys Exposed to 8-Aminoquinolines (Plasmocid, Pentaquine, Pamaquine): Corresponding Incidence in Human Subjects during Tafenoquine Clinical Trials

	Clinical Signs Associated with Brain Lesions in Monkeys	MedDRA PT/ Code	Incidence at Tafenoquine Doses Administered in Clinical Trials, n (%)			
			Tafenoquine 200 mg OD x 3 days (n=491)	Tafenoquine 400 mg OD x 3 days (n=713)	Tafenoquine ACR (n=825)	Placebo (n=396)
Plasmocid						
Nervous System Disorders	Nystagmus	Nystagmus/ (b) (6)	0	0	0	0
	Loss of motor coordination	Coordination abnormal/ (b) (6)	0	0	2 (0.2%)	0
	Loss of equilibrium	Balance disorder/ (b) (6)	0	0	0	0
Eye Disorders	Loss of pupillary reflexes	Pupillary reflex impaired/ (b) (6)	0	0	0	
General Disorders and Administration Site Conditions	Death	Death/ (b) (6)	0	0	0	0

Table 14: Clinical Signs Associated with Brain Lesions in Monkeys Exposed to 8-Aminoquinolines (Plasmocid, Pentaquine, Pamaquine): Corresponding Incidence in Human Subjects during Tafenoquine Clinical Trials (Continued)

	Clinical Signs Associated with Brain Lesions in Monkeys	MedDRA PT/ Code	Incidence at Tafenoquine Doses Administered in Clinical Trials, n (%)			
			Tafenoquine 200 mg OD x 3 days (n=491)	Tafenoquine 400 mg OD x 3 days (n=713)	Tafenoquine ACR (n=825)	Placebo (n=396)
Pentaquine						
Nervous System Disorders	Syncope	Syncope/ (b) (6)	0	0	2 (0.2%)	0
Vascular Disorders	Persistent hypotension	Hypotension/ (b) (6)	0	1 (0.1%)	0	0
Reproductive System and Breast Disorders	Erectile dysfunction	Erectile Dysfunction/ (b) (6)	0	0	1 (0.1%)	1 (0.3%)
Pamaquine						
Nervous System Disorders	Paralyzed palate	Areflexia/ (b) (6)	0	0	0	0

7.3. Nonclinical Assessment of Cardiotoxicity

In vitro studies with tafenoquine suggested potential effect on heart conductance as it inhibited hERG tail current in a dose-dependent manner (IC_{50} 0.51 μg/mL) and at 100-fold higher concentrations (46.4 μg/mL) caused a non-specific effect on the conduction through heart Purkinje fibres of the dog. In vivo, tafenoquine caused systemic vasodilation when given by intravenous (IV) infusion to anaesthetized dogs but at oral doses up to 16 mg/kg had no cardiovascular effect in the conscious dog. The dog $AUC_{0\text{-}1week}$ of 116 μg.hr/mL following 16 mg/kg is approximately 5-times higher than the clinical AUC following a clinical dose of 600 mg. Thus the cardiovascular liability of tafenoquine is expected to be low.

8. Evaluation of Efficacy

8.1. Definition of Endpoints

The primary efficacy endpoint in all clinical trials was confirmed parasitemia. Confirmed parasitemia signifies that the presence of parasites in the blood smears had to be confirmed by two independent microscopists.

8.2. Derivation of the Recommended Prophylaxis Regimen

The recommended prophylaxis regimen (also the investigated ACR) consists of a loading dose of 200 mg per day x 3 days followed by a maintenance dose of 200 mg weekly.

Phase 2 studies that preceded the key trials and that together led to the ultimate generation of the recommended prophylaxis regimen were studies 053 and 054, 006, 044, and 043.

Studies 053 and 054 were small challenge studies that provided useful PK data in the sense that it was possible to correlate parasitological failure with trough drug levels.

Study 006 investigated different loading doses for semi-immunes in Africa. Loading doses using dose levels of 50 mg to 200 mg were equally protective for 7 weeks after dosing. This study suggested that for prolonged prophylaxis, a loading dose would have to be supplemented with maintenance doses.

Study 044 investigated a complete prophylactic regimen (loading dose followed by maintenance doses) with however higher dose levels (400 mg) than the clinical regimen ultimately chosen. One individual failed prophylaxis and trough levels for this individual were recorded.

Study 043 was the study from which the ultimate prophylactic regimen was first derived. In study 043, complete prophylactic regimens (loading dose followed by maintenance dose) based on 200 mg per dose or 400 mg per dose were evaluated. The 2 regimens were equally effective: protective efficacy of 88% for the 200 mg based regimen vs. protective efficacy of 90% for the 400 mg based regimen. Since tolerance data had by then showed that the 200 mg based regimen was better tolerated than the 400 mg based regimen, the 200 mg based regimen was recognized as appropriate for the proposed prophylactic regimen since it was the highest dose level that was well-tolerated.

In addition to having the highest dose-level that was well-tolerated, the recommended prophylaxis regimen was found to generate appropriate plasma concentrations in non-immune persons, the population for which prophylaxis is intended. As discussed in Section 5 above, a precautionary plasma concentration of 80 ng/mL was selected as the minimum target trough value for prevention of symptomatic malaria development in non-immune individuals (Edstein-2003). The population PK analysis (Section 5) showed that the recommended prophylaxis regimen was an appropriate regimen to achieve this targeted value, since trough levels are >80 ng/ml in 95% of individuals.

8.3. Pivotal/Key Prophylaxis Trials: Controlled Clinical Studies Pertinent to the Clinical Indication

Malaria prophylaxis includes two sequential phases: “Prevention of Malaria while in the endemic region” and “Prevention of malaria after leaving the endemic region (post-exposure prophylaxis).” The Applicant believes that the present dossier is unique for malaria prophylactic regimens in that it addresses both phases of malaria prophylaxis.

The Applicant’s designation of which trials should be considered as key/pivotal for efficacy is based on FDA 2007 general Malaria Guidance (FDA-2007), FDA tafenoquine-specific recommendations of 2004 (Section 4.3), and discussions related to the July 2017 pre-NDA meeting (Section 4.3). Briefly, the comparator-controlled Study 033 is considered pivotal, with support from 1 or more studies with each of the following designs: a placebo-controlled prophylactic study in semi-immune subjects (e.g., Studies 043, and 045); a placebo-controlled prophylactic study in non-immune subjects in a human challenge model (Study TQ-2016-02); and by a treatment study (Study 058). Therefore, for “Prevention of Malaria while in the endemic region”, the Applicant's pivotal/key efficacy trials consist of 5 studies collectively designated as “Controlled Clinical Studies Pertinent to the Clinical Indication”. These studies are:

- Study 033: Active comparator-controlled prophylactic trial in non-immune subjects. This was a randomized, double-blind, comparative study to evaluate the anticipated clinical regimen of tafenoquine in comparison with mefloquine for the prophylaxis of *Pf* and *Pv* malaria in non-immune Australian soldiers deployed to East Timor (now Timor-Leste).
- Study 043: Placebo-controlled prophylactic trial in semi-immune subjects. This was a randomized, placebo-controlled comparison of different loading doses and “full prophylactic regimens” (i.e., loading dose followed by weekly or monthly dosing) for semi-immune subjects in Africa. One of the regimens was the anticipated clinical regimen.
- Study 045: Placebo controlled prophylactic trial in semi-immune subjects. This was a randomized, double-blind, placebo-controlled evaluation of tafenoquine compared to mefloquine for chemoprophylaxis of *Pf* in northern Ghana. One of the regimens was the anticipated clinical regimen.
- Study TQ-2016-02: Placebo-controlled prophylactic study against *Pf* in non-immune subjects in a human challenge model.
- Study 058: Treatment study of *Pv* in semi-immune subjects.

In Study 043, Study 045, Study 033, and study TQ-2016-02, tafenoquine-treated subjects received the anticipated clinical regimen proposed for malaria prevention. The anticipated clinical regimen (ACR) consists of a loading dose of tafenoquine 200 mg per day for 3 days, followed by tafenoquine 200 mg once per week for up to 24 weeks. In Study 058, patients received 400 mg per day for 3 days and were followed for cure. This 1200 mg-total-dose regimen results in the same cumulative dose as the anticipated clinical regimen being

administered for the 28-day period during which the primary efficacy endpoint (cure) was assessed.

In 2004 guidance (Section 4.3, FDA Type B Meeting Minutes, 17Dec2004), FDA advised that subjects should be enrolled from 2 or more distinct geographical regions. The above key trials address efficacy against both *Pf* and *Pv*, and exposure to *Pf* occurred both in African semi-immunes and in Southeast Asia/Oceania non-immunes and mixed immunes.

Phase 2/supporting studies that preceded and support the key trials listed above consist of the following:

- Studies 053 and 054: Prophylactic efficacy of single-dose (Study 053) and early multiple dose
- (Study 054) tafenoquine regimens in the human *Pf* challenge model;
- Study 006: Different loading doses for semi-immunes in Africa;
- Study 030: Placebo-controlled prophylactic trial in semi-immune subjects. This was a randomized, double-blind, placebo-controlled evaluation of tafenoquine compared to mefloquine for chemoprophylaxis of *Pf* in western Kenya. One of the tested regimens was the anticipated clinical regimen.
- Study 044: “Full prophylactic regimen” with a higher dose than the final clinical dose for non-immunes in Southeast Asia.

Taken together, the above studies led to the determination that tafenoquine 200 mg per day x 3 days followed by 200 mg weekly provides effective prophylaxis against malaria for subjects exposed to *Plasmodia* and support the proposed prophylactic regimen in the prescribing instructions.

Because parasites may emerge from the liver after the subject leaves the endemic region, a post-exposure regimen to prevent malaria after leaving the endemic region is also important. *Pf* and *Pv* liver forms emerge from the liver to enter the blood beginning at 6 to 7 days and continuing for as long as 23 days after sporozoite inoculation (Fairly-1945). Some *Pv* liver forms, however, become dormant hypnozoites and do not emerge for weeks (tropical strains) to many months or (temperate strains) years after liver infection (Baird-2011). Relapse is defined as recurrent *Pv* blood infection due to emergence of dormant liver forms into the blood. Evaluation of relapse prevention is relevant to the issue of how long to continue tafenoquine prophylaxis after an individual leaves the endemic region.

For “Prophylaxis of malaria after leaving the endemic region”, 5 relevant studies have been performed. These studies are:

- Study 033: After the malaria prevention phase of the study, tafenoquine was compared to primaquine for relapse prevention in non-immune subjects;
- Study 058: In addition to evaluating the treatment effect of tafenoquine against Pv already present in the blood, follow-up was extended to 120 days, thus assessing relapse in tafenoquine patients compared to primaquine patients up to that time;

- Study 047: Wide range of short tafenoquine regimens compared with primaquine for relapse prevention in non-immune subjects in Southeast Asia
- Study 049: Several short tafenoquine regimens were compared with primaquine for relapse prevention in Australian non-immune subjects; and
- Study 046: Full prophylactic regimen for relapse prevention in Australian non-immunes.

8.4. Demographics and Baseline Characteristics

The baseline characteristics of the populations utilized in the prophylactic field studies that comprise the tafenoquine dossier are summarized in Table 15. Males (3,232 subjects) predominated overall and in each study grouping; however, 771 total females also participated in these studies. The mean age of 29 years, mean weight of 69 kg, and mean BMI of 23 kg/mm^2 signifies a healthy young adult population. Subjects ranged in age from 12 years to 70 years. The populations were uniformly healthy upon entrance into the study without clinically significant abnormalities in entrance laboratory values and without clinically significant concomitant disease. Although pre-existing parasitemia was cleared with antimalarial drugs prior to institution of prophylaxis, subjects were not administered drugs with possible antimalarial activity during the prophylactic phase of the studies. The baseline health characteristics (lack of clinical malaria) in these field studies are representative of the general population who will utilize anti-malarial prophylaxis with tafenoquine. In addition, study subjects in Studies 044 and 033 had the mixed-or-non-immunity status characteristic of persons who also could undertake tafenoquine prophylaxis.

Table 15: Baseline Characteristics of Efficacy Study Subjects in Primary Analytic Populations

Baseline Characteristics[a]	**Prophylactic African Studies 006 / 043 / 045 / 030**	**Prophylactic SE Asia / Oceania Studies 044 / 033**	**All Field Prophylactic Studies Using Loading Plus Weekly Dosing 043 / 044 / 045 / 030 / 033**	***P vivax* Hypnozoite and Blood Stage Treatment Studies 046 / 047 / 049 / 058**	**All Field Efficacy Studies 006 / 043 / 030 / 044 / 033 / 047 / 049 / 058**
Gender					
Female, N (%)	594 (40.9)	21 (2.5)	394 (20.9)	156 (9.1)	771 (19.3)
Male, N (%)	857 (59.1)	824 (97.5)	1487 (79.1)	1551 (90.9)	3232 (80.7)
Age (Years)					
N	1451	845	1881	1707	4003
Mean (SD)	31.4 (14.8)	26.3 (6.31)	32.4 (12.1)	27.4 (6.77)	28.6 (10.6)
Range	12.0 – 70.0	18.0 – 51.0	14.0 – 70.0	16.0 – 58.0	12.0 – 70.0
Weight (kg)					
N	1447	844	1880	1704	3995
Mean (SD)	56.4 (9.34)	75.8 (14.2)	65.3 (15.1)	76.7 (13.5)	69.2 (15.7)
Range	32.0 – 97.0	45.0 – 135.0	33.0 – 135.0	36.5 – 140.0	32.0 – 140.0

Table 15: Baseline Characteristics of Efficacy Study Subjects in Primary Analytic Populations (Continued)

Baseline Characteristics[a]	Prophylactic African Studies 006 / 043 / 045 / 030	Prophylactic SE Asia / Oceania Studies 044 / 033	All Field Prophylactic Studies Using Loading Plus Weekly Dosing 043 / 044 / 045 / 030 / 033	*P vivax* Hypnozoite and Blood Stage Treatment Studies 046 / 047 / 049 / 058	All Field Efficacy Studies 006 / 043 / 030 / 044 / 033 / 047 / 049 / 058
Height (cm)					
N	1161	640	1388	1704	3505
Mean (SD)	166 (8.92)	178 (6.91)	172 (9.34)	177 (9.89)	173 (10.5)
Range	120.0 – 194.0	154.5 – 198.0	145.0 – 198.0	143.0 – 208.0	120.0 – 208.0
BMI					
N	1159	640	1388	1703	3502
Mean (SD)	20.0 (2.66)	25.6 (3.26)	22.4 (4.14)	24.4 (2.97)	23.2 (3.70)
Range	12.7 – 35.4	17.5 – 39.0	12.7 – 39.0	11.4 – 36.3	11.4 – 39.0

[a] The primary analytic populations for each study were: 006 – ITT known data set population; 043 – ITT population; 044 – ITT population; 045 – ITT population; 030 – mITT population; 033 – PP population; 047 – ITT population; 049 – ITT population; 058 – Per Protocol population.

8.5. Efficacy in Key Studies Supporting the Intended Use of the Product for Prophylaxis of Malaria in the Endemic Region

8.5.1. Phase 3 Prophylaxis Study (Study 033)

Design: This study compared tafenoquine with mefloquine for the prophylaxis of both *Pf* and *Pv* malaria in non-immune Australian soldiers deployed to East Timor (now Timor-Leste). The study was divided into 2 phases. The first, or prophylactic phase, consisted of a 26-week period during deployment where subjects received prophylactic study medication (tafenoquine 200 mg capsule or mefloquine 250 mg). At the end of the deployment to the malarious area and once the subjects had returned to barracks in Townsville, Australia, the subjects entered a 24-week relapse follow-up phase. During this follow-up phase, subjects who had been on mefloquine prophylaxis received 14-days of primaquine (15 mg bid) while subjects on tafenoquine prophylaxis received placebo capsules for 14 days.

Dosing:

- Prophylactic phase: full prophylactic regimens of tafenoquine (loading dose of 200 mg daily x 3 days followed by 200 mg weekly) vs. mefloquine (loading dose of 250 mg daily x 3 days followed by 200 mg weekly).
- Relapse follow-up phase: tafenoquine subjects received placebo. Mefloquine-treated subjects received a standard primaquine regimen (primaquine l 5mg bid for 14 days).

Demographics: In the ITT population, subjects were 97% male and 99% White, with 59% between 18 and 35 years of age.

Results: The primary efficacy endpoint was failure during the prophylactic phase, up to and including the first day of primaquine eradication medication. Failure ("prophylactic failure") was defined by parasitological and clinical criteria: a single microscopically-confirmed positive smear (any species) with concurrent clinical signs and symptoms consistent with malaria infection. Slides were read by 2 readers, and by a third microscopist in case of disagreement.

For the principal analysis, the prophylactic outcome for each treatment group during prophylactic treatment in summarized in Table 16 for the Per-Protocol (PP) population (defined as all randomized subjects who satisfied inclusion/exclusion criteria and subsequently adhered to the protocol), the pre-specified primary analytic population. All subjects were prophylactic successes during the prophylactic phase.

Table 16: Prophylactic Outcome Based on Clinical Malaria (All Species) During Prophylactic Treatment Phase (PP Population) for Study 033

Prophylactic Outcome	Treatment Group	
	Tafenoquine 200 mg[a] N = 462	**Mefloquine 250 mg[b] N = 153**
Number of Subjects	462	153
Prophylactic failure	0 (0%)	0 (0%)
Prophylactic Success	462 (100%)	153 (100%)
Treatment Difference (Tafenoquine – Mefloquine)	0%	

[a] Subjects received a loading dose of tafenoquine 200 mg per day for 3 days, followed by tafenoquine 200 mg once a week for the 26-week prophylactic phase. Subjects who entered the follow-up phase received placebo bid for 14 days.

[b] Subjects received a loading dose of mefloquine 250 mg per day for 3 days, followed by mefloquine 250 mg once a week for the 26-week prophylactic phase. Subjects who entered the follow-up phase received primaquine 15 mg bid for 14 days.

NB: Clinical malaria = single positive smear with concurrent symptoms of malaria.

During the study's relapse follow-up phase, there were 5 cases of malaria, with 4 occurring in the tafenoquine group and 1 in the mefloquine group. All were cases of *Pv* malaria. This equates to less than 1% of subjects being prophylactic failures at any time during the study, and there were no differences between the groups. There were no reports of mixed species malaria infections.

8.5.1.1. Study 033: Tafenoquine Noninferiority vs. Mefloquine

In a retrospective analysis of the Study 033 trial results, the all species malaria attack rate was estimated for the prophylactic phase of the study, which was defined as the period between administration of the first prophylactic dose and the first dose of post-deployment medication (Table 17, derived from Dow-2014). First, the *Pv* relapse rate post-prophylaxis was enlarged from 5 (see Section 8.5.1 above) to 8 by extending the period of follow-up from 6 months to 1 year, as is appropriate for temperate-strains of *Pv*. Then, the *Pv* attack rate during the prophylactic phase of the deployment was calculated from the observed *Pv* relapse rate during post-deployment and the estimated anti-relapse effectiveness (82%) of the investigational products determined from prior studies. Since *Pf* does not relapse, the *Pf* attack rate during the

prophylactic phase of the deployment was calculated from the ratio of *Pf* to *Pv* attack rates in prior studies (ratio = 0.146: Dow-2014). Finally, the estimated *Pv* plus *Pf* attack rate during the prophylactic phase of deployment was calculated from the sum of the 2 individual species estimated attack rates: 6.88% + 4.91% = 11.79%.

Table 17: Estimation of Malaria Attack (*Pv*, *Pf*, all species) during the Prophylactic Phase (12 month) of Study 033

Data[a]	Value[b]
Post deployment *Pv* relapse rate (%) amongst Study 033 subjects	1.23
Anti-relapse effectiveness (%) of primaquine	69.5
Anti-relapse efficacy (%) of tafenoquine	86.3
Anti-relapse efficacy of combined Study 033 post-exposure prophylaxis regimens	82.1
Pv attack rate (%) during prophylactic phase of Study 033	6.88
Ratio of *Pf* cases to *Pv* cases in concomitant malaria survey of East Timor resident population	0.714
Pf attack rate (%) during prophylactic phase of Study 033	4.91
All malaria attack rate (%) during prophylactic phase of Study 033	11.79

[a] Observed in Study 033, ADF deployment, assumed from literature or derived.
[b] Rounded after calculation.
Sources are provided in Dow-2014.

The PE of tafenoquine and mefloquine, with corresponding 95% CI, vs. this 11.79% calculated placebo attack rate were determined to be 100% (95% to 100%) and 100% (86% to 100%), respectively.

Discussion: In non-immunes, the full prophylactic regimen of tafenoquine had efficacy similar to that of the active comparator drug, mefloquine: No subject had parasitemia in either group over 6 months of prophylaxis. Historic control data indicate that 11.79% of subjects would have become infected (6.9% with *Pv*, 4.91% with *Pf*). As usual for non-inferiority calculations, "M1 [the margin between active control and placebo] is estimated based on the historical experience with the active control drug" [Non-Inferiority Trials to Establish Effectiveness 2016 (UCM 202140)] not on comparison between active control and placebo within the study. The report by Dow (2014) suggests that the historic control data would have been duplicated had a placebo group been entered in the present study, i.e., that the "constancy assumption" [UCM202140] holds.

For Study 033 failure rates in the prospectively defined primary analytic population (the per protocol population) were Tafenoquine 0/462 [95% CI (0%, 1%)] and Mefloquine 0/153 [95% CI (0%, 2.4%)], and the difference Tafenoquine - Mefloquine was 0% [95% CI (-2%, 1%)]. The CI for Tafenoquine and Mefloquine were computed using the Clopper-Pearson (1934) exact binomial confidence limits. The CI for the difference is computed without continuity correction (Newcombe-1998). The historical control is 11.79%. Even if we assume that the non-inferiority margin is 25% of the efficacy margin of 11.79% -- this is 11.79% - 0% -- then the non-inferiority margin would be 2.95%. The upper limit of the 95% CI of the difference between Tafenoquine and Mefloquine is 1% which is below the non-inferiority margin. We can conclude that Tafenoquine is non-inferior to Mefloquine.

8.5.2. Study 043

Design/Objective: PE of low and high full prophylactic tafenoquine regimens (loading plus weekly dosing) in preventing *Pf* parasitemia in African semi-immunes.

Dosing: Tafenoquine load-only (400 mg of tafenoquine for 3 days followed by placebo for up to 15 weeks); tafenoquine low dose full prophylactic regimen (200 mg of tafenoquine for 3 days followed by tafenoquine 200 mg weekly for 15 weeks); tafenoquine high dose full prophylactic regimen (400 mg tafenoquine for 3 days followed by tafenoquine 400 mg weekly for 15 weeks); or placebo (for 3 days and then weekly).

Demographics: Subjects were Africans semi-immune of approximately of equal gender and of mean age 32 years.

Results: The primary efficacy endpoint was confirmed parasitemia. The primary efficacy analytic endpoint, protective efficacy (PE) based on failure rates at the end of prophylaxis, was determined for the ITT population (defined as a subject who had supplied at least one blood smear for parasitemia assessment after starting weekly dosing). The incidence of confirmed parasitemia over the complete treatment period of 15 weeks and the PE of the treatment groups relative to placebo are summarized in Table 18.

Table 18: Protective Efficacy at End of Study 043 (Efficacy Population)

	Treatment Group[a]			
	Placebo N = 59	**Load-Only Tafenoquine 400 mg N = 54**	**Low Dose Tafenoquine 200 mg N = 53**	**High Dose Tafenoquine 400 mg N = 57**
Positive for Parasitemia[b]	54 (92%)	14 (26%)	6 (11%)	5 (9%)
PE (%)		71.7	87.6	90.4
95% CI		(57.0%, 82.5%)	(75.2%, 94.2%)	(79.2%, 95.9%)

[a] All Subjects were treated for 3 days with halofantrine 250 mg to clear any existing parasitemia. Subjects then received a loading dose of investigational product according to group assignment for 3 days, followed by the same treatment once-a-week for 15 weeks.

[b] Subjects with confirmed parasitemia in the period from the last loading dose to the end of the 15 week study, who had received all clearance and loading medication and at least one weekly dose of investigational product.

The rate of parasitemia (92%) in the placebo group was markedly higher than in the tafenoquine treatment groups. *Pf* accounted for all the cases of parasitemia except for a single case of *P malariae* (a subject in the tafenoquine load-only group). PE relative to placebo over the entire treatment period was lower in the tafenoquine load-only group (71.7%) compared to the low dose (87.6%) and high dose (90.4%) full prophylactic tafenoquine regimens.

8.5.3. Study 045

Design/Objective: The objectives of the study were to determine the PE of full prophylactic regimens (loading-plus-weekly) of tafenoquine between 25 and 200 mg each dose in preventing *Pf* parasitemia in African semi-immunes compared to placebo and secondarily to mefloquine. This design means that study 045 has both “Phase 2” and “Phase 3” features. The “Phase 2” feature was the comparison of each regimen between 25 mg and 200 mg to each other. The

"Phase 3" feature was comparison of the 200 mg regimen, the eventual anticipated clinical regimen, to both negative control (placebo) and to positive comparator (mefloquine).

Dosing: After treating existing parasitemia with quinine/doxycycline/primaquine during the "radical cure phase," subjects were randomized into 1 of 6 groups to receive full prophylactic regimens (3 days loading dose then weekly) of tafenoquine (25, 50, 100 or 200 mg each dose), mefloquine (250 mg each dose), or placebo.

