APPENDIX 1: ABSTRACTS OF SELECTED LITERATURE

Med J Aust. 2000 Dec 4-18;173(11-12):583-5.

Malaria in the Australian Defence Force during and after participation in the International Force in East Timor (INTERFET).

Kitchener SJ[1], Auliff AM, Rieckmann KH.

Author information

Abstract

Malaria in Australian Defence Force members has been far more common in East Timor than in other recent overseas deployments. By six months after all 5,500 members of the International Force in East Timor had returned to Australia, 267 malaria infections had been reported to the Army Malaria Institute. Only 64 of those affected had their first clinical episode during their 4-5 months in East Timor, and about two-thirds of these infections were caused by Plasmodium falciparum. The remaining 212 soldiers developed their first symptoms after returning to Australia, and all but two infections were caused by P. vivax. After treatment, 44 soldiers had relapses of their vivax infections; 11 had a second relapse and two had a third relapse. These findings raise several issues about prevention and management of malaria in the ADF.

Malar J. 2014 Feb 6;13:49. doi: 10.1186/1475-2875-13-49.

A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic anti-malarials in non-immune individuals during deployment to a malaria-endemic area.

Dow GS[1], McCarthy WF, Reid M, Smith B, Tang D, Shanks GD.

Author information

Abstract

BACKGROUND:

In 2000/2001, the Australian Defense Forces (ADF), in collaboration with SmithKline Beecham and the United States Army, conducted a field trial to evaluate the safety, tolerability and efficacy of tafenoquine and mefloquine/primaquine for the prophylaxis of malaria amongst non-immune Australian soldiers deployed to East Timor (now called Timor Leste) for peacekeeping operations. The lack of a concurrent placebo control arm prevented an internal estimate of the malaria attack rate and so the protective efficacy of the study regimens was not determined at the time.

METHODS:

In a retrospective analysis of the 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. First, the Plasmodium vivax attack rate was estimated during the prophylactic phase of the deployment by adjusting the observed P. vivax relapse rate during post-deployment to account for the known anti-relapse efficacies (or effectiveness) of the study medications (determined from prior studies). The all species malaria attack rate (P. vivax and Plasmodium falciparum) was then determined by adjusting the P. vivax attack rate based on the ratio of P. falciparum to P. vivax observed during prior ADF deployments to Timor Leste. This estimated all species malaria attack rate was then used as the 'constant estimated attack rate' in the calculation of the protective efficacy of tafenoquine and mefloquine during the prophylactic phase of the deployment.

RESULTS:

The estimated attack rate during the prophylactic phase of the study was determined to be 7.88%. The protective efficacies of tafenoquine and mefloquine, with corresponding 95% confidence intervals (95% CI), were determined to be 100% (93%-100%) and 100% (79%-100%) respectively.

CONCLUSIONS:

The protective efficacy of tafenoquine (200 mg per day for three days, followed by weekly 200 mg maintenance doses) is similar to that of the weekly standard of care (mefloquine, 250 mg).

Anaesth Intensive Care. 2001 Aug;29(4):426-34.

Severe falciparum malaria in five soldiers from East Timor: a case series and literature review.

Blum PG[1], Stephens D.

Author information

Abstract

Despite chemoprophylaxis, malaria remains a serious threat for large numbers of non-immune soldiers deployed in endemic areas. Five adult cases of severe falciparum malaria are reported. Three cases were complicated by multiorgan failure and one of these patients died from cerebral malaria. These cases serve to highlight issues, in an Australian intensive care unit, associated with the management of severe malaria, an uncommon disease in our country. The need for rapid diagnosis and commencement of appropriate treatment is paramount in preventing further morbidity and mortality. Understanding and management of malaria continues to evolve rapidly. The pathophysiology of acute lung injury, shock and brain injury associated with malaria are examined in light of recent research. This article discusses the current controversies of exchange blood transfusion and the use of the new artemisinin derivatives.

Am J Trop Med Hyg. 2015 Sep;93(3):584-90. doi: 10.4269/ajtmh.15-0245. Epub 2015 Jun 29.

Safety, Tolerability, and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan.

Saunders DL[1], Garges E[2], Manning JE[2], Bennett K[2], Schaffer S[2], Kosmowski AJ[2], Magill AJ[2].

Author information

Abstract

Long-term antimalarial chemoprophylaxis is currently used by deployed U.S. military personnel. Previous small, short-term efficacy studies have shown variable rates of side effects among patients taking various forms of chemoprophylaxis, though reliable safety and tolerability data on long-term use are limited. We conducted a survey of troops returning to Fort Drum, NY following a 12-month deployment to Operation Enduring Freedom, Afghanistan from 2006 to 2007. Of the 2,351 respondents, 95% reported taking at least one form of prophylaxis during their deployment, and 90% were deployed for > 10 months. Compliance with daily doxycycline was poor (60%) compared with 80% with weekly mefloquine (MQ). Adverse events (AEs) were reported by approximately 30% with both MQ and doxycycline, with 10% discontinuing doxycycline compared with 4% of MQ users. Only 6% and 31% of soldiers reported use of bed nets and skin repellents, respectively. Compliance with long-term malaria prophylaxis was poor, and there were substantial tolerability issues based on these anonymous survey results, though fewer with MQ than doxycycline. Given few long-term antimalarial chemoprophylaxis options, there is an unmet medical need for new antimalarials safe for long-term use.

Antimicrob Agents Chemother. 2010 Feb;54(2):792-8. doi: 10.1128/AAC.00354-09. Epub 2009 Dec 7.

Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects.

Nasveld PE[1], Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team.

Collaborators (14)

Author information

Abstract

This study represents the first phase III trial of the safety, tolerability, and effectiveness of tafenoquine for malaria prophylaxis. In a randomized (3:1), double-blinded study, Australian soldiers received weekly malaria prophylaxis with 200 mg tafenoquine (492 subjects) or 250 mg mefloquine (162 subjects) for 6 months on a peacekeeping deployment to East Timor. After returning to Australia, tafenoquine-receiving subjects received a placebo and mefloquine-receiving subjects received 30 mg primaquine daily for 14 days. There were no clinically significant differences between hematological and biochemical parameters of the treatment groups. Treatment-related adverse events for the two groups were similar (tafenoquine, 13.4%; mefloquine, 11.7%). Three subjects on tafenoquine (0.6%) and none on mefloquine discontinued prophylaxis because of possible drug-related adverse events. No diagnoses of malaria occurred for either group during deployment, but 4 cases (0.9%) and 1 case (0.7%) of Plasmodium vivax infection occurred among the tafenoquine and mefloquine groups, respectively, up to 20 weeks after discontinuation of medication. In a subset of subjects recruited for detailed safety assessments, treatment-related mild vortex keratopathy was detected in 93% (69 of 74) of tafenoquine subjects but none of the 21 mefloquine subjects. The vortex keratopathy was not associated with any effect on visual acuity and was fully resolved in all subjects by 1 year. Tafenoquine appears to be safe and well tolerated as malaria prophylaxis. Although the volunteers' precise exposure to malaria could not be proven in this study, tafenoquine appears to be a highly efficacious drug for malaria prophylaxis

Trans R Soc Trop Med Hyg. 2008 Nov;102(11):1095-101. doi: 10.1016/j.trstmh.2008.04.024. Epub 2008 Jun 9.

The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of Plasmodium vivax malaria in the Southwest Pacific.

Elmes NJ[1], Nasveld PE, Kitchener SJ, Kocisko DA, Edstein MD.

Author information

Abstract

Tafenoquine is being developed for radical cure and post-exposure prophylaxis of Plasmodium vivax malaria. In an open-label study, 1512 Australian Defence Force personnel received one of three tafenoquine 3 d regimens [400 mg once daily (od), 200 mg twice daily (bid), 200 mg od] or daily primaquine (22.5 mg) plus doxycycline (100 mg) over 14 d in Bougainville and in Timor-Leste for post-exposure prophylaxis. The relapse rate of subjects treated in Bougainville with tafenoquine (n=173) was 1.2% (200 mg bid x 3 d) and 2.3% (400 mg od x 3 d), while primaquine plus doxycycline (n=175) was 3.4%. For subjects treated in Timor-Leste with tafenoquine (n=636), the relapse rate was 4.9% (200 mg od x 3 d), 5.3% (200 mg bid x 3 d) and 11.0% (400 mg od x 3d), while primaquine plus doxycycline (n=289) was 10.0%. The most frequent adverse events reported across all groups were nausea, abdominal distress and diarrhoea. There was a dose-dependent reduction in adverse events with a reduced dose of tafenoquine, with the lowest dose (total 600 mg over 3 d) producing rates of adverse events equivalent to that of primaquine plus doxycycline. The much shorter dosing regimen of tafenoquine should increase compliance, which is often suboptimal with primaquine after leaving an endemic area. [Australian New Zealand Clinical Trials Registry Number 12607000588493].

Am J Trop Med Hyg. 2007 Mar;76(3):494-6.

Tafenoquine for the treatment of recurrent Plasmodium vivax malaria.

Kitchener S[1], Nasveld P, Edstein MD.

Author information

Abstract

Tafenoquine was used to treat Plasmodium vivax malaria cases who had previously failed treatment with chloroquine and primaquine. Chloroquine was followed by a loading dose of tafenoquine (200 mg base/day for 3 days) and 200 mg a week was given for 8 weeks. One of 27 treated patients relapsed after 6 months of observation. A standard course of chloroquine administered with 8 weeks of tafenoquine may be more effective than chloroquine with primaquine (22.5 mg/day for 14 days) in preventing additional P. vivax relapses. Larger studies are required to optimize the combination, but our findings suggest that an extended use of tafenoquine may be required to prevent relapses of primaquine-tolerant strains of P. vivax malaria.

Lancet. 1995 Nov 4;346(8984):1190-3.

Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria.

Fryauff DJ[1], Baird JK, Basri H, Sumawinata I, Purnomo, Richie TL, Ohrt CK, Mouzin E, Church CJ, Richards AL, et al.

Author information

Abstract

Drug resistance has made malaria prevention difficult and the new agents are too expensive for widespread use. Primaquine, an established drug for treatment, is potentially useful for prevention. Malaria prophylaxis with primaquine was evaluated in Irian Jaya during one year in Javanese men who were not deficient in glucose-6-phosphate dehydrogenase (G-6-PD). 126 volunteers were randomised to receive 0.5 mg/kg primaquine base or placebo daily (double-blinded), or 300 mg chloroquine base weekly (open). The protective efficacy of primaquine relative to placebo was 94.5% (95% confidence interval 57-99) for Plasmodium falciparum and 90.4% (95% CI 58-98) for P vivax. Attack rates for either parasite did not differ significantly between the chloroquine and placebo groups. Incidence density of physical complaints not associated with parasitaemia was low (17-18 complaints/person-year) and was about the same in all groups except for cough, which was increased in the primaquine group. Complete blood counts were normal and no evidence of hepatic or renal dysfunction was found with primaquine. However, at 50 weeks the primaquine group had a mean methaemoglobin of 5.8% (range 1.4-13%), which declined by half within 7 days of ending prophylaxis. When used daily for one year by men with normal G-6-PD activity, primaquine was well tolerated and effective for prevention of malaria.

Clin Infect Dis. 2001 Dec 15;33(12):1990-7. Epub 2001 Nov 12.

Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia.

Baird JK[1], Lacy MD, Basri H, Barcus MJ, Maguire JD, Bangs MJ, Gramzinski R, Sismadi P, Krisin, Ling J, Wiady I, Kusumaningsih M, Jones TR, Fryauff DJ, Hoffman SL; United States Naval Medical Research Unit 2 Clinical Trials Team.

Author information

Abstract

Malaria causes illness or death in unprotected travelers. Primaquine prevents malaria by attacking liver-stage parasites, a property distinguishing it from most chemoprophylactics and obviating 4-week postexposure dosing. A daily adult regimen of 30 mg primaquine prevented malaria caused by Plasmodium falciparum and P. vivax for 20 weeks in 95 of 97 glucose-6-phosphate dehydrogenase (G6PD)-normal Javanese transmigrants in Papua, Indonesia. In comparison, 37 of 149 subjects taking placebo in a parallel trial became parasitemic. The protective efficacy of primaquine against malaria was 93% (95% confidence interval [CI] 71%-98%); against P. falciparum it was 88% (95% CI 48%-97%), and >92% for P. vivax (95% CI >37%-99%). Primaquine was as well tolerated as placebo. Mild methemoglobinemia (mean of 3.4%) returned to normal within 2 weeks. Blood chemistry and hematological parameters revealed no evidence of toxicity. Good safety, tolerance, and efficacy, along with key advantages in dosing requirements, make primaquine an excellent drug for preventing malaria in nonpregnant, G6PD-normal travelers.

Am J Trop Med Hyg. 2006 Sep;75(3):402-15.

Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I.

Hill DR[1], Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ.

Author information

Abstract

Primaquine phosphate has been used for preventing relapse of Plasmodium vivax and P. ovale malaria since the early 1950s, based on its ability to kill latent (hypnozoite) and developing liver stages of these parasites. There are three uses for primaquine in malaria: radical cure of established infection with P. vivax or P. ovale malaria; presumptive anti-relapse therapy (PART; terminal prophylaxis) in persons with extensive exposure to these parasites; and primary prophylaxis against all malaria species. All persons for whom primaquine is being considered must have a glucose-6-phosphate dehydrogenase (G6PD) enzyme level checked before use, and persons who have a deficiency of G6PD must not take primaquine for prophylaxis or PART. The recommended adult dose for PART based on clinical trials and expert opinion is 30 mg base daily for 14 days, started on return from a malarious region and overlapping with a blood schizonticide. The adult dose for primary prophylaxis is 30 mg daily begun 1 day before travel and continued for 7 days after return. This review will examine the evidence for these recommendations.

Recht et al 2015 WHO Report on 8-Aminoquinoline Safety

Executive summary Conclusions Primaquine currently holds a unique place in antimalarial therapeutics. It is the only generally available drug that kills hypnozoites (radical curative activity) in vivax or ovale malaria and the only drug with potent activity against mature gametocytes of P. falciparum. It also has causal prophylactic and weak asexual stage activity. The antimalarial activity of primaquine results from its metabolism to reactive intermediate compounds, which have not been well characterized. In addition to its therapeutic effect, primaquine induces haemolysis among people with reduced defences against oxidant compounds, mainly those with the common X-linked genetic defect of glucose-6-phosphate dehydrogenase (G6PD). Over 180 genetic variants of G6PD deficiency have been described, each of which confers a different level of deficiency. Some haemolysis always occurs when primaquine is given to G6PD-deficient individuals, but the extent of haemolysis depends on the dose and duration of exposure and the degree of deficiency.

Although primaquine has been used widely for over 60 years, estimates of the risks remain imprecise. In total, 14 deaths have been ascribed to primaquine, all following treatment with multiple doses. If the population denominator is all patients given any dose of primaquine or during mass drug administration in published studies, the risk for death associated with primaquine treatment would be 1 in 621 428, with an upper 95% confidence limit of 1 in 407 807. In studies involving testing for G6PD, the incidence of severe adverse events (nearly all related to severe haemolysis) was 11.2% (27/241) in G6PD-deficient individuals and almost zero in G6PD-normal people.

The gametocytocidal effect of primaquine requires only a single dose, and a review of dose–response relations suggests that, when given with artemisinin-based combination therapy (ACT), a single dose of 0.25 mg of base/kg (adult dose, 15 mg) has maximum effects. Current evidence suggests that this dose is unlikely to result in dangerous haemolysis, even in people with severe G6PD deficiency. For radical cure of vivax or ovale malaria, a 2-week course of treatment is required (current recommendations are 0.25 mg base/kg per day for temperate strains and 0.5 mg base/ kg for tropical strains). Shorter, higher-dose regimens may be as effective, but all regimens carry a risk for inducing potentially dangerous haemolysis in G6PD-deficient individuals, and G6PD testing is required (but is seldom available in endemic areas). The simple NADPH "spot test" identifies deficiency that is < 30% of normal activity and thus identifies people at haemolytic risk. Semi-quantitative rapid tests are being developed, but more information is needed on the relations between….

Cochrane Database Syst Rev. 2017 Oct 30;10:CD006491. doi: 10.1002/14651858.CD006491.pub4.

Mefloquine for preventing malaria during travel to endemic areas.

Tickell-Painter M[1], Maayan N, Saunders R, Pace C, Sinclair D.

Author information

Abstract

BACKGROUND:

Mefloquine is one of four antimalarial agents commonly recommended for preventing malaria in travellers to malaria-endemic areas. Despite its high efficacy, there is controversy about its psychological side effects.

OBJECTIVES:

To summarize the efficacy and safety of mefloquine used as prophylaxis for malaria in travellers.

SEARCH METHODS:

We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published on the Cochrane Library; MEDLINE; Embase (OVID); TOXLINE (https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm); and LILACS. We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) for trials in progress, using 'mefloquine', 'Lariam', and 'malaria' as search terms. The search date was 22 June 2017.

SELECTION CRITERIA:

We included randomized controlled trials (for efficacy and safety) and non-randomized cohort studies (for safety). We compared prophylactic mefloquine with placebo, no treatment, or an alternative recommended antimalarial agent. Our study populations included all adults and children, including pregnant women.