Demographics: Subjects were all African semi-immune subjects, and approximately two thirds were male. Mean age was 37 years for males and 52 years for females.

Results: The primary efficacy endpoint was first occurrence of a blood smear positive for asexual stage *Pf* parasites. The full analysis dataset (the protocol specified primary analytic population) comprised data from all subjects who completed the radical cure phase successfully, were randomized to receive any of the investigational products, completed the loading period, received at least one dose of weekly prophylactic medication, and had at least one efficacy assessment.

The incidence of parasitemia (i.e., the proportion of subjects with at least one positive blood smear) and PE based on first positive blood smear during prophylaxis treatment are summarized in Table 19. In the placebo group, 91.5% of subjects had a positive smear within the 13 weeks of observation. In terms of the Phase 2 dose-ranging aspect of this trial: there appeared to be some protection offered by tafenoquine at a dose of 25 mg, but the greatest protection was afforded by the highest 3 doses of tafenoquine which all provided a PE of between 84.4% and 87.2%, similar to that of mefloquine (85.7%).

The time between first loading dose and the first positive smear is summarized in Table 20. In the placebo and low dose tafenoquine groups, a majority of subjects who developed positive smears did so within 6 weeks of starting investigational products. In terms of the Phase 3 nature of this trial, we note that for each of placebo, tafenoquine 200 mg, and mefloquine, the most frequent time to first positive smear was 3 – 6 weeks.

Table 19: Incidence of Parasitemia and Protective Efficacy for Study 045

Parasitemia	Treatment Group[a]					
	Placebo	Tafenoquine 25 mg	Tafenoquine 50 mg	Tafenoquine 100 mg	Tafenoquine 200 mg	Mefloquine 250 mg
Full Analysis Dataset						
Total No.	94	93	91	94	91	46
No. With Positive Smear	86	58	13	11	12	6
Incidence (%)	91.5	62.4	14.3	11.7	13.2	13.0
PE (%)	–	31.8	84.4	87.2	85.6	85.7
95% CI for PE	–	(20.2%, 43.4%)	(74.8%, 90.7%)	(78.3%, 92.7%)	(76.2%, 91.6%)	(71.9%, 93.3%)

[a] All subjects were treated with presumptive eradication therapy (quinine sulfate (10 mg (salt) / kg tid) for 4 days, followed on the fifth day by a 7-day course of doxycycline (100 mg po pd) and a 14-day course of primaquine phosphate (30 mg (base) daily). Five days later subjects then received investigational products. Investigational products were given as a loading dose for 3 days, followed by a single dose once-a-week for 12 weeks.

Table 20: Time to First Positive Smear – Full Analysis Dataset (Study 045)

Time to First Positive Smear	Treatment Group[a]					
	Placebo N = 94	Tafenoquine 25 mg N = 93	Tafenoquine 50 mg N = 91	Tafenoquine 100 mg N = 94	Tafenoquine 200 mg N = 91	Mefloquine 250 mg N = 46
No. With Positive Smear	86	58	13	11	12	6
≤ 3 weeks	9 (9.6%)	4 (4.3%)	4 (4.4%)	0	0	1 (2.2%)
3 – 6 weeks	63 (67.0%)	30 (32.3%)	4 (4.4%)	4 (4.3%)	6 (6.6%)	4 (8.7%)
6 – 9 weeks	11 (11.7%)	18 (19.4%)	2 (2.2%)	6 (6.4%)	3 (3.3%)	0
9 – 12 weeks	3 (3.2%)	4 (4.3%)	1 (1.1%)	1 (1.1%)	2 (2.2%)	1 (2.2%)
> 12 weeks	0	2 (2.2%)	2 (2.2%)	0	1 (1.1%)	0

[a] All subjects were treated with presumptive eradication therapy (quinine sulfate (10 mg (salt)/kg tid) for 4 days followed on the fifth day by a 7-day course of doxycyline (100 mg po bid) and a 14-day course of primaquine phosphate (30 mg (base) daily). Five days later subjects then received investigational products. Investigational products were given as a loading dose for 3 days, followed by a single dose once-a-week for 12 weeks.

Discussion: For semi-immune African subjects, full prophylactic regimens employing 50 mg to 200 mg per dose had PE similar to that of the mefloquine active comparator control. More specifically, the efficacy of the anticipated clinical regimen of tafenoquine 200 mg was very similar to that of the positive control mefloquine. PE on a cumulative attack basis was 86% for both regimens. For a non-inferiority analysis based on cumulative incidence: Tafenoquine (200 mg) failures were 12/91 [95% CI (7%, 22%)], Mefloquine failures were 6/46 [95% CI (5%, 26%)], and Placebo failures were 86/94 [95% CI (84%, 96%)]. With respect to differences: Placebo - Tafenoquine (200 mg) is 78.6% [95% CI (68%, 86%)], Placebo - Mefloquine is 76.8% [95% CI (63%, 86%)], and Tafenoquine - Mefloquine is 0.1% [95% CI (-11%, 14%)]. These

data indicate that either Tafenoquine or Mefloquine are superior to Placebo with the difference CI excluding 0% by a large margin. If the difference between Placebo and Mefloquine is the efficacy margin and we assume a very conservative 25% of that margin to be the non-inferiority margin, then 0.25 x 76.8% is 19.2%. Since the upper limit of the 95% CI for the difference between Tafenoquine and Mefloquine is 14% which is below the non-inferiority margin then we can conclude that Tafenoquine is non-inferior to Mefloquine.

8.5.4. Study 044

Study 044 is included in this list of "key studies", even though the studied regimen was not the ACR, because data from this study have an impact on the comparative efficacy of tafenoquine against *Pv* and *Pf*, and also on efficacy in non-immune subjects.

Design/Objective: Efficacy of a novel full prophylactic regimen of tafenoquine (high dose given monthly) in the prophylaxis of *Pf* and *Pv* infections in a mixed-immune population in Southeast Asia.

Dosing: Subjects were randomized to a relatively high tafenoquine loading dose followed by the same dose administered infrequently (400 mg daily for 3 days followed by 400 mg monthly for 5 consecutive months) or to placebo.

Demographics*:* Subjects were all Asian males, of mean age 29 years. The subjects may be considered non-immune to mixed immune because 53% reported never having had malaria and only 23% had had malaria in the prior year.

Results: The primary efficacy endpoint was confirmed parasitemia during the double blind tafenoquine vs. placebo treatment period. Efficacy analyses were performed on the ITT population, defined as subjects who had received at least one dose of randomized study medication and who had at least one on-therapy assessment of parasitemia (blood smear). Table 21 summarizes the incidence of parasitemia in the 2 treatment groups (tafenoquine 400 mg and placebo) and PE of tafenoquine relative to placebo. There was one case (1.0%) of parasitemia (*Pv*) in subjects who received tafenoquine compared with 30 (29.7%) cases in the placebo group. Within the placebo group, there was a higher incidence of *Pv* compared with *Pf* but nevertheless a substantial representation of *Pf* (21 *Pv*, 8 *Pf*, 1 mixed infection). The PE (95% CI) of tafenoquine relative to placebo was 96.7% (82.0%, 99.4%) for all *Plasmodium* species, 95.3% (73.9%, 99.2%) for *Pv* and 100% (54.5%, 99.9%) for *Pf*. The single case of *Pv* in the tafenoquine group was detected 35 days after the second monthly tafenoquine dose. The subject missed the third monthly dose due to leaving the site.

Table 21: Protective Efficacy against *Pv* and *Pf* Infection Based on Cumulative Malaria Attack Rates for Study 044 (ITT Population)

	Treatment Group[a]	
	Tafenoquine 400 mg[b] N = 104	**Placebo[c] N = 101**
Total Cases		
All Species	1 (1.0%)	30 (29.7%)
P f	0 (0.0%)	8 (7.9%)
P v	1 (1.0%)	21 (20.8%)
Mixed[d]	0 (0.0%)	1 (1.0%)
PE (%) (95% CI)		
All Species	96.7 (82.0%, 99.4%)	
P f	100 (54.5%, 99.9%)	
P v	95.3 (73.9%, 99.2%)	

[a] Subjects were treated with presumptive eradication therapy (doxycycline 200 mg /day for 7 days).
[b] Subjects then received a loading dose of tafenoquine 400 mg for 3 days, followed by tafenoquine 400 mg once a month for 5 consecutive months beginning one month after the loading dose.
[c] Subjects then received a loading dose of placebo for 3 days, followed by placebo once a month for 5 consecutive months beginning one month after the loading dose.
[d] Mixed parasitemia counted as both *Pf* and *Pf* for calculations of crude attack rate and PE.

Discussion*:* For the first month, the total dose in this study (1200 mg) was equivalent to the total dose for the ACR. For months 2-5, the total dose in this study (400 mg) was half the total dose of the ACR (800 mg per month). This relatively low dose was very effective against all malaria in this predominately non-immune population, and was similarly effective vs. *Pf* as vs *Pv*.

8.5.5. *Pf* Treatment Study in the Human Challenge Model Study TQ-2016-02

Design/Objective: Study TQ-2016-02 was a randomized, double-blinded, placebo-controlled study to evaluate the blood schizonticidal activity of tafenoquine administered orally against challenge with blood stage *Pf* in healthy, non-immune participants. Healthy volunteers were randomized to receive tafenoquine or placebo in a 6:2 ratio for a sufficient amount of time to reach steady state (in the tafenoquine group) comparable to that achieved with the anticipated clinical regimen, after which approximately 3,000 blood stage parasites were administered and the volunteers monitored for parasitemia by quantitative polymerase chain reaction (qPCR).

Dosing: Tafenoquine was administered as one 200 mg dose per day for 3 consecutive days (loading doses; Days 1-3) given after the subject's normal breakfast. This was followed by another 200 mg base dose 7 days later given after the subject's normal breakfast (Day 10). Subjects were then inoculated with erythrocytes (blood type O-) containing approximately 2800 viable *Pf* parasites of strain 3D7 (Riamet® and Primacin™ sensitive) on Day 13.

Demographics: Of the 12 tafenoquine subjects and 4 placebo subjects, approximately 60% were female; mean age was 25-34 years. Most subjects were of the White race.

Results: The mean plasma concentration on the day of parasite inoculation, Day 13, was slightly less than 400 ng/mL, as intended, since the mean plasma concentration at steady state has this value. No parasites were seen at any time in any of the subjects administered tafenoquine, but

parasites were seen in the blood of each of the 4 placebo subjects. Parasitemia exceeded the protocol defined threshold for rescue on days 21-22 for each placebo volunteer, at which time the placebo volunteers were administered co-artemether rescue therapy.

The observed difference in the proportion of participants experiencing Malaria Failure between the tafenoquine and placebo groups was highly statistically significant (Fisher's Exact Test p=0.0005: Table 22). Based on no occurrences of Malaria Failure with tafenoquine, the PE of active treatment was determined to be 100.0%.

Table 22: Malaria Failure Rate in Study TQ-2016-02

Statistics	Tafenoquine (N=12)	Placebo (N=4)
Malaria Failure (%)	0 (0.0%)	4 (100.0%)
95% CI for Malaria Failure Rate[a]	0.0%, 26.5%	39.8%, 100.0%
p-value (Fisher's Exact Test)	0.0005	
Relative Risk[b]	0.00	
Protective Efficacy	100.0	

[a] 95% CI for Malaria Failure Rate = Clopper-Pearson exact confidence interval.
[b] Relative risk = (Incidence of Malaria in Tafenoquine group) / (Incidence of Malaria in Placebo group). 95% CI for Relative Risk and Protective Efficacy are not available because there was no occurrence of malaria with tafenoquine.

Discussion: Tafenoquine steady state drug concentrations were completely effective against approximately 2,800 *Pf* blood stage parasites inoculated into non-immune normal volunteers in the human challenge model. This study suggests that after challenge in the field by *Plasmodium* sporozoites, parasites that escape killing being killed by tafenoquine in the liver will be killed by tafenoquine in the blood.

8.5.6. *Plasmodium vivax* Treatment Study in the Field: Study 058

Design/Objective: Study 058 was a randomized, active-control, double-blind, double-dummy study to evaluate the efficacy and safety of tafenoquine for the treatment of *Pv* parasitemia in adults in Thailand. The primary objective of this study was to assess whether (Cohort 1) 400 mg/day for 3 days or (Cohort 2) a single 600 mg dose of tafenoquine alone could clear/cure *Pv* blood stage infections.

Dosing: Only the initial regimen of Cohort 1 (400 mg per day x 3 days) was ultimately investigated. Subjects in Cohort 1 were randomized 2:1 to receive tafenoquine 400 mg/day for 3 days, or the standard blood schizonticidal dosing regimen of chloroquine (1000 mg chloroquine phosphate for 2 days followed by 500 mg chloroquine phosphate for one day) followed by a standard hypnozoite eradication dosing regimen for primaquine (15 mg base per day for 14 days).

Demographics: Approximately 80% were male, median age was 28 years. All subjects were of the Asian race.

Results: The subjects can be considered semi-immune since approximately 2/3 of all randomized subjects had a previous episode of malaria, and 53% of subjects randomized to receive tafenoquine had an episode within the previous 6 months. Parasitemia at baseline was [mean (SD)] 8000 (9415) parasites/μL for tafenoquine group and 6020 (7886) parasites/μL for the chloroquine/primaquine group.

The primary efficacy endpoint was the day 28 cure rate. Cure at Day 28 ("Adequate Clinical Response") required no microscopically-confirmed parasites seen on Day 7 (no "Early Treatment Failure") followed by no recurrence of homologous parasites between Day 7 and 28 (no "Late Treatment Failure"). As the primary efficacy population seems undefined in the protocol, 2 populations were considered: ITT and PP. In the ITT population a 'worst case' approach was taken: subjects who were not evaluable for the Day 7 evaluation were categorized as Early Treatment Failures and subjects who were evaluable for the Day 7 PP population but not the Day 28 evaluation were categorized as Late Treatment Failures. The Day 7 and Day 28 PP populations consisted of those subjects in the ITT population who were present for the Day 7 and Day 28 day evaluations.

After all subjects in Cohort 1 had completed the Day 28 assessment, an independent data monitoring committee (IDMC) evaluated the efficacy and safety of the Cohort 1 regimen. During its review of efficacy, the IDMC determined that the dosing regimen of tafenoquine used in Cohort 1 failed to meet the pre-specified endpoint for the Day 28 cure rate due to 3 early treatment failures, and recommended enrollment into Cohort 2 not be initiated but that follow-up in Cohort 1 should be completed according to the protocol. It is worth noting that while these 3 subjects met the definition of Early Treatment Failure, all 3 had low parasitemia levels on Day 7 (40 – 60 parasites/μL) and cleared their parasitemia by Day 8 without additional anti-malarial treatment.

For the PP population of Cohort 1, 40 of 43 tafenoquine-treated subjects had an adequate clinical response. For the chloroquine + primaquine PP population, all 22 of 22 subjects had an adequate clinical response. The ITT population included another 3 subjects for tafenoquine and another 2 subjects for chloroquine + primaquine. The Day 28 cure rate in the ITT population was 87% and 92% in the tafenoquine and chloroquine plus primaquine treatment arms, respectively (Table 23). The difference in Day 28 cure rates between the 2 treatments was 7% for the PP population and 5% for the ITT population. The 95% CI for these treatment differences included zero in both cases.

Table 23: Summary of Day 28 Cure Rate Study 058

	Tafenoquine % [a] N (%)	Chloroquine + Primaquine [b] N (%)	Treatment Difference (95% CI)
Per Protocol			
	43	22	
Adequate Clinical Response	40 (93.0)	22 (100.0)	
Early Treatment Failure	3 (7.0)	0 (0)	-7.0% (-14.6%, 0.6%)
Late Treatment Failure	0	0	
90% CI for Adequate Clinical Response	(82.9%, 98.1%)	(87.3%, 100.0%)	
Intent-To-Treat			
	46	24	
Adequate Clinical Response	40 (87.0)	22 (91.7)	
Early Treatment Failure	5 (10.9)	0 (0)	-4.7% (-19.4%, 10.0%)
Late Treatment Failure	1 (2.2)	2 (8.3)	
90% CI for Adequate Clinical Response	(75.9%, 94.2%)	(76.0%, 98.5%)	

[a] Subjects received tafenoquine 400 mg once a day for 3 days.
[b] Subjects received chloroquine (1000 mg chloroquine phosphate for 2 days followed by 500 mg chloroquine phosphate for 1 day) followed primaquine (15 mg base per day).

Because follow-up extended to 120 days, it was possible to assess relapse in this study. Tafenoquine was highly effective (100%) for the prevention of *Pv* relapse, as none of the 35 subjects receiving tafenoquine with an adequate clinical response at Day 28 and who remained evaluable during the follow-up period to Day 120 had a relapse of *Pv* malaria. Among the 20 such evaluable subjects receiving chloroquine plus primaquine, there was one relapse (on Day 63) during the follow-up period.

While tafenoquine demonstrated significant schizonticidal and gametocytocidal activity, its onset of action was noticeably slower than that of the standard treatment regimen of chloroquine plus primaquine. In both the PP and ITT populations, 100% of subjects receiving chloroquine plus primaquine cleared their parasitemia within 96 hours of the start of treatment. In comparison, 54% (PP) and 52 % (ITT) of subjects receiving tafenoquine cleared their parasitemia within 96 hours of start of treatment. In both the PP and ITT populations, the mean asexual parasite clearance time was twice as long in subjects treated with tafenoquine (83 and 83 hours, respectively: excluding the three tafenoquine subjects with early treatment failure) than in subjects treated with chloroquine plus primaquine (40 and 40 hours, respectively). Similarly, the mean gametocyte clearance time in subjects treated with tafenoquine was twice as long in PP and ITT subjects treated with tafenoquine (49 and 48 hours, respectively) than in subjects treated with chloroquine plus primaquine (23 and 23 hours, respectively).

Discussion: When tafenoquine was given alone, a relatively high loading dose of 400 mg per day x 3 days was active against blood stages of *Pv*. In the PP population of the tafenoquine group, 40 of 43 patients were cured at day 28. The 3 PP subjects that had parasites at 7 days were aparasitemic at 8 days without further antimalarial therapy. All 43 tafenoquine PP subjects were aparasitemic at 28 days and none that were followed for 120 days experienced recrudescence or relapse up that time. We note that although initial exposure in this study would be twice the

initial exposure of the proposed prophylactic regimen (loading dose = 200 mg per day x 3 days), subjects in this study received no further tafenoquine. The total amount of drug administered to Cohort 1 over the 28 day period over which the primary endpoint was evaluated (1200 mg) equals the amount of drug in the proposed prophylactic regimen (200 mg per day x 3 days followed by 200 mg weekly) when taken for one month.

Prophylactic antimalarial regimens need to be effective only against the relatively few parasites that initially infect the blood and commonly use a fraction (1/4 to 1/5) of the antimalarial treatment dose administered approximately every half-life. The 4 classical and present prophylactic drugs are chloroquine, mefloquine, Malarone (atovaquone and proguanil), and doxycycline. The treatment dose of chloroquine is 1500 mg whereas the prophylactic regimen is 300 mg weekly. The treatment dose of mefloquine is 1250 mg whereas the prophylactic dose is 250 mg weekly. The treatment dose of Malarone is 4 tablets per day (for 3 days) whereas the prophylactic dose is one tablet daily. The treatment dose of doxycycline is 100 mg bid plus another drug [quinine] (for 7 days) whereas the prophylactic dose is 100 mg daily alone. Expressed in a different way: 10,000 parasites/μL are routinely seen when a patient presents for *treatment*, but only approximately 300,000 total parasites normally exit the liver to infect the 5 L blood volume, thus the parasite burden in the *prophylactic* situation is about 0.06 parasites/μL blood, and only a small fraction of the treatment regimen is required for the prophylactic regimen.

Tafenoquine did not kill *Pv* as fast as the standard regimen of chloroquine-plus-primaquine. Nevertheless, it is possible to suggest from the data of this treatment study that the proposed prophylactic regimen is likely to be effective prophylaxis against *Pv*. In this treatment trial, initial parasitemia was 8000 parasites/μL and tafenoquine at 400 mg/day x 3 days eliminated all blood stages of *Pv* by Day 8. In the prophylactic situation, the parasite burden is calculated to be lower than 1 parasite/μL blood. In contrast to this many orders-of-magnitude diminished parasite burden from the treatment situation to the prophylactic situation, tafenoquine exposure for the 200 mg-based prophylactic regimen would be similar to the exposure in Study 058. The results of Study 058 suggest that the proposed tafenoquine prophylactic regimen will be effective against the relatively low *Pv* parasite burden present in the blood during prophylaxis.

9. Comparison and Analysis Across Studies

9.1. Study Populations

The baseline characteristics of the populations utilized in the prophylactic field studies that comprise this dossier are summarized in Table 24. Males (3,232 subjects) predominated overall and in each study grouping; however, 771 total females also participated in these studies. The mean age of 29 years, mean weight of 69 kg, and mean BMI of 23 kg/mm^2 signifies a healthy young adult population. Subjects ranged in age from 12 years to 70 years. The populations were uniformly healthy upon entrance into the study without clinically significant abnormalities in entrance laboratory values and without clinically significant concomitant disease. Although pre-existing parasitemia was cleared with antimalarial drugs prior to institution of prophylaxis, subjects were not administered drugs with possible antimalarial activity during the prophylactic phase of the studies. The baseline health characteristics (lack of clinical malaria) in these field studies are representative of the general population who will utilize anti-malarial prophylaxis with tafenoquine. In addition, study subjects in Studies 044 and 033 had the mixed-or-non-immunity status characteristic of persons who also could undertake tafenoquine prophylaxis.

Table 24: Baseline Characteristics of Efficacy Study Subjects in Primary Analytic Populations

Baseline Characteristics[a]	Prophylactic African Studies 006 / 043 / 045 / 030	Prophylactic SE Asia / Oceania Studies 044 / 033	All Field Prophylactic Studies Using Loading Plus Weekly Dosing 043 / 044 / 045 / 030 / 033	*P vivax* Hypnozoite and Blood Stage Treatment Studies 046 / 047 / 049 / 058	All Field Efficacy Studies 006 / 043 / 030 / 044 / 033 / 047 / 049 / 058
Gender					
Female, N (%)	594 (40.9)	21 (2.5)	394 (20.9)	156 (9.1)	771 (19.3)
Male, N (%)	857 (59.1)	824 (97.5)	1487 (79.1)	1551 (90.9)	3232 (80.7)
Age (Years)					
N	1451	845	1881	1707	4003
Mean (SD)	31.4 (14.8)	26.3 (6.31)	32.4 (12.1)	27.4 (6.77)	28.6 (10.6)
Range	12.0 – 70.0	18.0 – 51.0	14.0 – 70.0	16.0 – 58.0	12.0 – 70.0
Weight (kg)					
N	1447	844	1880	1704	3995
Mean (SD)	56.4 (9.34)	75.8 (14.2)	65.3 (15.1)	76.7 (13.5)	69.2 (15.7)
Range	32.0 – 97.0	45.0 – 135.0	33.0 – 135.0	36.5 – 140.0	32.0 – 140.0
Height (cm)					
N	1161	640	1388	1704	3505
Mean (SD)	166 (8.92)	178 (6.91)	172 (9.34)	177 (9.89)	173 (10.5)
Range	120.0 – 194.0	154.5 – 198.0	145.0 – 198.0	143.0 – 208.0	120.0 – 208.0

Table 24: Baseline Characteristics of Efficacy Study Subjects in Primary Analytic Populations (Continued)

Baseline Characteristics[a]	Prophylactic African Studies 006 / 043 / 045 / 030	Prophylactic SE Asia / Oceania Studies 044 / 033	All Field Prophylactic Studies Using Loading Plus Weekly Dosing 043 / 044 / 045 / 030 / 033	*P vivax* Hypnozoite and Blood Stage Treatment Studies 046 / 047 / 049 / 058	All Field Efficacy Studies 006 / 043 / 030 / 044 / 033 / 047 / 049 / 058
BMI					
N	1159	640	1388	1703	3502
Mean (SD)	20.0 (2.66)	25.6 (3.26)	22.4 (4.14)	24.4 (2.97)	23.2 (3.70)
Range	12.7 – 35.4	17.5 – 39.0	12.7 – 39.0	11.4 – 36.3	11.4 – 39.0

[a] The primary analytic populations for each study were: 006 – ITT known data set population; 043 – ITT population; 044 – ITT population; 045 – ITT population; 030 – mITT population; 033 – PP population; 047 – ITT population; 049 – ITT population; 058 – Per Protocol population

Subjects lost to follow-up are summarized in Table 25. Drop outs were few (approximately 2.5%).

Table 25: Dropouts for Reasons other than Lack of Efficacy in Primary Analytic Population of Efficacy Studies

Baseline Characteristic[a]	Prophylactic African Studies 006 / 043 / 045 / 030	Prophylactic SE Asia / Oceania Studies 044 / 033	All Field Prophylactic Studies Using Loading Plus Weekly Dosing 043 / 044 / 045 / 030 / 033	*P vivax* Hypnozoite and Blood Stage Treatment Studies 047 / 049 / 058	All Field Efficacy Studies 006 / 043 / 030 / 044 / 033 / 047 / 049 / 058
Number of Subjects in Efficacy Studies					
N	1451	845	1881	1702	3998
Dropouts, Reasons for Withdrawal N (%)					
Adverse Experience	12 (0.8)	1 (0.1)	3 (0.2)	0(0)	13 (0.3)
Lost to Follow-up	25 (1.7)	3 (0.4)	22 (1.2)	3 (0.2)	31 (0.8)
Moved	0(0)	21 (2.5)	21 (1.1)	0 (0)	21 (0.5)
Other	5 (0.3)	0(0)	5 (0.3)	0 (0)	5 (0.1)
Protocol Deviation	13 (0.9)	0 (0)	10 (0.5)	0 (0)	13 (0.3)
Unknown	18 (1.2)	0 (0)	18 (1.0)	0 (0)	18 (0.5)

[a] The Primary Analytic Populations for each study were: 006 – ITT known data set population; 043 – ITT population; 044 – ITT population; 045 – ITT population; 030 – mITT population; 033– PP population; 047 – ITT population; 049 – ITT population; 058 – PP population.

9.2. Comparison of Efficacy Results of Prophylaxis Studies in the Endemic Region

We first investigated whether a 3-day loading dose alone would provide sufficient prophylactic efficacy. Although in Study 006, a loading dose of 50 to 200 mg per day for 3 days alone was sufficient to provide 100% PE in semi-immunes for 7 weeks, in Study 043, a loading dose of 400 mg per day for 3 days had only 72% efficacy in semi-immunes over a period of 15 weeks, indicating that for long-term protection, loading doses need to be followed by additional dosing.

Evaluation of full prophylactic regimens (loading dose followed by weekly or monthly doses) of 25 to 400 mg each dose then ensued. Data from study 045 indicates that administration of 25 mg (for each loading and weekly dose) does not provide sufficient protection**.** In contrast, protection with 50, 100, and 200 mg was similar to each other and to the mefloquine comparator, in the semi-immunes of Study 045. Data from studies 043 and 044 indicate that 400 mg (loading dose) followed by weekly (Study 043) or monthly (Study 044) dosing is perhaps more effective than 200 mg. However, regimens based on 400 mg dosing had higher gastrointestinal AEs than regimens based on 200 mg dosing (see Section 12.3 below). The 200 mg regimen was chosen for pivotal trials because 200 mg (200 mg per day for 3 days, followed by 200 mg weekly) was the regimen employing the highest dose of drug that was well tolerated.

Efficacy data based on attack rates for all studies using full prophylactic regimens of tafenoquine (loading dose followed by weekly/monthly dosing) are summarized in Table 26.

Table 26: Comparison of Efficacy Results across Studies

Study	Analysis Set	Treatment	N	No. of Prophylactic Failures	% Fail (95% CI)	%PE (95%CI)
043[a]	ITT	Placebo	59	54	92 (82 – 96)	–
		Tafenoquine 200 mg	53	7	13 (7 – 25)	86 (73 – 93)
044	ITT	Placebo	101	30[b]	30 (22 – 39)	–
		Tafenoquine 400 mg Monthly	104	1[b]	1 (0 – 5)	97 (82 – 99)
045	ITT	Placebo	94	86	92 (84 – 96)	–
		Tafenoquine 25 mg	93	58	62 (52 –72)	32 (20 – 43)
		Tafenoquine 50 mg	91	13	14 (9 – 23)	84 (75 – 91)
		Tafenoquine 100 mg	94	11	12 (7 – 20)	87 (78 – 93)
		Tafenoquine 200 mg	91	12	13 (8 – 22)	86 (76 – 92)
		Mefloquine 250 mg	46	6	13 (6 – 26)	86 (72 – 93)
033	PP	Tafenoquine 200 mg	462	0	0 (0 – 1)	–
		Mefloquine 250 mg	153	0	0 (0 – 2)	–

Table 26: Comparison of Efficacy Results across Studies (Continued)

Study	Analysis Set	Treatment	N	No. of Prophylactic Failures	% Fail (95% CI)	%PE (95%CI)
043 045	(As Above)	Placebo	246	172	70 (64 –75)	–
044 033	(As Above)	Tafenoquine 200 mg / 400 mg	566	1	< 1	–

[a] Parasitemia through one week post prophylaxis.
[b] In the placebo group, there were 8 *Pf*, 21 *Pv*, and one mixed infection. In the tafenoquine group, there was one *Pv* infection.

In key studies 045 and 033 against the positive comparator mefloquine, point estimates of efficacy of tafenoquine vs. comparator were essentially the same within each study. In Study 045 for *Pf* in semi-immunes, PE compared to placebo was 86% for tafenoquine and 86 % for mefloquine. Tafenoquine was statistically non-inferior to mefloquine for *Pf* in this study population. In study 033 primarily for *Pv* but also with substantial calculated incidence of *Pf* in non-immunes, the full prophylactic regimen of tafenoquine had efficacy identical to that of the standard mefloquine comparator: no subject had parasitemia in either group over 6 months of prophylaxis. Historic control data indicate that 11.79 % of subjects would have become infected (6.9% with *Pv*, 4.91% with *Pf*) under those conditions. Here also, tafenoquine was statistically non-inferior to mefloquine.

9.3. Comparison of Results of Subpopulations Relevant to Prophylaxis Studies in the Endemic Region

For the proposed indication of prophylaxis against *Pf* and relapse prevention of *Pv*, several subpopulations are of interest:

a. *Pf* alone vs. *Pv* combined with *Pf*.
b. Different geographic regions, since parasites may differ in drug sensitivity between regions.
c. Non-immune vs. semi-immune. Demonstration that tafenoquine protection does not differ between non-immunes and semi-immunes would indicate that prior exposure to *Plasmodium* is not needed for efficacy in either non-immunes or persons with an unknown degree of immunity.
d. Race
e. Gender
f. Weight

Analysis a) / b) / c) / d) with respect to studies of prophylaxis in the endemic region: since Studies 043 and 045 were performed vs. *Pf* in Africa in a semi-immune racially black population, and Studies 044 and 033 were performed vs. *Pv*-plus-*Pf* in SE Asia-plus-Oceania in a mixed and non-immune racially Asian-plus-Caucasian population, comparing efficacy data in pooled Studies 030, 043 and 045 vs. pooled studies 044 and 033 simultaneously implements subpopulation analyses a), b), c), and d).

Efficacy and PE were high and similar across Studies 033, 043, 044, and 045.

With respect to anti-malarial immunity: in the non-immune population studied in 033 the efficacy rate of tafenoquine 200 mg was 100%, and in the mixed-to-non- immune population studied in 044 the efficacy rate of tafenoquine 400 mg was 99%. Because there was a placebo group in Study 044, PE could be calculated and was 97% in that study. In comparison, in the semi-immune populations studied in placebo-controlled Studies 043 and 045, the PEs of tafenoquine 200 mg were 86% and 94%, respectively.

Since parasite species, geographic region, and race are associated with population immunity in these studies, it can be inferred that efficacy vs. *Pf* is similar to that vs. *Pv*, efficacy in SE Asia/Oceania is similar to that in Africa, and efficacy in Asians/Caucasians is similar to that in Black Africans.

Analysis e) with respect to all prophylactic studies: Efficacy in males vs. females is shown in Table 27. Overall, the failure rate for all field studies in males was similar to that in females (7% to 8% for both genders).

Table 27: Efficacy of Tafenoquine of Males vs. Females in Primary Analytic Populations

Baseline Characteristic[a]	Prophylactic African Studies 006 / 043 / 045 / 030	Prophylactic SE Asia / Oceania Studies 044 / 033	All Field Prophylactic Studies Using Loading Plus Weekly Dosing 043 / 044 / 045 / 030 / 033	*P vivax* Hypnozoite and Blood Stage Treatment Studies 047 / 049 / 058	All Field Efficacy Studies 006 / 043 / 030 / 044 / 033 / 047 / 049 / 058
Efficacy in Males					
Number of	564	571	983	1043	2178
Failure, N (%)	103 (18.3)	1 (0.2)	95 (9.7)	54 (5.2)[b]	158 (7.3)
Efficacy in Females					
Number of	414	14	248	104	532
Failure, N (%)	41 (9.9)	0(0)	31 (12.5)	1 (1.0)	42 (7.9)

[a] The primary analytic populations for each study were: 006 – ITT known data set population; 043 – ITT population; 044 – ITT population; 045 – ITT population; 030 – mITT population; 033 – PP population; 047 – ITT population; 049 – ITT population; 058 – PP population.

[b] During FDA audit, 1 more subject failure was identified to bring total to 54 rather than 53 (number in Sponsor's database).

Analysis f) with respect to studies of prophylaxis in the endemic region: Few subjects of high weight were included in the clinical studies in this dossier. However, one study of the full prophylactic regimen varied dose by a factor of 4, so that meant dose per unit weight also varied by a factor of 4. In Study 045, mean weight in each group between tafenoquine 200 mg was 54 kg to 57 kg (males) and 45 kg to 50 kg (females). These narrow weight ranges mean that subjects in the 50 mg dose group received approximately 1 mg/kg each dose for both males and females and subjects in the 200 mg dose group received approximately 4 mg/kg each dose for both males and females. In spite of the difference in dosing on a weight basis, PE was almost the same: 84% in the 50 mg dose group and 86% in the 200 mg dose group. The comparative efficacy between subjects receiving 1 mg/kg each dose and 4 mg/kg each dose in Study 045 suggests that even

subjects weighing 100 kg, who would receive 2 mg/kg each dose with the proposed prophylactic regimen of 200 mg each dose, would not be more likely to fail than a 65 kg person who would receive 3 mg/kg each dose.

The predicted comparability of efficacy in heavier individuals in consistent with PK/PD relationships. In subjects for whom trough levels were measured, no patient with trough levels > 80 ng/mL has failed tafenoquine prophylaxis (see Section 5.1). In the final population PK model based on clinical data from Studies 001, 002, 003, 004, 005, 014, 015, 033, 044, and 058, tafenoquine 200 mg once daily for 3 days followed by tafenoquine 200 mg weekly generated plasma tafenoquine concentrations > 80 ng/mL immediately after the loading dose in 95% of individuals and in all individuals post-first trough. The simulated tafenoquine concentration was sustained above 80 ng/mL irrespective of weight (or meal schedule or age).

10. Analysis of Clinical Information Relevant to Dosing Recommendations

The dosage recommendations for malaria prophylaxis are as follows:

a. *Before arrival in an endemic area, to ensure sufficient concentration in the blood, it is recommended to start tafenoquine prophylaxis, 200 mg daily on the 3 days prior to arrival. Subsequent doses should be taken once every 7 days thereafter for the duration of travel and for one dose post-exposure.*

   The basis for this proposed dosing regimen has been summarized in Section 9.2. The recommended dosage regimen utilizes the highest well tolerated dose of drug providing maximum tafenoquine efficacy. Although population subgroups could in theory have differing protection, tafenoquine PE did not differ between subgroups. There was no substantial or statistical difference between PE based on parasite (*Pf* vs. *Pv*) which is synonymous with endemic region (Africa vs. SE Asia-plus-Oceania) and with race (Black vs Asian-White), on gender (male vs. female), on preexisting immunity (non-immune vs. semi-immune), or on weight.

b. *No specific adaptation of the usual adult dosage is required for elderly patients or subjects with existing semi-immunity to malaria.*

   Tafenoquine clinical trials have enrolled subjects as old as age 70 with no alterations required in the usual adult dosage of tafenoquine and no obvious age-related impact on efficacy. As previously stated, preexisting immunity (non-immune vs semi-immune) derived from prior exposure to *Plasmodium* did not affect the PE of tafenoquine.

c. *The maximum recommended duration of administration of tafenoquine is 6 months.*

   This was the duration of prophylaxis used in Pivotal Trial 033.

d. *On leaving a malarious area, tafenoquine should be continued for one additional weekly dose.*

   Prophylaxis after the last possible day of contact with an infected mosquito requires protection against 2 forms of *Plasmodium*:

   - Initial liver forms of *Pf* and *Pv* that have not yet exited the liver to infect the blood. Initial liver forms begin to exit the liver on Day 7 after sporozoite inoculation into the human host, but may exit up to Day 23 (Fairly-1945).
   - Dormant liver forms (“hypnozoites”) of *Pv* that can exit the liver and infect the blood causing clinical “relapse.”

Post-exposure prophylaxis to eliminate initial liver forms of *Pf* and *Pv* that have yet to leave the liver requires 4 weeks of drugs if the drug only kills blood parasites (“schizonticidal drug”) but only 7 days for drugs that kill initial liver forms *in situ* (“causal drug”). Malarone® administered on the day of sporozoite inoculation plus 6 days thereafter was shown to be 100% protective in a human challenge study (Berman-2001), and the US CDC recommends stopping Malarone

prophylaxis 7 days after leaving the endemic region. Primaquine, another causal prophylactic agent, is similarly recommended to be taken only for 7 days after the last day of exposure for that purpose (Magill-2015).

Post-exposure prophylaxis to kill *Pv* dormant forms thus preventing relapse requires an 8-aminoquinoline, the only category of antimalarial agents known to have clinical anti-hypnozoite activity. For this purpose, primaquine dosing (30 mg per day for an adult) is extended to 14 days after leaving the endemic region (Magill-2015).

Considerations related to causal activity (killing of initial liver forms) and anti-relapse activity (killing of hypnozoites) by tafenoquine are presented below.

Causal activity of tafenoquine: Due to the long half-life of this drug in humans (approximately 2 weeks), drug administered at the time of sporozoite inoculation will be present during the 7 days of initial liver infection and also during the subsequent weeks when it might kill parasites that escape from the liver. Thus, separating tafenoquine's causal activity from its suppressive activity is difficult in humans. However, in a mouse model, tafenoquine pharmacodynamics have been separately determined for liver vs. blood. A transgenic *Plasmodium berghei* parasite expressing the bioluminescent reporter protein luciferase has been utilized to visualize and quantify parasite development in C57BL/6 albino mouse liver using a real-time *in vivo* imaging system. Blood stage parasitemia was separately monitored by flow cytometry (Li-2014). When one dose of tafenoquine (5 mg/kg) was administered one day prior to sporozoite inoculation, 10 of 10 animals were protected. In these animals, liver imaging showed that 98.6% of parasites were eliminated compared to controls at 48 hrs after sporozoite challenge. Because parasites begin to emerge from the liver to enter the blood at 48 hours in this model, some of the remaining 1.4% of liver parasites had entered the blood after that time and the 100% prophylactic efficacy of this regimen was due to elimination of a few blood parasites by tafenoquine ($t_{½}$ = 51 hour) remaining in the blood after 48 hours. The overwhelming preponderance of causal activity as a component of total tafenoquine prophylactic activity suggests that tafenoquine, like Malarone and primaquine, need only be continued for 7 days after the last date of exposure to successfully protect against emergence of initial liver forms.

Anti-hypnozoiticidal activity of tafenoquine: Certain of the relapse-prevention studies accomplished as part of this dossier provided data delineating how long tafenoquine should be continued post-exposure to kill hypnozoites. In particular, Study 033, in addition to comparing the effect of tafenoquine to mefloquine during exposure, also compared the effect of tafenoquine ending when the subjects exited the endemic region to standard of care primaquine for 14 days after existing the endemic region on *Pv* relapse. Neither the 6-month data (4 failures of 462 tafenoquine subjects vs. 1 failure of 153 mefloquine subjects: p>0.99) nor the 1 year data (7 failures of 462 tafenoquine subjects versus 1 failure of 153 mefloquine subjects: p=0.69) showed statistical significance between the groups. This suggests that exposure consequent to the proposed prophylactic regimen of tafenoquine will be as effective as standard primaquine therapy with respect to anti-hypnozoite activity.

Another source of data comes from the DETECTIVE study publication (study TAF112582) in which several tafenoquine dosing regimens were compared to primaquine (Llanos-Cuentas-2014). Study TAF112582 was a multi-centre, double-blind, double-dummy, randomized, parallel-group, active-controlled study with the primary objective to compare the efficacy of

tafenoquine as a radical cure for *Pv* malaria relative to the primaquine standard. Eligible subjects were treated with chloroquine on Days 1 to 3 to treat the blood stage malaria infection. The subjects were then randomized into 6 treatment groups (50 to 57 per group) to receive single doses of either 50 mg, 100 mg, 300 mg or 600 mg of tafenoquine, 15 mg primaquine (once daily for 14 days), or the initial 3-day chloroquine regimen only. The primary endpoint was relapse-free efficacy at 6 months post-dosing. Tafenoquine regimens of 300 mg once or 600 mg once were more effective than the standard primaquine regimen to prevent relapse in this study. The number of subjects who were relapse-free at 6 months in the tafenoquine 300 mg group, tafenoquine 600 mg group, and primaquine group was 89%, 91%, and 77%, respectively. Our study 051 showed that plasma concentrations (AUC, C_{max}) of tafenoquine are dose proportional between 200 mg and 400 mg single dose. Thus, tafenoquine concentrations after the 300 mg dose used in DETECTIVE is approximately 1.5-times the concentrations after 200 mg single dose. But with its long half live, the tafenoquine accumulation ratio is approximately 4, and after the 200 mg x3 days loading dose and certainly after further weeks of 200 mg tafenoquine administration, tafenoquine exposure is more than twice the level achieved by 300 mg once in DETECTIVE. This PK analysis indicates that tafenoquine exposure due to the recommended prophylactic regimen will be at least as effective as the 300 mg tafenoquine dose proposed in DETECTIVE for an anti-relapse indication.

In summary, the primary causal basis of tafenoquine prophylaxis indicates that tafenoquine needs be continued, as Malarone and primaquine are continued, only one week post-exposure to kill initial liver forms. The comparison to primaquine as an anti-relapse agent in this dossier and in the literature indicates that in subjects taking the recommended tafenoquine prophylactic regimen, only one further dose of tafenoquine post-exposure is needed to kill hypnozoites and prevent relapse. Overall, the recommendation is that tafenoquine prophylaxis (200 mg weekly) be continued for one dose post the last day of parasite exposure.

11. Persistence of Efficacy and/or Tolerance Effects

Data from pooled Studies 043, 045, 030, and 033, showed that, for the recommended prophylactic regimen, failures did not increase with time on treatment beyond 6 weeks, suggesting that prophylactic efficacy did not diminish with time on prophylaxis drug (Table 28).

Table 28: Time to Parasitemia (ITT) - Pooled Studies 043, 045, 030 and 033

	Tafenoquine 200 Load + Weekly (Studies 030, 033, 043, 045 (N = 740)
Time to parasitemia (Weeks)	
N	21
Min/Max	1.00, 12.71
≤ 3 weeks	4 (0.5%)
> 3 weeks, ≤ 6 weeks	9 (1.2%)
> 6 weeks, ≤ 9 weeks	4 (0.5%)
> 9 weeks, ≤ 12 weeks	3 (0.4%)
> 12 weeks	1 (0.1%)

These data support dosage recommendation e): “If one tafenoquine dose is missed, replace that dose up to the time of the next weekly dose. If 2 tafenoquine doses are missed, replace with one tafenoquine dose on the day before the next weekly dose. If 3 or more tafenoquine doses are missed, replace with 2 daily doses before the next weekly dose.”

The rationale for these recommendations is based on PK considerations. The median tafenoquine blood concentration at steady state is approximately 250 ng/mL and $t_{½}$ ~ = 2 weeks. If one weekly dose is missed, replacement of that dose at any time prior to the next weekly dose should maintain the approximate steady state. If 2 weekly doses are missed, median concentrations fall to approximately 125 ng/mL, the value after one 200-mg tafenoquine dose (Study 022), thus 200 mg per day x 2 days are needed to raise drug concentrations to the level achieved after the original loading regimen. If 3 or more weekly doses are missed, drug levels are approximately ¼ the steady state value, and the original loading regimen should be re-administered.

12. Evaluation of Safety

The Sponsor's safety database includes data from 3184 subjects who were exposed to tafenoquine, of whom 825 were administered the Tafenoquine ACR. For integrated analyses of safety, studies were grouped by those studies where subjects received the anticipated clinical regimen (ACR) of tafenoquine for malaria prophylaxis (200 mg per day for 3 days followed by 200 mg weekly for up to 6 months) and by other studies that evaluated alternate/different tafenoquine doses or administration regimens.

Safety Studies of the Anticipated Clinical Regimen (ACR)

- Study 030: A Randomized, Double-Blind, Placebo-Controlled Evaluation of Weekly Tafenoquine Compared to Mefloquine for Chemosuppression of *Plasmodium falciparum* in Western Kenya
- Study 033: A Randomized, Double-Blind, Comparative Study to Evaluate the Safety, Tolerability and Effectiveness of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-immune Australian Soldiers Deployed to East Timor
- Study 043: Evaluation of Weekly Tafenoquine Compared to Placebo for Chemosuppression of *Plasmodium falciparum* in Western Kenya
- Study 045: A Randomized, Double-Blind, Placebo-Controlled Evaluation of Increasing Doses of Weekly Tafenoquine for Chemosuppression of Plasmodium falciparum in Semi-Immune Adults Living in the Kassena-Nankana District of Northern Ghana
- Study 057: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability, specifically Renal and Ophthalmic Effects, of Tafenoquine 200 mg for 6 months, in Healthy Volunteers

Other Safety Studies Included in The Safety Analyses

- Study 003: A Study to Determine the Effect of Food and Sex on the Pharmacokinetics of Tafenoquine in Healthy Adult Volunteers
- Study 006: Dose Down Range Placebo-Controlled, Double-Blind Study of Oral Tafenoquine for Prophylactic Efficacy, Safety and Tolerance in Subjects Resident in a Malarious Area of Gabon
- Study 014: An Open-Label, Randomized Study in Healthy Male and Female Volunteers to Assess the Tolerability and Relative Bioavailability of Three Consecutive Single-Daily Doses of the Existing Capsule Formulation and Novel Tablet and Capsule Formulations of Tafenoquine
- Study 022: An Open, Single Dose, Two Parallel-Group Study to Investigate the Effect of Food on the Bioavailability of the Tafenoquine Final Capsule Formulation, in Healthy Male and Female Volunteers

- Study 040: Evaluation of the Effect of Tafenoquine on the Metabolism of Multiple Cytochrome P450 Substrates
- Study 044: A Randomized, Double-Blind, Placebo-Controlled Evaluation of Tafenoquine for Chemosuppression of Plasmodium falciparum and Plasmodium vivax in Thai Army Soldiers
- Study 047: A Dose Ranging Study for the Safety and Efficacy of Tafenoquine in the Prevention of Relapse of Plasmodium vivax Infection in Thailand
- Study 049: Evaluation of Tafenoquine for the Post-Exposure Prophylaxis of Vivax Malaria (Southwest Pacific Type) in Non-Immune Australian Soldiers
- Study 050: Rising, Single Oral Dose Safety and Tolerance Study of Tafenoquine - Part I
- Study 051: A Multiple Dose Safety, Tolerance, and Pharmacokinetic Study of Tafenoquine when given to Healthy Male and Female Subjects
- Study 052: Pharmacokinetics, Pharmacodynamics, Safety and Tolerance of a Single Oral Dose of Tafenoquine
- Study 053: Evaluation of Tafenoquine as a Prophylactic Agent against Induced P. falciparum Malaria Infection in Healthy Non-Immune Subjects: A Dose-Ranging Study
- Study 054: Evaluation of Tafenoquine as a Prophylactic Agent against Induced P. falciparum Malaria Infection in Healthy Non-Immune Subjects II: A Multiple-Dose Causal Versus Suppressive Study
- Study 058: A Randomized, Active-Control, Double-Blind, Double-Dummy Study to Evaluate the Efficacy and Safety of Tafenoquine for the Treatment of Plasmodium vivax in Adults
- Study 933: Long Term Renal Follow-up Protocol for Subjects in Protocol 033

Supportive information regarding the safety of tafenoquine is primarily drawn from healthy volunteers (not only in Phase 1 studies but also in Phase 2-3 prophylaxis studies), with prophylaxis populations including subjects with varying levels of inherent malarial immunity (non-immune Australian military personnel to semi immune African residents). In these studies, safety was assessed through vital sign measurements, monitoring of clinical signs/symptoms, physical examinations, clinical laboratory testing, and monitoring of AEs. Selected studies have also included targeted assessments for effects on renal, ocular, pulmonary, or cardiac function, as well as for methemoglobin level.

All of the safety studies listed above in both safety groupings are included in the Integrated Summary of Safety as described in Section 12.1 below.

12.1. Analysis of Clinical Safety: Pooling of Studies with a Focus on the Anticipated Clinical Regimen (ACR)

Safety analyses for the studies in the tafenoquine NDA were provided in the form of an Integrated Summary of Safety (ISS) and a Summary of Clinical Safety (Module 2.7.4). To establish a comprehensive profile of the safety of tafenoquine throughout its clinical

development history, the ISS included all Phase 1-3 tafenoquine clinical trials conducted through 30 April 2016. These 17 studies were pooled into 3 specific analysis groups (Table 29) according to the doses of investigational product received and the dosing duration. The Summary of Clinical Safety included all studies analyzed in the ISS, plus a description of the safety outcomes of 2 tafenoquine studies that were conducted later in 2016, Study TQ-0216-01 (a PK study) and Study TQ-2016-02 (a malaria challenge study).