DATA COLLECTION AND ANALYSIS:

Two review authors independently assessed the eligibility and risk of bias of trials, extracted and analysed data. We compared dichotomous outcomes using risk ratios (RR) with 95% confidence intervals (CI). Prespecified adverse outcomes are included in 'Summary of findings' tables, with the best available estimate of the absolute frequency of each outcome in short-term international travellers. We assessed the certainty of the evidence using the GRADE approach.

MAIN RESULTS:

We included 20 RCTs (11,470 participants); 35 cohort studies (198,493 participants); and four large retrospective analyses of health records (800,652 participants). Nine RCTs explicitly excluded participants with a psychiatric history, and 25 cohort studies stated that the choice of antimalarial agent was based on medical history and personal preference. Most RCTs and cohort studies collected data on self-reported or clinician-assessed symptoms, rather than formal medical diagnoses. Mefloquine efficacyOf 12 trials comparing mefloquine and placebo, none were performed in short-term international travellers, and most populations had a degree of immunity to malaria. The percentage of people developing a malaria episode in the control arm varied from 1% to 82% (median 22%) and 0% to 13% in the mefloquine group (median 1%).In four RCTs that directly compared mefloquine, atovaquone-proguanil and doxycycline in non-immune, short-term international travellers, only one clinical case of

malaria occurred (4 trials, 1822 participants). Mefloquine safety versus atovaquone-proguanil Participants receiving mefloquine were more likely to discontinue their medication due to adverse effects than atovaquone-proguanil users (RR 2.86, 95% CI 1.53 to 5.31; 3 RCTs, 1438 participants; high-certainty evidence). There were few serious adverse effects reported with mefloquine (15/2651 travellers) and none with atovaquone-proguanil (940 travellers).One RCT and six cohort studies reported on our prespecified adverse effects. In the RCT with short-term travellers, mefloquine users were more likely to report abnormal dreams (RR 2.04, 95% CI 1.37 to 3.04, moderate-certainty evidence), insomnia (RR 4.42, 95% CI 2.56 to 7.64, moderate-certainty evidence), anxiety (RR 6.12, 95% CI 1.82 to 20.66, moderate-certainty evidence), and depressed mood during travel (RR 5.78, 95% CI 1.71 to 19.61, moderate-certainty evidence). The cohort studies in longer-term travellers were consistent with this finding but most had larger effect sizes. Mefloquine users were also more likely to report nausea (high-certainty evidence) and dizziness (high-certainty evidence).Based on the available evidence, our best estimates of absolute effect sizes for mefloquine versus atovaquone-proguanil are 6% versus 2% for discontinuation of the drug, 13% versus 3% for insomnia, 14% versus 7% for abnormal dreams, 6% versus 1% for anxiety, and 6% versus 1% for depressed mood. Mefloquine safety versus doxycyclineNo difference was found in numbers of serious adverse effects with mefloquine and doxycycline (low-certainty evidence) or numbers of discontinuations due to adverse effects (RR 1.08, 95% CI 0.41 to 2.87; 4 RCTs, 763 participants; low-certainty evidence).Six cohort studies in longer-term occupational travellers reported our prespecified adverse effects; one RCT in military personnel and one cohort study in short-term travellers reported adverse events. Mefloquine users were more likely to report abnormal dreams (RR 10.49, 95% CI 3.79 to 29.10; 4 cohort studies, 2588 participants, very low-certainty evidence), insomnia (RR 4.14, 95% CI 1.19 to 14.44; 4 cohort studies, 3212 participants, very low-certainty evidence), anxiety (RR 18.04, 95% CI 9.32 to 34.93; 3 cohort studies, 2559 participants, very low-certainty evidence), and depressed mood (RR 11.43, 95% CI 5.21 to 25.07; 2 cohort studies, 2445 participants, very low-certainty evidence). The findings of the single cohort study reporting adverse events in short-term international travellers were consistent with this finding but the single RCT in military personnel did not demonstrate a difference between groups in frequencies of abnormal dreams or insomnia.Mefloquine users were less likely to report dyspepsia (RR 0.26, 95% CI 0.09 to 0.74; 5 cohort studies, 5104 participants, low certainty-evidence), photosensitivity (RR 0.08, 95% CI 0.05 to 0.11; 2 cohort studies, 1875 participants, very low-certainty evidence), vomiting (RR 0.18, 95% CI 0.12 to 0.27; 4 cohort studies, 5071 participants, very low-certainty evidence), and vaginal thrush (RR 0.10, 95% CI 0.06 to 0.16; 1 cohort study, 1761 participants, very low-certainty evidence).Based on the available evidence, our best estimates of absolute effect for mefloquine versus doxycyline were: 2% versus 2% for discontinuation, 12% versus 3% for insomnia, 31% versus 3% for abnormal dreams, 18% versus 1% for anxiety, 11% versus 1% for depressed mood, 4% versus 14% for dyspepsia, 2% versus 19% for photosensitivity, 1% versus 5% for vomiting, and 2% versus 16% for vaginal thrush.Additional analyses, including comparisons of mefloquine with chloroquine, added no new information. Subgroup analysis by study design, duration of travel, and military versus non-military participants, provided no conclusive findings.

AUTHORS' CONCLUSIONS:

The absolute risk of malaria during short-term travel appears low with all three established antimalarial agents (mefloquine, doxycycline, and atovaquone-proguanil).The choice of antimalarial agent depends on how individual travellers assess the importance of specific adverse effects, pill burden, and cost. Some

travellers will prefer mefloquine for its once-weekly regimen, but this should be balanced against the increased frequency of abnormal dreams, anxiety, insomnia, and depressed mood.

Travel Med Infect Dis. 2017 May - Jun;17:28-34. doi: 10.1016/j.tmaid.2017.05.006. Epub 2017 May 8.

Tafenoquine is not neurotoxic following supertherapeutic dosing in rats.

Dow GS[1], Brown T[2], Reid M[2], Smith B[3], Toovey S[4].

Author information

Abstract

BACKGROUND:

Tafenoquine is a new drug for malaria prevention. The goal of the present work was to conduct a specific neurobehavioral study in rats with histopathological assessment of the brain.

METHODS:

The clinical, hematological, behavioral, motor activity, and neurohistopathologic changes induced by different dose levels of tafenoquine were evaluated following single super-therapeutic dose administration. Toxicokinetic data were generated to allow extrapolation to clinical exposures.

RESULTS:

At the highest dose (500 mg/kg), two animals (of 12) died. Surviving animals showed clinical signs of toxicity and had reduced body weight 7-8 days after dosing. Decreases in motor activity were observed on more than one occasion at doses > 9-fold higher than the clinical exposure. No statistically significant changes were observed for other behavioral endpoints. No neurohistopathological changes were noted. Changes in hematological and clinical pathology endpoints were observed at the lowest dose level (125 mg/kg). For context, the human dosing regimen is a 10 mg/kg load followed by 3.3 mg/kg weekly (in a 60 kg person).

CONCLUSIONS:

As in humans, adverse events other than neurotoxicity were dose-limiting for tafenoquine in rats. This raises the prospect that a new weekly prophylactic, without neurologic liability, may become available in the near future.

Travel Med Infect Dis. 2017 May - Jun;17:19-27. doi: 10.1016/j.tmaid.2017.05.008. Epub 2017 May 8.

Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis.

Novitt-Moreno A[1], Ransom J[1], Dow G[2], Smith B[3], Read LT[4], Toovey S[5].

Author information

Abstract

BACKGROUND:

Tafenoquine is a new prophylactic antimalarial drug. The current analysis presents an integrated safety assessment of the Tafenoquine Anticipated Clinical Regimen (Tafenoquine ACR) from 5 clinical trials, including 1 conducted in deployed military personnel and 4 in non-deployed residents, which also incorporated placebo and mefloquine comparator groups.

METHODS:

Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®, Version 15.0) and summarized. Among all subjects who had received the Tafenoquine ACR, safety findings were compared for subjects who were deployed military personnel from the Australian Defence Force (Deployed ADF) versus non-deployed residents (Resident Non-ADF).

RESULTS:

The incidence of at least one AE was 80.6%, 64.1%, 67.6% and 94.9% in the mefloquine, placebo, tafenoquine Resident Non-ADF and tafenoquine Deployed ADF groups, respectively. The latter group had a higher incidence of AEs related to military deployment. AEs that occurred at ≥ 1% incidence in both tafenoquine sub-groups and at a higher frequency than placebo included diarrhea, nausea, vomiting, gastroenteritis, nasopharyngeal tract infections, and back/neck pain.

CONCLUSIONS:

Weekly administration of tafenoquine for up to six months increased the incidence of gastrointestinal AEs, certain infections, and back/neck pain, but not the overall incidence of AEs versus placebo. CLINICAL TRIAL REGISTRATION NUMBERS/CLINICALTRIALS.

GOV IDENTIFIERS:

NCT02491606; NCT02488980; NCT02488902.

Am J Trop Med Hyg. 2017 Jan 11;96(1):159-166. doi: 10.4269/ajtmh.16-0390. Epub 2016 Nov 14.

Neuropsychiatric Outcomes After Mefloquine Exposure Among U.S. Military Service Members.

Eick-Cost AA[1], Hu Z[2], Rohrbeck P[2], Clark LL[2].

Author information

Abstract

Mefloquine was widely prescribed to U.S. military service members until 2009 when use was limited to personnel with contraindications to doxycycline and no contraindications to mefloquine. The need to estimate the occurrence of neuropsychiatric outcomes (NPOs) in service members prescribed mefloquine warranted a comprehensive evaluation of this issue. Active component service members filling a prescription for mefloquine, doxycycline, or atovaquone/proguanil (A/P) between January 1, 2008 and June 30, 2013, were included in the analysis. The risk of developing incident NPOs and the risk of subsequent NPOs among subjects with a history of the condition were assessed. A total of 367,840 individuals were evaluated (36,538 received mefloquine, 318,421 received doxycycline, and 12,881 received A/P). Among deployed individuals prescribed mefloquine, an increased risk of incident anxiety was seen when compared with doxycycline recipients (incidence rate ratio [IRR] = 1.12 [1.01-1.24]). Among nondeployed mefloquine recipients, an increased risk of posttraumatic stress disorder (PTSD) was seen when compared with A/P recipients (IRR = 1.83 [1.07-3.14]). An increased risk of tinnitus was seen for both deployed and nondeployed mefloquine recipients compared with A/P recipients (IRR = 1.81 [1.18-2.79]), 1.51 (1.13-2.03), respectively). Six percent of the mefloquine cohort had an NPO in the year before receiving mefloquine. When comparing individuals with a prior neuropsychiatric history to those without, the ratio of relative risks for adjustment disorder, anxiety, insomnia, and PTSD were higher (not statistically significant) for mefloquine compared with doxycycline. These findings emphasize the continued need for physicians prescribing mefloquine to conduct contraindication screening.

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NEUROTOXICITY OF THE 8-AMINOQUINOLINES

III. THE EFFECTS OF PENTAQUINE, ISOPENTAQUINE, PRIMAQUINE, AND PAMAQUINE ON THE CENTRAL NERVOUS SYSTEM OF THE RHESUS MONKEY*†

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AND
L. H. SCHMIDT, PH.D.
[*Cincinnati, Ohio*]

SUMMARY

The effects on the central nervous system of the rhesus monkey of the newer antimalarial drugs pentaquine, isopentaquine, and primaquine were studied, and compared with those of the older drug, pamaquine. The effects of the four compounds were generally similar in that the principal lesions were produced in the dorsal motor, supraoptic and paraventricular nuclei, and in a small group of cells associated with Meynert's commissure.

The dorsal motor nucleus was more severely injured after fatal doses of pentaquine than after fatal doses of the other three drugs. Lesions in the supraoptic and paraventricular nuclei, and in Meynert's group were severe after higher fatal doses of all four drugs, but somewhat less extensive after isopentaquine and primaquine than after pentaquine and pamaquine. Pamaquine differed from the other three drugs in that it consistently induced lesions of moderate severity in the abducens, trochlear, and lateral oculomotor nuclei.

Each of the four compounds produced minor lesions in a few areas other than those mentioned above. The magnocellular nucleus ruber and the hypoglossal nucleus were most commonly affected.

NEUROTOXICITY OF THE 8-AMINOQUINOLINES

I. Lesions in the Central Nervous System of the Rhesus Monkey Induced by Administration of Plasmocid*

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SUMMARY

This report has dealt with a study of the occurrence and development of lesions in the central nervous system of the rhesus monkey resulting from fatal and subfatal intoxication with Plasmocid (6-methoxy-8-(3-diethylamino-propylamino)-quinoline). These lesions have been correlated with symptoms of central nervous system injury.

Rapidly fatal intoxication with Plasmocid produced severe degenerative lesions in the proprioceptive pathways, the auditory pathway, vestibulo-cerebellar pathway, visual reflex pathways, extrapyramidal motor pathways, and to some extent in the olfactory system. Some or all of the principal nuclei of these pathways were involved, as well as other nuclear groups associated with these. Lesions were limited to the spinal cord, brain stem, diencephalon, and the corpus striatum. In most of the injured nuclei, there was extreme degeneration of all neuron cell bodies.

Subacute intoxication with Plasmocid modified this picture somewhat. At the maximum tolerated dose, lesions occurred in the same pathways as after fatal doses. Degeneration was comparable in the nuclei of the proprioceptive and visual reflex pathways, and in some nuclei of the pain-temperature-touch pathway. Outside of the main pathways, the extent and severity of the lesions were often less on the subfatal dosage. There was a striking difference in involvement in the auditory and vestibulo-cerebellar systems, and especially in

the extrapyramidal motor pathways and in the olfactory areas; these areas were much less affected by the subfatal doses.

At half the maximum tolerated doses, Plasmocid produced more specific lesions. These were limited to the spinal cord and brain stem, and involved primarily the nuclei of the proprioceptive pathways, the oculomotor system, and to a lesser extent the vestibular nuclei and some associated nuclei.

At one fourth the maximum tolerated doses, less severe and less extensive injury was found in these same nuclei (proprioceptive and oculomotor group) and only scattered degenerating cells in the vestibular nuclei.

After chronic intoxication with maximum or half the subfatal dose, degenerated neurons were no longer present. The areas involved contained numerous astrocytes and fine neuroglia fibers, but very little microglia. After chronic intoxication followed by a long recovery period, injured areas were massed with microglia, as well as with astrocytes and neuroglia fibers.

Serial studies of changes in the central nervous system during minimum fatal and maximum subfatal intoxication have outlined the sequence with which various regions became involved. The first areas to show degenerative changes were again the proprioceptive nuclei of the cord and medulla, the vestibular nuclei, and on the fatal dosage of Plasmocid, some of the visual reflex nuclei and the cochlear nuclei. Ultimately, the same nuclear groups became involved after both dosage levels, but lesions appeared more slowly after the subfatal doses and were definitely less extensive in the auditory and the vestibulo-cerebellar pathways and in the extrapyramidal motor system.

The above effects of Plasmocid appeared to be the results of specific toxic action on selected neurons. Injury occurred with little if any evidence of circulatory disturbance.

NEUROTOXICITY OF THE 8-AMINOQUINOLINES

II. REACTIONS OF VARIOUS EXPERIMENTAL ANIMALS TO PLASMOCID [1]

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SUMMARY

A comparative study has been made of the lesions in the central nervous system which developed following administration of minimal fatal doses of Plasmocid to various species of monkeys, dogs, rats, and mice.

Rhesus and cynomolgus monkeys exhibited a similar and striking group of neurological symptoms, which were associated with acute and severe degenerative lesions involving practically all neurons in many of the principal nuclei of the proprioceptive and tactile, auditory, vestibulo-cerebellar, visual-reflex, and extrapyramidal motor pathways, in the olfactory areas, and in associated regions. These lesions were limited to the brain stem, cerebellum, and spinal cord.

Mangabey monkeys, although much less susceptible to the action of Plasmocid than rhesus and cynomolgus monkeys, showed the same general pattern of central nervous system intoxication. The primary lesions in the mangabeys were located in the eye muscle nuclei and in those vestibular nuclei concerned with equilibrium mechanisms; these lesions were much less severe than those associated with fatal Plasmocid intoxication in the other simian species.

In dogs, fatal Plasmocid intoxication induced no distinct symptoms of central nervous system dysfunction and no lesions in those regions which were severely affected in various monkeys. However, there was drastic degeneration in the dorsal motor nucleus and some loss of cells in the lateral sympathetic columns.

Rats and mice tolerated much larger doses of Plasmocid than the above animals. Both rodents exhibited paralysis of the tongue and lower jaw as the major symptom of central nervous system dysfunction. The only significant lesion was in the mesencephalic V nucleus.

It is clear from these findings that there are marked differences in the effects of Plasmocid on the central nervous systems of various experimental animals. The explanation for the diverse behaviors is not apparent as yet.

THE TOXICITY OF LARGE DOSES OF PENTAQUINE (SN–13,276), A NEW ANTIMALARIAL DRUG [1]

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(Received for publication January 4, 1947)

This paper reports observations on the toxicity of pentaquine [3] when administered in amounts higher than the recommended therapeutic dose (1). The purpose of the observations was to define the margin of safety of the drug in clinical use.