Table 29: Pooled Analysis Groups of Clinical Trials included in the Integrated Summary of Safety and Summary of Clinical Safety

Pooled Analysis Group	Population of Analysis Group	Studies Contributing
Short Term Exposure Data Set	Subjects receiving daily tafenoquine for a period of only 1-3 days. Group includes the majority of Phase 1 studies and 4 Phase 2 studies. Study doses ranged from 2 mg (single dose) to 500 mg daily x 3 days.	003, 006, 014, 022, 040, 043, 047, 049, 050, 052, 053, 058
Clinical Use Studies[a]	Phase 2- 3 prophylaxis and treatment studies (006, 030, 033, 043, 044, 045, 049) plus Phase 1Study 057 (the Renal-ocular Safety Study) which utilized the ACR of Tafenoquine.	006, 030, 033, 043, 044, 045, 049, 057 and 058
Extended Dosing Safety Set[b]	Subjects receiving a 3-day loading dose of tafenoquine followed by weekly or monthly exposure in controlled trials. All studies that utilized extended (weekly or monthly) dosing regimens of tafenoquine were included in this group, including the ACR. Group consists of the majority of Malaria Prophylaxis Studies (Studies 030, 033, 043, 044, and 045) and the Phase 1 Renal-ocular Safety Study (Study 057).	030, 033, 043, 044, 045, 057

[a] Included studies relevant to tafenoquine dose response
[b] Included all comparator controlled studies that utilized the tafenoquine ACR of 200 mg daily for 3 days followed by once weekly dosing of 100 mg for up to 26 weeks.

As presented in Table 29, the Short Term Exposure Data Set (Studies 003, 006, 014, 022, 040, 043, 047, 049, 050, 052, 053, and 058) allowed for the comparison of the anticipated daily dose of tafenoquine (200 mg) with doses <200 mg and doses >200 mg. In this group, which included the majority of Phase 1 studies, doses ranged from 2 mg to 500 mg daily.

The group of Clinical Use Studies included 7 Phase 2-3 prophylaxis and treatment studies (006, 030, 033, 043, 044, 045, and 049) plus one Phase 1 study (Study 057). Study 057, termed the "Renal-Ocular Safety Study", assessed specific renal and ophthalmologic safety parameters in volunteers administered the ACR of tafenoquine. The Clinical Use Studies allowed for the comparison of the tafenoquine ACR versus two different tafenoquine "loading dose only" regimens (200 mg x 3 days or 400 mg x 3 days) and versus an extended dosing regimen that utilized a higher dose than the ACR (i.e., 400 mg daily x 3 days, followed by 400 mg weekly). Placebo and Mefloquine groups were also included as comparators.

The Extended Dosing Safety Set was comprised of the majority of malaria prophylaxis studies (Studies 030, 033, 043, 044, and 045) plus the Phase 1 Renal-Ocular Safety Study (Study 057).

All controlled studies that utilized extended dosing regimens of tafenoquine, including the tafenoquine ACR, were included in this analysis group. Comparisons of subgroups within this data set allowed for the comparison of safety outcomes in subjects who received the ACR with no malaria pre-treatment medications (Studies 033 and 057) versus subjects who received the ACR after pre-treatments (subjects in three African studies - Studies 030, 043, and 045). Also, within those subjects who received the ACR, analyses of AEs in deployed military subjects (Study 033) versus non-deployed subjects (Studies 030, 043, 045, and 057) allowed for the assessment of the impact of unique deployment-related extrinsic factors.

12.2. Overall Exposure to Tafenoquine

Drug exposure by dose and duration for all clinical trials is presented in Table 30.

12.3. Safety in the Short-Term Studies: Establishing a Safe Daily Dose of Tafenoquine

In the Short-term Studies, safety was compared for tafenoquine 3-day loading doses of 200 mg once daily (OD), 200 mg twice daily (BID), and 400 mg OD. The demographics of the 3 dosage groups were comparable, with the majority of subjects being males between the ages of 20 and 49. Race was not reported in over 80% of cases.

Safety data from the Short-term Studies confirmed the superior safety/tolerability profile of the 200 mg OD loading dose as compared to either the 400 mg OD loading dose or the split-dose loading regimen (200 mg BID x 3 days). Overall, a lower percentage of subjects (31.4%) who received the 200 mg OD loading dose experienced AEs than did subjects who received either the higher 400 mg OD loading dose (56.0% subjects with AEs) or the 200 mg BID split-dose (41.0% of subjects with AEs).

Increasing the daily dose from 200 mg to 400 mg also increased the percentages of subjects who experienced gastrointestinal disorders (20.8% subjects with AEs at 200 mg OD vs. 45.3% at 400 mg OD), with dose-dependence observed for nausea, abdominal pain, diarrhea, gastrointestinal reflux disease (GERD), and flatulence.

New types of AEs that were documented at the 400 mg OD loading dose but not at the 200 mg OD loading dose included anemia, thrombocytopenia, hemolysis, increased methemoglobinemia, and keratopathy.

Although splitting the 400 mg daily dose to 200 mg BID appeared to reduce the frequency of some AEs, nevertheless, the safety profile of the 200 mg OD loading dose reduced these percentages further, offering the best safety profile over the other 2 loading regimens. Aside from safety considerations, efficacy and PK data also supported use of the 200 mg OD loading dose (to be completed pre-travel), as it ensured sufficient prophylactic concentrations of tafenoquine in the blood prior to arrival in an endemic area.

Table 30: Study Subject Drug Exposure by Dose and Duration of Exposure

Duration	Number of Subjects who Received this Tafenoquine Dosing Regimen (Study No.)									Total
	< 200 mg OD	200 mg OD	<200 mg OD x 3 days, then <200 mg weekly	200 mg OD x 3 days, then 200 mg weekly[a]	200 mg BID	Other >200 mg OD	>200 mg OD once weekly	400 mg OD x 3 days, then 400 weekly	400 mg OD x 3 days, then 400 monthly	
1 day	27 (050, 052) 10 (001)	46 (022, 052) (TQ-2016-01)	--	--	--	93 (003, 047, 050, 052, 053)		--	--	246
3 days	248 (006)	490 (006, 049)	--	--	161 (049)	610 (014, 043, 049, 058)		--	--	1509
4 days	12 (TQ-2016-02)									12
3 days with concomitant medication (DDI studies[b])	--	--	--	--	--	28 (040) 34 (015)		--	--	62
6 days	--	--	--			11 (047)		--	--	11
7 days	--	--	--		--	52 (047)		--	--	52

Table 30: Study Subject Drug Exposure by Dose and Duration of Exposure (Continued)

Duration	Number of Subjects who Received this Tafenoquine Dosing Regimen (Study No.)									Total
	< 200 mg OD	200mg OD	<200 mg OD x 3 days, then <200 mg weekly	200 mg OD x 3 days, then 200 mg weekly[a]	200 mg BID	Other >200 mg OD	>200 mg OD once weekly	400 mg OD x 3 days, then 400 weekly	400 mg OD x 3 days, then 400 monthly	
10 weeks							24 (051)			24
10-15 weeks	--	--	--	55 (043)	--	--		--	--	55
10-25 weeks	--	--	--					59 (043)	--	59
12 weeks	--	--	280 (045)	93 (045)	--	--		--	--	373
20 weeks[c]									104 (044)	104
23 weeks	--	--		81 (057)	--	--		--	--	81
24 weeks	--	--		596 (030, 033)						596
Total (Any Duration)	285	536	280	825	161	828	24	59	104	3184

[a] Anticipated clinical regimen (ACR).
[b] DDI studies: Study 040 for DDI with midazolam, flurbiprofen, and caffeine; Study 015 for DDI with desipramine.
[c] Protocol stipulated a dosing duration of 5 months, equivalent to ~ 20 weeks.

12.4. Clinical Use Studies: Safety of Extended Weekly/Monthly Dosing vs. 3-Day Loading Dose Alone

Because malaria prophylaxis must continue for the duration of an individual's stay in a malarious region, the safety of prolonged dosing was evaluated. The Clinical Use Dataset (defined in Section 12.1) was comprised of 8 studies (Studies 006, 030, 033, 043, 045, 049, 057, and 058) that allow for the comparison of two different tafenoquine "loading dose only" regimens (200 mg x 3 days or 400 mg x 3 days) versus two different prolonged dosing regimens – the ACR and an extended dosing regimen that utilized a higher dose than the ACR (i.e., 400 mg daily x 3 days, followed by 400 mg weekly). Placebo subjects were also included as comparators. In addition, Study 044 is included with the Clinical Use Studies in this analysis to allow for the comparison of monthly dosing.

As with the Short-term Studies (Section 12.3), the majority of subjects in the Clinical Use Studies were males between the ages of 20 and 49 years.

Drug exposure is presented in Table 31. Among the weekly dosing regimens, the planned prophylactic durations for Studies 033, 043, 044, 045, and 057 were 26, 10-15, 24, 12, and 24 weeks respectively. The planned prophylactic duration for Study 030 was 24 weeks. Overall, a total of 988 subjects across 6 studies (Studies 030, 033, 043, 044, 045, and 057) received tafenoquine regimens that called for either weekly or monthly dosing. These subjects showed good compliance with their extended dosing regimens, with 83.6% to 90.4% completing their prophylactic dosing as planned.

Table 31: Drug Exposure in Clinical Use Studies (Studies 006, 030, 033, 043, 045, 049, 057, and 058) and Study 044

	Tafenoquine Dosing Groups				
	Loading Dose Only		Extended Dosing (Loading Dose, then Weekly)		Extended Dosing (Loading Dose, then Monthly)
	200 mg x 3 days	400 mg x 3 days	200 mg x 3 days, then 200 mg weekly (ACR)	400 mg x 3 days, then 400 mg weekly	400 mg x 3 days, then 400 mg monthly
Studies	**006, 049**	**043, 049, 058**	**030, 033, 043, 045, 057**	**043**	**044**
N	491	713	825	59	104
Duration of Exposure (weeks)					
Mean (SD)	0.41 (0.19)	0.44 (0.09)	21.22 (8.55)	11.71 (2.68)	17.69 (5.18)
Median	0.40	0.40	26.40	12.4	20.10
Min, Max	0.3, 4.7	0.1, 1.3	0.1, 29.6	0.1, 13.4	0.4, 20.9
Subjects (n, %) with Exposure					
<3 weeks	490 (99.8%)	713 (100.0%)	25 (3.0%)	2 (3.4%)	1 (1.0%)
≥3 and <12 weeks	1 (0.2%)	0	102 (12.4%)	8 (13.6%)	18 (17.3%)
≥12 and <24 weeks	0	0	223 (27.0%)	49 (83.1%)	85 (81.7%)
≥24 weeks	0	0	475 (57.6%)	0	0
Number of Study Doses					
Mean (SD)	3.0 (0.00)	3.7 (1.26)	23.8 (8.60)	14.2 (2.91)	7.4 (1.39)
Median	3.0	3.0	29.0	15.0	8.0
Min, Max	3, 3	1, 6	1, 32	1, 16	3, 8
Completed Prophylactic Phase	491 (100%)	658 (92.3%)	690 (83.6%)	52 (88.1%)	94 (90.4%)

12.4.1. AEs in the Clinical Use Dataset

Table 32 presents selected safety findings from the Clinical Use Studies that are relevant to the choice of a tafenoquine extended dosing regimen. First among the data presented is a comparison of the percentages of subjects with AEs across the various dosing regimens. The percentages of subjects who experienced AEs in the two loading dose groups (31.4% and 56.0%) were lower than in any of the 3 extended doing regimens (83.9%, 94.9%, or 71.2%). However, when AEs were examined according to causality ("relationship to study drug"), it became apparent that, although the numbers of subjects with AEs increased with extended dosing, much of this increase was accounted for by AEs that had little or no relationship to tafenoquine. For example, in the 2 loading dose groups where tafenoquine was administered for only 3 days, 24.4% of subjects in the 200 mg group and 50.4% in the 400 mg group had an AE that was considered "related" to study drug. In the 2 extended dosing groups, where weekly tafenoquine was administered for a protracted duration, 41.4% of subjects in the 200 mg group and 52.5% in the 400 mg group reported AEs that were considered "related" to tafenoquine. Thus, less than 10% of subjects in the 3-day loading groups had AEs that were not related to tafenoquine, in comparison to over 40% of subjects in the extended dosing groups (ACR subjects and 400 mg). These findings for the extended dosing groups likely reflect the impact of subjects' random life events (eg, unrelated headaches, upper respiratory infections, accidents, injuries, etc) on safety data collection, as safety surveillance continued over many months.

Extended weekly dosing with the ACR did not increase the percentage of gastrointestinal AEs (16.2%) as compared to the 200 mg loading dose (18.5%). This positive finding anticipated good subject compliance with the oral dosing regimen, which in fact did occur, as evidenced by exposure data for the ACR group (Table 32).

Table 32: Selected Safety Findings: Clinical Use Safety Set (Studies 006, 030, 033, 043, 045, 049, 058 and 057) and Study 044

	Tafenoquine Dosing Groups			
	Loading Dose Only		Loading Dose followed by Extended Weekly Dosing	
	200 mg daily x 3 days	400 mg daily x 3 days	200 mg daily x 3 days, then 200 mg weekly (ACR)	400 mg daily x 3 days, then 400 mg weekly
Included Studies	**006, 049**	**043, 049, 058**	**030, 033, 043, 045, 057**	**043**
N	491	713	825	59
Number (%) of Subjects with at Least One AE	154 (31.4%)	399 (56.0%)	692 (83.9%)	56 (94.9%)
Number (%) of Subjects with at least One AE Related to Study Drug				
Any AE	120 (24.4%)	359 (50.4%)	340 (41.2%)	31 (52.5%)
Gastrointestinal Disorders	91 (18.5%)	295 (41.4%)	134 (16.2%)	20 (33.9%)
Infections and Infestations	2 (0.4%)	7 (1.0%)	65 (7.9%)	5 (8.5%)
Nervous System Disorders	21 (4.3%)	82 (11.5%)	104 (12.6%)	4 (6.8%)
Musculoskeletal and Connective Tissue Disorders	3 (0.6%)	5 (0.7%)	47 (5.7%)	3 (5.1%)
Injury, Poisoning, and Procedural Complications	0	0	5 (0.6%)	0
Skin and Subcutaneous Tissue Disorders	1 (0.2%)	11 (1.5%)	28 (3.4%)	9 (15.3%)
Eye Disorders	1 (0.2%)[a]	18 (2.5%)[b]	86 (10.4%)[c]	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (0.2%)	0	38 (4.6%)	0
General Disorders and Administration Site Conditions	4 (0.8%)	2 (0.3%)	26 (3.2%)	3 (5.1%)
Investigations	1 (0.2%)	24 (3.4%)	21 (2.5%)	0
Blood and Lymphatic Tissue Disorders	0	4 (0.6%)	13 (1.6%)	0
Ear and Labyrinth Disorders	0	0	15 (1.8%)	0
Psychiatric Disorders	1 (0.2%)[d]	6 (0.8%)[e]	22 (2.7%)[f]	1 (1.7%)[g]
Metabolism and Nutrition Disorders	3 (0.6%)	1 (0.1%)	13 (1.6%)	0

Table 32: Selected Safety Findings: Clinical Use Safety Set (Studies 006, 030, 033, 043, 045, 049, 058 and 057) and Study 044 (Continued)

	Tafenoquine Dosing Groups			
	Loading Dose Only		Loading Dose followed by Extended Weekly Dosing	
	200 mg daily x 3 days	400 mg daily x 3 days	200 mg daily x 3 days, then 200 mg weekly (ACR)	400 mg daily x 3 days, then 400 mg weekly
Renal and Urinary Disorders	0	0	1 (0.1%)	0
Hepatobiliary Disorders	0	0	3 (0.4%)	0
Immune System Disorders	0	0	1 (0.1%)	0

[a] One case of eye pain
[b] Includes 14 (2.0%) cases of keratopathy
[c] Includes 68 (8.2%) cases of keratopathy
[d] One subject with insomnia
[e] Five cases of insomnia and 1 case of altered mood
[f] Seven cases of insomnia, 5 abnormal dreams, 2 nightmares, 1 sleep disorder, 2 agitation, 2 depression, 2 euphoric mood, 1 bipolar disorder, 1 depressed mood, 1 neurosis
[g] One case of insomnia

12.5. Extended Dosing Set: Evaluation of the Anticipated Clinical Regimen (ACR)

The Extended Dosing Safety Set was comprised of the majority of malaria prophylaxis studies (Studies 030, 033, 043, 044, and 045) plus the Phase 1 Renal-Ocular Safety Study (Study 057). All controlled studies that utilized extended dosing regimens of tafenoquine, including the tafenoquine ACR, were included in this analysis group. Comparisons of subgroups within this data set allowed for the comparison of safety outcomes in subjects who received the ACR with no malaria pre-treatment medications (Studies 033 and 057) versus subjects who received the ACR after pre-treatments (subjects in three African studies - Studies 030, 043, and 045). Also, within those subjects who received the ACR, analyses of AEs in deployed military subjects (Study 033) versus non-deployed subjects (Studies 030, 043, 045, and 057) allowed for the assessment of the impact of unique deployment-related extrinsic factors.

12.5.1. Demographics: Extended Dosing Dataset

Table 33 compares the demographics of subjects who received the Tafenoquine ACR, Placebo, and Mefloquine. The majority of subjects in the 3 groups were male (72.0 - 83.9%) and between the ages of 20 and 49 (75.6% to 82.1%).

Among subjects who received the tafenoquine ACR, the majority were White (63.8%) and male (83.9%), with a mean age of 29.4 years. The youngest subject to receive the Tafenoquine ACR was 17 years of age; the oldest was 69. The Tafenoquine ACR and Mefloquine comparator groups were well matched with respect to age and sex; however, the ACR group included a higher percentage of Whites than the Mefloquine group (63.8% vs 51.8%) and fewer African/Black subjects (33.7% vs 47.6%). The Placebo group included a greater percentage of African/Black subjects (67.1%) and Asians (25.5%) than either the Tafenoquine ACR or Mefloquine groups.

Table 33: Subject Demographics: Tafenoquine ACR vs Placebo and Mefloquine

	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**	**030, 033, 045**
Age Categories (years)			
<20	81 (9.8%)	40 (10.1%)	41 (13.3%)
20-49	677 (82.1%)	299 (75.6%)	246 (79.6%)
≥50	67 (8.1%)	57 (14.8%)	22 (7.1%)
Mean (Range)	29.4 (17-69)	34.3 (17-60)	29.3 (17-68)
Sex (n, %)			
Male	692 (83.9%)	285 (72.0%)	254 (82.2%)
Female	133 (16.1%)	111 28.0%)	55 (17.8%)

Table 33: Subject Demographics: Tafenoquine ACR vs Placebo and Mefloquine (Continued)

	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=396)	Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)
Race (n, %)			
African	252 (30.5%)	256 (64.6%)	147 (47.6%)
Asian	9 (1.1%)	101 (25.5%)	0
Black	26 (3.2%)	10 (2.5%)	0
Hispanic/Latino	3 (0.4%)	1 (0.3%)	0
White	526 (63.8%)	26 (6.6%)	160 (51.8%)
Other	9 (1.1%)	0	2 (0.6%)

12.5.2. Treatment-Emergent Adverse Events

12.5.3. Deaths

No deaths occurred among subjects who received the Tafenoquine ACR (200 mg OD x 3 days, then 200 mg weekly).

[Note: In the tafenoquine program as a whole, one death was recorded in the safety database through 01 February 2017. This death occurred in a 53-year-old African (Ghanaian) male who had been randomized to receive tafenoquine 50 mg weekly. At 75 days after receiving his first tafenoquine dose, the subject was hospitalized for abdominal pain that had been present prior to study entry but had not been disclosed to investigators. After appropriate treatment, the subject was discharged from the hospital with the diagnosis of hepatocellular carcinoma, and he expired soon afterwards. The investigator reported the death as unrelated to tafenoquine.]

12.5.4. Treatment-Related Adverse Events Leading to Subject Discontinuation in the Tafenoquine ACR Group

In tafenoquine studies, treatment-related AEs were defined very conservatively to include even those AEs that were assessed as “unlikely” to be related to tafenoquine. The most common treatment-related adverse reactions leading to treatment discontinuation (Table 34) in Tafenoquine ACR-treated subjects were increased alanine aminotransferase (ALT) (6 subjects), decreased hemoglobin (3 subjects), and decreased glomerular filtration rate (GFR) (2 subjects). Only 1 to 2 subjects were discontinued due to AEs in other body systems. Treatment-related adverse reactions leading to treatment discontinuation in placebo-treated subjects were increased ALT (1 subject), decreased hemoglobin (1 subject), decreased platelet count (1 subject), headache (1 subject), and metamorphopsia (1 subject).

Table 34: Treatment-Related Adverse Reactions Leading to Discontinuation: Tafenoquine ACR vs. Placebo

	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly(n=825)	Placebo (n=396)
Investigations	11 (1.3)	3 (0.8)
ALT increased	6 (0.7)	1 (0.3)
Hemoglobin decreased	3 (0.4)	1 (0.3)
GFR decreased	2 (0.2)	0
Platelet count decreased	0	1 (0.3)
Infections and Infestations	1 (0.1)	0
Gastrointestinal Disorders	2 (0.2)	0
Abdominal pain upper	1 (0.1)	0
Irritable bowel syndrome	1 (0.1)	0
Nervous System Disorders	2 (0.2)	1 (0.3)
Headache	0	1 (0.3)
Hyperesthesia	1 (0.1)	0
Visual field defect	1 (0.1)	0
Psychiatric Disorders	2 (0.2)	0
Depression	1 (0.1)	0
Blood and Lymphatic System Disorders	2 (0.2)	0
Hemolytic anemia	2 (0.2)	0
Eye Disorders	3 (0.4)	1 (0.3)
Visual field defect	1 (0.1)[a]	0
Visual acuity reduced	1 (0.1)[a]	0
Night blindness	1 (0.1)[a]	0
Metamorphopsia	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	1 (0.1)	0
Hepatobiliary Disorders	1 (0.1)	0
Metabolism and Nutrition Disorders	1 (0.1)	0

[a]One of 3Eye Disorders that simultaneously affected a single subject

Among the 34 withdrawn subjects, only 16 (47.1%) were discontinued due to AEs that were considered “possibly”, “probably”, or “suspected” related to tafenoquine. The most common of these were “investigations” AEs, including increased ALT (6 cases) and decreased hemoglobin (3 cases).

Five of the 34 withdrawn subjects continued to have ongoing issues related to their AEs that persisted after their studies closed. These “ongoing” AEs included one case of lactose intolerance (Study 030), 2 cases of injuries (Study 033), and 2 cases of arthralgia of the shoulder (Study 033). All of these ongoing AEs were considered unrelated or unlikely related to tafenoquine. The remaining 29 of 34 discontinued subjects experienced full resolution of the AEs that led to their withdrawal.

12.5.5. Treatment-Related Serious Adverse Events in Subjects who Received the Tafenoquine ACR

Among subjects who received the Tafenoquine ACR, a total of 49 SAEs were reported, affecting 5.9 per 100 subjects compared to 23 SAEs in placebo-treated subjects (5.8 per 100 subjects). However, although 49 (5.7%) of subjects in the Tafenoquine ACR group experienced an SAE, only 22 (2.7%) experienced an SAE that was considered treatment-related (Table 35). [Note: As in Section 12.5.4 above, treatment-related AEs were defined very conservatively to include even those AEs that were assessed as "unlikely" to be related to tafenoquine.] Of the 23 SAEs: 7 were an eye disorder, 5 were decreased glomerular filtration rate, 4 were an infection or infestation, 4 were gastrointestinal disorders, 2 were a nervous system disorder, and 1 was a blood/lymphatic system disorder. Of the 23 SAEs in Placebo subjects, 10 were considered "treatment-related", affecting 9 (2.3%) subjects. Of these 10 treatment-related SAEs: 1 was an eye disorder, 2 were decreased glomerular filtration rate, 3 were an infection or infestation, 1 was a gastrointestinal disorder, 1 was a nervous system disorder, and 2 were general disorders and administration site conditions.

No SAE was considered to be related to tafenoquine in the following categories: psychiatric disorders; skin and subcutaneous tissue disorders, or general disorders and administration site conditions.

Table 35: Treatment-Related Serious Adverse Events: Tafenoquine ACR versus Placebo

	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045**
Total Number of SAE	49	23
Total Number (%) of Subjects with at Least One SAE	47 (5.7%)	17 (4.3%)
Total Number of Treatment-Related SAE	23	10
Number (%) of Subjects with at Least One Treatment-Related SAE	22 (2.7%)	9 (2.3%)
Eye Disorders	7 (0.8%)	1 (0.3%)
Keratopathy	5 (0.6%)	0
Retinal Disorder	2 (0.2%)	0
Metamorphopsia	0	1 (0.3%)
Infections and Infestations	4 (0.5%)	3 (0.8%)
Pneumonia	1 (0.1%)	1 (0.3%)
Gastroenteritis	1 (0.1%)	0
Helminth infections	1 (0.1%)	0
Malaria	0	1 (0.3%)
Tonsillitis	0	1 (0.3%)
Urinary tract infection	1 (0.1%)	0

Table 35: Treatment-Related Serious Adverse Events: Tafenoquine ACR versus Placebo (Continued)

	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=396)
Investigations	5 (0.6%)	2 (0.5%)
GFR decreased	5 (0.6%)	2 (0.5%)
Gastrointestinal Disorders	3 (0.4%)	1 (0.3%)
Diarrhea	1 (0.1%)	0
Abdominal pain	1 (0.1%)	0
Abdominal pain upper	1 (0.1%)	0
Irritable Bowel Syndrome	1 (0.1%)	0
Vomiting	0	1 (0.3%)
Nervous System Disorders	2 (0.2%)	1 (0.3%)
Headache	1 (0.1%)	0
Loss of Consciousness	0	1 (0.3%)
Visual Field Defect	1 (0.1%)	0
Blood and Lymphatic System Disorders	1 (0.1%)	0
Hemolytic anemia	1 (0.1%)	0
General Disorders and Administration Site Conditions	0	1 (0.3%)
Chills	0	1 (0.3%)
Pyrexia	0	1 (0.3%)

12.5.6. Adverse Events Occurring in ≥1% of Subjects in the Tafenoquine ACR Group

Adverse reactions occurring in ≥1% of subjects in the tafenoquine group and at a greater incidence than in the placebo group (Table 36) were the following: diarrhea, GERD, vomiting, chest pain, seasonal allergy, body tinea, motion sickness, keratopathy, gastroenteritis, impetigo, nasopharyngitis, otitis externa, sinusitis, tinea infection, tinea pedis, tonsillitis, viral infection, arthropod bite, heat illness, joint injury, laceration, ligament sprain, muscle strain, soft tissue injury, thermal burn, arthralgia, back pain, neck pain, lethargy, insomnia, oropharyngeal pain, heat rash, in-growing nail, and rash. Within the tafenoquine-treated subjects, subjects in study 033 were deployed military personnel who were exposed to unique deployment-related extrinsic factors whereas subjects in studies 030, 043, 045, and 057 were non-deployed and not exposed to these external stressors. The incidence of AEs in non-deployed tafenoquine-treated subjects was lower than in all subjects including the deployed soldiers, and in some cases was lower than the placebo group (Table 36).

Table 36: Adverse Events occurring in ≥1% of Subjects in the Tafenoquine ACR Group with an Incidence Numerically Greater than in the Placebo Group, Deployed vs Non-Deployed Subjects

Adverse Reaction	All Tafenoquine subjects (N=825)	Non-Deployed Tafenoquine subjects (N=333)	Placebo (N=396)
Gastroenteritis	209 (25.3%)	26 (7.8%)	17 (4.3%)
Back pain	116 (14.1%)	47 (14.1%)	26 (6.6%)
Nasopharyngitis	108 (13.1%)	11 (3.3%)	9 (2.3%)
Diarrhea	105 (12.7%)	16 (4.8%)	23 (5.8%)
Keratopathy*	68 (8.2%)	0	0
Soft tissue injury	62 (7.5%)	2 (0.6%)	0
Arthralgia	61 (7.4%)	14 (4.2%)	15 (3.8%)
Heat rash	53 (6.4%)	0	0
Viral infection	48 (5.8%)	8 (2.4%)	6 (1.5%)
Laceration	37 (4.5%)	8 (2.4%)	6 (1.5%)
Vomiting	31 (3.8%)	7 (2.1%)	6 (1.5%)
Oropharyngeal pain	30 (3.6%)	18 (5.4%)	12 (3.0%)
Tonsillitis	27 (3.3%)	11 (3.3%)	2 (0.5%)
Rash	25 (3.0%)	5 (1.5%)	2 (0.5%)
Tinea pedis	24 (2.9%)	0	0
Lethargy	24 (2.9%)	1 (0.3%)	0
Motion sickness	21 (2.5%)	0	0
Joint injury	21 (2.5%)	3 (0.9%)	0
Seasonal allergy	20 (2.4%)	1 (0.3%)	0
Chest pain	18 (2.2%)	17 (5.1%)	5 (1.3%)
Body tinea	17 (2.1%)	5 (1.5%)	4 (1.0%)
Sinusitis	17 (2.1%)	5 (1.5%)	2 (0.5%)
Muscle strain	17 (2.1%)	3 (0.9%)	2 (0.5%)
Neck pain	17 (2.1%)	5 (1.5%)	4 (1.0%)
GERD	14 (1.7%)	1 (0.3%)	1 (0.3%)
Arthropod bite	14 (1.7%)	2 (0.6%)	2 (0.5%)
Ingrowing nail	12 (1.5%)	0	0
Ear pain	11 (1.3%)	5 (1.5%)	4 (1.0%)
Otitis externa	11 (1.3%)	2 (0.6%)	4 (1.0%)
Heat illness	11 (1.3%)	0	0
Ligament sprain	10 (1.2%)	4 (1.2%)	0
Thermal burn	10 (1.2%)	1 (0.3%)	0
Insomnia	10 (1.2%)	2 (0.6%)	3 (0.8%)

Table 36: Adverse Events occurring in ≥1% of Subjects in the Tafenoquine ACR Group with an Incidence Numerically Greater than in the Placebo Group, Deployed vs Non-Deployed Subjects (Continued)

Adverse Reaction	All Tafenoquine subjects (N=825)	Non-Deployed Tafenoquine subjects (N=333)	Placebo (N=396)
Impetigo	8 (1.0%)	0	0
Tinea infection	9 (1.1%)	2 (0.6%)	0

*Early reports of corneal deposits thought to be secondary to phopholipidosis were initially reported as keratopathy and reported as SAEs. Once these were determined to be benign and reversible, later reports of keratopathy were not reported as SAEs.

12.6. Adverse Events Relevant to Prescribing Information

12.6.1. Gastrointestinal Effects

As an analogue of primaquine, tafenoquine might be expected to share some aspects of primaquine's adverse effect profile, which includes gastrointestinal side effects (nausea, vomiting, epigastric distress, and abdominal cramps (Sanofi-Aventis-2016). Nonclinical repeat-dose studies of oral tafenoquine in 3 animal species (mice, rats and dogs) linked tafenoquine to mild gastrointestinal effects (reduced food consumption and reduced weight gain). In addition, early clinical studies (Section 12.3 and Section 12.4.1) to establish the prophylactic ACR of tafenoquine suggested that gastrointestinal AEs could be anticipated with the Tafenoquine ACR, including nausea, abdominal pain, diarrhea, GERD, and flatulence.

Gastrointestinal AEs reported during clinical trials of the Tafenoquine ACR are summarized in Table 37. Gastrointestinal AEs that occurred at incidences ≥1% at the Tafenoquine ACR included: abdominal pain, abdominal pain upper, constipation, dental caries, diarrhea, dyspepsia, gastritis, GERD, nausea, and vomiting. However, among these 10 AEs, only diarrhea, GERD, and vomiting occurred at a higher incidence than in the Placebo group. These 3 AEs (diarrhea, GERD, vomiting) showed symptomatic comparability to gastrointestinal AEs seen with primaquine (abdominal cramps, epigastric distress, vomiting) and appeared to occur at a lower incidences than with primaquine (Hill et al-2006). For example, severe gastrointestinal adverse drug reactions affected up to 3% of primaquine-treated subjects in a review by Hill et al (2006). In comparison, overall discontinuations due to gastrointestinal AEs and gastrointestinal SAEs occurred in only 0.2% to 0.4% of subjects who received the tafenoquine ACR (Table 37). With respect to specific gastrointestinal SAEs or AEs that led to study discontinuation, each affected one study subject (incidence 0.1%) in the Tafenoquine ACR group.

In summary, as with primaquine, gastrointestinal AEs did occur in subjects who received the Tafenoquine ACR. However, these gastrointestinal AEs rarely led to discontinuation of tafenoquine dosing.

Table 37: Summary of Gastrointestinal Adverse Events: Tafenoquine ACR versus Placebo

	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR)(n=825)	Placebo (n=396)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**
Number (%) of Subjects with Gastrointestinal AEs leading to Discontinuation	2 (0.2%)	0
Abdominal pain	0	0
Abdominal pain upper	1 (0.1%)	0
Irritable bowel syndrome	1 (0.1%)	0
Number (%) of Subjects with Gastrointestinal SAEs	3 (0.4%)	1 (0.3%)
Abdominal pain	1 (0.1%)	0
Diarrhea	1 (0.1%)	0
Vomiting	0	1 (0.3%)
Abdominal pain upper	1 (0.1%)	0
Irritable bowel syndrome	1 (0.1%)	0
Abdominal Pain	49 (5.9%)	45 (11.4%)
Abdominal pain upper	16 (1.9%)	9 (2.3%)
Constipation	20 (2.4%)	10 (2.5%)
Dental Caries	9 (1.1%)	10 (2.5%)
Diarrhea	105 (12.7%)	23 (5.8%)
Dyspepsia	13 (1.6%)	13 (3.3%)
Gastritis	13 (1.6%)	8 (2.0%)
GERD	14 (1.7%)	1 (0.3%)
Nausea	50 (6.1%)	25 (6.3%)
Vomiting	31 (3.8%)	6 (1.5%)

12.6.2. Effects on Hematological Parameters

As an analogue of primaquine, tafenoquine might be expected to share primaquine's profile for hematological AEs, including anemia, methemoglobinemia, leukopenia, and hemolytic anemia in individuals with G6PD deficiency (Sanofi-Aventis-2016). Consistent with this, nonclinical repeat-dose studies of oral tafenoquine in 3 animal species (mice, rats and dogs) have linked tafenoquine to hematological changes (methemoglobinemia and decreased red cell parameter values, with bone marrow hyperplasia) (Section 7).

Following a review of available clinical data from malaria treatment or prophylactic studies of tafenoquine, it was concluded that tafenoquine did appear to cause mild decreases in hemoglobin (Table 38). However, in only 3 subjects (0.4% of the ACR population) did a decrease in hemoglobin lead to discontinuation of tafenoquine dosing. This 0.4% percentage was only marginally higher than in the Placebo group (0.3%). Overall, any trend for decline in hemoglobin during tafenoquine dosing had no appreciable clinical impact at the doses utilized in the Tafenoquine ACR.

As with primaquine, increased methemoglobin levels may occur with tafenoquine. In normal individuals, enzymes inside RBCs typically maintain physiological concentrations of methemoglobin at approximately 1–2%, and methemoglobin levels of 1%-3% are usually asymptomatic (Hunter-2011). Higher methemoglobin levels of 3%-15% may also be asymptomatic; however, at levels above 15%, cyanosis may occur, and at levels of 20% to 50%, patients often show dyspnea, headache, fatigue, dizziness, syncope, and weakness (Hunter-2011). Among subjects who received the Tafenoquine ACR, methemoglobin levels ≥1% were observed in 13.9% of subjects, indicating that methemoglobin levels may have mildly exceeded the physiological norm. However, no subject developed methemoglobin levels ≥ 10% (Table 38).

Hemolytic anemia occurred only rarely in the Tafenoquine ACR group, affecting 2 (0.2%) subjects.

Table 38: Incidence of Specific Hematological Findings: Tafenoquine ACR Group vs Placebo

	Number (%) of Subjects with Specific Hematological Findings	
	Tafenoquine 200 mg x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**
Studies Included	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**
Hemoglobin Decreased[a] ≥0.66 g/dL	496 (60.1%)	166 (41.9%)
Hemolytic anemia[b]	2 (0.2%)	0
Methemoglobin ≥1%	115 (13.9%)[c]	3 (6.0%)
Methemoglobin ≥10%	0	0

[a]Percentages are based on the total number of subjects in the treatment group.
[b]Hemolytic anemia was defined as a ≥15% decrease from Baseline in hemoglobin or hematocrit, together with a ≥50% decrease from Baseline in haptoglobin.
[c]Only studies 033 and 043 contributed data to the incidence of methemoglobin ≥1%.

Hematological AEs reported during Tafenoquine ACR clinical trials are summarized in Table 39. Hematological AEs leading to study discontinuation were decreased hemoglobin and hemolytic anemia, reported in 3 (0.4%) and 2 (0.2%) subjects, respectively, in the Tafenoquine ACR group. All 3 withdrawals due to decreased hemoglobin occurred in Study 045, where nontraditional withdrawal criteria directed that subjects be discontinued for even minor changes in laboratory parameters. In all 3 cases, the decrease in hemoglobin was considered mild and "non-serious", did not require treatment, and resolved in 28-50 days. Two (2) withdrawals due to hemolytic anemia occurred in Study 057, affecting a 31 year old female and a 40 year old male. Neither subject required treatment and hemoglobin normalized in both subjects within 1 month.

Although 3 hematological AEs occurred at incidences ≥1% in the Tafenoquine ACR group (anemia, leukocytosis, and thrombocytopenia), none had a higher incidence than in the Placebo group.

Similar to what was seen for gastrointestinal AEs (Section 12.6.1), although mild decreases in hemoglobin and mild increases in methemoglobin were seen in the Tafenoquine ACR group, these effects rarely led to discontinuation of tafenoquine dosing.

Table 39: Summary of Hematological Adverse Events: Tafenoquine ACR Group versus Placebo

	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR)(n=825)	Placebo (n=396)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**
Number (%) of Subjects with Hematological AEs leading to Discontinuation		
Hemoglobin decreased	3 (0.4%)	1 (0.3%)
Hemolytic anemia	2 (0.2%)	0
Number (%) of Subjects with Hematological SAEs		
Hemolytic anemia	1 (0.1%)	0
Hematological AEs Occurring in ≥1% of Study Subjects		
Anemia	10 (1.2%)	7 (1.8%)
Leukocytosis	8 (1.0%)	5 (1.3%)
Thrombocytopenia	10 (1.2%)	9 (2.3%)

12.6.2.1. Outcomes in G6PD-Deficient Subjects

Although all tafenoquine studies have routinely excluded subjects with G6PD deficiency, 8 subjects with G6PD deficiency or other hemoglobinopathies were inadvertently recruited in 5 of the tafenoquine clinical trials and received tafenoquine regimens (Table 40). In most cases, this inadvertent recruitment was due to the inherent limitations of G6PD phenotyping tests or to human error. Many of the subjects showed no signs or symptoms of hemolysis, and any who were symptomatic ultimately recovered, typically after receiving outpatient oral treatments. Only one subject, a 34-year-old Black female in Study 043, required hospitalization and transfusions. This subject had received 400 mg tafenoquine in the 3-day load-only group, a dose that is twice that of the 200 mg loading dose used in the Tafenoquine ACR.

Table 40: Subjects with G6PD Deficiency Who Inadvertently Received Tafenoquine in Sponsor's Clinical Trials

Study No. Phase G6PD Exclusion?	Details of Hematologic Adverse Event				
	Source of AE Details	**TQ Dose Received by Subject**	**Subject Demographics**	**Details on Subject's G6PD Status**	**Description of Adverse Event**
Study 043 Phase 2 G6PD deficient subjects excluded	Study 043	TQ 400 mg x 3 days (loading dose)	34 year-old Black, female, semi-immune	Subject was G6PD deficient and was mistakenly entered into study through administrative error. Subject later found to be heterozygous for the A- G6PD variant (double mutation at positions 202 and 376G).	SAE: Subject developed hemolytic anemia 2 days after starting her TQ 400 mg loading dose. Although not acutely ill, she was hospitalized, with presenting symptoms of yellow sclerae and dark brown urine. Blood tests on Day 3 showed hemoglobin had decreased from 12.6 g/dL at screening to 7.9 g/dL, hematocrit had decreased from 39% to 22%, and creatinine increased from 0.8 to 1.4 mg/dL. TQ was discontinued, and the subject recovered following a blood transfusion. She was discharged from hospital after a 3-day stay. SAE was considered definitely related to study medication.
		TQ 400 mg x 3 days (loading dose)	39-year-old Black female, semi-immune	G6PD blood test taken at screening indicated the subject was normal for G6PD deficiency. However genotyping later showed her to be G6PD homozygous for the A- variant.	Subject experienced an episode of anemia of moderate intensity within three weeks of receiving TQ 400 mg x 3 days (loading dose). This episode was at study week 3 when routine blood test showed hemoglobin of 9.1 g/dL compared to 12.2 g/dL at baseline. Subject's anemia was treated with PO medications (an iron supplement and folic acid) and was considered resolved 2 months later (hemoglobin 12.9 g/dL). This AE was considered non-serious and probably related to TQ.

Table 40: Subjects with G6PD Deficiency Who Inadvertently Received Tafenoquine in Sponsor's Clinical Trials (Continued)

Study No. Phase G6PD Exclusion?	Details of Hematologic Adverse Event				
	Source of AE Details	**TQ Dose Received by Subject**	**Subject Demographics**	**Details on Subject's G6PD Status**	**Description of Adverse Event**
Study 030 Phase 2 Exclusion for G6PD deficiency	Study 030	TQ 200 mg x 3 days (loading dose)	31-year-old Black female, semi-immune	G6PD status recorded as normal on two occasions pre-study	SAE: Subject developed mild hemolytic anemia on Day 3 of the study. At that time, bilirubin was 174.42 µmol/L compared to 38.48 µmol/L at baseline. At baseline, hemoglobin (144 g/L) and hematocrit (44%) values were within reference range, but 6 days later both had decreased [hemoglobin 90 g/L (ref 100-180 g/L), hematocrit 28.1% (ref 31-51%)]. The subject was suspected of having acute hepatitis, but investigators ultimately diagnosed the event as hemolytic anemia. Subject was treated with multivitamins and ferrous sulphate and the event resolved after 25 days. The investigator considered the hemolytic anemia to be a SAE with a suspected relationship to study treatment. Subject was withdrawn from the study.
Study TAF106491 Phase 1 Exclusion for G6PD Deficiency based on a "quantitative enzyme assay"	Study TAF106491 Miller-2013, GSK-2012	TQ 450 mg x 2 days	23-year-old, African American female, healthy volunteer	Subject passed the phenotyping test for study inclusion, but had G6PD enzyme activity at the low end of the normal range After her hemoglobin decrease, subject was retrospectively genotyped and identified as being G6PD deficient (G6PD A Santamaria phenotype).	On Day 10, the subject experienced a maximum decline in hemoglobin of 2.8 g/dL compared to baseline, without any signs or symptoms of hemolysis. The subject did not receive any concomitant medications; however, her hemoglobin values returned to baseline by Day 56.

Table 40: Subjects with G6PD Deficiency Who Inadvertently Received Tafenoquine in Sponsor's Clinical Trials (Continued)

Study No. Phase G6PD Exclusion?	Details of Hematologic Adverse Event				
	Source of AE Details	**TQ Dose Received by Subject**	**Subject Demographics**	**Details on Subject's G6PD Status**	**Description of Adverse Event**
		450 mg x 2 days	20-year-old, African American female, healthy volunteer	Passed the phenotyping test for study inclusion. After her hemoglobin decrease, subject was retrospectively genotyped and identified as being G6PD deficient (G6PD A- phenotype)	On Day 10, the subject experienced a maximum decline in hemoglobin of 3.0 g/dL compared to baseline, without any signs or symptoms of hemolysis. The subject did not receive any concomitant medications; however, her hemoglobin values returned to baseline by Day 56.
Study TAF114582 Phase 1 Subjects with <90% G6PD enzyme activity (based on site median) were excluded	Study TAF114582; Green-2014	TQ 300 mg	40- year- old Native Hawaiian female, healthy volunteer	Subject had G6PD activity screening assay showing 81% of site median (ie, a protocol violation). Subject was later found to be heterozygous WHO Class II Vanua Lava genotype	Subject showed a maximum decrease in hemoglobin of 2.1 g/dL on Day 6. Subject demonstrated reticulocytosis but recovered without any clinical symptoms or sequelae. Clinically she did not show any symptoms or signs of hemolytic anaemia. The subject recovered without sequelae.
		TQ 600 mg	28-year-old African-American female, healthy volunteer	Subject had a screening G6PD assay showing 102% of site median, consistent with protocol eligibility. Subject was found to have aWHO class III A-968 mutation	Subject had a maximum decline in her Hb of 1.9 g/dL on Day 8, associated with reticulocytosis and a rise in bilirubin. Clinically she did not show any symptoms or signs of haemolytic anaemia. No clinical AEs were recorded. The subject recovered without sequelae.

Table 40: Subjects with G6PD Deficiency Who Inadvertently Received Tafenoquine in Sponsor's Clinical Trials (Continued)

Study No. Phase G6PD Exclusion?	Details of Hematologic Adverse Event				
	Source of AE Details	**TQ Dose Received by Subject**	**Subject Demographics**	**Details on Subject's G6PD Status**	**Description of Adverse Event**
Study TAF112582 Phase 2b Subjects excluded if their G6PD enzyme activity was less than 70% of the derived site median.	Llanos-Cuentas-2014	TQ 300 mg plus chloroquine	Unidentified adult female, unspecified race, patient with *P vivax* monoinfection	Subject was identified by genotyping as heterozygous for the G6PD-deficient Mahidol variant.	Subject experienced no AEs related to hemolysis

12.6.3. Hepatic Effects

Tafenoquine PK have not been studied in persons with hepatic impairment, and persons with serum levels of ALT >60 U/L and bilirubin levels>2.0 mg/gL were excluded or infrequently entered in the pivotal clinical studies of tafenoquine. For those subjects who were enrolled in tafenoquine ACR studies under the typical exclusion criteria, no hepatic SAEs were reported in the Tafenoquine ACR group and no hepatic AEs occurred at a frequency ≥1% in that population.

As previously described (Section12.5.4), 6 subjects in the Tafenoquine ACR group of Study 045 were discontinued due to ALT elevations. This study had a high withdrawal rate due to its nontraditional withdrawal criteria, which removed any subject from study participation if their laboratory values drifted outside of those listed in the study's entry criteria (for ALT, study exclusion occurred for values > 60 U/L). Consequently, even minor, non-serious, alterations in ALT (including some ALT values below 60 U/L) became grounds for withdrawal in Study 045. As an example, the specific peak ALT values for the withdrawn subjects in Study 045 were as follows: 51 U/L, 82 U/L, 47 U/L, 68 U/L, 145 U/L, and 61 U/L. For 4 of these 6 subjects, repeat ALT values were available for the period after tafenoquine was discontinued, and all 4 subjects had normalized ALT by study's end.

As further discussed in Section 12.8, elevated ALT was reported in 12 (1.5%) subjects in the Tafenoquine ACR group; however, this was exactly the same percentage as in the Placebo group.

12.6.4. Renal Effects

Persons with serum creatinine >1.8 mg/dL were excluded from the pivotal clinical studies of tafenoquine, and tafenoquine pharmacokinetics have not been studied in persons with renal impairment.

Safety findings from nonclinical studies of tafenoquine suggested that the drug might have renal effects (tubular nephropathy, necrosis, and dilation). However, short-term dosing in clinical studies did not uncover a renal risk for tafenoquine doses of 200 mg OD (Section 12.3). Although decreased GFR was reported as an SAE in 5 (0.6%) subjects in the Tafenoquine ACR group, this percentage was comparable to Placebo (0.5%) (Section 12.5.5). Furthermore, no renal AEs were reported at incidences ≥1%, in the Tafenoquine ACR group (Section 12.5.6).

Change from baseline in GFR (mean, SD) during the first week of Tafenoquine dosing and during extended dosing periods are presented in Table 41 and Table 42, respectively, for pooled Studies 006, 030, 033, 043, 045, 049, 057, 058 and 933. Mild decreases in mean GFR over time were seen in all dosage groups in Table 41, including in the Tafenoquine ACR group, but these changes often reflected very small sample populations and did not place the overall mean GFR outside the normal range.

Table 41: Change From Baseline in GFR (Pooled Studies 006, 030, 033, 043, 045, 049, 057, 058 and 933) -- First Week

Dosage Group	Studies	First Week of Dosing: Mean (SD) Change from Baseline							
		Mean Baseline GFR[a] (SD)	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Tafenoquine 200 mg Loading Only (N=491)	006 and 049	93.3 (14.6)	0.68 (22.9)	-18.4 (14.6)	-7.54 (11.1)	-2.09 (10.5)	--	--	21.2[b] (-)
Tafenoquine 400 mg Loading Only (N=713)	043, 049, and 058	93.6 (17.0)	-8.5 (16.5)	-10.1 (15.1)	-9.9 (13.2)	-10.0 (16.9)	-8.6 (6.2)	--	--
ACR – Tafenoquine 200 mg load and weekly (N=825)	030, 033, 043, 045, and 057	105.2 (16.1)	-1.3 (11.6)	--	-7.5 (11.1)	-6.2 (8.8) (n=2)	--	--	--

[a] Expressed in mL/min/1.73 m²
[b] Represents data from 1 subject only

Table 42: Change From Baseline in GFR (Pooled Studies 006, 030, 033, 043, 045, 049, 057, 058 and 933) – Extended Dosing after Week 1

			Mean (SD) Change from Baseline									
Period after First Week of Dosing			**Week2**	**Week 3-4**	**Week 6-8**	**Week 10**	**Week 12**	**Week 16-18**	**Week 24-26**	**Follow-up Week 1-2**	**Follow-up Week 3-4**	**Follow-up Week 12**
Dosage Group	**Studies**	**Mean Baseline GFR[a] (SD)**										
Tafenoquine 200 mg Loading Only (N=491)	006 and 049	93.3 (14.6)	1.3 (25.6)	-0.4 (22.7)	--	20.1 (38.5)	--	--	--	--	--	-
Tafenoquine 400 mg Loading Only (N=713)	043, 049, and 058	93.6 (17.0)	-2.9 (16.8)	4.1 (13.3)	21.0 (14.6)	22.9 (11.4)	4.9 (14.5)	-	-	15.6 (10.0)	14.4 (11.3)	-
ACR – Tafenoquine 200 mg load and weekly (N=825)	030, 033, 043, 045, and 057	105.2 (16.1)	-6.46 (--)[b]	-13.2 (14.1)	-11.9 (14.67)	5.8 (18.4)	-5.8 (11.6)	-10.6 (12.3)	-13.4 (12.5)	11.6 (11.2)	-5.9 (14.4)	-8.0 (12.2)

[a] Expressed in mL/min/1.73 m²
[b] Only 1 subject had data for this time point.