Pentaquine (SN–13,276) offers considerable promise as a radical cure of *vivax* malaria (1, 2). It is closely related chemically to pamaquin (Figure 1). At dosage levels *within* the therapeutic range, the drug has seldom caused serious toxic reactions in white subjects. We have reported therapeutic results in 88 patients treated with 60 mgm. of base per day for 14 days (2). Most of them had few or no symptoms; only two subjects had severe symptoms, but not such as to make discontinuance of medication advisable. Symptoms, when they occurred, were similar to those produced by pamaquin: methemoglobinemia, abdominal discomfort or pain, anorexia, nausea, and vomiting. No hemolytic crisis occurred, but none of the subjects were negroes, in whom the incidence of hemolytic episodes is high with pamaquin (1). Sixty mgm. of pentaquine base have a toxicity approximately equivalent to 30 mgm. of pamaquin base.

Pentaquine was administered in double or triple the maximal therapeutic dose of 60 mgm. per day in order to explore the prophylactic (3) and curative effect of the drug in *vivax* malaria and to define the upper dosage limits tolerated in man.

PROCEDURE

Details of the routine procedures used in these studies are reported elsewhere (4). The subjects were healthy, white, inmate volunteers [4] in the Illinois State Penitentiary at Stateville. In prophylactic tests, the drug was administered to ten subjects at four-hour intervals for eight days at a daily dose of 120 or 180 mgm. of base.

PAMAQUINE POISONING IN MAN, WITH A CLINICOPATHOLOGIC STUDY OF ONE CASE[1]

AAGOT CHRISTIE LÖKEN[2] AND WEBB HAYMAKER

Since the introduction of pamaquine (plasmochin) in the treatment of malaria in 1926 by Mühlens (15), there have been numerous reports on its toxic effect. Le Heux and Wijngaarden (13) observed that tolerance to the drug varies in different species. In rabbits, for instance, the lethal oral dose was 225 mg. per kg. body weight; in dogs it was 20 mg., and in cats only 7.5 mg. Pamaquine poisoning was characterized in its early stages by slow respiration, dyspnea, and slow pulse rate, and in later stages by methemoglobinemia and cyanosis. The concentration of methemoglobin in the blood varied: in cats it was at its height approximately 16 hours after administration and gradually fell to zero in about 7 days. Urinary secretion of the drug was found to be very scant and the mode of destruction in the body uncertain. *In vitro* experiments with blood to which pamaquine was added disclosed that methemoglobin formed more readily in hemolyzed than in nonhemolyzed blood. Pamaquine in a concentration of 0.01 per cent produced methemoglobinemia and slight hemolysis; in concentration of 0.1 per cent or higher methemoglobin formation was found to precede hemolysis.

Tskimanauri (20) observed in dogs and rabbits that therapeutic doses of pamaquine caused temporary tachycardia, slight elevation of blood pressure, and increase in depth and rate of respiration. In animals given pamaquine after bilateral vagotomy a slight elevation of blood pressure and bradycardia occurred. In pamaquine-treated animals with the vagi intact there was tachycardia rather than bradycardia. Moreover, larger doses of pamaquine had no material effect on the cardiac rhythm. These observations were taken to mean that pamaquine acted directly on the vagal center. Goodman and Gilman (8) have stated that pamaquine is toxic to the heart, causing tachycardia, extrasystoles and other arrhythmias, but they did not disclose the source of their information. Heimann and Shapiro (9) found in man that pamaquine increased the amplitude of the various deflections in electrocardiograms, particularly the T wave.

There does not seem to be any generally accepted dosage of pamaquine. According to Goodman and Gilman (8), the dose of pamaquine from which adults obtain maximum benefit is 0.02 gm. 3 times a day. Cecil (3) advised giving pamaquine in conjunction with quinine, or following the administration of quinacrine, in biweekly doses of 0.02 gm. until gametocytes had disappeared. Strong (19) and Mackie, Hunter and Worth (14) recommended 0.01 gm. by mouth 3 times a day for 4 days. In the United States Army's "combined QAP treatment," quinine is given first, then quinacrine, and after a lapse of 2 days, 0.01 gm. of pamaquine 3 times a day for 5 days (Jarcho (11)).

As to toxic effects of pamaquine in man, Berliner and Butler (1) have observed

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Relationships between chemical structures of 8-aminoquinolines and their capacities for radical cure of infections with Plasmodium cynomolgi in rhesus monkeys.

Schmidt LH.

Abstract

Evaluation of 200 8-aminoquinolines for the capacities to effect radical cure of infections with sporozoites of Plasmodium cynomolgi in rhesus monkeys led to identification of 34 derivatives with activity equal or superior to that of primaquine and to characterization of substituents on the quinoline nucleus and side chain that favored or prejudiced curative activity. Of the 34 derivatives, 19 were as active as primaquine, 9 were twice as active, and 6 were four times as active. With respect to nuclear substituents, all were methoxy substituted at position 6; 24 had one and 10 had two additional substituents. The additions with most favorable impact on activity included methyl substituents at positions 4 and 2 and alkoxy, fluoro, and a group of 3- or 4-substituted phenoxy substituents at position 5. With respect to 8-amino substituents, 14 of the 15 derivatives more active than primaquine, and 13 of the 19 as active as primaquine, carried a branched alkyl chain, four to five carbons in length, between the 8- and terminal amino groups. Proximity of branching to the 8-amino group could be an important determinant of curative activity; however, the effect of such branching was not predictable. All 15 derivatives more active than primaquine and a substantial fraction of those comparable to primaquine in activity have sufficient structural novelty to merit evaluation for tolerability and radical curative activity in humans, with reasonable prospects that one or more would be better tolerated than primaquine and superior to this drug for cure of Plasmodium vivax infections.

III. Delineation of the Potentials of Primaquine as a Radical Curative and Prophylactic Drug

L. H. SCHMIDT,* ROCHELLE FRADKIN,* CLARA S. GENTHER,* AND HETTIE B. HUGHES

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Abstract. This report summarizes the results of experimental studies that underpinned evaluation of primaquine in human volunteers inoculated with sporozoites of the Chesson strain of *Plasmodium vivax* and current uses of this 8-aminoquinoline for curative and preventive purposes. These experimental studies dealt with both the curative and prophylactic activities of selected 8-aminoquinolines in rhesus monkeys infected or challenged with sporozoites of *P. cynomolgi* and the toxicities of these agents for non-infected monkeys. They began with preliminary assessments of the curative activities and toxicities of five 6-methoxyquinolines differing from each other with respect to alkyl substituent in the 8-aminoalkylamino side chain. Primaquine, one of these five derivatives, was the most active and had the best therapeutic index. Results of expanded evaluations of its curative activity and toxicity, compared with results of earlier appraisals of the activities and toxicities of pamaquine, pentaquine, and isopentaquine, indicated that, with respect to therapeutic indexes, primaquine was superior to these older compounds. Evaluations of primaquine for prophylactic activity followed, with emphasis on the influence of the dosage regimen. Results showed that protection against infection with sporozoites could be attained not only by daily dosage throughout the incubation period, but also by one or two well tolerated doses at appropriate times during this period or by dosage twice weekly for 4 weeks after sporozoite challenge.

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Traumatic events, other operational stressors and physical and mental health reported by Australian Defence Force personnel following peacekeeping and war-like deployments.

Waller M[1], Treloar SA, Sim MR, McFarlane AC, McGuire AC, Bleier J, Dobson AJ.

Author information

Abstract

BACKGROUND:

The association between stressful events on warlike deployments and subsequent mental health problems has been established. Less is known about the effects of stressful events on peacekeeping deployments.

METHODS:

Two cross sectional studies of the Australian Defence Force were used to contrast the prevalence of exposures reported by a group deployed on a peacekeeping operation (Bougainville, n = 1704) and those reported by a group deployed on operations which included warlike and non-warlike exposures (East Timor, n = 1333). A principal components analysis was used to identify groupings of non-traumatic exposures on deployment. Multiple regression models were used to assess the association between self-reported objective and subjective exposures, stressors on deployment and subsequent physical and mental health outcomes.

RESULTS:

The principal components analysis produced four groups of non-traumatic stressors which were consistent between the peacekeeping and more warlike deployments. These were labelled 'separation', 'different culture', 'other people' and 'work frustration'. Higher levels of traumatic and non-traumatic exposures were reported by veterans of East Timor compared to Bougainville. Higher levels of subjective traumatic exposures were associated with increased rates of PTSD in East Timor veterans and more physical and psychological health symptoms in both deployed groups. In Bougainville and East Timor veterans some non-traumatic deployment stressors were also associated with worse health outcomes.

CONCLUSION:

Strategies to best prepare, identify and treat those exposed to traumatic events and other stressors on deployment should be considered for Defence personnel deployed on both warlike and peacekeeping operations.

60 Degrees Pharmaceuticals LLC
ARAKODA for Malaria Prophylaxis
Antimicrobial Drugs Advisory Committee Meeting

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

NDA 210607

Briefing Document for the Antimicrobial Drugs Advisory Committee

Meeting Date: July 26, 2018

Sponsor:
60 Degrees Pharmaceuticals, LLC
1025 Connecticut Ave. NW, Suite 1000
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ADVISORY COMMITTEE BRIEFING MATERIALS AVAILABLE FOR PUBLIC RELEASE

60 Degrees Pharmaceuticals LLC
ARAKODA for Malaria Prophylaxis
Antimicrobial Drugs Advisory Committee Meeting

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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.

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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

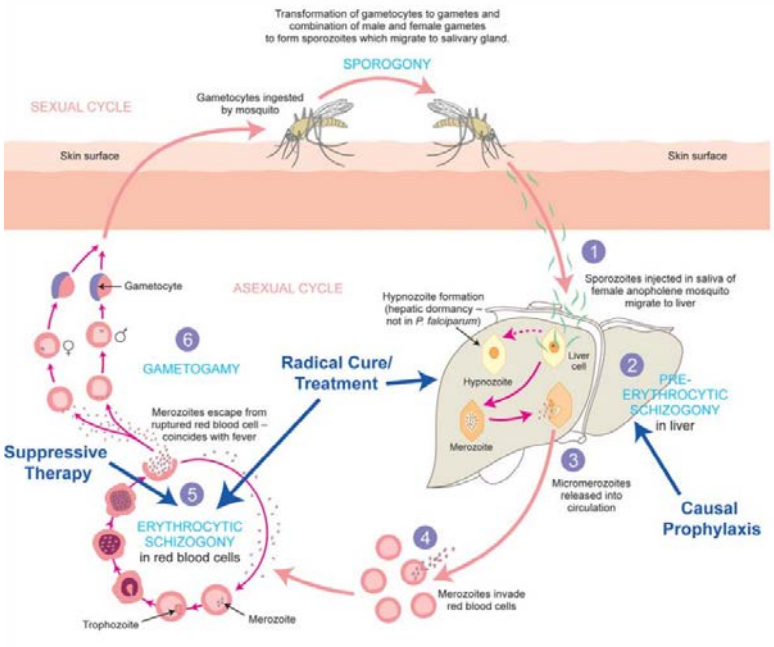
Malaria is a potentially fatal illness caused by protozoal infection of RBC with parasites belonging to the genus *Plasmodium*, transmitted to humans by the bite of a *Plasmodium*-infected mosquito. Five species of *Plasmodium* infect humans, namely, *P. falciparum* (*Pf*), *P. vivax* (*Pv*), *P. ovale*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

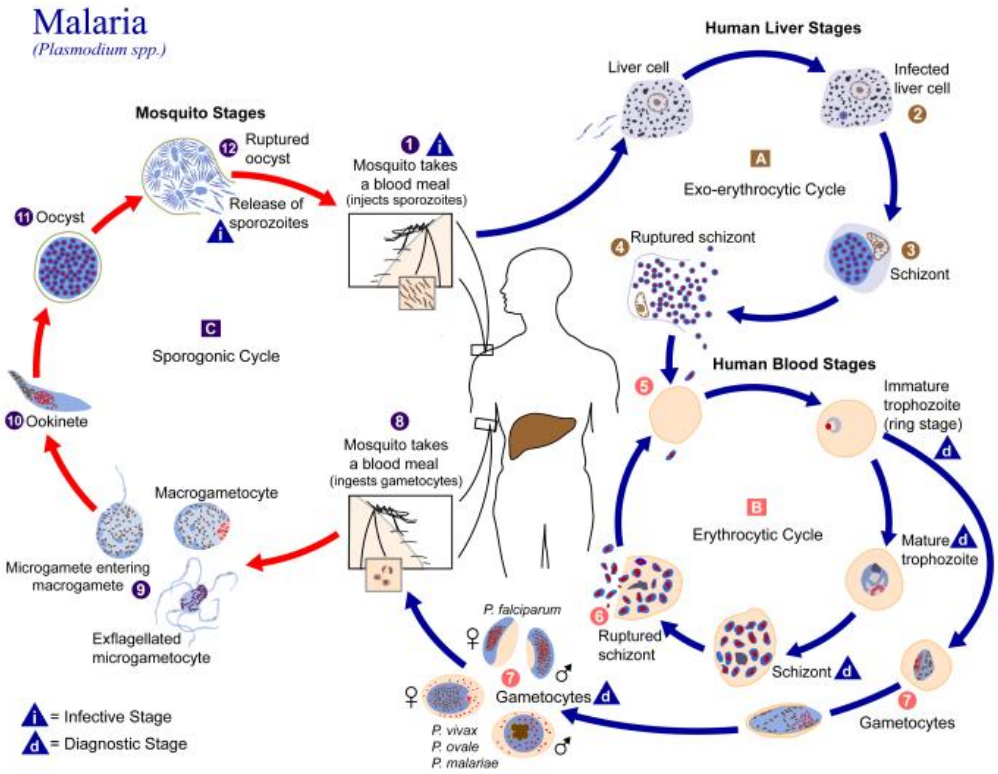
In terms of life cycle, *Pf* differs from that of *Pv* in not having a hypnozoite stage. Hypnozoites are forms of the malaria parasite that lie dormant in the liver, eventually awakening to cause malaria symptoms in the future (i.e., a malaria "relapse").

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.

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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).

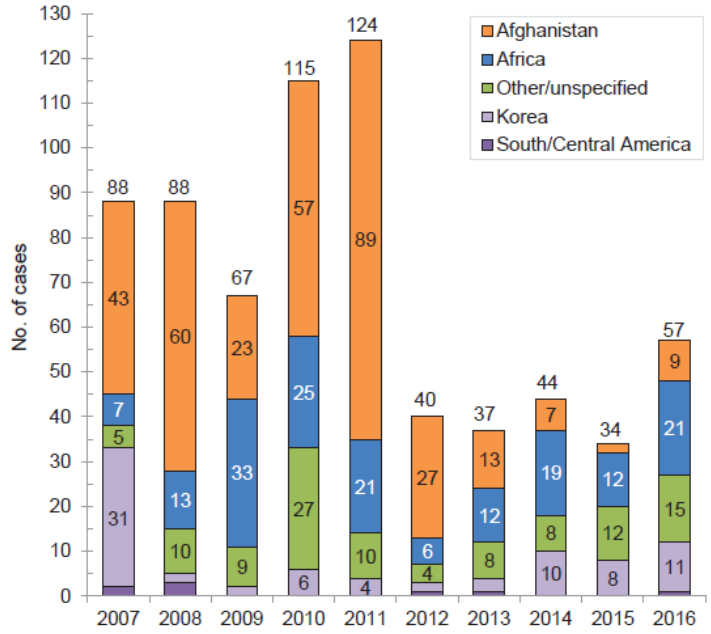
Table 4: Top Five Vector-Borne Diseases: Numbers of Confirmed, Possible, and Suspected Cases, active and reserve components , US Armed Forces, 2010-2016

	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

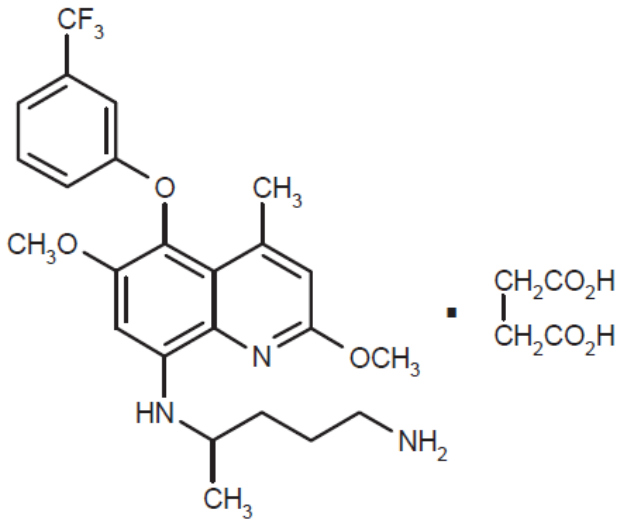
The antimalarial tafenoquine succinate is a new chemical entity belonging to the 8-aminoquinoline group of medicines and is a synthetic analogue of primaquine. Tafenoquine is a primaquine congener synthesized by adding a methoxy group at the 2 position, a methyl group at the 4 position, and a 3-trifluoromethylphenoxy 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.

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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.

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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).

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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)

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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

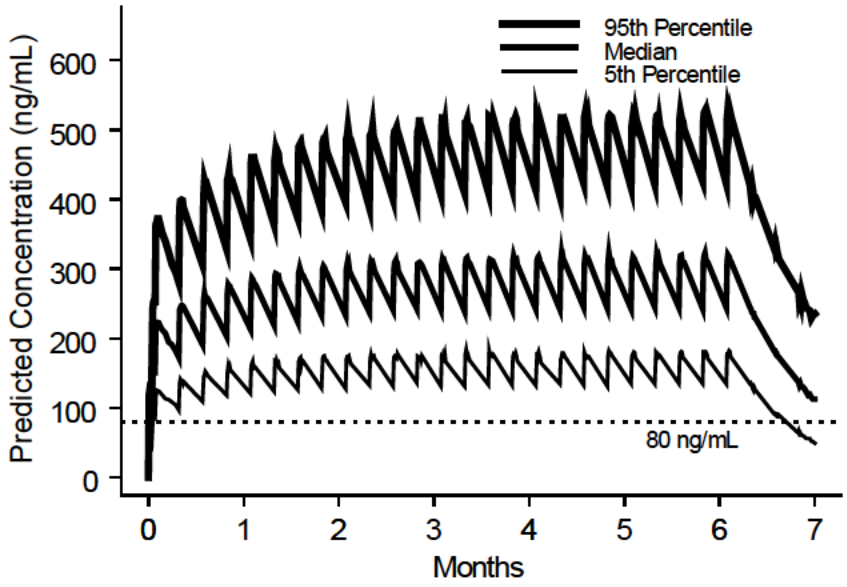
Studies conducted in non-immune persons, which is a population similar to the population for which prophylaxis is intended, showed that symptomatic breakthrough of malaria occurred when tafenoquine plasma concentrations were < 50 ng/mL. In Study 053, one subject became parasitemic on Study Day 31 with 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.

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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.

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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

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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.

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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).

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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

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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.

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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.

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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.

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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.

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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

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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).

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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.

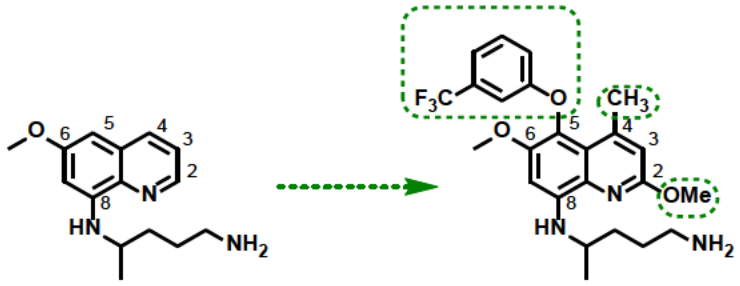
Seven (7) of the 8 had no psychiatric AEs reported during study participation, and all 8 subjects identified by DOB successfully completed their full regimen (26-28 weeks) of tafenoquine dosing.

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

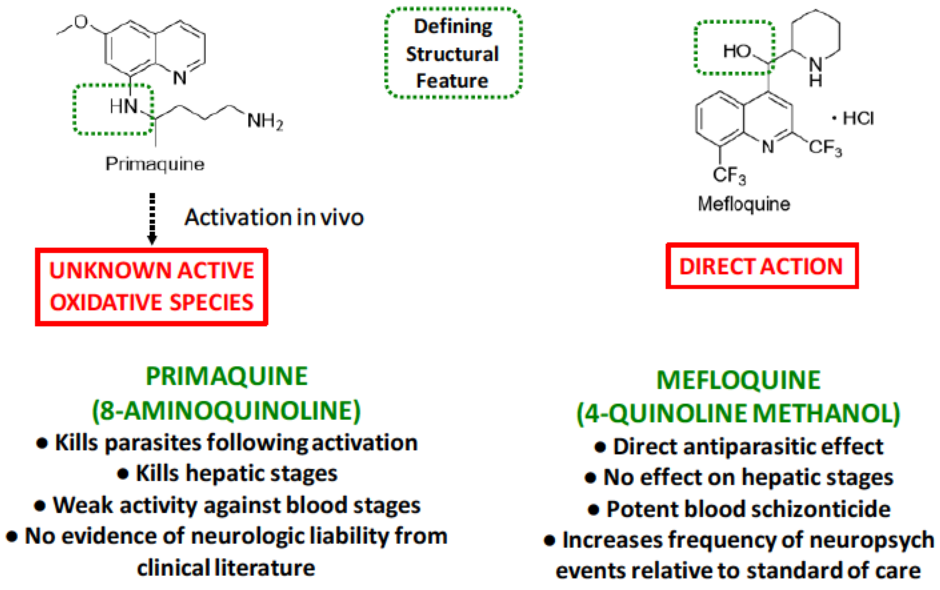


PRIMAQUINE
- **Half-Life: 6h**
- **Kills hepatic stages**
- **Weak activity against blood stages**
- **No evidence of neurologic liability from clinical literature**

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.

13. References

Armed Forces Health Surveillance Branch. Update: Malaria, U.S. Armed Forces, 2016. MSMR. 2017; 24:2-7.

Armed Forces Health Surveillance Branch (US). Update: Malaria, US Armed Forces, 2017. MSMR. 2018;25(2):2.

Baird JK. Radical cure: the case for anti-relapse therapy against all malarias. Clin Infec Dis. 2011;52:621-3.

Baumann-Birkbeck L, Grant GD, Anoopkumar-Dukie S, Kavanagh JJ. Drowsiness and motor responses to consecutive daily doses of promethazine and loratadine. Clin Neurophysiol. 2014;125:2390-6.Benson AJ. Chapter 35: Motion Sickness. In Lounsbury DE (editor), Medical Aspects of Harsh Environments, Volume 2. Office of the Surgeon General, Department of the Army, United States of America, Falls Church, VA: 2002.

Berman JD, Nielsen R, Chulay JD, Dowler M, Kain KC, et al. Causal prophylactic efficacy of atovaquone-proguanil (MalaroneTM) in a human challenge model. Trans R Soc Trop Med Hyg. 2001;95:429-32.

Beutler E. Drug induced hemolytic anemia. Pharm Rev. 1969;21:73-103.

Brueckner RP1, Lasseter KC, Lin ET, Schuster BG. First-time-in-humans safety and pharmacokinetics of WR 238605, a new antimalarial. Am J Trop Med Hyg. 1998a;58:645 9.

Brueckner RP, Coster T, Wesche DL, Shmuklarsky M, Schuster BG. Prophylaxis of Plasmodium falciparum infection in a human challenge model with WR 238605, a new 8-aminoquinoline antimalarial. Antimicrob Agents Chemother. 1998b;42:1293-94.

Burrows JN, Duparc S, Gutteridge WE, van Huijsduijnen RH, Kaszubska W, Macintyre F, Mazzuri S, Möhrle JJ, Wells TN. New developments in anti-malarial target candidate and product profiles. Malaria J. 2017;16:26.

CDC. About Malaria: Disease. Last Updated October 7, 2015. Available from: https://www.cdc.gov/malaria/about/disease.html. Accessed: 14 June 2018.

Erskine SK. CDC. Yellow Book. Chapter 2. The Pre-Travel Consultation: Self-Treatable Conditions - Motion Sickness.. Last updated: July 10, 2015. Available from: http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/motion-sickness Accessed: 14 November 2016.

CDC. DPDx - Laboratory Identification of Parasites of Public Health Concern: Malaria. Last updated: December 29, 2017a. Available from: https://www.cdc.gov/dpdx/malaria/index.html. Accessed: 11 June, 2018.

CDC. Yellow Book: Chapter 3 - Infectious Diseases Related to Travel. Malaria. Last Updated: June 12, 2017b. Available from: https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria. Accessed: 11 June 2018.

CDC. Yellow Book. Chapter 8. Advising Travelers with Specific Needs. Special Considerations for US Military Deployments. Last updated: June 13, 2017c. Available from:

https://wwwnc.cdc.gov/travel/yellowbook/2018/advising-travelers-with-specific-needs/special-considerations-for-us-military-deployments. Accessed 15 May 2018.

CDC. Choosing a Drug to Prevent Malaria. Last updated April 25, 2018. Available from: https://www.cdc.gov/malaria/travelers/drugs.html. Accessed 11 June 2018.

Charles BG, Miller AK, Nasveld PE, Reid MG, Harris IE, Edstein MD. Population pharmacokinetics of tafenoquine during malaria prophylaxis in healthy subjects. Antimicrob Agents Chemo. 2007;51:2709-17.

Clayman CB, Arnold J, Hockwald RS, Yount EH, Edgcomb JH, Alving AS. 3. Toxicity of primaquine in caucasians. JAMA. 1952;149:1563-8.

Coyne JT, Stripling R, Rovira E, Hunter D, Cohn JV, Brendley K, Zwick G, Carter G. Mitigating Motion Sickness in Ground Vehicles. U.S. Naval Research Laboratory (NRL) Review 2008. Available from U.S. Naval Research Laboratory: https://www.nrl.navy.mil/content_images/08Information_Coyne.pdf. Accessed: 14 November 2016.

Craige BJR, Eichelberger L, Jones RJR, Alving AS, Pullman TN, Whorton MC. The toxicity of large doses of pentaquine (SN13276), a new antimalarial drug. J Clin Invest. 1948;27:17-24.

Cullen KA, Mace KE, Arguin PM. Malaria surveillance—United States, 2013. MMWR Surveill Summ 2016;65(No. SS-2):1–22. https://doi. org/10.15585/mmwr.ss6502a1

DiTusa C, Kozar MP, Pybus B, Sousa J, Berman J, Gettayacamin M, Im-erbsin R, Tungtaeng A, Ohrt C. Causal prophylactic efficacy of primaquine, tafenoquine, and atovaquone-proguanil against Plasmodium cynomolgi in a rhesus monkey model. J Parasitol. 2014;100:671-3. doi: 10.1645/13-480.1. Epub 2014 Apr 29.

Dow G, Bauman R, Caridha D, Cabezas M, Du F, Gomez-Lobo R, Park M, Smith K, Cannard K. Mefloquine induces dose-related neurological effects in a rat model. Antimicrob Agents Chemother. 2006;50:1045-53.

Dow GS, Gettayacamin M, Hansukjariya P, Imerbsin R, Komcharoen S, Sattabongkot J, Kyle D, Milhous W, Cozens S, Kenworthy D, Miller A. Radical curative efficacy of tafenoquine combination regimens in Plasmodium cynomolgi-infected Rhesus monkeys (Macaca mulatta). Malaria J. 2011;10:212.

Dow GS, McCarthy WF, Reid M, Smith B, Tang D, Shanks GD. A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic antimalarials in non-immune individuals. Malar J. 2014;13:49. doi: 10.1186/1475-2875-13-49.

Dow GS, Brown T, Reid M, Smith B, Toovey S. Tafenoquine is not neurotoxic following supertherapeutic dosing in rats. Travel medicine and infectious disease. 2017;17:28-34.

Edstein MD, Kocisko DA, Brewer TG, Walsh DS, Eamsila C, Charles BG Population pharmacokinetics of the new antimalarial agent tafenoquine in Thai soldiers. Br J Clin Pharmacol. 2001;52:663-70.

Edstein MD, Kocisko DA, Walsh DS, Eamsila C, Charles BG, Rieckmann KH. Plasma concentrations of tafenoquine, a new long-acting antimalarial agent, in Thai soldiers receiving monthly prophylaxis. Clin Inf Dis. 2003;37:1654-8.

Edstein MD, Nasveld PE, Kocisko DA, Kitchener SJ, Gatton ML, Rieckmann KH. Gender differences in gastrointestinal disturbances and plasma concentrations of tafenoquine in healthy volunteers after tafenoquine administration for post-exposure vivax malaria prophylaxis. Trans R Soc Trop Med Hyg 2007;101:226-30.

Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL. Neuropsychiatric outcomes after mefloquine exposure among US military service members. Am J Trop Med Hyg. 2017;96:159-66.

Elmes NJ, Nasveld PE, Kitchener SJ, Kocisko DA, Edstein MD. The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of Plasmodium vivax malaria in the Southwest Pacific. Trans R Soc Trop Med Hyg. 2008;102:1095 1101.

Fairley BN. Chemotherpeutic suppression and prophylaxis in Malaria. An experimental investigation undertaken by medical research teams in Australia. Trans R Soc Trop MedHyg. 1945;38:311-65.

FDA. Guidance for Industry Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis. June 2007.

FDA. FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. Communication dated: July 29, 2013. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362232.pdf. Accessed: 19 January 2016.

Gill J, Lee H, Barr T, Baxter T, Heinzelmann M, Rak H, Mysliwiec V. Lower health related quality of life in US military personnel is associated with service-related disorders and inflammation. Psychiatry Res. 2014;216:116-22.

GlaxoSmithKline (GSK). Tafenoquine Study TAF115051. Last updated: 26 March 2012. Available from: https://gsk.sylogent.com/files/2a28d0ad-c5c0-4f7e-8f2a-6ac897f6f954. Accessed on 24 August 2016.

GSK. MALARONE- atovaquone and proguanil hydrochloride tablet, film coated. Highlights of Prescribing Information. Issued 2016. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Malarone/pdf/MALARONE.PDF. Accessed 11 June 2018.

Gorka AP, Jacobs LM, Roepe PD. Cytostatic versus cytocidal profiling of quinoline drug combinations via modified fixed-ratio isobologram analysis. Malar J. 2013;12:332. doi: 10.1186/1475-2875-12-332.

Green JA, Patel AK, Patel BR, Hussaini A, Harrell EJ, McDonald MJ, Carter N, Mohamed K, Duparc S, Miller AK. Tafenoquine at therapeutic concentrations does not prolong Fridericia corrected QT interval in healthy subjects. J Clin Pharmacol. 2014;54:995-1005.

Hale BR, Owusu-Agyei S, Fryauff DJ, Koram KA, Adjuik M, Oduro AR, Prescott WR, Baird JK, Nkrumah F, Ritchie TL, Franke ED, Binka FN, Horton J, Hoffman SL. A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against *Plasmodium falciparum*. Clin Infect Dis. 2003;36:541-549.

Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg. 2006;75:402-15.

Hoebe C, De Munter J, Thijs C. Adverse effects and compliance with mefloquine or proguanil antimalarial chemoprophylaxis. Eur J Clin Pharm. 19971;52:269-75.

Hunter L, Gordge L, Dargan P I, Wood D M. Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: a review. British J Clin Pharm. 2011;72:18–26. http://doi.org/10.1111/j.1365-2125.2011.03950.x

Karle JM, Olmeda R, Freeman SG, Schroeder AC. Quantification of the individual enantiomer plasma concentrations of the candidate antimalarial agent N4-[2,6-dimethoxy-4methyl-5-[(3-trifluoromethyl)phenoxy]-8-quinolinyl]-1,4-pentanediamine (WR238,605). Chromatogr. Biomed. 1995; 670:251-257.

Kavanagh JJ, Grant GD, Anoopkumar-Dukie S. Low dosage promethazine and loratadine negatively affect neuromotor function. Clin Neurophysiol. 2012;123:780-6.

Kersgard CM, Hickey PW. Adult malaria chemoprophylaxis prescribing patterns in the military health system from 2007–2011. Am J Trop Med Hyg. 2013;89:317-25.

Khuu D, Eberhard ML, Bristow BN, Javanbakht M, Ash LR, Shafir SC, Sorvillo FJ. Malaria-related hospitalizations in the United States, 2000–2014. Am J Trop Med Hyg. 2017;97:213-21.

Kirk KM, McGuire A, Nielsen L, Cosgrove T, McClintock C, Nasveld PE, Treloar SA. Self-reported tinnitus and ototoxic exposures among deployed Australian Defence Force personnel. Military Medicine. 2011;176:461-7.

Kitchener SJ, Nasveld PE, Gregory RM, Edstein MD. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. Med J Aust. 2005;182(4):168-71.

Kocisko DA, Walsh DS, Eamsila C, Edstein MD. Measurement of tafenoquine (WR 238605) in human plasma and venous blood by high pressure liquid chromatography. Ther Drug Monitoring. 2000; 22:184–89.

Leary KJ, Riel MA, Roy MJ, Cantilena LR, Bi D, Brater DC, van de Pol C, Pruett K, Kerr C, Veazey JM, Jr., Beboso R, Ohrt C. A randomized, double-blind, safety and tolerability study to assess the ophthalmic and renal effects of tafenoquine 200 mg weekly versus placebo for 6 months in healthy volunteers. Am J Trop Med Hyg. 2009;81:356-62.

Lell B, Faucher JF, Missinou MA, Borrmann S, Dangelmaier O, Horton J, Kremsner PG. Malaria chemoprophylaxis with tafenoquine: a randomised study. Lancet. 2000;355:2041-45.

Li Q, O'Neil M, Xie L, Caridha D, Zeng Q, Zhang J, Pybus B, Hickman M, Melendez V. Assessment of the prophylactic activity and pharmacokinetic profile of oral tafenoquine compared to primaquine for inhibition of liver stage malaria infections. Malar J. 2014;13:141.

Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, Krudsood S, Gupta SK, Kochar SK, Arthur P, Chuenchom N, Mohrle JJ, Duparc S, Ugwuegbulam C, Kleim JP, Carter N, Green JA, Kellam L. Tafenoquine plus chloroquine for the treatment and relapse prevention of Plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, Phase 2b dose-selection study. Lancet. 2014;383:1049-58.

Loken A. Pamaquine poisoning in man, with a clinicopathologic study of one case. Am J Trop Med Hyg. 1949;29:341-52.

Magill A. For the Record: A History of Malaria Chemoprophylaxis - Chapter 3 - 2016 CDC Yellow Book. Last updated: June 09, 2015.

McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in US service members returning from military deployments. Military Medicine. 2010;175:759-62.

Miller A et al. Pharmacokinetics (PK) and QTc changes after co-administration of tafenoquine and chloroquine in healthy volunteers. Abstract 711, 59th annual meeting of the American Society of Tropical Medicine and Hygiene, 3-7 Nov 2010, Atlanta, Georgia.

Miller AK, Harrell E, Ye L, Baptiste-Brown S, Kleim JP, Ohrt C, Duparc S, Mohrle JJ, Webster A, Stinnett S, Hughes A, Griffith S, Beelen AP. Pharmacokinetic interactions and safety evaluations of coadministered tafenoquine and chloroquine in healthy subjects. Br J Clin Pharmacol. 2013;76:858-867.

Nasveld P, Brennan L, Edstein M, Kitchener S, Leggat P, Rieckmann K. A randomised, double blind comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxix of malaria in non-immune Australian soldiers. Abstract 326. Am J Trop Med Hyg. 2002a;67:255-256.

Nasveld P, Kitchener S, Edstein M, Rieckmann K. Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. Trans R Soc Trop Med Hyg 2002b;96:683-684.

Nasveld P, Kitchener S. Treatment of acute vivax malaria with tafenoquine. Trans R Soc Trop Med Hyg. 2005;99:2-5.

Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. 2010;54:792–798.

Nevin RL, Byrd AM. Neuropsychiatric adverse reactions to mefloquine: a systematic comparison of prescribing and patient safety guidance in the US, UK, Ireland, Australia, New Zealand, and Canada. Neurology and therapy. 2016;5:69-83.

Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Statistics in medicine. 1998;17:873-90.

Novitt-Moreno A, Ransom J, Dow G, Smith B, Read LT, Toovey S. Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis. Travel medicine and infectious disease. 2017;17:19-27.

Overbosch D, Schilthuis H, Bienzle U, Behrens RH, Kain KC, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. ClinInfect Dis. 2001;33:1015-21.

Peterson AL, Goodie JL, Satterfield WA, Brim WL. Sleep disturbance during military deployment. Military Medicine. 2008;173:230-5.

Phillips MA, Kass RB. User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. J Travel Medicine. 1996;3:40-5.

Plumb TR, Peachey JT, Zelman DC. Sleep disturbance is common among servicemembers and veterans of Operations Enduring Freedom and Iraqi Freedom. Psychological services. 2014 ;11:209.

Pradines B, Mamfoumbi MM, Tall A, Sokhna C, Koeck JL, Fusai T, Mosnier J, Czarnecki E, Spiegel A, Trape J-F, Kombila M, Rogier M. In vitro activity of tafenoquine against the asexual blood stages of Plasmodium falciparum isolates from Gabon, Senegal, and Djibouti. Antimicrob Agents Chemother. 2006;50:3225-3226.

Puri SK, Dutta GP. Blood schizontocidal activity of WR 238605 (Tafenoquine) against Plasmodium cynomolgi and Plasmodium fragile infections in rhesus monkeys. Acta tropica. 2003;86:35-40.

Quashie NB, Duah NO, Abuaku B, Quaye L, Ayanful-Torgby R, Akwoviah GA, Kweku M, Johnson JD, Lucchi NW, Udhayakumar V, Duplessis C, Kronmann KC, Koram KA. A SYBR Green 1-based in vitro test of susceptibility of Ghanaian Plasmodium falciparum clinical isolates to a panel of anti-malarial drugs. Malar J. 2013;12:450. doi: 10.1186/1475-2875-12-450.

Ramharter M, Noedl H, Thimasarn K, Wiedermann G, Wernsdorfer G, Wernsdorfer WH. In vitro activity of tafenoquine alone and in combination with artemisinin against Plasmodium falciparum. Am J Trop Med Hyg. 2002:67;1:39-43.

Recht J, Ashley E, White N. Safety of 8-aminoquinoline Antimalarial Medicines. World Health Organization. 2014

Roche Products Pty Ltd. Lariam® (mefloquine hydrochloride). Prescribing Information. Date of Most Recent Amendment: 10 January 2018.Available from: http://www.guildlink.com.au/gc/ws/ro/pi.cfm?product=roplaria11114. Accessed: 11 June 2018.

Rueangweerayut R, Bancone G, Beelen A, Carter N, Duparc S, Green JA, Harrell EJ, Kleim JP, Miller A, Mohrle J, Qureshi A, Yubon N, Luzzatto L, Nosten F, Kongpatanakul S. A Phase I study to investigate the haemolytic potential of tafenoquine in healthy subjects with glucose 6 phosphate dehydrogenase deficiency (TAF110027). Abstract 435. Am J Trop Med Hyg. 2012;87:130.

Saunders DL, Garges E, Manning JE, Bennett K, Schaffer S, Kosmowski AJ, Magill AJ Safety, Tolerability, and Compliance with Long-Term Antimalarial;93:584-90.

Sanofi-Aventis U.S. LLC. Primaquine Phosphate (tablet, film coated) Drug Label Information. Revised: August 2016. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1BFBF4AE-81B8-4160-A00D-6322AADD4B59. Accessed: October 31, 2016.

Schmidt LH. Relationships between chemical structures of 8-aminoquinolines and their capacities for radical cure of infections with Plasmodium cynomolgi in rhesus monkeys. Antimicrob Agents Chemother. 1983;24:615-52.

Schmidt IG, Schmidt LH. Neurotoxicity of the 8-aminoquinolines I. Lesions in the central nervous system of Rhesus monkeys induced by administration of plasmocid. J Neuropathol Exp Neurol. 1948;7:368-398.

Schmidt IG, Schmidt LH. Neurotoxicity of the 8-aminoquinolines. II. Reactions of various experimental animals. J Comp Neurol. 1949;91:337-367.

Schmidt IG, Schmidt LH. Neurotoxicity of the 8-aminoquinolines. III. The effects of pentaquine, isopentaquine, primaquine and pamaquine on the central nervous system of the Rhesus monkey. J Neuropath Exp Neurol 1951;10:231-256.

Shanks GD, Oloo AJ, Aleman GM, Ohrt C, Klotz FW, Braitman D, Horton J, Brueckner R. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. Clin Infect Dis. 2001;33:1968-74.

St Jean PL, Xue Z, Carter N, Koh GC, Duparc S, Taylor M, Beaumont C, Llanos-Cuentas A, Rueangweerayut R, Krudsood S, Green JA, Rubio JP. Tafenoquine treatment of Plasmodium vivax malaria: suggestive evidence that CYP2D6 reduced metabolism is not associated with relapse in the Phase 2b DETECTIVE trial. Malar J. 2016;15:97.

Takeuchi R, Lawpoolsri S, Imwong M, Kobayashi J, Kaewkungwal J, Pukrittayakamee S, Puangsa-Art S, Thanyavanich N, Maneeboonyang W, Day NP, Singhasivanon P. Directly-observed therapy (DOT) for the radical 14-day primaquine treatment of Plasmodium vivax malaria on the Thai-Myanmar border. Malar J. 2010;9:308.

Tan KR, Magill AJ, Parise ME, Arguin PM. Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC expert meeting on malaria chemoprophylaxis. Am J Trop Med Hyg. 2011;84:517-31.

Tenero D, Green JA, Goyal N. Exposure-response analyses for tafenoquine after administration to patients with Plasmodium vivax malaria. Antimicrob Agents Chemother. 2015;59:6188-94.

Tickell-Painter M, Maayan N, Saunders R, Pace C, Sinclair D. Mefloquine for preventing malaria during travel to endemic areas. The Cochrane Library. 2017 Oct 30.

TEVA Pharmaceuticals USA, Inc. Mefloquine Hydrochloride Tablets USP. Prescribing Information. Revised: December 2017. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=09716a24-d7da-42b2-af29-c03a1b6670bd. Accessed: 23 May 2018.

Troxel WM, Shih RA, Pedersen ER, Geyer L, Fisher MP, Griffin BA, Haas AC, Kurz J, Steinberg PS. Sleep in the military: Promoting healthy sleep among US servicemembers. Rand health quarterly. 2015;5(2).

US Department of Veterans Affairs. New treatment options for tinnitus sufferers. Updated April 17, 2015. Available from: http://www.va.gov/health/NewsFeatures/20110524a.asp. Accessed: 28 September, 2016.

Vennerstrom JL, Nuzum EO, Miller RE, Dorn A, Gerena L, Dande RA et al. 8-aminoquinolines active against blood stage Plasmodium falciparum in vitro inhibit haematin polymerization. Antimicrobial Agents and Chemotherapy. 1999;43:598-60.

Waller M, Treloar SA, Sim MR, McFarlane AC, McGuire AC, Bleier J, Dobson AJ. Traumatic events, other operational stressors and physical and mental health reported by Australian Defence Force personnel following peacekeeping and war-like deployments. BMC psychiatry. 2012;12:1.

Walsh DS, Looareesuwan S, Wilairatana P, Heppner DG, Jr., Tang DB, Brewer TG, Chokejindachai W, Viriyavejakul P, Kyle DE, Milhous WK, Schuster BG, Horton J, Braitman DJ, Brueckner RP. Randomized dose-ranging study of the safety and efficacy of WR 238605 (Tafenoquine) in the prevention of relapse of Plasmodium vivax malaria in Thailand. J Infect Dis. 1999;180:1282-87.

Walsh DS, Eamsila C, Sasiprapha T, Sangkharomya S, Khaewsathien P, Supakalin P, Tang DB, Jarasrumgsichol P, Cherdchu C, Edstein MD, Rieckmann KH, Brewer TG. Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multidrug-resistant *P. falciparum* malaria. J Infect Dis. 2004a;190:1456-63.

Walsh DS, Wilairatana P, Tang DB, Heppner DG, Jr., Brewer TG, Krudsood S, Silachamroon U, Phumratanaprapin W, Siriyanonda D, Looareesuwan S. Randomized trial of 3-dose regimens of tafenoquine (WR238605) versus low-dose primaquine for preventing Plasmodium vivax malaria relapse. Clin Infect Dis. 2004b;39:1095-1103.

WHO. World Malaria Report 2015. Available from : http://who.int/malaria/publications/world-malaria-report-2015/report/en/. Accessed: 16 January 2016.

World Health Organization (WHO). World Malaria Report 2017. Available from: http://www.afro.who.int/publications/world-malaria-report-2017. Accessed on 20 April, 2018.

WHO. Malaria Fact Sheet. Updated April 2017. Available from http://www.who.int/mediacentre/factsheets/fs094/en/. Accessed 19 October 2017.

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.

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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.

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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.

FDA Briefing Document

Tafenoquine Tablet, 100 mg
Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

July 26, 2018

The committee will discuss new drug application (NDA) 210607 for tafenoquine tablet, 100 mg, sponsored by 60 Degrees Pharmaceuticals, for the proposed indication of prevention of malaria in adults for up to 6 months of continuous dosing.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The FDA have brought tafenoquine tablets to this Advisory Committee to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

1 Introduction

This briefing document describing the safety and efficacy data for tafenoquine (TQ) was prepared by the FDA for panel members of the Antimicrobial Drugs Advisory Committee. The FDA would like the committee to discuss whether the data are adequate to support the safety and efficacy of TQ for the prevention of malaria in adults for up to 6 months of continuous dosing.

2 Background

TQ is an 8-aminoquinoline antimalarial. TQ possesses activity against all pre-erythrocytic and erythrocytic stages of the *Plasmodium* species, including *P. falciparum* and *P. vivax*. The proposed indication is the prevention of malaria in adults for up to 6 months of continuous dosing. The indication encompasses all species of *Plasmodia* and includes prophylaxis while in the endemic region and post-exposure.

The proposed regimen for TQ includes a loading dose of 200 mg (two 100 mg tablets) once daily for 3 days before travel to a malarious area, followed by 200 mg maintenance weekly dose while in the malarious area, followed by a single 200 mg dose in the week following exit from the malarious area.

3 Product Information

TQ is an 8-aminoquinoline antimalarial drug, a synthetic analog of primaquine (PQ), for oral administration. Each immediate release TQ tablet contains 100 mg of tafenoquine (equivalent to 125.5 mg tafenoquine succinate).

Other quinoline antimalarials approved in the US include quinine, chloroquine (CQ), hydroxychloroquine, and mefloquine (MQ).

4 Regulatory History

This application was granted a Priority Review Designation. Among six clinical trials submitted to support TQ effectiveness for the indication of malaria prophylaxis, the source data for the two placebo-controlled trials (Studies 043 and 045) were not available for FDA audit.

5 Clinical Pharmacology

Pharmacokinetics

Table 1 provides the pharmacokinetics (PK) of TQ following administration of a single 200 mg dose (two 100 mg tablets) in healthy adult subjects under fed conditions. A

dedicated fed / fasted food effect study was not conducted with the to-be-marketed 100 mg TQ tablet. However, in majority of the clinical trials, TQ was administered under fed conditions.

Table 1. Mean (%CV) Pharmacokinetic Parameters of TQ Following Single Oral Administration of Two 100 mg TQ Tablets with Food in Healthy Subjects[a]

Parameter	Value
C_{max}	147 ng/mL (20.7%)[b]
T_{max}	14 hours (6.05 – 72 hours)[c]
AUC∞	70.1 hr*µg/mL (24.6%)[b]

[a] The PK parameters of TQ are reported from a PK study, where TQ tablet was administered with high-fat meal to 65 healthy subjects.
[b] Coefficient of Variance (CV)
[c] Median and (Range)

Following the administration of a single oral dose under fasted conditions in healthy adult subjects, TQ AUC and C_{max} increased dose proportionally over the dose range from 100 mg to 400 mg. When healthy adult subjects received 200 mg TQ once-weekly for ten weeks without a loading dose under fasting conditions, the mean plasma accumulation ratio of TQ was approximately 4.4. In humans, TQ protein binding is >99.5%. The apparent volume of distribution of TQ in healthy adult subjects is approximately 2470 L [interindividual variability (IIV): 24.1%]. The apparent oral clearance of TQ is approximately 4.17 L/h (IIV = 23.6%) in healthy adult subjects. The mean terminal half-life is approximately 16.5 days in healthy adult subjects. Negligible metabolism was observed *in vitro* in human liver microsomes and hepatocytes. The major route(s) of excretion of TQ in humans is unknown.

Specific Populations
Population PK analyses indicated that the PK of TQ were not significantly affected by body weight, gender, age, and race. The PK of TQ have not been studied in patients with renal or hepatic impairment.

Drug-Drug Interactions
TQ does not significantly inhibit CYP2D6, CYP3A4, CYP2C9, or CYP1A2 in drug interaction studies.

The effect of co-administration of TQ on the PK of organic cation transporter-2 (OCT2) and multidrug and toxin extrusion-1 (MATE) substrates in humans is unknown. However, *in vitro* studies indicate the potential for increased concentrations of OCT2 and MATE substrates (e.g., metformin) which may increase the risk of toxicity of these drugs. Co-administration with OCT2 and MATE substrates (e.g., dofetilide, metformin) should be avoided.

In vitro studies indicated that TQ is not likely to inhibit human BCRP, P-gp, OAT1, OAT3, OATP1B1, and/or OATP1B3-mediated transport or to be a substrate for human OATP1B1 and/or OATP1B3.

6 Microbiology

Mechanism of Action
The precise mechanism by which TQ exhibits activity against *Plasmodium* species is not known. Studies with *P. falciparum* and other protozoa, such as *Leishmania donovani* and *Trypanosoma brucei,* suggest that TQ may exert its effect by inhibiting hematin polymerization[1] and inducing apoptotic like death of the parasite[2,3,4]. The apoptotic like death of the parasite may be associated with mitochondrial dysfunction and increased oxidative stress. In addition to its effect on the parasite, TQ causes red blood cell shrinkage[5].

Activity against Plasmodium species
TQ is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species that include *P. falciparum* and *P. vivax*. The activity of TQ against the pre-erythrocytic liver stages of the parasite prevents the development of the erythrocytic forms of the parasite, which are responsible for relapses in *P. vivax* malaria.

Resistance
A potential for development of resistance of *Plasmodium* species to TQ was not evaluated. However, studies with another protozoan, *Leishmania major*, suggest a potential for development of resistance to TQ; the mechanism of resistance appears to be due to increased glycolytic ATP synthesis[1, 6].

Studies with *P. falciparum* strains/isolates suggest a potential for cross-resistance with PQ. Clinical relevance of such findings is not known.