Table 43 summarizes renal AEs for the Tafenoquine ACR group vs Placebo. In the Tafenoquine ACR group, no subject was discontinued due to a renal or urinary tract AE, and none experienced a renal or urinary tract SAE. Also, there were no renal or urinary tract AEs that occurred in ≥1% of Tafenoquine ACR subjects. With respect to renal investigations AEs (ie, investigations AEs affecting renal laboratory parameters), decreased GFR was observed in 0.6% of subjects in the Tafenoquine ACR group, but this was only slightly higher than the 0.5% percentage seen in the Placebo group. Two (0.2%) subjects in the Tafenoquine ACR group were discontinued due to decreased GFR, and both were in Study 057 (the targeted renal-ocular safety study). In both discontinued subjects, serum creatinine remained within the normal range throughout the study, and neither subject had clinically significant urinalysis findings. In both cases, the decrease in GFR was considered mild, resolved without treatment, and was considered unlikely to be related to tafenoquine. In addition to decreased GFR, mild increases in creatinine were noted. These occurred in 0.2% of the Tafenoquine ACR group, a percentage that was lower than in Mefloquine subjects (0.6%).

Table 43: Summary of Renal Adverse Events: Tafenoquine ACR Group versus Placebo and Mefloquine

	Number (%) of Subjects	
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**
Subjects with Renal AEs Leading to Discontinuation	0	0
Subjects with Renal and Urinary Tract SAEs	0	0
Renal and Urinary Tract AEs Occurring in ≥1% of Study Subjects	0	0
Number (%) of Subjects with Renal Investigations AEs leading to Discontinuation[a]	2 (0.2%)	0
GFR decreased	2 (0.2%)	0
Number (%) of Subjects with Renal Investigations SAEs	5 (0.6%)	2 (0.5%)
GFR decreased	5 (0.6%)	2 (0.5%)
Renal AEs Occurring in ≥1% of Study Subjects	0	0
Renal AEs Occurring in <1% of Study Subjects		
GFR decreased	5 (0.6%)	2 (0.5%)
Creatinine increased	2 (0.2%)	1 (0.3%)
Creatinine abnormal	1 (0.1%)	0

[a] Renal Investigations AEs include Investigations AEs that were changes in renal laboratory parameters.

Focused renal safety testing was incorporated into the protocol of Study 057 (the “renal-ocular safety study”). Study 057 was a randomized, double-blind, placebo-controlled study evaluating

the safety and tolerability (renal and ophthalmic effects) of the Tafenoquine ACR administered for 6 months in healthy males and females aged 18 to 55 years. The primary endpoint of Study 057 was the mean change from baseline GFR at 24 weeks for tafenoquine versus placebo. GFR was measured using an iothalamate clearance technique. In Study 057, it was prospectively defined that if the mean change in GFR was greater than 15% lower in the Tafenoquine group compared with the Placebo group, such a difference would be considered clinically significant. The non-inferiority limit was established as -0.247 mL/s/1.73m^2, which was -15% of the mean GFR for all subjects at Baseline. [Note: The lower boundary of the 95% CI for the observed treatment difference would need to be greater than the non-inferiority limit in order for non-inferiority to be met.] Results from the Tafenoquine ACR group and the Placebo group were compared using an analysis of covariance (ANCOVA) model, adjusting for Baseline GFR, age, gender, race, and center. It was found that the adjusted GFR increased from Baseline to Week 24 in both treatment groups. The results of the analysis clearly demonstrated that tafenoquine was non-inferior to Placebo, since the lower bound of the CI for the treatment difference (-0.168 mL/s/1.73 m^2) was greater than the established non-inferiority margin of -0.247 mL/s/1.73 m^2.

As with the primary endpoint, no notable differences between treatment groups with respect to secondary renal endpoints were observed. Specifically, mean changes in GFR at weeks 12 and 24 were similar for the Tafenoquine ACR and Placebo groups.

12.7. Other Adverse Events Affecting Specific Body Systems and Organs

12.7.1. Cardiac Effects

As an analogue of primaquine, there is the possibility that tafenoquine could share primaquine's risk for cardiac side effects, including cardiac arrhythmia and prolongation of the QT interval on ECG (Sanofi-Aventis-2016). However, based on nonclinical studies, the cardiovascular liability of tafenoquine was expected to be low (Section 7.3). Consistent with nonclinical findings, in subjects who received the Tafenoquine ACR (n=825) in 5 pooled clinical trials (Studies 030, 033, 043, 045, 057), there were no reported cardiac SAEs and no study discontinuations due to cardiac AEs. Furthermore, no cardiac AEs occurred at an incidence ≥1% in subjects who received the Tafenoquine ACR.

In a non-sponsor clinical study (TAF114582, n=260), there was no effect on Fridericia corrected QT (QTcF) prolongation after a single tafenoquine dose of 300 mg or 600 mg (Green-2014). However, a mean 6.6 msec prolongation of QTcF compared to Placebo was seen at 72 hours post-final-dose in a group that received a total tafenoquine dose of 1200 mg over 3 days (tafenoquine 400 mg x 3 days). Notably, all of these tafenoquine doses were above the tafenoquine 200 mg OD dose employed in the sponsor's Tafenoquine ACR.

12.7.1.1. Sponsor's Summary of QTc Interval and Other Electrocardiographic Findings in Six Tafenoquine Studies (Studies 014, 015, 022, 033, 050, and 051)

In the Sponsor's database, 6 l studies systematically evaluated the electrocardiographic (ECG) effects of tafenoquine.. Two (Studies 050 and 022) evaluated single doses of tafenoquine, and 4 studies evaluated multiple doses of tafenoquine (Studies 014, 015, 033, and 051. Study 033 was a tafenoquine ACR study and Study 051 assessed high-dose tafenoquine administered once-weekly. A total of 340 subjects participated in these 6 studies, with 276 subjects receiving

tafenoquine, 42 placebo, 1 no treatment, and 21 mefloquine. Tafenoquine single doses ranged from 4 mg to 600 mg. The highest cumulative dose (6000 mg) was administered in Study 051, where 600 mg tafenoquine was administered once weekly for 10 weeks.

QTcF Prolongation in Individual Subjects: Overall, among the 276 tafenoquine-exposed subjects, only 4 (1.4%) had a QTcF measurement >450 msec that occurred only at a time point other than at screening or baseline, in comparison to 2 (4.8%) of the 42 Placebo subjects. No subject at any time point had a QTcF value >480 msec.

QTcF Prolongation in Single Dose Studies: There was no dose-related increase in mean QTc change from baseline for tafenoquine single doses of 250 mg to 600 mg.

QTcF Prologation in Multiple Dose Studies: For the Tafenoquine ACR in Study 033, mean plasma tafenoquine concentration at the final prophylaxis visit was 315.88 ± 74.84 ng/mL. At this tafenoquine concentration, after 26 weeks of Tafenoquine ACR dosing, the mean QTcF interval change from baseline was -4.5 msec (-9.7, 0.7) msec, arguing against any QTc prolongation effect. At tafenoquine weekly doses of up to 600 mg for 10 weeks (Study 051), where tafenoquine C_{max} after Dose 10 (range 455-783 ng/mL) was up to 2.5 times higher than the C_{max} observed in Tafenoquine ACR Study 033 (315.88 ± 74.84 ng/mL), there was no consistent evidence of QTcF prolongation. These findings are consistent with the results of a previously published tafenoquine thorough QT/QTc study (Green-2014), which concluded that tafenoquine did not have a clinically meaningful effect on cardiac repolarization.

12.7.2. Respiratory, Thoracic, and Mediastinal Disorders

In animals, findings in repeat dose studies of tafenoquine included effects in the lung indicative of phospholipidosis (proteinosis, edema, macrophage accumulation and increased lung weight). As part of the Phase 3 program, monitoring for the effects of phospholipidosis was performed on a subset of troops (n=95) in Study 033. In this subset, baseline pulmonary assessments (chest x-rays and lung function testing) were performed, and then repeated after 6 months dosing with investigational product. No abnormalities were found.

Among the overall population of subjects who received the Tafenoquine ACR (n=825) in 5 pooled clinical trials (Studies 030, 033, 043, 045, 057), there were no reported study discontinuations or SAEs in the category of Respiratory, Thoracic, and Mediastinal Disorders. Among the 3 AEs in that category that occurred at an incidence ≥1% in subjects who received the Tafenoquine ACR (cough, nasal congestion, and oropharyngeal pain), only one (oropharyngeal pain) occurred at a higher incidence than in Placebo subjects (3.6% vs 3.0%, respectively).

12.7.3. Visual Disorders

Ophthalmologic AEs reported during clinical trials of the Tafenoquine ACR are summarized in Table 44. Ophthalmologic AEs leading to study discontinuation were night blindness and reduced visual acuity, both of which affected the same patient (incidence 0.1%) in the Tafenoquine ACR group. Keratopathy was reported as an SAE in 0.6% of subjects in the Tafenoquine ACR group, and the SAE of “retinal disorders” occurred in 0.2%.

Eye disorders that occurred at incidences ≥1% in the Tafenoquine ACR group were conjunctivitis and keratopathy. Conjunctivitis occurred at a lower incidence (2.9%) than in the Placebo population (4.5%). Keratopathy is discussed in Section 12.7.3.1.

Table 44: Summary of Ophthalmologic Adverse Events: Tafenoquine ACR Group versus Placebo

	Number (%) of Subjects	
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR)(n=825)	**Placebo (n=396)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**
AEs leading to Discontinuation		
Metamorphopsia	0	1 (0.3%)
Night blindness	1 (0.1%)	0
Visual acuity reduced	1 (0.1%)	0
Number (%) of Subjects with Ophthalmologic SAEs	7 (0.8%)	1 (0.3%)
Keratopathy	5 (0.6%)	0
Retinal disorder	2 (0.2%)	0
Metamorphopsia	0	1 (0.3%)
Ophthalmologic AEs Occurring in ≥1% of Study Subjects		
Conjunctivitis	24 (2.9%)	18 (4.5%)
Keratopathy	68 (8.2%)[a]	0

[a]All reports are from Study 033.

12.7.3.1. Keratopathy

Keratopathy was noted in early clinical studies of tafenoquine at daily doses higher than the dose (200 mg) employed in the Tafenoquine ACR (Section 12.3). Subsequently, 5 cases of keratopathy were identified in an early cohort of the Tafenoquine ACR group in Study 033. As a result, 74 of the 492 subjects in the Tafenoquine ACR group of Study 033 underwent more detailed ophthalmic assessments to identify vortex keratopathy at screening and at the 6-month visit. At the end of the study's prophylactic period (6-month visit), 69 (93.2%) of the 74 subjects had developed keratopathy. However, there were no changes in tests of visual fields, visual acuity, or color vision in these subjects. The majority of subjects with keratopathy (42 of 69) had resolution at 3 months after the end of the prophylactic period, while the remainder had complete resolution of their keratopathy within 1 year after the end of tafenoquine dosing. An expert ophthalmology advisory board reviewed the ophthalmologic findings from Study 033 and concluded that the observed corneal changes were benign and fully reversible.

As a follow-up to Study 033, the aim of Study 057 was to provide further evidence of the ophthalmic safety of tafenoquine for its use as an antimalarial agent (Leary-2009). Although the corneal deposits observed in Study 033 had resulted in no evident effects on vision, their possible effect on night vision had not been evaluated. Since impairment of night vision would prevent active duty soldiers from fully performing their duties, the possibility of tafenoquine adversely affecting night vision was investigated in Study 057. Retinal and night vision effects were

assessed using multiple tests including measurement of forward light scatter (FLS), low contrast visual acuity (LCVA), mesopic contrast threshold (MCT), and scotopic contrast threshold (SCT). The primary ophthalmic safety endpoint was the number of subjects with impaired night vision due to corneal deposits, as measured by the FLS test. The corneal deposits themselves were documented as abnormal eye test results and were not reported as AEs. Overall, there were no FLS test failures in either treatment group. The results of the primary ophthalmic safety analysis clearly showed that night vision was unimpaired in the tafenoquine-treated group. The secondary ophthalmic safety endpoints that assessed deterioration in night vision via LCVA, MCT, and SCT testing showed similar findings for tafenoquine ACR subjects and Placebo subjects. In summary, there was no evidence in this study that exposure to tafenoquine had an adverse effect on the retina.

In Study 057, 10 (14.3%) subjects in the Tafenoquine ACR group and 7 (21.9%) subjects in the Placebo group had evidence of corneal deposits in either eye at screening. After the screening visit, 15 (2l.4%) subjects receiving tafenoquine and 4 (12.5%) subjects receiving placebo developed new-onset corneal deposits in one or both eyes during the study. Approximately 60% of the cases among subjects receiving tafenoquine and 100% of the cases among subjects receiving placebo emerged by Week 12 of the study. No trends were apparent with respect to the time to onset of new corneal deposits in subjects who did not have these deposits at screening. New-onset corneal deposits in all 4 subjects in the Placebo group resolved within 6 weeks of onset, while in the Tafenoquine ACR group, corneal deposits resolved within 12 weeks of onset in all but one subject. Corneal deposits in the remaining tafenoquine-treated subject resolved by Week 48.

In summary, although there is no evidence that exposure to tafenoquine has an adverse effect on the retina, vortex keratopathy (manifesting as benign corneal deposits) has been noted in some subjects treated with the tafenoquine ACR. These corneal changes did not impact vision, and they resolved within 1 year in all cases.

12.7.3.2. Retinal Effects

When cases of keratopathy were identified in an early cohort of subjects (healthy adult volunteers) in Study 033, selected subjects underwent more detailed ophthalmic assessments. These included fundoscopy, which was performed at baseline (before tafenoquine dosing) and at 3 months post-prophylaxis (ie, at 3 months after the last tafenoquine dose) in 69 subjects in the Tafenoquine ACR group and 17 in the Mefloquine group. Examiners who performed the fundoscopy were aware of subjects' corneal deposits (if present) and were therefore unblinded in that respect. Fundoscopic examinations revealed abnormalities (eg, granularity/pigmentation of retinal pigment epithelium, hard drusen) in 27 of 69 (39.1%) Tafenoquine ACR subjects and in 4 of 17 (23.5%) Mefloquine subjects. Vision was not affected in any of these individuals. Among the subjects with retinal findings, fundus fluorescein angiograms (FFA) were performed in 15 of the 31 cases and were considered abnormal in 4 of 14 (28.6%) of the Tafenoquine ACR subjects and in 1of 1 (100%) Mefloquine subjects. When an expert ophthalmology board was asked to review this data, relevance of the retinal findings (based on fundoscopy and FFA) could not be ascertained because no baseline retinal photography data was available. The ophthalmology board noted that the results observed could reflect normal variability and the subjective nature of the examinations. They did not consider that the FFA results provided evidence of a drug effect.

In Study 058, adult subjects with confirmed *Pv* malaria received either tafenoquine 400 mg/day for 3 days (Days 1 – 3), or combination treatment with chloroquine and primaquine (chloroquine 100 mg on Days 1 and 2, chloroquine 500 mg on Day 3, and primaquine 15 mg on Days 3 through 16). Retinal safety assessments were performed at baseline (before dosing with investigational product) and on Study Days 28 and Day 90. Retinal pigmentation was documented at the Day 28 assessment in 9 (19.6%) of patients with *P vivax* malaria who received tafenoquine 400 mg/day x 3 days, and this pigmentation was still present in 8 of the 9 tafenoquine-treated malaria subjects at Day 90. In comparison, 1 (4.2%) of the *P vivax* subjects who received chloroquine with primaquine developed retinal findings. As in Study 033, the presence of retinal findings was not associated with any change in vision. An IDMC, which included 2 ophthalmic experts, reviewed all of the ophthalmologic safety data for all subjects through the Day 28 assessment. Both ophthalmic experts concurred that there was no difference in visual function tests between the tafenoquine 400 mg group and the chloroquine with primaquine group. They also had no major concerns regarding findings in the digital photographs of the corneas or retinas, and they agreed that the eye findings did not raise undue concern, since visual function did not change. In addition, a blinded review of the retinal digital photographs conducted at the Fundus Photograph Reading Center, University of Wisconsin, found no evidence of anatomical changes consistent with retinal toxicity. The findings of the IDMC and blinded review of the digital retinal photographs were confirmed by an ophthalmology advisory board, which reviewed all of the ophthalmology safety data from the study and were in unanimous agreement that there was no evidence from the data presented of any impact on vision in subjects taking tafenoquine. The board also concluded that there was no evidence from assessment of the digital fundus images for any retinal toxicity.

To provide further evidence of the ophthalmic safety of tafenoquine at the dose used for antimalarial prophylaxis, a 6-month study (Study 057) was conducted in healthy volunteers to compare the Tafenoquine ACR versus Placebo. Retinal examinations were performed at the following time points: at baseline (before dosing with tafenoquine); during the 6-month dosing phase of the study (at 3 weeks, 6 weeks, 12 weeks, 18 weeks, and 24 weeks); and at the Follow-up safety visit (at 12 weeks after tafenoquine dosing was completed). Retinal changes and impact on macular function were documented at each time point for each eye of every subject. Macular function tests included Amsler Grid, Humphrey Perimetry Test, high contrast visual acuity (HCVA), and color vision “color assessment and diagnosis” (CAD) test. There was no evidence in this study that exposure to tafenoquine had any adverse effect on the retina.

Assessment of macular function via the Amsler Grid Test, demonstrated no abnormalities in either eye for any subject in the tafenoquine group. Sporadic abnormalities across both treatment groups with the Humphrey Perimetry Test revealed no trends with respect to study treatment. Failures with the HCVA Test were more frequent among tafenoquine subjects at the Week 6 and Week 12 time points; however, at Follow-up, the incidence of failures was higher in the Placebo group. A retinal abnormality (described as an area of retinal pigmentation that was not near the fovea) was identified by digital photography in the right eye of 1 subject (1.8 % of the population) who received the Tafenoquine ACR. In that subject, the retinal changes were seen only at the Follow-up visit. There were no retinal abnormalities in any subject in the Tafenoquine ACR group during the dosing phase of the study. In the Placebo group, 1 subject (3.7% of the population) also had a retinal abnormality, which was similarly detected at the Follow-up visit.

This study confirmed that administration of the Tafenoquine ACR for 6 months did not cause retinal toxicity in healthy subjects.

12.7.4. Nervous System Effects

Nervous system AEs reported during clinical trials of the Tafenoquine ACR are summarized in Table 45. Nervous system AEs leading to study discontinuation in the Tafenoquine ACR group were hyperesthesia and visual field defect, each of which affected 1 (0.1%) subject. Neither of these AEs was considered severe. They are described as follows:

- In Study 033, a 26-year-old White male ADF soldier, hepatitis B carrier positive, reported hyperesthesia of moderate intensity on Study Day 12. Before experiencing hyperesthesia, study personnel had documented at least 1 episode of heavy alcohol use in this subject, together with alcohol-associated malaise while on study (reported as AEs on Study Day 2). Hyperesthesia, considered "suspected" related to tafenoquine, was treated by unspecified non-medicinal modalities and resolved after 130 days.
- In Study 057, a 45-year-old White female was discovered to have a mild visual field defect on ophthalmologic testing, together with mild night blindness and mildly reduced visual acuity on Study Day 21. The subject was withdrawn from the study, and her AEs resolved without treatment approximately 6 weeks after onset. All three AEs were considered "suspected" related to tafenoquine.

The two SAEs in the ACR group were visual field defect and headache, each of which occurred in 1 (0.1%) subject. The subject with visual field defect has been described above. The single subject with the SAE of headache is described below:

- In Study 030, a 50-year-old female with a history of abdominal-pelvic pain was enrolled in the trial's Tafenoquine ACR arm and was experiencing sinusitis at baseline. She developed gastroenteritis approximately 1 month later (Day 34), together with a severe headache beginning on Study Day 37. She reported using multiple non-prescription medicinal products, including turpentine oil, clove oil, eucalyptus oil, menthol, camphor, and capsaicin. After reporting her headache, she remained in the study and was treated with non-prescription analgesics. The subject's headache resolved after 49 days, during which time she also reported abdominal pain, backaches, and an upper respiratory tract infection. Her SAE of headache was considered unlikely related to tafenoquine.

Headache, dizziness, or lethargy affected ≥1% of the Tafenoquine ACR population (Table 45). Headache and dizziness were reported in a smaller percentage of Tafenoquine ACR subjects than Placebo and Mefloquine-treated subjects.

Table 45: Summary of Nervous System Adverse Events: Tafenoquine ACR Group vs Placebo and Mefloquine

	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR)(n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**	**030, 033, 045**
Number (%) of Subjects with AEs leading to Discontinuation			
Headache	0	1(0.3%)	0
Hyperesthesia	1 (0.1%)	0	0
Visual field defect	1 (0.1%)	0	0
Number (%) of Subjects with Nervous System SAEs			
Headache	1(0.1%)	0	0
Loss of consciousness	0	1(0.3%)	0
Visual field defect	1 (0.1%)	0	0
AEs Occurring in ≥1% of Study Subjects			
Headache	178 (21.6%)	125 (31.6%)	92 (29.8%)
Dizziness	22 (2.7%)	25 (6.3%)	17(5.5%)
Lethargy	24 (2.9%)	0	11 (3.6%)

When only treatment-related nervous system AEs were compared for the Tafenoquine ACR vs. Placebo (Table 46), the overall percentages were comparable for the 2 groups (3.8% vs. 3.5%, respectively). Percentages with headache (1.9%) and dizziness (0.8%) in the Tafenoquine group were lower than in the Placebo (2.5% and 1.0%) and Mefloquine (2.6% and 2.3%) groups. Only lethargy occurred more frequently in the tafenoquine ACR population (1.1%) compared to Placebo (0%) and Mefloquine (0.3%). Notably, all cases of lethargy reported among Tafenoquine subjects occurred in deployed military subjects in Study 033. These soldiers were limited to sleeping in 4-hour shifts due to their participation in patrols and combat during the night. In contrast, no cases of lethargy were reported among non-deployed resident populations who received the Tafenoquine ACR.

Table 46: Treatment-Related Nervous System AEs Occurring in ≥1% of Study Subjects

Nervous System Adverse Events[a]	Subjects with Adverse Event, n(%)		
	Tafenoquine ACR (n=825)	Placebo (n=396)	Mefloquine (n=309)
Headache	16 (1.9%)	10 (2.5%)	8 (2.6%)
Dizziness	7 (0.8%)	4 (1.0%)	7 (2.3%)
Lethargy	9 (1.1%)*	0	1 (0.3%)*
Total	32 (3.8%)	14 (3.5%)	16(5.2%)

* All cases of Treatment-Related Lethargy occurred in Deployed troops. None occurred in Non-Deployed Resident populations

[a] Includes AEs that were considered possibly, probably, or definitely related to study drug.

12.7.5. Ear and Labyrinth Disorders

Motion sickness was reported in 21 (2.5%) subjects in the Tafenoquine ACR population. All 21 of these cases occurred in deployed military personnel in Study 033; none occurred in non deployed subjects. In 4 of the 21 military cases, the verbatim term “sea sickness” was used to describe the AE. In these 4 cases, the sea sickness was reported as continuous but short-lived (1 day duration), which is consistent with a brief period of transport in a ship. All AEs of sea sickness were successfully treated with either Kwells® (hyoscine hydrobromide), or Maxolon™ (metoclopramide hydrochloride), and all were considered “not related” to tafenoquine.

Among the remaining 17 military subjects with motion sickness, the AE was reported as mild and intermittent, and, in the majority of cases (11 of 17, or 64.7%), it was considered “not related” to tafenoquine. About half of the affected subjects (8 of 17, or 47.1%) did not require treatment, while the remainder were successfully treated with hyoscine hydrobromide, prochlorperazine, or metoclopramide hydrochloride. In 10 of the 17 cases, the condition resolved either on the soldier’s day of departure from East Timor, or within 7 days post-departure, suggesting that the motion sickness was triggered or exacerbated by deployment-related travel (in ground vehicles, in aircraft, or by ship). This type of deployment-related travel is a recognized risk factor for motion sickness among military populations (Coyne-2008; Benson-2002).

Also in Study 033, the potential for concomitant medications to either cause, or contribute to, subjects’ motion sickness cannot be ruled out. For example, antiparasitic medications (albendazole and ivermectin) were routinely administered prophylactically to all deployed soldiers, and antiparasitic medications are known to exacerbate motion sickness (Erskine-2015).

12.7.5.1. Tinnitus in the Tafenoquine ACR Population

There were 3 reports of tinnitus among subjects who received the tafenoquine ACR, and 2 of these occurred in military personnel enrolled in Study 033. In both military cases, the tinnitus was assessed as mild, did not require treatment, and was considered unrelated to study medication. Attributing causality in military cases of tinnitus is confounded by the fact that military deployment is known to present a high risk for tinnitus as a result of exposure to the

loud noises associated with firing weapons and explosions, as well as soldiers' close proximity to noisy vehicles and heavy equipment (US Department of Veterans Affairs-2015). In the retrospective East Timor Health Study of ADF personnel who had been deployed to East Timor (1999-2005), the prevalence of self-reported symptoms of tinnitus was 38% (Kirk-2011). In addition to exposure to loud noises, the authors of this study concluded that a variety of chemical exposures (e.g., heavy metals, intense smoke, and engine exhaust) may have also affected the development of tinnitus in ADF personnel deployed to East Timor.

The third reported case of tinnitus occurred in the right ear of a healthy female volunteer during the safety follow-up phase of Study 057. Onset was several weeks after tafenoquine dosing had ended. As in the 2 military cases, the tinnitus was described as mild, and it did not require treatment. Relationship to study drug was considered unlikely.

12.7.6. Psychiatric Adverse Events

Psychiatric AEs reported during clinical trials of the Tafenoquine ACR are summarized in Table 47 . Psychiatric AEs leading to study discontinuation in the Tafenoquine ACR group included depression and a suicide attempt, each of which occurred in 1 (0.1%) subject as follows:

- In Study 043, a 24-year-old Kenyan male subject was withdrawn due to the SAE of alcohol intoxication/intentional self-injury (coded as a "suicide attempt") that occurred on Study Day 7 (total of 3 loading doses and 1 weekly dose of tafenoquine 200 mg). While acutely intoxicated with ethanol, the subject's self destructive actions ("taking poison") had been reportedly prompted by marital problems. The subject was hospitalized, tafenoquine was discontinued, and the SAE was considered resolved in 2 days. The suicide attempt was considered to be of "severe" intensity but "not related" to tafenoquine.
- In Study 033, a 28 year-old White ADF soldier with a history of intracranial head injury, reported moderate depression beginning on Study Day 24. He was withdrawn from the study and treated with paroxetine, and his depression resolved after 87 days. The subject's depression was considered "suspected" related to tafenoquine.

In comparison, there were no psychiatric discontinuations in the Placebo group, while in the Mefloquine group, one subject was discontinued due to anxiety.

Only one psychiatric AE occurred at an incidence ≥1% in the Tafenoquine ACR group. This was insomnia, which affected 1.2% of subjects in the Tafenoquine ACR group (Table 47).

Notably, both the Tafenoquine ACR group and the Mefloquine groups included deployed military populations exposed to hostile environments, which may have increased their risk for psychiatric AEs. This issue is discussed in Section 12.7.6.1.

Table 47: Summary of Psychiatric Adverse Events: Tafenoquine ACR Group versus Placebo and Mefloquine

	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**	**030, 033, 045**
Number (%) of Subjects with Psychiatric AEs leading to Discontinuation			
Anxiety	0	0	1 (0.3%)
Depression	1 (0.1%)	0	0
Suicide attempt	1 (0.1%)*	0	0
Number (%) of Subjects with Psychiatric SAEs			
Anxiety	0	0	1 (0.3%)[a]
Suicide attempt	1 (0.1%)[a]*	0	0
Psychiatric AEs Occurring in ≥1% of Study Subjects			
Insomnia	10 (1.2%)	3 (0.8%)	1(0.3%)
Psychiatric AEs Occurring in ≤1% of Study Subjects			
Abnormal dreams	5 (0.6%)	0	2 (0.6%)
Sleep disorder	3 (0.4%)	0	2 (0.6%)
Nightmare	3 (0.4%)	0	1 (0.3%)
Depression	2 (0.2%)	0	1 (0.3%)
Agitation	2 (0.2%)	0	0
Anxiety	0	0	2 (0.6%)
Anxiety Disorder	2 (0.2%)	0	0
Euphoric mood	2 (0.2%)*	0	0
Bipolar disorder	1 (0.1%)*	0	0
Depressed mood	1 (0.1%)*	0	0
Neurosis	1 (0.1%)	0	0
Panic attack	1 (0.1%)*	0	0
Stress	1 (0.1%)*	0	0
Suicide attempt	1 (0.1%)*	0	0
Somnambulism	0	0	1 (0.3%)
Loss of libido	0	0	1 (0.3%)

[a]SAE led to discontinuation

*Indicates that all AEs in this category were considered unrelated or unlikely related to tafenoquine. Categories with no asterisk included some AEs that were considered possibly or probably related to tafenoquine.

12.7.6.1. Impact of Military Deployment on Psychiatric Adverse Effects

When monitoring the tolerability of a drug under military operational conditions, investigators must consider the physiological and psychological stressors associated with such activities that may affect reports of psychiatric AEs (Kitchener-2005). In studies of prophylactic antimalarial drugs in military populations, there is evidence that the incidence of neuropsychiatric AEs (eg, adjustment disorder, insomnia, anxiety disorder) is higher in deployed versus non-deployed populations, especially when deployment occurs under combat conditions (Eick-Cost-2017, Kitchener-2005). An elevated risk for neuropsychiatric symptoms and conditions is expected in deployed populations, and this risk is evident even for FDA-approved antimalarials with no known neuropsychiatric AE profile (eg, doxycycline, atovaquone/proguanil) (Eick-Cost-2017, Kitchener -2005).

A review of psychiatric data from Study 033 revealed that the military subjects in that study had a unique psychiatric AE profile compared to subjects in other Tafenoquine ACR studies. This suggested that subjects in Study 033 might have been exposed to factors that placed them at a higher risk for psychiatric AEs. It should be noted that this study did not include a placebo control group for ethical reasons. Therefore, the placebo-controlled comparator studies did not include deployed soldiers, making the placebo-controls under representing those events occurring in this unique population.

The study population of Study 033 was comprised of ADF soldiers deployed on United Nations peacekeeping duties in East Timor from October 2000 to April 2001. All participants were healthy adults, ages 18-55, G6PD normal, with no history of psychiatric disorders or seizures.

An independent study by Waller (2012), has detailed the specific types of psychological stressors to which Study 033 ADF forces were likely exposed as part of their peacekeeping deployment in East Timor. The subjects' type of military operation was described as “warlike” (Waller-2012). Warlike operations, as defined by the Australian Government, are those military activities where the application of force is authorized and where there is an expectation of casualties (Kirk-2011). Consistent with this violent environment, specific traumatic exposures reported by ADF personnel deployed to East Timor during the time at which Study 033 was conducted included the following (Waller-2012):

- danger of being injured (71% of ADF reported this);
- danger of being killed (71%);
- witness to human degradation and misery on a large scale (58%);
- saw dead bodies (49%);
- feared that you had been exposed to a toxic agent, contagious disease, or injury (31%);
- heard of a close friend or co-worker injured or killed (30%);
- handled dead bodies (28%); and
- present when a close friend or co-worker was injured or killed (13%).

Non-traumatic stressors included the threat of danger (67%) and health concerns (52%) (Waller-2012).

Among ADF personnel deployed to East Timor, independent research has indicated that 7.2% eventually developed symptoms of post-traumatic stress disorder (PTSD) and 6.9% had a long-term high level of psychological stress, based on data gathered in 2007-2009 (7-9 years after deployment) (Waller-2012).

Overall, these findings support the hypothesis that the environment to which Tafenoquine ACR subjects and Mefloquine subjects in Study 033 were exposed was a psychologically hostile environment that could potentially foster the development of neuropsychiatric AEs (Novitt-Moreno-2017). This same effect was documented in a similar population of ADF peacekeeping forces in East Timor who took part in a study of mefloquine versus doxycycline (Kitchener-2005).

Compounding this psychologically hostile environment were the actual physical insults and injuries which the soldiers experienced as a result of their warlike deployment (Table 48). For example, subjects in the Tafenoquine ACR and Mefloquine groups had roughly five times (28.0% and 26.2%, respectively) the risk for injuries/poisonings/complications than those in the Placebo group (5.8%). Combined moderate and severe injuries/poisonings/complications were also much higher for the Tafenoquine ACR group (8.7%) and Mefloquine Group (4.5%) versus Placebo (1.3%).

In terms of causality, over 97% of the injuries/poisonings/complications in the Tafenoquine ACR and Mefloquine Groups were considered “not related” to the study drug (Table 48), supporting the fact that these AEs reflected the effects of war rather than drug effects. In reality, the subjects in Study 033 not only experienced the psychological threat of injury, but also the true physical experience of injury. Notably, AEs which were seen only in the Tafenoquine ACR or Mefloquine Groups, but not in the Placebo Group, included the following: soft tissue injury, joint injury, heat illness, ligament sprain, thermal burn, arthropod sting, limb injury, animal bite, excoriation, injury, joint dislocation, gas poisoning, back injury, foreign body, gunshot wound, foreign body in eye, limb crushing injury, craniocerebral injury, foot fracture, heat exhaustion, neck injury, procedural pain, respiratory fume inhalation disorder, barotitis media, chemical eye injury, corneal abrasion, facial bones fracture, hand fracture, meniscus lesion, radius fracture, sports injury, animal scratch, ankle fracture, avulsion fracture, chemical burn of skin, chest injury, concussion, electric shock, epicondylitis, eye injury, face injury, lip injury, lower limb fracture, multiple fractures, muscle injury, nail injury, post-procedural hemorrhage, post-traumatic pain, tendon injury, tooth injury, upper limb fracture, and wrist fracture.

Unique deployment-related psychological stressors and combat-related injuries are among the influential “extrinsic factors” to which subjects in Study 033 were exposed and which did not affect subjects in other Tafenoquine ACR studies (Novitt-Moreno-2017). However, in spite of the stressful environment to which the Tafenoquine ACR Deployed subjects were exposed, the incidence of psychiatric AEs was less than 4% in the Tafenoquine ACR Total Population (Table 48), and the majority of psychiatric AEs were mild (84.4%) (Table 49).

Table 48: Number (%) of Subjects with Injury-Related AEs vs Psychiatric AEs: Tafenoquine ACR Group vs Placebo and Mefloquine

	Total Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**	**030, 033, 045**
Total Number (%) of Subjects with AES: Injury, Poisoning, and Procedural Complications	231 (28.0%)	23 (5.8%)	81 (26.2%)
Total Number (%) of Subjects with Moderate or Severe AES: Injury, Poisoning, and Procedural Complications	72 (8,7%)	5 (1,3%)	14 (4.5%)
Total Number (%) of Subjects with Psychiatric AES	32 (3.9%)	3 (0.8%)	10 (3.2%)

Table 49 presents psychiatric AEs by severity grade and relationship to study drug for the Tafenoquine ACR Group compared to Placebo and Mefloquine. Within the Tafenoquine ACR and Mefloquine populations, Deployed and Non-Deployed groups are compared as well.

Deployed subjects accounted for the majority of subjects with psychiatric AEs in both the Tafenoquine ACR and Mefloquine populations, representing 25 (78.1%) of 32 in the Tafenoquine ACR group and 7 (70.0%) of 10 in the Mefloquine group. Among both the Deployed Tafenoquine ACR and Deployed Mefloquine populations, the majority of psychiatric AEs (84.0% and 85.7%, respectively) were assessed as mild, and the majority were considered not related or unlikely related to the study drug (52.0% and 57.2%, respectively).

Table 49: Psychiatric AEs, Severity Grade and Relationship to Study Drug, Tafenoquine ACR Group vs Placebo and Mefloquine

		Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR)			Mefloquine 250 mg daily x 3 days, then 250 mg weekly		
	Placebo (n=396)	**Total ACR Population (n=825)**	**Deployed Subjects in Study 033 (n=492)**	**Non-Deployed Subjects (n=333)**	**Total Mefloquine Population (n=309)**	**Deployed Subjects in Study 033 (n=162)**	**Non-Deployed Subjects (n=147)**
Total Number (%) of Subjects with Psychiatric AES	3 (0.8%)	32 (3.9%)	25 (5.1%)	7 (2.1%)	10 (3.2%)	7 (4.3%)	3 (2.0%)
AE Severity							
Total No. of Subjects Reporting AEs	3	32	25	7	10	7	3
Mild	2 (66.7%)	27 (84.4%)	21 (84.0%)	6 (85.7%)	8 (80.0%)	6 (85.7%)	2 (66.7%)
Moderate	1 (33.3%)	4 (12.5%)	4 (16.0%)	0	1 (10.0%)	1 (14.3%)	0
Severe	0	1 (3.1%)	0	1 (14.3%)	1 (10.0%)	0	1 (33.3%)
AE Relationship to Study Drug: Psychiatric AEs							
Total No. of Subjects Reporting AEs	3	32	25	7	10	7	3
Not Related	0	10 (31.3%)	9 (36.0%)	1 (14.3%)	4 (40.0%)	3 (42.9%)	1 (33.3%)
Unlikely	2 (66.7%)	8 (25.0%)	4 (16.0%)	4 (57.1%)	2 (20.0%)	1 (14.3%)	1 (33.3%)
Possibly	1 (33.3%)	13 (40.6%)	11 (44.0%)	2 (28.6%)	4 (40.0%)	3 (42.9%)	1 (33.3%)
Probably	0	1 (3.1%)	1 (4.0%)	0	0	0	0
Definitely	0	0	0	0	0	0	0

To further explore the potential impact of a hostile environment on psychiatric AEs among military personnel in the Tafenoquine ACR group, the percentages of subjects with specific types of AEs were compared (Table 50) for the Tafenoquine ACR group as a whole (n=825) versus the Deployed military subjects in Study 033 (n=492), Non-Deployed non-ADF subjects who received the Tafenoquine ACR (n=333), and Placebo (n=396). Among Deployed ADF forces in Study 033, injuries impacted 39.8% of subjects overall, while psychiatric AEs occurred in 5.1%. In comparison, in non-deployed non-ADF subjects who received the Tafenoquine ACR, injuries occurred in only 10.5% of subjects, while psychiatric AEs affected about 2.1%. Hence, the military subjects of Study 033, with a much higher injury-related environmental stress level and overall psychiatric stress level, showed a higher level of psychiatric AEs than did the non-military subjects in the other Tafenoquine ACR studies. In subjects who received Placebo, only 5.8% reported injuries/poisonings/procedural complications, and the incidence of psychiatric AEs was correspondingly low (0.8%). However, 3 out of 3 (i.e., 100%) cases of psychiatric AEs were considered related to the study drug in the Placebo group, compared to only 22 of 32 (i.e., 69%) in Deployed ACR subjects.

Table 50 also presents the percentages of subjects with specific types of psychiatric disorders, comparing deployed ADF subjects who received the Tafenoquine ACR in Study 033 to those who received Placebo. Among the reported psychiatric disorders, only insomnia occurred at a rate of > 1% of subjects in both groups. Among the 25 deployed ADF subjects who experienced psychiatric disorders, the majority [18 (72%) of 25] developed problems impacting sleep (insomnia, abnormal dreams, nightmares, sleep disorder). In comparison, among non-deployed subjects, sleep AEs affected only 3 (43%) of 7 subjects with psychiatric AEs. This finding that sleep-related AEs impacted deployed military subjects underscores the potentially dramatic effect that deployment can have on sleep in military populations (Peterson-2008, Plumb-2014). All (100%) of sleep disturbance AEs were considered related to the study medication in the Placebo and Non-Deployed ACR groups, while a lower percentage (66.7%) was considered related to tafenoquine in the Deployed ACR group.

Table 50: Subjects with Psychiatric AEs in Tafenoquine ACR Populations: Deployed Military (ADF) Subjects in Study 033 versus Placebo Subjects and Non-Deployed Subjects Who Received Tafenoquine ACR

	Placebo (n=396)	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR)		
		All Subjects (n=825)	Deployed ADF Military (ADF) Subjects (n=492)	Non-Deployed Subjects (n=333)
Number (%) of Subjects with Injury, Poisoning, and Procedural Complications	23 (5.8%)	231 (28.0%)	196 (39.8%)	35 (10.5%)
Number (%) of Subjects with Psychiatric Disorders	3 (0.8%)	32 (3.9%)	25 (5.1%)	7 (2.1%)
Psychiatric Disorders Considered Related to Study Drug[a]	*3 (0.8%)*	*22 (2.7%)*	*16 (3.3%)*	*6 (1.8%)*
Number (%) of Subjects with Psychiatric Disorders Affecting Sleep	3 (0.8%)	21 (2.5%)	18 (3.7%)	3 (0.9%)
Sleep Disorders Considered Related to Study Medication	*3 (0.8%)*	*15 (1.8%)*	*12 (2.4%)*	*3 (0.9%)*
No. (%) of Subjects with Psychiatric AEs Affecting Sleep				
Insomnia	3 (0.8%)	10 (1.2%)	8 (1.6%)	2 (0.6%)
Abnormal dreams	0	5 (0.6%)	5 (1.0%)	0
Nightmares	0	3 (0.4%)	3 (0.6%)	0
Sleep Disorder	0	3 (0.4%)	2 (0.4%)	1 (0.3%)
Number (%) of Subjects with Other Psychiatric Disorders (i.e., not specifically affecting Sleep)				
Agitation	0	2 (0.2%)	2 (0.4%)	0
Anxiety disorder	0	2 (0.2%)	2 (0.4%)	0
Depression	0	2 (0.2%)	1 (0.2%)	1 (0.3%)
Euphoric mood	0	2 (0.2%)*	2 (0.4%)*	0
Bipolar disorder	0	1 (0.1%)*	0	1 (0.3%)*
Depressed mood	0	1 (0.1%)*	0	1 (0.3%)*
Neurosis	0	1 (0.1%)	0	1 (0.3%)*
Panic attack	0	1 (0.1%)*	1 (0.2%)*	0
Stress	0	1 (0.1%)*	1 (0.2%)*	0
Suicide attempt	0	1 (0.1%)*	0	1 (0.3%)*

[a] "Related" includes unlikely, possibly, probably or definitely related.
*Indicates that all AEs in this category were considered unrelated or unlikely related to tafenoquine.

12.7.6.2. Adverse Events Affecting Sleep in the Deployed ACR Population: Relationship to Study Medication

Sleep problems, particularly insomnia, are highly prevalent during military deployments and insomnia is often reported, not only during actual combat operations (Gill-2014), but also post-deployment after combat ends (McLay-2010). In a recent exhaustive study sponsored by the US Secretary of Defense, the RAND National Defense Research Institute (US) concluded that sleep problems—particularly insomnia, short sleep duration, and nightmares—are highly prevalent during combat operations (Troxel-2015). These findings are relevant to the present analysis, as they support the conclusion that tafenoquine exposure was not the cause of an increased burden of sleep-related AEs in the deployed ADF population,

To examine whether specific extrinsic factors could be identified in subjects who reported psychiatric AEs in the Deployed ACR subgroup versus the Resident Non-Deployed subgroup, medical histories and non-psychiatric AEs were reviewed for mitigating factors (Table 51 and Table 52).

As shown in Table 51, concurrent gastrointestinal illnesses, active pain, or upper respiratory illnesses affected 8 out of 10 subjects with insomnia or sleep disorders in the Deployed ADF subgroup and 2 of 3 subjects in the Non-Deployed subgroup. When these confounding illnesses and events were eliminated, comparable percentages (0.3%-0.4%) of the two subgroups experienced insomnia or sleep disorders. In terms of the Tafenoquine ACR Overall population, although insomnia or sleep disorder was reported in 1.6% of this population, only 3 of 825 subjects (0.4% of the Tafenoquine ACR Overall population) did not have an identifiable concurrent illness or injury that might have contributed to their inability to sleep.

Table 51: Mitigating Factors among Subjects with Adverse Events of Insomnia or Sleep Disorder: Tafenoquine ACR Population

Subgroup	Subjects with Insomnia or Sleep Disorder, n (%)	No. Subjects with Concurrent Illness/Injury, n (%)[a]			
		Gastrointestinal	Active Pain[b]	Upper Respiratory	None
Deployed Subjects (n=492)	10 (2.0%)	5 (1.0%)[c]	6 (1.2%)	2 (0.4%)[d]	2 (0.4%)
Non-Deployed Subjects (n=333)	3 (0.9%)	0	2 (0.6%)	0	1 (0.3%)
Tafenoquine ACR Total Population (n=825)	13 (1.6%)	5 (0.6%)	8 (1.0%)	2 (0.2%)	3 (0.4%)

[a] Some subjects had illnesses or injuries in more than one category
[b] Includes back pain, various musculoskeletal complaints, and pain due to injuries
[c] Includes gastroenteritis, diarrheal illness, and abdominal pain
[d] Includes upper respiratory tract infections, allergies, and hay fever

As shown in Table 52, abnormal dreams/nightmares affected only Deployed subjects and did not occur in the Non-Deployed Group. Either head injuries or active pain affected 4 (50%) of the 8 Deployed subjects with abnormal dreams/nightmares. Only 3 subjects had no mitigating factors in play.

Table 52: Mitigating Factors among Subjects with Abnormal Dreams/Nightmares: Tafenoquine ACR Population

Subgroup	Subjects with Abnormal Dreams/ Nightmares n (%)	No. Subjects with Concurrent Illness/Injury, n (%)[a]				
		Head Injury	Gastrointestinal	Active Pain[b]	Upper Respiratory	None
Deployed Subjects (n=492)	8 (1.6%)	2 (0.4%)	0	2 (0.4%)	1 (0.2%)	3 (0.6%)
Non-Deployed Subjects (n=333)	0	0	0	0	0	0
Tafenoquine ACR Total Population (n=825)	8 (1.0%)	2 (0.2%)	0	2 (0.2%)	1(0.1%)	3 (0.4%)

[a] Some subjects had illnesses or injuries in more than one category.
[b] Includes back pain, various musculoskeletal complaints, and pain due to injuries.
[c] Includes gastroenteritis, diarrheal illness, and abdominal pain.
[d] Includes upper respiratory tract infections, allergies, and hay fever.

12.7.6.3. Neuropsychiatric "Prodromal Symptoms" in the Tafenoquine ACR Population

As discussed in Section 2.4.1 above, a cluster of prodromal symptoms has been identified for mefloquine neuropsychiatric toxicity, including the following: abnormal dreams/nightmares, insomnia or sleep disorder, depression or depressed mood, and anxiety or anxiety or anxiety disorder. The incidences of these types of events is presented in Table 53 below for the Tafenoquine ACR population (Deployed and Non-deployed) compared to Placebo. Prodromal symptoms in subjects who received the Tafenoquine ACR were almost entirely limited to the Deployed ACR population. This population was exposed to military stressors, as discussed above (Section 12.7.6.1), and were likely influenced by combat conditions (Novitt-Moreno-2017). In contrast, only one Non-deployed ACR subject had any prodromal symptom. This was insomnia, which occurred at the same incidence (0.3%) in both the Non-Deployed ACR and Placebo groups.

Table 53: Incidence of Neuropsychiatric Prodromal Symptoms in Tafenoquine ACR Populations (Deployed and Non-deployed) vs. Placebo

Prodromal Neuropsychiatric Treatment-related[a] Adverse Events	N (%) Placebo (n=396)	Tafenoquine ACR Deployed (n=492)	Tafenoquine ACR Non-Deployed Residents (n=333)
Abnormal dreams or nightmares	0	7 (1.4%)	0
Insomnia or sleep disorder	1 (0.3%)	4 (0.8%)	1 (0.3%)
Depression or depressed mood	0	1 (0.2%)	0
Anxiety or anxiety disorder	0	0	0
Total	1 (0.3%)	0	1 (0.3%)

[a] Assessed as possibly, probably, or definitely related to study drug.

12.7.6.4. Neuropsychiatric Adverse Events Reported to the Australian Therapeutic Goods Administration (TGA) Related to Study 033 in Australian Military Personnel

Between February 18th and 23rd, 2017, a total of 17 cases referencing tafenoquine and involving potential neuropsychiatric AEs were reported to the Australian Therapeutic Goods Administration (TGA). GSK shared information internationally for 4 of these 17 cases in the form of 4 IND Safety Reports (INDSR), which were provided to the Sponsor and to all investigators worldwide on 08 June 2017. GSK indicated that the four INDSR referred to four of their CSD Safety Database Numbers. Details of these 4 cases are provided in Appendix A, Table 56, which summarizes the AE information that was reported to the TGA for each subject and compares this information to the trial safety information that is contained in the Sponsor's database. Based on Sponsor's information, 1 of the 4 subjects had no neuropsychiatric ARs reported during the study, while 2 of the subjects had only mild symptoms (motion sickness/vertigo or anxiety) that were considered to be unrelated to tafenoquine. Only one subject had AEs (mild abnormal dreams and mild-moderate insomnia) that were suspected of having a relationship to the study drug. However, these sleep disturbances began on Study Day 0 and occurred in the context of the subject's ongoing back pain (present at enrollment) and new-onset shoulder pain that were concurrent medical problems during the trial.

Aside from the 4 subjects described above, there were 12 additional subjects with TGA reports whose identification information was limited to date of birth (DOB). By using DOB, 8 of these 12 subjects were tentatively matched to a subject who had participated in Study 033. Only 1 of the 8 DOB-matched subjects had any psychiatric AEs reported during Study 033. This subject reported 15 days of lethargy/somnolence that began 4 days after he received his final tafenoquine dose and coincided with his post-deployment return home. Notably, the subject also reported AEs of "increased appetite", "increased thirst", and "nausea" for the same 15 days during this same post-deployment period. In contrast, no lethargy/somnolence was reported by this subject during his 27 weeks of tafenoquine dosing.