[1] Vennerstrom JL, Nuzum EO, Miller RE, Dorn A, Gerena L, Dande PA, Ellis WY, Ridley RG, and Milhous WK, 1999, 8-aminoquinolines active against blood stage *Plasmodium falciparum i*n vitro inhibit hematin polymerization. AAC 43 (3): 598-602.
[2] Lanners NH, 1991, Effect of the 8-aminoquinoline primaquine on culture-derived gametocytes of the malaria parasite *Plasmodium falciparum.* Parasitol Res 77: 478-481.
[3] Carvalho L, Luque-Ortega JR, Manzano JI, Castanys S, Rivas L, and Gamarro F, 2010, Tafenoquine, an antiplasmodial 8-aminoquinoline, targets *Leishmania* respiratory complex III and induces apoptosis. AAC 54 (12): 5344-5351.
[4] Carvalho L, Martínez-García M, Pérez-Victoria I, Manzano JI, Yardley V, Gamarro F, and Pérez-Victoria JM, 2015, The oral antimalarial drug tafenoquine shows activity against *Trypanosoma brucei.* AAC 59 (10): 6151-6160.
[5] Bhuyan AAM, Bissinger R, Stockinger K, and Lang F, 2016, Stimulation of suicidal erythrocyte death by tafenoquine. Cellular Physiology and Biochemistry 39: 2464-2476.
[6] Manzano JI, Carvalho L, Perez-Victoria JM, Castanys S, and Gamarro F, 2011, Increased glycolytic ATP synthesis is associated with tafenoquine resistance in *Leishmania major*. AAC 55 (3): 1045-1052.

7 Pharmacology/Toxicology (Nonclinical Neurobehavioral Assessment)

Rats dosed orally with [^{14}C]-tafenoquine showed low but measurable drug-related radioactivity in the brain, indicating some minimal penetration of the blood brain barrier. Two studies were conducted to determine if TQ administration was associated with any adverse neurobehavioral effects in rats.

Tafenoquine Succinate: Neurobehavioral Assessment when Administered Orally in Rats

Rats were given a single oral gavage dose of vehicle or TQ (125, 250, or 500 mg/kg). The neurofunctional assessment consisted of a functional observational battery (FOB), pretest and at 0.5, 3, 6, 24, and 48 hours post dose and a quantitative 60-minute locomotor activity assessment, performed following the FOB pretest and at 6, 24, and 48-hours post dose. Viability, clinical observations, body weights and microscopic pathology of the brain tissues were also recorded. On Days 4 and 8, up to 3 animals/sex/group were sacrificed and brains were removed and fixed for histopathology examination. Among other things, the FOB evaluated posture, reactivity to handling, gait, ease of locomotion, arousal, response to visual approach, pain perception, air righting, landing foot splay, and motor movements (tremors, fasciculation, convulsions, stereotypy). Motor activity was measured over a 60-minute session at 5-minute intervals as the total number of horizontal and vertical movements.

Transient, statistically significant decreases and increases in horizontal activity were observed in some animals at or greater than 6 hours following dosing. These findings were seen at doses 13 times the proposed human dose. Although these findings were statistically significant, motor activity varied greatly. There was no difference between the controls and TQ-treated animals on any measures in the FOB assessment. There were also no microscopic differences in the brains of TQ treated rats compared to controls as evaluated by H&E staining or Bielschowsky silver stain.

Oral Juvenile Toxicity Study in the CRL:CD(SD) Rat

To evaluate potential effects on growth and development, TQ (0,5, 15, or 25 mg/kg/dose) was administered orally every five days between postnatal day (PND) 7 and 22. The dose levels were then increased to 0, 10, 20, or 50 mg/kg/ between PND 27 and 62. After at least two weeks without treatment, animals were evaluated for motor activity, pre-pulse inhibition of auditory startle response, and learning and memory ability (Morris water maze), to assess latent effects of dosing on behavior. Motor activity was assessed on PND 77/78 over a 1-hour period, with the automated activity monitoring system collecting data over each successive 6-minute interval.

There was no difference in neurobehavioral function in juvenile rats treated with TQ over 62 days (into adulthood) compared to controls. Motor activity scores after at least two weeks of drug-free recovery showed no effect of TQ administration on horizontal or vertical activity. There were also no adverse findings on brain histopathology. The C_{max} at the highest dose was about 7 times the C_{max} in patients at the clinical dose.

TQ administration was associated with transient reductions in motor activity in rats at high, single doses but no such effects were observed in repeat-dose studies at doses up to 7-fold higher than the anticipated clinical exposure based on C_{max} comparisons.

8 Overview of Clinical Development Program for the Prevention of Malaria

This NDA contains 6 randomized, double-blind, controlled, efficacy studies, as shown in Table 2. There was one active-controlled trial in non-immune subjects (Study 033), three placebo-controlled trials in semi-immune subjects (Studies 043, 045, and 030), one placebo-controlled *P. falciparum* challenge study in non-immune subjects (Study TQ-2016-02), and a treatment trial of *P. vivax* (Study 058).

Electronic data was not submitted for Study 030. The initial analysis of Study 030 was unable to demonstrate efficacy for the test product or an active control. After investigation of the results, it was determined that there was a problem with the initial reading of the malaria slides and a blinded central site conducted a re-read of the slides. This study will be considered as supportive and is included for completeness.

Study 058, the treatment trial, used a different dose of TQ than that used for the prophylaxis indication and did not plan to compare the similarity of a TQ regimen to a CQ and PQ regimen. Additionally, the study did not meet the pre-specified criteria for success. As such, this study is not informative with regard to the efficacy of TQ prophylaxis and will not be reviewed as part of the efficacy section of this review.

Table 2. Clinical Trials Relevant to Efficacy Assessment

Trial #	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Randomized	Study Population	No. of Centers/ Countries
033	MC, R, DB, DD, PG, AC in non-immune subjects (Phase 3)	TQ (200 mg x3 days, then weekly x25 weeks) MQ /Oral	Prophylactic success at Week 26	26 weeks/ 24 weeks	492 162	Australian soldiers	7 sites/1 country
043	Single-center, R, DB, PG, PC in semi-immune subjects	TQ loading dose only (200 mg once daily x3 days) TQ (200 mg once daily x3 days, then weekly x10-15 weeks) TQ (400 mg once daily x3 days, then weekly x10-15 weeks) Placebo /Oral	Parasitemia during 15-week prophylaxis	15 weeks/ 4 weeks	64 61 62 62	G6PD normal adults aged 18-55 years, in good health	1 center/ 1 country (Kenya)
045	Single-center,	TQ (25, 50, 100, 200	Parasitemia	12 weeks/	95	Male subjects	1 center/

Trial #	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Randomized	Study Population	No. of Centers/ Countries
	R, DB, PG, PC, AC in semi-immune subjects	mg once daily x3 days, then weekly x12 weeks) MQ Placebo /Oral	during 12-week prophylaxis	4 weeks	94 94 94 48 96	aged 18-60 and female subjects aged 50-60 years, in good health	1 country (Ghana)
058	R, DB, DD, PG, AC, treatment of *P. vivax* in semi-immune subjects (Phase 2)	TQ 400 mg once daily x3 days CQ+PQ /Oral	Cure at Day 28	3 days/ 120 days	46 24	Subjects with positive smear for *P. vivax*, parasite density between 500-200,000/µL, aged 20-60 years	1 center/ 1 country (Thailand)
TQ-2016-02	R, DB, PC, PG, challenge study (blood stage *P. falciparum* challenge inoculum on Day 13, Phase 1b)	TQ (200 mg x3 days (Days 1-3) and Day 10 Placebo /Oral	Parasitemia from Day 17 to 34	10 days/ 22-24 days (End of Study on Day 32 to 34)	12 4	Males or females, aged 18-55 years, in good health	1 center/ 1 country (Australia)
030	R, DB, PC, AC, PG in semi-immune subjects. Only study report submitted (no datasets). Potential error in outcome assessment.	TQ (200 mg, once daily x3 days, then weekly x24 weeks) MQ Placebo /Oral	Parasitemia within 7 days after 24 weeks	24 weeks/4 weeks	104 101 101	Healthy volunteers aged 18-55 years.	1 center/ 1 country (Kenya)

8.1 Study 033

8.1.1 Study Design

Study 033 was a Phase 3, randomized, double-blind, double-dummy, active-controlled trial assessing the effectiveness, safety and tolerability of weekly TQ and MQ for chemoprophylaxis of *P. falciparum* and *P. vivax* malaria in East Timor in non-immune Australian soldiers.

The trial had two phases: a prophylactic phase, consisting of a 26-week period during deployment and a 24-week relapse follow-up phase that started at the end of the deployment to the malarious area once the subjects had returned to barracks. Study visits included Days 0, 1, and 2; Weeks 4, 9, 16, 26, 32, 38, 44 (phone), and 50 (phone).

Subjects were randomized in a 3:1 ratio to the following two groups:

Table 3. Study 033: Treatment Groups and Study Phases

Group	Prophylactic Phase (26 weeks)	Relapse Follow-up Phase (24 weeks)
TQ	Loading dose of 200 mg daily x 3 days followed by 200 mg weekly	Placebo
MQ	Loading dose of 250 mg daily x 3 days followed by 200 mg weekly	Standard PQ regimen (15 mg twice a day for 14 days)

Block randomization was used and was stratified by company (an army unit).

Primary Efficacy Endpoint

The primary efficacy endpoint was prophylactic success/failure during the prophylactic phase up to and including the first day of PQ eradication medication.

Prophylactic Success: No clinical malaria (single positive smear, any species, with concurrent clinical signs and symptoms consistent with malaria infection).

Prophylactic Failure: Clinical malaria (single positive smear, any species, with concurrent clinical signs and symptoms consistent with malaria infection).

Key Inclusion Criteria and Exclusion Criteria

Inclusion Criteria

- Healthy subjects between the ages of 18 and 55 years inclusive.

Exclusion Criteria

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- History of allergy or intolerance to MQ, PQ or any other 8-aminoquinolines.
- Clinically significant abnormalities as determined by history, physical examination, or laboratory testing of blood chemistry and hematology.

8.1.2 Statistical Methodologies

Analysis Populations

The Applicant's principal efficacy analysis was based on the per-protocol (PP) population. The intention-to-treat (ITT) population was used to confirm the findings of the principal analysis. The ITT population is used for the primary efficacy analysis by the FDA.

PP population: All randomized subjects who satisfied inclusion/exclusion criteria and adhered to the protocol.

ITT population: All subjects who took at least one dose of study medication during the prophylaxis treatment period.

Statistical Methods

The plan was to calculate the treatment difference in prophylactic failure rates along with a 95% CI stratified by company for the difference, and a conclusion of noninferiority (NI) of TQ would be drawn if the upper limit of this CI was no more than 10%. The Applicant calculated the effect of MQ compared to placebo to be 7.88%, assuming an attack rate of 7.88% and 100% protective efficacy for MQ. With M2 being 50% or 25% of M1, a margin could be 3.94% or 1.97%. However, given the unknown placebo attack rate, it is difficult to fully justify a NI margin in the setting of malaria prophylaxis. The Applicant's summary of the evidence for the malaria prevalence in the region at the time of the trial is discussed below.

Planned analyses involving occurrence of clinical malaria and a single positive smear (*P. falciparum* only and *P. vivax* only) were not performed as there were no subjects with clinical malaria or a positive smear during prophylactic treatment. Missing values for efficacy evaluation were not discussed in the protocol. The FDA considered the subjects with missing efficacy endpoints as prophylactic failures in its analysis.

8.1.3 Patient Disposition

The study was conducted between October 2000 to May 2001 during a military deployment of the Australian Defense Force (ADF) in Townsville, Australia, and in East Timor (at 7 sites). The first dose was taken 5.5 days (from 4 to 12 days) before arriving in East Timor. Table 4 shows the numbers of subjects screened, randomized, and included in the analysis populations. All randomized subjects were included in the ITT population. A total of 30 (6.1%) and 9 (5.6%) subjects in the ITT population from the TQ and MQ groups were excluded from the PP population, respectively. The majority of subjects in the ITT population completed the study.

Table 4. Study 033: Patient Disposition and Study Populations

	TQ	MQ	Total
Screened			663
Randomized	492	162	654
Safety	492	162	654
ITT	492	162	654
PP	462	153	615
Completed prophylactic phase	473 (96.1%)	157 (96.9%)	630 (96.3%)
Completed Study	472 (95.9%)	157 (96.9%)	629 (96.2%)
Reason for withdrawal from study			
AE	12 (2.4%)	4 (2.5%)	16 (2.4%)
Protocol deviation	1 (0.2%)	0	1 (0.2%)
Loss to follow-up	1 (0.2%)	0	1 (0.2%)
Moving out of the endemic area with no reported malaria infection	6 (1.2%)	1 (0.6%)	7 (1.1%)

AE=Adverse Event

Demographic Characteristics

Demographic characteristics were similar between the study groups and are listed Table 5. All subjects were younger than 65 years old. The majority of subjects were White males.

Table 5. Study 033: Demographic Characteristics in the ITT Population

	TQ (N=492)	MQ (N=162)	Total (N=654)
Age (years)			
Mean (SD)	25.4 (5.2)	26.0 (6.5)	25.5 (5.6)
Median	24.0	24.0	24.0
Range	18.0, 47.0	18.0, 51.0	18.0, 51.0
Age group, n (%)			
18-25	286 (58.1)	97 (59.9)	383 (58.6)
26-35	178 (36.2)	48 (29.6)	226 (34.6)
36-45	27 (5.5)	16 (9.9)	43 (6.6)
46-55	1 (0.2)	1 (0.6)	2 (0.3)
Sex, n (%)			
Female	14 (2.8)	8 (4.9)	22 (3.4)
Male	478 (97.2)	154 (95.1)	632 (96.6)
Weight (kg)			
Mean (SD)	80.95 (11.88)	81.34 (12.20)	81.04 (11.95)
Median	80.0	80.0	80.0
Range	50.0, 135.0	53.0, 135.0	50.0, 135.0
Race, n (%)			
Black or African American	4 (0.8)	1 (0.6)	5 (0.8)
Other	4 (0.8)	1 (0.6)	5 (0.8)
White	484 (98.4)	160 (98.8)	644 (98.5)

Other Baseline Characteristics

Malaria history is summarized in Table 6. Only a small proportion (<3%) of the subjects had a history of malaria and the two groups were not statistically significantly different.

Table 6. Study 033: Malaria History in the ITT Population

	TQ (N=492)	MQ (N=162)
History of malaria, n (%)		
Yes	15 (3.0%)	4 (2.5%)
Attacks in last 6 months, n (%)	9 (1.8%)	1 (0.6%)

The proportions of subject with various medical conditions were comparable between the two groups (data not shown).

8.1.4 Efficacy Results

There were no cases of clinical malaria during the prophylactic phase. The FDA analyzed the primary efficacy endpoint in the ITT population and considered as prophylactic failures all subjects who withdrew during the prophylactic phase and the three subjects who did not complete the prophylactic phase due to AE. This analysis indicated that the prophylactic success was greater than 96% for both groups.

Table 7. Study 033: Prophylactic Outcome based on Clinical Malaria (all species) during Prophylactic Treatment Phase (26 weeks)

Prophylactic Outcome, n (%)	**TQ (N=492)**	**MQ (N=162)**
FDA ITT analysis		
Prophylactic success	473 (96.1%)	157 (96.9%)
Missing	19	5
Difference in success proportion (TQ-MQ) [Exact 95% CI]	-0.78% [-3.71%, 3.57%]	
Applicant PP analysis	N=462	N=153
Prophylactic success	462 (100%)	153 (100%)
Difference in success proportion (TQ-MQ) [Exact 95% CI][a]	0% [-1%, 2%]	

Efficacy Results – Secondary and Other Relevant Endpoints

Prophylactic outcome for each treatment group during the prophylactic and relapse follow-up phases is summarized in Table 8 for the ITT population and PP population. All prophylactic failures were cases of *P. vivax* malaria occurring in the follow-up phase, resulting in less than 1% failures during the study. The time to relapse for these subjects ranged from 12.3 to 19.9 weeks from the end of the treatment. Per study protocol, subjects in the TQ group did not receive active treatment (TQ or PQ) in the follow-up phase, while the subjects in the MQ group received PQ for 14 days. There were 25 subjects with missing outcome (one more than in the prophylactic phase due to loss to follow-up at the end of the relapse follow-up phase). Some of the 24 subjects not completing the prophylactic phase were followed-up in the relapse follow-up phase. However, none of these 25 subjects had smear results or malaria symptom data available during the follow-up. Therefore, these subjects were not considered as prophylactic successes in the FDA's ITT analysis.