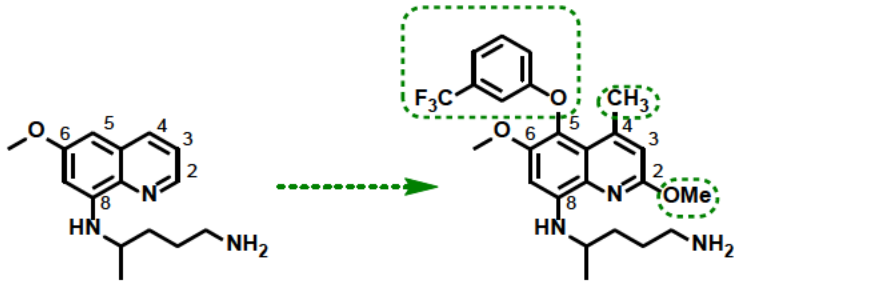
Seven (7) of the 8 had no psychiatric AEs reported during study participation, and all 8 subjects identified by DOB successfully completed their full regimen (26-28 weeks) of tafenoquine dosing.

12.7.7. Summary: Tafenoquine Does not have a Neurologic Liability

The utility of mefloquine in malaria chemoprophylaxis has been hampered by its neuropsychiatric liability. Evidence from the literature and presented herein does not suggest tafenoquine has a neurologic liability:

- Tafenoquine is congener of primaquine, an 8-aminoquinoline used for 70 years without any known neurotoxicity (Hill-2006, Recht-2014) (Figure 6). Reflecting this consensus, the label for primaquine does not contain specific language or a boxed warning in relation to neuropsychiatric events (Sanofi-aventis-2017).

Figure 6: Comparison of the Structure of Tafenoquine with Primaquine

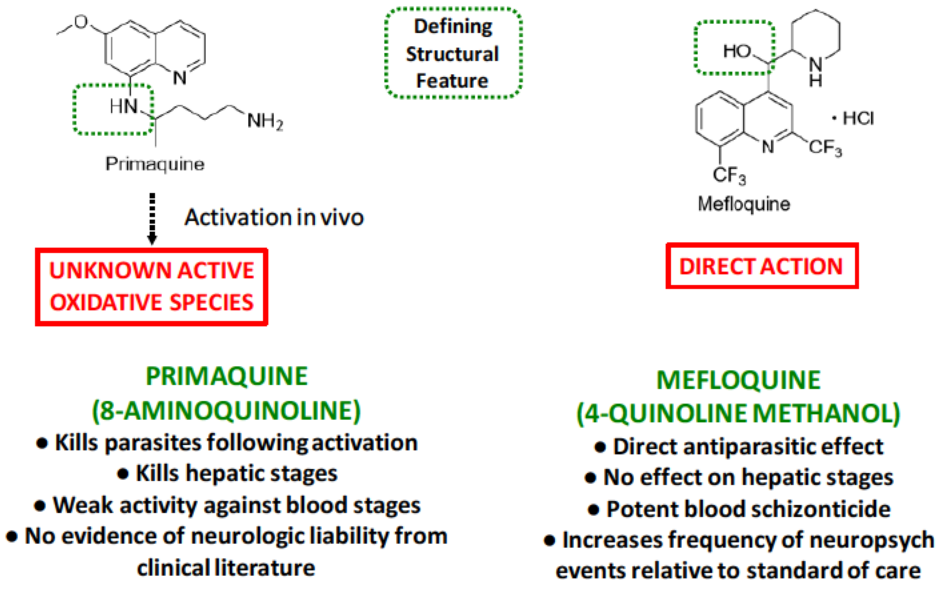


PRIMAQUINE
- **Half-Life: 6h**
- **Kills hepatic stages**
- **Weak activity against blood stages**
- **No evidence of neurologic liability from clinical literature**

TAFENOQUINE
- **Half-Life: 14 days**
- **Kills hepatic stages**
- **Kills blood stages in vivo**
- **No evidence of neurologic liability from Sponsor database**

- In contrast, mefloquine is a 4-quinoline-methanol with a different mechanism of action that is intrinsically linked to its substantially different chemical structure (Figure 7)

Figure 7: Pharmacodynamics of Primaquine Compared with Mefloquine



- In terms of its chemical structure, tafenoquine is 4-methy substituted, a substitution that has been proven to abolish neurotoxicity in Rhesus monkeys (Schmidt-1983)
- Although mefloquine showed behavioral neurotoxicity and produced histopathologic brain abnormalities in rats (Dow-2006), tafenoquine was free from both of these effects (Dow-2017) (Section 7.1).
- Clinical signs of neurotoxicity can occur when the 8-aminoquinolines plasmocid, pentaquine, or pamaquine are administered to monkeys and humans. However, no such signs were observed with primaquine, the 8-aminoquinoline most closely related to tafenoquine (Section 7.2). In three published studies (Puri-2003; Dow-2011 and Ditusa-2014), and a toxicokinetic study (submitted with NDA 210607), in which 55 Rhesus monkeys were given tafenoquine at various doses up to a total dose of 48 mg/kg (27x higher than the 95% radically curative dose of tafenoquine), no plasmocid, pamaquine or pentaquine-like neurologic signs were reported. Furthermore, at the minimum lethal dose, the cause of death was hepatotoxicity (not neurotoxicity), and no CNS lesions were observed in those animals for which necropsy was performed. Therefore, in Rhesus monkeys, tafenoquine exhibited a safety margin consistent with that of primaquine.
- Nasveld et al (2010) reported an overall incidence of AEs (including neuropsychiatric AEs) that was similar in the tafenoquine and mefloquine arms of Study 033. However, it is erroneous to conclude that both drugs result in the same number of adverse drug reactions (as opposed to adverse events), because no placebo could be included in Study 033 as it involved a non-immune population on active military deployment (Section 12.7.6). The observations of Nasveld are not surprising given that military deployment is a major risk factor for neuropsychiatric events (Section

12.7.6.1 and Section 12.7.6.2) and the environment of Study 033 (Timor Leste) was considered a "war-like" by the Australian government (Section 12.7.6.1). In that context (i.e., deployed soldiers exposed to the stressors of war), military studies have shown that the burden of neuropsychiatric illness is similarly increased regardless of the chemoprophylactic drug used to prevent malaria (Eick-Cost-2017). Also, because mefloquine is a nocebo (Overbosch-2001), the relative risk of neuropsychiatric events would be expected to increase in the tafenoquine arm of any study where mefloquine was a comparator.

- Although the incidence of insomnia and abnormal dreams increased with deployment in Study 033, this is not surprising given the war-like environment (Section 12.7.6.2). Moreover, the absolute incidence of these events decreased to the level of placebo once mitigating factors that could contribute to sleep disturbances were taken into account (Table 51 and Table 52 above).
- There is also no evidence of an increase in nervous system AEs for tafenoquine relative to placebo in non-deployed populations (Table 46).
- A cluster of prodromal symptoms has been identified for mefloquine neuropsychiatric toxicity (Section 12.7.6.3). However, there is no evidence that tafenoquine increases the incidence of such events relative to placebo in a resident population not exposed to military stressors.
- Tafenoquine has been administered to n=2192 subjects at doses equivalent or higher than the anticipated prophylactic dose. To date, there has been only one severe neuropsychiatric SAE among Tafenoquine ACR subjects that has not been considered "unrelated" to tafenoquine. This was an episode of severe headache in a subject in Study 030, which occurred in the context of longstanding sinusitis and use of multiple non-prescription medicinal products (turpentine oil, clove oil, eucalyptus oil, menthol, camphor, capsaicin). The headache did not result in the subject's discontinuing medication and was considered "unlikely" related to tafenoquine. Case histories for each subject experiencing "neuropsychiatric AEs" in Study 033 showed that many were directly attributable to other factors in the study regardless of blinded treatment assignment.
- There is no evidence that the neuropsychiatric AEs reported to regulatory authorities by ADF veterans constitute adverse drug reactions. Events alleged to have contemporaneously occurred with drug administration in Studies 033 and 049 could not be verified, were mild in nature, or unrelated to study medication. Events alleged to have occurred many years after these studies have no temporal relationship with tafenoquine administration. It is therefore not plausible that they represent adverse drug reactions.

12.8. Clinical Laboratory Evaluations

Table 54 presents a summary of clinical laboratory AEs reported for the Tafenoquine ACR group versus Placebo and Mefloquine. Overall, AEs in this category were observed in fewer subjects in the Tafenoquine ACR group (3.4%) than in either the Placebo Group (5.6%) or the Mefloquine

Group (5.5%). The majority of Investigations AEs in the Tafenoquine ACR group were graded as mild (19 of 28), and the most frequently observed were abnormalities in hepatic enzymes (affected 1.6% of Tafenoquine ACR subjects).

As previously described (Section 12.6.3), 6 subjects in the Tafenoquine ACR group of Study 045 were discontinued due to mild ALT elevations to comply with nontraditional protocol procedures. However, for the ACR group as a whole (Table 54), elevated ALT AEs were reported in only 12 (1.5%) subjects the same percentage as in the Placebo group.

Compared to Placebo subjects or Mefloquine subjects, subjects in the Tafenoquine ACR group experienced fewer AEs related to hepatic enzyme abnormalities, bilirubin changes, or changes in hematology parameters.

Decreased GFR was noted in 5 subjects in the Tafenoquine ACR group (Table 54). As previously discussed (Section 12.6.4), focused renal safety testing was incorporated into the protocol of Study 057 (the "renal-ocular safety study") to further examine the renal safety of tafenoquine. Study 057 was a randomized, double-blind, placebo-controlled study evaluating the safety and tolerability (renal and ophthalmic effects) of the Tafenoquine ACR versus Placebo administered for 6 months in healthy adult volunteers. The study demonstrated that tafenoquine was not inferior to placebo in its primary endpoint, which was the mean change from baseline GFR at 24 weeks for tafenoquine versus placebo. Additionally, no notable differences between treatment groups with respect to the multiple secondary renal endpoints were observed.

Table 54: Summary of Investigations AEs: Tafenoquine ACR Group versus Placebo and Mefloquine

	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**	**030, 033, 045**
Number (%) of Subjects with Investigations AEs	28 (3.4%)	22 (5.6%)	17 (5.5%)
Mild	19 (2.3%)	15 (3.8%)	14 (4.5%)
Moderate	0	2 (0.5%)	2 (0.6%)
Severe	0	0	0
AE Intensity Missing	9 (1.1%)	5 (1.3%)	1 (0.3%)
Number (%) of Subjects with Specific Investigations AEs			
Any Hepatic Enzyme AE	13 (1.6%)	7 (1.8%)	6 (1.9%)
ALT increased	12 (1.5%)	6 (1.5%)	4 (1.3%)
ALT abnormal	1 (0.1%)	1 (0.3%)	1 (0.3%)
Liver function test abnormal	0	0	1 (0.3%)

Table 54: Summary of "Investigations" AEs: Tafenoquine ACR Group vs Placebo and Mefloquine (Continued)

	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Any Bilirubin AE	3 (0.4%)	5 (1.3%)	6 (1.9%)
Blood bilirubin abnormal	1 (0.1%)	4 (1.0%)	3 (1.0%)
Blood bilirubin increased	2 (0.2%)	1 (0.3%)	3 (1.0%)
Any Renal Function AE	9 (1.1%)	3 (0.8%)	4 (1.3%)
GFR decreased	5 (0.6%)	2 (0.5%)	0
Blood creatinine increased	2 (0.2%)	1 (0.3%)	2 (0.6%)
Blood creatinine abnormal	1 (0.1%)	0	1 (0.3%)
Blood creatinine decreased	0	0	1 (0.3%)
Urine analysis abnormal	1 (0.1%)	0	0
Any Hematology AE	4 (0.5%)	6 (1.5%)	3 (1.0%)
Hemoglobin decreased	3 (0.4%)	1 (0.3%)	0
Platelet count decreased	0	2 (0.5%)	2 (0.6%)
Hematocrit increased	0	1 (0.3%)	1 (0.3%)
Full blood count abnormal	1 (0.1%)	0	0
Hematocrit abnormal	0	1 (0.3%)	0
Hematocrit decreased	0	1 (0.3%)	0

12.9. Ongoing Study of Long-Term Dosing with Tafenoquine

The Sponsor has proposed that the initial label allow for 6 months of continuous dosing, which reflects the duration of the Phase 3 study. However, military deployments often exceed 6 months, and therefore ongoing Study 60PH04 was conceived to support a proposed future label change to allow for up to 12 months continuous dosing. The Sponsor elected to initiate this study prior to submission of the NDA due to the anticipated long duration of the study.

Ongoing Study 60PH04 is a randomized, double-blind, placebo-controlled study in 600 healthy G6PD-normal volunteers. Participants who meet the eligibility criteria are randomized (ratio 1:1 to receive a loading dose of either tafenoquine 200 mg (2 x 100 mg tablets) or placebo daily for three consecutive days, followed by study treatment (tafenoquine 200 mg or placebo) once per week for 51 weeks, with safety follow-up visits at Weeks 4, 12, 24, and 52. Due to the long half-life of tafenoquine, all participants will return to the clinic at Week 64 for their end-of-study visit. If a participant has an ongoing AE, they will continue with additional safety assessments for up to 3 more times at approximately 12-week intervals or until resolution or stabilization of the AE, whichever is earlier.

The primary objective of Study 60PH04 is to assess the ophthalmic safety of tafenoquine after 12 months of exposure versus placebo. Secondary objectives are to assess the long-term safety and tolerability of tafenoquine versus placebo by clinical monitoring of vital signs, ECG, laboratory data, reporting of AEs, and psychiatric changes (baseline vs end of study). Study 60PH04 tracks psychiatric safety during long-term tafenoquine administration through use of the M.I.N.I. 7.0.2 (Mini International Neuropsychiatric Interview, Version 7.0.2). The study also assesses sleep disturbances through administration of the Leeds Sleep Evaluation Questionnaire (LSEQ).

12.10. Safety Analysis by Race

To facilitate safety comparisons by race for extended dosing with the tafenoquine 200 mg regimen, the AE profiles by racial group for 5 studies was compared (Table 55) as follows: 3 studies with an entirely (100%) Black/African population (Studies 030, 043, 045); 1 study with a 98.4% White population (Study 033); and 1 study with a 100% Asian population (Study 058). Although subjects in Study 058 received a dose of 400 mg tafenoquine for 3 days, this 1200 mg-total-dose regimen results in the same cumulative dose as the ACR being administered for the 28-day period during which the primary efficacy endpoint (cure) was assessed.

Among the 3 studies that enrolled entirely Black/African populations, the percentages of subjects with at least 1 AE ranged from 11.8% in Study 045 to 94.2% in Study 030. (Note: The unusually low percentage of AEs in Study 045 was a direct result of that study's nontraditional definitions for AEs, which were primarily based on fluctuations in laboratory parameters.) In comparison, the percentages of subjects with AEs in the predominantly White population of Study 033 and the entirely Asian population of Study 058 were 92.3%, and 100%, respectively.

Except for nontraditional Study 045, the number of withdrawals across races was similar in the 5 studies and amounted to <5% of subjects. With respect to SAEs, these occurred in 0 to 10.9% of subjects, with the highest percentage being in the Asian population of Study 058.

Table 55: Comparison of Tafenoquine Safety Outcomes in Five Studies that Enrolled Three Different Racial/Ethnic Groups

Study	Safety Population (n)	Predominant Race	Subjects with at Least 1 AE (n,%)	Subjects with an SAE (n,%)	Subjects Withdrawn due to an AE (n,%)
030	104	Black/African (100%)	98 (94.2%)	8 (7.7%)	5 (4.8%)
043	55	Black/African (100%)	50 (90.9%)	1 (1.8%)	1 (1.8%)
045	93	Black/African (100%)	11 (11.8%)	2 (2.2%)	10 (10.8%)
033	492	White (98.4%)	454 (92.3%)	18 (3.7%)	11 (2.2%)
058	46	Asian (100%)	46 (100%)	5 (10.9%)	0

12.11. Safety Analysis by Gender

Among subjects in the Tafenoquine ACR group (n=825), there were 692 (83.9%) males and 133 (16.1%) females. Overall, females had a lower incidence of AEs (74.4%) than did males (85.7%).

The frequencies of those AEs occurring in ≥1% of the subjects in these studies were mostly similar between males and females with some exceptions. AEs reported in males but not in females were keratopathy, body tinea, impetigo, otitis externa, tinea pedis, heat illness, muscle strain, and ingrowing nail. Dysmenorrhea was the only AE reported in females but not in males.

Other differences between the genders where there was ≥ 5% difference in incidence were the following:

Higher Incidence in Females

- anemia (6.0% females vs 0.3% males);
- fatigue (6.0% females vs 1.0% males);
- abdominal pain (11.3% females vs 4.9% males);
- decreased appetite (6.0% females vs 1.0% males);
- back pain (19.5% females vs 13.0% males);
- headache (36.1% females vs 18.8% males);
- cough (10.5% females vs 5.2% males).

Higher Incidence in Males

- gastroenteritis (28.5% males vs 9.0% females);
- diarrhea (13.9% males vs 6.8% females);
- nasopharyngitis (14.6% males vs 5.3% females); and
- heat rash (7.4% males vs 1.5% females).

Higher incidences of anemia and fatigue in females may have been linked to menstrual blood loss, while higher incidences of gastroenteritis, diarrhea, nasopharyngitis, and heat rash in males were likely related to the rigors of military deployment in a jungle setting (Study 033).

12.12. Pediatric Use

Safety and effectiveness in children have not been established.

12.13. Geriatric Use

Clinical studies did not include sufficient numbers of subjects 65 years of age and over to determine if they respond differently than younger subjects.

Only one subject over age 65 received tafenoquine in any of the Sponsor's clinical trials. This subject was a 69-year-old Black female who was administered the Tafenoquine ACR in Study 045. She successfully completed the study and experienced no AEs.

12.14. Pregnancy and Lactation

In nonclinical reproductive toxicology studies of tafenoquine, no adverse effects on fertility or embryofetal development (including at maternally toxic doses), or on post-natal survival, were observed. Tafenoquine was not teratogenic in segment II (embryo-fetal) studies in rats or rabbits, including at 30 mg/kg/day in rats which is equivalent to 8-times the daily human dose based on comparison of human equivalent. In a Segment I study in rats, there were no effects on mating and fertility indices, estrous cycles, sperm motility, sperm count or morphology, nor on any caesarean section parameters, including embryofetal development, when tafenoquine was given at doses of 5 mg/kg/day.

In clinical trials of tafenoquine, pregnant women have been routinely excluded. However, as of October 2014, there had been a total of 25 pregnancies reported in association with tafenoquine clinical studies, 18 of which were in subjects who had received tafenoquine. Outcomes of these 18 were as follows:

- Four had uncomplicated pregnancies, with uncomplicated deliveries of healthy offspring. Three of these subjects had first trimester tafenoquine exposure, while the fourth conceived at approximately 6 weeks after the last tafenoquine dose.
- Two had spontaneous abortions that occurred in the first trimester and both abortions were considered unrelated to tafenoquine. The first subject developed menorrhagia 11 days after a positive pregnancy test, and a subsequent ultrasound revealed no fetus. Similarly, the second subject also experienced vaginal bleeding (a “menstrual period”) at 8 weeks gestation, and a subsequent pregnancy test was negative.
- Six pregnancies ended in elective abortions.
- One pregnant subject was lost to follow-up.
- Five reported suspected pregnancies were not confirmed by subsequent laboratory tests. These were considered probable false positive results.

Females of reproductive potential should use effective contraception while taking tafenoquine for malaria prevention. In addition, consistent with the long half-life of tafenoquine, use of effective contraception should continue for 5 half- lives (3 months) after the end of treatment.

No preclinical studies have been conducted to determine if tafenoquine or any of its metabolites are excreted in breast milk.

Prescribing information proposed by Sponsor for Pregnancy and Lactation is consistent with the above preclinical data and clinical review. In the absence of clinical data on lactation risk and risk to persons of reproductive potential, Sponsor has taken a conservative and proposed the risks reported for the congener drug primaquine (Hill-2006). That is, the Sponsor proposes that tafenoquine should not be administered to lactating women unless the infant tests negative for G6PD deficiency (Hill-2006), and that tafenoquine is contraindicated in pregnancy because the status of the fetus with respect to G6PD deficiency is unknown.

12.15. Drug-Drug Interactions

An in vitro assessment was conducted of the effect of tafenoquine on the renal transporters multidrug and toxin extrusion transporter 1 (MATE1), MATE2-K and organic cation transporter 2 (OCT2), and tafenoquine was found to be a more potent inhibitor of these renal transporters than the positive control, cimetidine. Because inhibition of renal transporters may result in increased exposure to the medications they excrete, the risk for adverse effects may increase as well. Examples of medications excreted by OCT2, MATE1 and MATE2-K include dofetilide and procainamide. To date, no subject administered the Tafenoquine ACR has concomitantly received any of these medications.

Tafenoquine may inhibit drug transporters in the kidney. Since inhibition of these transporters may lead to increased exposure to medications that they excrete, when tafenoquine is co-administered with, substrates or inhibitors of MATE or OCT2, it may be advisable to re-evaluate safety and/or efficacy of the latter drugs.

Drugs/foods such as sulfonamides, dapsone, furazolidone, fava beans, and nalidixic acid may, like tafenoquine, cause hemolytic anemia in G6PD-deficient individuals (Beutler-1969). It is possible that these drugs in combination with tafenoquine might cause hemolysis in G6PD-normal individuals. If these drugs are administered in combination with tafenoquine, monitor urine for dark color and perform periodic checks of hematocrit.

12.16. Overdosage

There have been no reported cases of tafenoquine overdose. However, based on clinical experience with individual doses above 200 mg (Section 12.3), early symptoms of tafenoquine overdose are likely to be gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain). Hematologic events (hemolytic anemia and methemoglobinemia) may also be seen. Hemolytic anemia is also to be expected if normal tafenoquine doses are administered in error to persons deficient in G6PD (Section 12.6.2.1).

Persons should contact their health care provider if they have darker lips or urine [see Nonclinical Toxicology (Section 7)] as these may be signs of RBC hemolysis or methemoglobinemia.

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Appendix A. GSK INDSR Cases

Table 56: Summary of Safety Information Reported to Regulatory Authorities vs. Sponsor's Clinical Trial Safety Information for Four Subjects Described in GSK INDSR Communication (08 June 2017)

GSK CSD Safety Database	Sponsor's Studies		Australian TGA Report		Sponsor's Database			
	Study No.	Subject Age/Sex	Condition (s) Reported to TGA	Reported Date of Event/Onset of Symptoms	Medical History/ Prior Meds	Tafenoquine Treatment (Year)	No. of Weekly Tafenoquine Doses[a]	Neuropsychiatric AEs and Other Relevant Information Reported in Sponsor's Database
Case 1	049	29/Male	Encephalopathy, malaria, drug ineffective	Onset (not specified which events) within 1 month of the start of dosing.	None/ None	3 doses of tafenoquine 400 mg (1999)	No weekly dosing in this study	None
Case 2	033	26/Male	Multiple neurologic and other disorders	2007	None/ Ivermectin	Tafenoquine ACR (2000-2001)	27	Motion sickness/vertigo Onset Day 64; Mild Not treated: Resolved after 130 days. Considered "not related" to study drug.

Table 56: Summary of Safety Information Reported to Regulatory Authorities vs. Sponsor's Clinical Trial Safety Information for Four Subjects Described in GSK INDSR Communication (08 June 2017) (Continued)

GSK CSD Safety Database	Sponsor's Studies		Australian TGA Report		Sponsor's Database			
	Study No.	Subject Age/Sex	Condition (s) Reported to TGA	Reported Date of Event/Onset of Symptoms	Medical History/ Prior Meds	Tafenoquine Treatment (Year)	No. of Weekly Tafenoquine Doses[a]	Neuropsychiatric AEs and Other Relevant Information Reported in Sponsor's Database
Case 3	033	25/Male	Anxiety, anger, panic attack, PTSD, nightmare	30-11-2000 (30Nov2000)	Vivax malaria, onset 2000, past/ Ivermectin	Tafenoquine ACR (2000-2001)	26	Anxiety Onset Day 108; Mild; Not Treated; Continuing; "Not related" to study drug Other AEs included gastroenteritis on Day 29 (required IV treatment) followed by a laceration on Day 35. Subject also developed sinusitis on Day 117, and was treated for >4 months with multiple meds, including dextromethorphan pseudoephedrine, and oxymetazoline.

Table 56: Summary of Safety Information Reported to Regulatory Authorities vs. Sponsor's Clinical Trial Safety Information for Four Subjects Described in GSK INDSR Communication (08 June 2017) (Continued)

GSK CSD Safety Database	Sponsor's Studies		Australian TGA Report		Sponsor's Database			
	Study No.	Subject Age/Sex	Condition (s) Reported to TGA	Reported Date of Event/Onset of Symptoms	Medical History/ Prior Meds	Tafenoquine Treatment (Year)	No. of Weekly Tafenoquine Doses[a]	Neuropsychiatric AEs and Other Relevant Information Reported in Sponsor's Database
Case 4	033	20/Male	Anger, insomnia, liver function test abnormal, mental disorder, blood calcium increased	01-12-2000 (01Dec2000)	Back Pain, onset 2000, ongoing/ Ivermectin	Tafenoquine ACR (2000-20001)	27	Abnormal Dreams Onset Day 0; Mild; Not treated; Resolved after 210 days; "Suspected related" to study drug. Insomnia Onset Day 0; Mild-Moderate: Not treated; Continuing; "Suspected related" to study drug. Subject also reported AE of "shoulder pain", and received meds for back pain (ibuprofen) and shoulder pain (diclofenac).

Note: Weekly dosing with 200 mg was completed according to protocol for all subjects in Study 033.