Table 8. Study 033: Prophylactic Outcome Based on Clinical Malaria (all species) at any Time During the Study (50 weeks)

Prophylactic Outcome, n (%)	**TQ (N=492)**	**MQ (N=162)**
ITT Population (FDA Analysis)	492	162
Prophylactic success	468 (95.1%)	156 (96.3%)
Prophylactic failure	4	1
Missing	20	5
Difference in success proportion (TQ-MQ) [95% CI]	-1.17% [-4.65%, 2.30%]	
PP Population (Applicant Analysis)	**462**	**153**
Prophylactic success	458 (99.1%)	152 (99.3%)
Prophylactic failure (all were *p. vivax*)	4 (0.9%)	1 (0.7%)
Difference in success proportion (TQ-MQ) [95% CI]	-0.21% [-1.74%, 1.32%,]	

Evidence of Malaria Prevalence

Cross-sectional survey

A community-based survey was conducted at sites within one kilometer of barracks at which subjects from Study 033 were stationed. Phase 1 was between January and February 2001, in the middle of the wet season, when Study 033 subjects had been in the area for about 16 weeks. The survey was repeated (Phase 2) at the end of the wet season in April and May 2001 as the prophylactic phase of Study 033 was close to the end. At each survey, approximately 200 local subjects (≥ 6 months) were selected at random from each of the seven sites and blood was collected for the preparation of malaria slides. Results showed that malaria was present in 6 of the 7 sites studied during both phases of the survey. The exception was a mountainous village where no malaria was seen. In areas where transmission occurred, rates of parasitemia were between 1% and 19.7% in Phase 1 and between 1.5% and 35.3% in Phase 2. The information from this survey suggested that the subjects in Study 033 were likely to have been exposed to malaria. However, due to the differences in study populations and the potential duration of malaria infections, it was not possible to use the prevalence of malaria in this survey to help justify the NI margin.

UN/WHO Malaria Report and Published Data

UN/WHO Malaria Report included figures for the number of weekly cases of malaria occurring between Week 44 of 1999[7] and Week 43 of 2000[8], immediately prior to the period of Study 033, and between Week 41 of 2000 and Week 39 of 2001, when Study 033 was conducted. In the year prior to the conduct of Study 033, the reported weekly cases ranged from about 700 to 6000 cases per week (about 2500 per week on average, as estimated by the reviewer). Data from the period when the 033 study was run showed a similar pattern but with fewer cases, with weekly cases ranging from about 0 to 3000 (about 1380 per week on average, as estimated by the reviewer).

The Applicant references literature that documents the incidence of malaria in East Timor. It states that though this is not conclusive evidence of exposure to malaria in Study 033, it does show that there is a high likelihood that subjects in Study 033 were exposed to both *P. falciparum* and *P. vivax*. The FDA agrees with this assessment.

Applicant's Justification of the Noninferiority Margin

In the justification of the NI margin, the Applicant claims that the attack rate in the region was 7.88%. This estimate used assumed relapse efficacy rates of both PQ and TQ along with the observed number of relapses seen during the 1-year follow-up of Study 033 to obtain a *P. vivax* attack rate of 6.88%. However, TQ was not used in the follow-up phase of Study 033, so it is not clear how relevant this calculation is. The ratio of *P. falciparum* to *P. vivax* attack rates was estimated (0.146) based on cases of malaria seen from deployments of soldiers in the previous year and was used to estimate the attack rate of *P.*

[7] https://reliefweb.int/updates?source=1275&country=230&date=19990101-20000101#content
[8] https://reliefweb.int/updates?source=1275&country=230&date=20000101-20010101#content

falciparum malaria (6.88%*0.146 = 1.00%). The *P. vivax* and *P. falciparum* attack rates were added together to obtain an overall attack rate for the trial (7.88%).

As stated above, the Applicant calculated the effect of MQ compared to placebo to be 7.88%, assuming an attack rate of 7.88% and 100% protective efficacy for MQ. With M2 being 50% or 25% of M1, a margin could be 3.94% or 1.97%.

The FDA finds this calculation of the attack rate in the untreated population problematic due to its reliance on some assumptions, including the treatment effect of TQ from the same study and the lack of consideration of the variability in various estimates.

Conclusions

In Study 033, the prophylactic failure proportions were very low in the two treatment groups. However, because the true malaria attack rate in the study area at that time was unknown, the FDA does not believe it is possible to justify a NI margin. Information provided by the Applicant does imply a high likelihood that the area was malarious around the time that the study was conducted and that subjects were likely exposed to malaria. Note that the information in females, older subjects, and in races other than White is limited in this study.

8.2 Study 043

8.2.1 Study Design

This study was a Phase 2b, placebo-controlled, randomized, double-blind parallel group, single center study in Kenya, in an area holoendemic for *P. falciparum* malaria.

Subjects who met the entry criteria were given a three-day presumptive course of halofantrine (250 mg daily for 3 days) to eliminate any existing *Plasmodium* parasitemia. Subjects were then randomized into one of four groups to receive one of three regimens of TQ or a placebo regimen.

- TQ load only: 400 mg of TQ for 3 days followed by placebo for 10-15 weeks.
- TQ low dose: 200 mg of TQ for 3 days, followed by TQ 200 mg weekly for 10-15 weeks.
- TQ high dose: 400 mg of TQ for 3 days, followed by TQ 400 mg weekly for 10-15 weeks.
- Placebo: weekly medication schedule was identical to the above TQ schedule.

Subjects were evaluated for *Plasmodium* parasitemia by weekly blood smears. Subjects were followed for an additional 4 weeks, starting 7 days after the last dose of study medication.

Primary Endpoint
The primary endpoint of the study was the protective efficacy (PE) of the TQ treatment regimens relative to placebo, where PE was derived from the proportion of subjects who

were prophylactic failures at any time during the double-blind prophylaxis treatment phase (15 weeks).

Key Inclusion and Exclusion Criteria

Inclusion Criteria

The following inclusion criteria were used:

1. Healthy subjects (male or female)
2. Age of 18-55 years
3. Residing in one of the study villages of the Nyanza Province in Kenya for the entire study

Exclusion Criteria

1. Any cardiovascular, liver, neurologic, or renal function abnormality which in the opinion of the clinical investigators would confound the outcome.
2. Use of antimalarial drugs not prescribed by study physicians within 2 weeks of study drug initiation.
3. Glucose-6-phosphate dehydrogenase (G6PD) deficiency.

8.2.2 Statistical Methodologies

Analysis Populations

The following analysis populations are defined:

ITT Efficacy Population: Subjects who received all clearance medication and loading medication and who received at least one dose in the weekly dosing regimen.

Efficacy Population: Subjects in the ITT Efficacy Population who provided at least one on-therapy malarial blood smear.

Safety Population: Subjects who received all three doses of halofantrine clearance medication and at least one loading dose of study medication.

The FDA considered all randomized subjects as the primary population for efficacy assessment.

Statistical Methods

The primary efficacy analysis was based on the PE of each TQ regimen relative to placebo. PE is defined as:

$$PE(\%) = \frac{I_{placebo} - I_{drug}}{I_{placebo}} * 100,$$

where I was cumulative incidence of parasitemia. The possible value for PE is between 0 (no protection) and 1 (complete protection). Corresponding 95% CIs for PE was calculated based on the method of Koopman. No adjustment was made to the level of the confidence interval for multiple comparisons due to multiple treatment groups in the study.

A chi-squared test was used to test for an overall difference in incidence of parasitemia across the four treatment groups. Additionally, Fisher's exact test was used to compare each active treatment arm to placebo. For these comparisons, to preserve the overall significance level at 5%, the pairwise comparisons were performed at the 0.017 level (Bonferroni adjustment for multiple comparisons). This value is calculated by dividing the type I error of 0.05 by 3 for the three treatment arms compared to placebo.

There was no plan for handling missing values. The FDA considered subjects with missing outcomes as prophylactic failures.

8.2.3 Patient Disposition

The study was conducted between May and September 1997 in one center (one village) in Kenya. Two hundred forty-nine subjects were randomized into the four treatment arms.

Patient disposition is listed in Table 9. The reasons for exclusions from the Safety/ITT or ITT Efficacy Populations were not provided in the dataset or the study report, although the reasons for discontinuation from the study were provided. Fourteen randomized subjects (5.6%) were excluded from the safety/ITT populations. These subjects had study discontinuation reasons that included that following: not taking (enough) clearance medications (halofantrine and etaquine), not starting/taking drug, or loss to follow-up (subject moved). Some of these reasons for discontinuation were not consistent with the Safety/ITT analysis population exclusions as defined. As stated above, the FDA does not agree with all exclusions from the Applicant's ITT population. Since the specific reasons for exclusion were not included in the datasets, the FDA's primary efficacy analysis included all randomized subjects. Subjects with missing data were considered prophylactic failures.

About 77% (182/235) of the subjects in the ITT population completed the study. Overall, lack of efficacy was the most common reason for discontinuation from the study. Most of the withdrawals were in the placebo group (27/67).

Table 9. Study 043: Patient Disposition

	Placebo	TQ Low Dose (200 mg)	TQ Load only (400 mg)	TQ High Dose (400 mg)
Randomized	62	61	64	62
Safety /ITT	61	55	60	59
ITT Efficacy	60	55	57	57
Efficacy Population	59	53	54	57
Completed	35	48	47	52
Discontinuation of study of randomized subjects	27	13	17	10
Reason discontinuation of study				
AE	0	1	1	0
Deviation from protocol*	1	8	2	6
Lack of efficacy	22	1	4	0
Loss to follow-up	4	3	9	4

	Placebo	TQ Low Dose (200 mg)	TQ Load only (400 mg)	TQ High Dose (400 mg)
Other	0	0	1	0

Source: Tables 3 and 4, Study Report. Study populations were from the study report.
*10 discontinued subjects with protocol deviation (1 prophylactic failure and 9 not failures) were included in the ITT analysis population. 7 discontinued subjects with protocol deviation (with no prophylactic failures) were not included in the ITT analysis. All randomized subjects will be included in FDA primary analysis.

Demographic Characteristics

As the low dose represents the regimen proposed for prophylaxis by the Applicant, the FDA focused its analysis on the low dose group. Table 10 shows that the low dose group had a somewhat higher proportion of males than the placebo group, but that other demographic characteristics were fairly similar between the TQ low dose and placebo groups.

Table 10. Study 043: Demographic Characteristics in all Randomized Subjects

	Placebo (N=62)	TQ Low Dose (200 mg) (N=61)	TQ Load only (400 mg) (N=64)	TQ High Dose (400 mg) (N=62)
Sex				
Male	34 (55%)	42 (69%)	38 (59%)	37 (60%)
Female*	28 (45%)	19 (31%)	26 (41%)	25 (40%)
Age (years)				
Mean (SD)	32.3 (11.6)	33.5 (12.4)	32.1 (11.9)	31.7 (10.1)
Median	32.0	34.0	33.5	34.0
Range	18-55	18-54	17-55	18-50
Race				
Black or African American	100%	100%	100%	100%

*The age of female subjects was between 18-55 years old with a mean of 36.4.

8.2.4 Efficacy Results

Table 11 contains the results of PE at the end of prophylaxis treatment in all randomized subjects (the FDA's primary efficacy analysis). In this analysis, subjects excluded from the Applicant's Efficacy Population were considered prophylactic failures. The differences in the incidence of parasitemia between the TQ groups and the placebo group were statistically significant. The p-values from the chi-square test, with multiplicity considered (using two-sided type I error of 0.05/3=0.017) were all less than 0.017. Even when using the most conservative method for handling missing data, where missing data in the TQ arm were considered as having parasitemia and in the placebo arm as not having parasitemia (a worst-case analysis), the results remained highly statistical significant (data not shown).

Table 11. Study 043: Incidence of Parasitemia and Protective Efficacy at the End of Treatment (15 Weeks) in all Randomized Subjects

	Placebo (N=62)	TQ Low Dose (200 mg) (N=61)	TQ Load only (400 mg) (N=64)	TQ High Dose (400 mg) (N=62)

	Placebo (N=62)	TQ Low Dose (200 mg) (N=61)	TQ Load only (400 mg) (N=64)	TQ High Dose (400 mg) (N=62)
Parasitemia (including missing data)	57 (91.9%)	15 (24.6%)	26 (40.6%)	11 (17.7%)
Actual Parasitemia	54 (87.1%)	7 (11.5%)	16 (25.0%)	6 (9.7%)
Missing value	3 (4.8%)	8 (13.1%)	10 (15.6%)	5 (8.1%)
Protective efficacy (PE) (%)		73.3	55.8	80.7
98.3% CI for PE (%)		54.0, 84.5	35.9, 61.5	62.7, 90.0
Chi-square p-value		<0.0001	<0.0001	<0.0001

Based on the study report, the majority 78/79 (99%) of subjects who developed malaria were infected with *P. falciparum*. *P. malariae* parasites were detected in a single subject in the TQ load only group.

Findings in Special/Subgroup Populations or Additional Analyses Conducted on the Individual Trial

Since all subjects were younger than 56 years of age, all subjects were of the same race, and no weight data were submitted, no analyses were performed by age, race, and weight. Incidence of parasitemia by gender were similar to the results seen in the overall population for the TQ low dose and placebo. See Table 11 and Table 12.

Table 12. Study 043: Incidence of Parasitemia at the End of Treatment (15 weeks) by Gender in all Randomized Subjects

	Placebo (N=62)	TQ Low Dose (200 mg) (N=61)	TQ Load only (400 mg) (N=64)	TQ High Dose (400 mg) (N=62)
Male	32/34 (94.1)	11/42 (26.2)	18/38 (47.4)	8/37 (21.6)
Female	25/28 (89.3)	4/19 (21.1)	8/26 (30.8)	3/25 (12.0)

The difference between the TQ low dose and placebo group was statistically significant for males and females, separately.

Conclusion

This study demonstrated that TQ 200 mg (for 3 days, followed by TQ 200 mg weekly for 10-15 weeks) achieved statistically significant protection against parasitemia compared with placebo (PE was 73.3% with a 98.3% CI [54.0%, 84.5%]), in semi-immune subjects in Kenya, where the primary species of the malarial parasite is *P. falciparum*.

8.3 Study 045

8.3.1 Study Design

This was a randomized, double-blind, placebo-controlled evaluation of multiple doses of weekly TQ in the Kassena-Nankana district of Northern Ghana.

Prior to study drug administration, subjects were given a regimen of antimalarial drugs intended to achieve 18-day radical cure (quinine for 4 days, followed by 7 days of doxycycline and 14 days of PQ). Subjects were randomized (2:2:2:2:2:1) to one of the following groups: placebo, TQ 25, 50, 100, 200 mg, and MQ 250 mg. At any given dose, TQ was administered initially as a loading dose of one capsule daily for 3 days, followed by a weekly dosing regimen at the same dose for 12 additional weeks. Similarly, MQ was administered as a loading dose of one tablet (250 mg) daily for 3 days, followed by one tablet weekly for 12 weeks. The loading dose started 5 days following the completion of radical cure. Study visits included Days 0 (enrollment), 23 (day 1 of load), 26 (1 day post-load), 33 to 111 (12 weekly visits while taking weekly doses, and weekly for 4 weeks).

The primary efficacy endpoint was the first occurrence of malaria infection as documented by a single positive blood smear. A smear was positive if both field microscopists' readings were positive.

Secondary measures of efficacy included the time to the first occurrence of malaria, the time to confirmation of parasitemia (confirmed parasitemia) as documented by two consecutive positive smears, and the incidence density of parasitemia.

Inclusion and Exclusion Criteria

Inclusion Criteria

Males aged 18 to 60 and females aged 50 to 60 years (to exclude women of reproductive age) in good health who planned to stay in the study area until the end of the study.

Exclusion Criteria

Exclusion criteria included, but were not limited to:

1. Any cardiovascular, liver, neurologic, or renal function abnormality
2. Receipt of antimalarial drugs for treatment within two weeks of study drug initiation.

8.3.2 Statistical Methodologies

Analysis Populations

The following analysis populations were defined. FDA analysis used the Safety Data Set for the primary efficacy analysis.

Full data set: all subjects who successfully completed the radical cure phase were randomized to receive any of the study medications, completed the loading dose period, received at least one dose of weekly prophylactic medication, and had at least one efficacy assessment. This was used for the Applicant's primary analysis.

PP data set: all subjects fully compliant with the study protocol who received the full course of treatment, unless they were withdrawn from randomized medication as a result

of developing parasitemia. This set was used for supplementary analysis.

Safety data set: all randomized subjects who successfully completed the radical cure phase and started the loading dose in the prophylaxis medication phase.

Analysis Methods

PE was defined in the same manner as in Study 043, with cumulative incidence of malaria up to 7 days after treatment with placebo or drug. The CIs for the estimates of PE were derived using the method described by Koopman. But the confidence level was not specified in the analysis plan, and 95% was used in the report. The FDA used a 98.75% level based on Bonferroni's method, as there were 4 comparisons (TQ vs. placebo) in the study (1-0.05/4).

Missing data were not discussed in the analysis plan. The FDA considered discontinued subjects with missing parasitemia results as failures.

8.3.3 Patient Disposition

Table 13. Study 045: Patient disposition

	Placebo	**TQ**				**MQ 250 mg**
		25 mg	**50 mg**	**100 mg**	**200 mg**	
Randomized	96	95	94	94	94	48
Safety	94	93	93	94	93	46
Full data set	94	93	91	94	91	46
PP data set	83	83	74	80	68	40
Completed prophylaxis phase	24	60	78	86	76	44
Total Withdrawn from the full data set	70(74.5%)	33(35.5%)	13(14.3%)	8(8.5%)	15(16.5%)	2(4.3%)
Reason for withdrawal						
Confirmed parasitemia	62(66.0%)	26(28.0%)	2(2.2%)	0	1(1.1%)	0
Discontinued*	8(8.5%)	7(7.5%)	11(12.1%)	8(8.5%)	14(15.4%)	2(4.3%)

*Discontinued due to AEs, non-compliance. From the data set the numbers for confirmed parasitemia and discontinued were 61 and 9, respectively for the placebo group; and 0 and 15 in the 200 mg TQ group.
Source: Tables 5 and 6, Study Report

Demographic Characteristics

Demographic characteristics are presented in Table 14. All variables were well-balanced among the groups. Note that the mean age for women was higher than the mean age for men because women <50 years old were not eligible for this study to exclude women of reproductive age.

Table 14. Study 045: Demographic Characteristics in the Safety Data Set

	Placebo (N=94)	**TQ**				**MQ 250 mg (N=46)**
		25 mg (N=93)	**50 mg (N=93)**	**100 mg (N=94)**	**200 mg (N=93)**	
Sex n(%)						
Male	62 (66.0)	55 (59.1)	56 (60.0)	66 (70.2)	61 (65.6)	32 (69.6)

	Placebo (N=94)	TQ				MQ 250 mg (N=46)
		25 mg (N=93)	50 mg (N=93)	100 mg (N=94)	200 mg (N=93)	
Female	32 (34.0)	38 (40.9)	37 (40.0)	28 (29.8)	32 (34.4)	14 (30.4)
Age (yrs) males						
Mean	39	40	36	38	40	36
Median	40	40	36	38	38	35
Range	17 – 60	14 – 63	18 – 58	18 – 60	18 – 63	19 – 58
Age (yrs) females						
Mean	53	53	53	54	54	53
Median	53	54	54	54	54	53
Range	46 – 60	45 – 59	38 – 63	46 – 70	46 – 69	45 – 68
Weight (kg) males						
Mean (SD)	54.8 (6.3)	56.3 (9.0)	55.6 (8.6)	55.4 (6.9)	54.3 (6.8)	56.7 (6.2)
Median	55	55	57	56	54	57
Range	35 – 73	37 – 90	33 – 77	36 – 68	36 – 72	42 – 69
Weight (kg) females						
Mean (SD)	48.0 (6.8)	46.0 (4.6)	50.2 (7.1)	47.6 (7.1)	44.9 (4.3)	48.8 (4.9)
Median	47	46	50	47	45	49
Range	35 – 65	35 – 54	40 – 71	35 – 62	35 – 55	40 – 57

Notes: Ages were not known precisely and were therefore approximate.

8.3.4 Efficacy Results

Table 15 shows the results from the FDA's primary efficacy analysis. As there were 4 TQ vs. placebo comparisons, to adjust for multiplicity, a type I error of 0.05/4=0.0125 was used using Bonferroni's approach, so 98.75% CI were calculated for all comparisons. The proposed dosing of TQ 200 mg was effective compared with placebo, as the 98.75% CI for the protective efficacy of 71.3% was [55.8%, 81.4%], much higher than 0, when considering discontinued subjects as prophylactic failures. Similar results were seen when considering discontinued subjects as non-events and with the worst-case analysis (discontinued subjects in the placebo group as having no parasitemia and discontinued subjects in other groups as having parasitemia, not shown), all the treatment groups compared to the placebo group indicated significant protection against parasitemia, demonstrating that the Applicant's handling of these discontinued patients was not an important source of bias with regard to efficacy. The results from the Applicant's analysis in the PP set (not shown) were very similar to the results in the safety data set.

Table 15. Study 045: Incidence of Parasitemia during 12-week Prophylaxis in the Safety Data Set (FDA's Analysis)

	Placebo (N=94)	TQ				MQ 250 mg (N=46)
		25 mg (N=93)	50 mg (N=93)	100 mg (N=94)	200 mg (N=93)	
Parasitemia	86	58	13	11	12	6
No parasitemia	8	35	80	83	81	40
Discontinued	*2*	*4*	*12*	*8*	*13*	*2*
AE	*1*	*4*	*6*	*6*	*8*	*0*
Non-compliance with study drug	*1*	*0*	*6*	*2*	*5*	*2*

	Placebo (N=94)	TQ				MQ 250 mg (N=46)
		25 mg (N=93)	50 mg (N=93)	100 mg (N=94)	200 mg (N=93)	
Discontinued subjects as parasitemia events						
Parasitemia	88	62	25	19	25	8
Incidence (%)	93.6	66.7	26.9	20.2	26.9	17.4
PE (%)		28.8	71.3	78.4	71.3	81.4
98.75% CI for PE (%)		13.4, 41.4	55.8, 81.4	63.8, 87.1	55.8, 81.4	58.4, 91.7
Discontinued subjects as not parasitemia events						
Parasitemia	86	58	13	11	12	6
Incidence (%)	91.5	62.4	14.0	11.7	12.9	13.0
PE (%)	-	31.8	84.7	87.2	85.9	85.7
98.75% CI for PE(%)		15.4, 45.1	70.8, 92.0	73.9, 93.7	72.2, 92.8	63.0, 94.5

Efficacy Results – Secondary and Other Relevant Endpoints

The incidence of confirmed parasitemia (i.e., two consecutive positive blood smears) and PE based on confirmed parasitemia are presented in Table 16 (FDA analysis, with discontinued subjects considered either as failures or as not having parasitemia, separately). As expected, the incidence of confirmed parasitemia was lower than the incidence based on single positive blood smear. The PEs were statistically significantly higher than 0, indicating a treatment effect. Note that when using this more strict definition of confirmed parasitemia, there were no observed parasitemia cases in the MQ arm or the two highest TQ arms.

Table 16. Study 045: Incidence of Confirmed Parasitemia during 12-week Prophylaxis in the Safety Data Set

	Placebo (N=94)	TQ				MQ 250 mg (N=46)
		25 mg (N=93)	50 mg (N=93)	100 mg (N=94)	200 mg (N=93)	
Parasitemia (missing as failure)	70	33	15	8	17	2
Incidence (%)	74.5	35.5	16.1	8.5	18.3	4.4
PE (%)	-	52.3	78.3	88.6	75.5	94.2
98.75% CI for PE (%)	-	30.3, 67.4	60.2,88.2	73.0, 95.2	56.7, 86.1	66.9, 99.0
Parasitemia (missing as no parasitemia)	61	26	2	0	0	0
Incidence (%)	64.9	28.0	2.2	0	0	0
PE (%)		56.9	96.7	100	100	100
98.75% CI for PE (%)		32.0, 72.7	80.8, 99.4	91.6, 100	90.2, 100	81.4, 100

Table 17 shows the categorized time to first positive smear in the safety set. The majority of the subjects who had parasitemia developed it during the first 9 weeks. All cases of parasitemia, were due to *P. falciparum* species with the exception of 4 subjects in the placebo group infected with *P. malariae.*

Table 17. Study 045: Time to First Positive Smear in the Safety Set

	Placebo (N=94)	TQ				MQ 250 mg (N=46)
		25 mg (N=93)	50 mg (N=93)	100 mg (N=94)	200 mg (N=93)	
Parasitemia	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
Missing time	2	4	12	8	13	2

Findings in Special/Subgroup Populations or Additional Analyses Conducted on the Individual Trial

Gender, Race, Age, Weight

In the subgroup analyses seen in Table 18, the FDA only included the relevant treatment groups: placebo, 200 mg TQ, and MQ, and considered discontinued subjects as failures. As this study only included one race, there was no subgroup analysis for race. There were almost no subjects 65 years of age or older to assess efficacy. For all other subgroups, results were comparable to the overall population.

Table 18. Study 045: Incidence of parasitemia during 12-week Prophylaxis by Gender, Age, and Weight in the Safety Set (missing=failure)

n/N(%)	Placebo (N=94)	TQ 200 mg (N=93)	MQ 250 mg (N=46)
Sex			
Male	58/62 (93.6)	19/61 (31.2)	7/32 (21.9)
Female	30/32 (93.8)	6/32 (18.8)	1/14 (7.1)
Age (yrs)			
<50	51/55 (92.7)	16/50 (32.0)	5/31 (16.1)
≥50-<65	37/39 (94.9)	9/42 (21.4)	2/14 (14.3)
≥65	0	0/1	1/1
Weight (kg)			
<50	29/29 (100)	6/42 (14.3)	2/11 (18.2)
≥50	59/65 (90.8)	19/51 (37.3)	6/35 (23.2)

Geographic Location (Site)

Table 20 shows the results by study site (discontinued subjects considered as failures). In the TQ 200 mg group, all sites, except for the smallest, showed very consistent results.

Table 19. Study 045: Incidence of Parasitemia During 12-week Prophylaxis by Study site in the Safety Set (missing=failure)

n/N(%)	Placebo (N=94)	TQ 200 mg (N=93)	MQ 250 mg (N=46)
Akuragu	10/11 (90.9)	2/10 (20.0)	0/3 (0)

n/N(%)	Placebo (N=94)	TQ 200 mg (N=93)	MQ 250 mg (N=46)
Biu	11/12 (91.7)	4/14 (28.6)	3/6 (50.0)
Gea	34/35 (97.1)	9/33 (27.3)	3/17 (17.7)
Korania	17/18 (94.4)	4/17 (23.5)	0/9 (0)
Nakolo	6/7 (85.7)	4/7 (57.1)	2/4 (50.0)
Sirigu	10/11 (90.9)	2/12 (16.7)	0/7 (0)

Conclusion

This study demonstrated that 200 mg TQ provided statistically significant protection against *P. falciparum* malaria in semi-immune subjects in Ghana. It is noted that this study did not enroll younger women.

8.4 Study 030

Study 030 was a placebo- and active-controlled study that did not show any efficacy of TQ or the active control MQ when initially assessed. For this reason, the sponsor submitted the study report without any electronic patient-level data.

8.4.1 Study Design

This was a randomized, double-blind, double-dummy, placebo-controlled study to evaluate weekly TQ for chemosuppression of *P. falciparum* compared to placebo in Western Kenya. A positive control, MQ, was included.

Subjects who met the study entry criteria were treated for three days with halofantrine to clear any existing parasitemia. At the end of the clearance period, subjects who did not have parasitemia were randomized to one of three arms, TQ 200 mg, MQ 250 mg, or placebo. Treatment consisted of daily treatment for three days followed by once weekly dosing for 24 weeks. After the treatment period, subjects were followed until Week 28.

The primary efficacy endpoint was prophylactic outcome (success/failure) at the end of the prophylactic treatment phase (time of last dose, Week 24, plus 7 days). Prophylactic outcome was based on absence/presence of asexual stage parasites of any *Plasmodium* species on a single blood smear.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Healthy male or female volunteers who provided informed consent, were 18-55 years of age and planning to reside in the study area for the entire study duration of approximately 70 weeks.

Exclusion Criteria

Exclusion criteria included, but were not limited to:

- positive parasitemia following halofantrine treatment for radical cure.

- any medical condition which, in the opinion of the investigator, made the subject unsuitable to enter the study.
- receipt of any antimalarial product other than halofantrine within the previous two weeks.
- receipt of an investigational drug within 30 days or 5 half-lives whichever was the longer.

8.4.2 Statistical Methodologies

Analysis Populations
The following analysis populations were defined:

ITT population: All randomized subjects who were free from parasitemia following clearance medication, took at least one dose of prophylactic study medication and attended at least one follow-up visit at which assessment of a blood smear took place. The FDA conducted an analysis based on all randomized subjects.

PP population: All randomized subjects who satisfied those inclusion/exclusion criteria with the potential to affect efficacy, and subsequently adhered to the protocol.

Analysis Methods
There was one interim analysis. Based on O'Brien and Fleming's method, a significance level of 0.0026 at the interim and a significance level of 0.048 (associated 95.2% CIs) at the final reporting stage were used. The primary efficacy analysis was based on PE of TQ, defined as before, and 95.2% CIs were constructed for the relative risk using Koopman's method at the final analysis.

8.4.3 Patient Disposition

This study was conducted at a single clinic in Kenya between May and November 2000. A total of 306 subjects were randomized and 300 were included in the ITT population. The reasons for exclusion from the ITT population are listed in Table 20.

Table 20. Study 030: Patient Disposition

	Placebo	TQ	MQ	Total
Screened				517
Randomized	101	104	101	306
ITT population	99	102	99	300
PP population	92	94	90	276
Safety population	101	104	101	306
Reason for randomized subjects' exclusion from the ITT population				
No negative smear before first dose	1 (1.0%)			1 (0.3%)
No smears post-first dose	1 (1.0%)	2 (1.9%)	2 (2.0%)	5 (1.6%)

Source: Tables 5 and 6, Study Report

Demographic Characteristics

Table 21 shows the demographic characteristics in the ITT population. These

characteristics were well-balanced across the three treatment groups.

Table 21. Study 030: Demographic Characteristics (ITT population)

	Placebo (N=99)	TQ (N=102)	MQ (N=99)
Sex, n(%)			
Male	63 (63.6)	66 (64.7)	66 (66.7)
Female	36 (36.4)	36 (35.3)	33 (33.3)
Age (years)			
Mean (SD)	32.0 (11.9)	29.5 (11.2)	29.4 (10.4)
Range	17-56	17-54	17-55
Race			
Black	99 (100)	102 (100)	99 (100)
Weight (kg)			
Mean (SD)	60.1 (7.9)	61.0 (8.5)	61.9 (10.0)
Range	44.0–84.0	42.0–90.0	40.0–97.0

Source: Table 7, Summary of Clinical Efficacy

8.4.4 Efficacy Results

Initial efficacy analyses were based on the slide-reading results from the US Army Medical Research Unit-Kenya. The results did not show any treatment effect. The low PE of the MQ (positive control) suggested that false-positive slide reading was likely to have occurred. While the study was still ongoing, 364 slide pairs were provided to the Naval Medical Research Unit-2 in Jakarta for blinded re-reading.

Table 22. Study 030: Protective Efficacy during the Prophylaxis Treatment Period (Week 25) based on First Positive Smear according to Original Slide Readers (ITT Population)

	Placebo (N=99)	TQ (N=102)	MQ (N=99)
Prophylactic failure	93 (93.9%)	90 (88.2%)	92 (92.9%)
PE (%)		6.1	1.1
95.2% CI for PE (%)		-2.8, 15	-7.4, 9.1

Based on the NAMRU-2 blinded slide reading, TQ was superior to placebo with PEs that were statistically significantly greater than zero (95.2% CIs did not include 0). The results appear comparable between TQ and MQ using the updated slide reading. Both the Applicant's and FDA analyses reached the same conclusion.

Table 23. Study 030: Protective Efficacy during the Prophylaxis Treatment Period based on First Positive Smear According to NAMRU-2 blinded Slide Readers (mITT Population, Applicant's analysis)

	Placebo (N=93)	TQ (N=99)	MQ (N=96)
Prophylactic failure	32 (34.4%)	2 (2%)	2 (2.1%)
PE (%)		94.1	93.9
95.2% CI for PE(%)		70.6, 98.8	70.0, 98.8

Source: Table 11, Summary of Clinical Efficacy. *Calculated by the reviewer.
The mITT population included all ITT subjects with at least one valid re-read smear result, i.e., a result with a classification of either positive or negative and with a collection date that was on or after the date of the first dose.

Table 24. Study 030: Protective Efficacy during the Prophylaxis Treatment Period Based on First Positive Smear according to NAMRU-2 blinded slide Readers (all randomized subjects, missing=failure, FDA's analysis)

	Placebo (N=101)	TQ (N=104)	MQ (N=101)
Prophylactic failure	40 (34.4%)	7 (2%)	7 (2.1%)
Prophylactic failure	32	2	2
Missing	8	5	5
PE (%)		83	92.5
95.2% CI for PE(%)		59.5, 92.9	58.3, 92.7

Calculated by FDA reviewer.

Conclusion

The original results of Study 030 did not show any treatment effect for either TQ or the positive control, MQ. After unplanned but blinded re-reading of the slides, the two active treatment groups showed significant protection against malaria by Week 25 in this semi-immune population of Western Kenyans. No datasets were submitted to allow a complete review of this study. Because the re-reading of smear slides was not pre-planned, this study provides only supportive evidence for efficacy.

8.5 Study TQ-2016-02

8.5.1 Study Design

This was a Phase 1b, randomized, double-blind, placebo-controlled study in healthy, non-immune adults to determine the schizonticidal activity of TQ after blood stage *P. falciparum* challenge (BSPC).

Two cohorts (21 days apart) of 8 subjects were randomized 6:2 into TQ 200 mg or placebo. Study drug was administered on Days 1 to 3, and 10. Note the regimen was the same as the first two weeks of the proposed regimen. Subjects were then inoculated with erythrocytes (blood type O-) containing approximately 2800 viable *P. falciparum* parasites of strain 3D7 (artemether/lumefantrine and PQ sensitive) on Day 13. All patients were treated with rescue therapy at the end of study visit or earlier in the event of malaria or at the discretion of the principal investigator. Study visits included Days 1, 2, 3, 4-9 (one visit), 10, 11-12 (one visit), 13, 14-16 (one visit), 17, 20, 24, 29, 32 (artemether/lumefantrine treatment), 33, and 34.

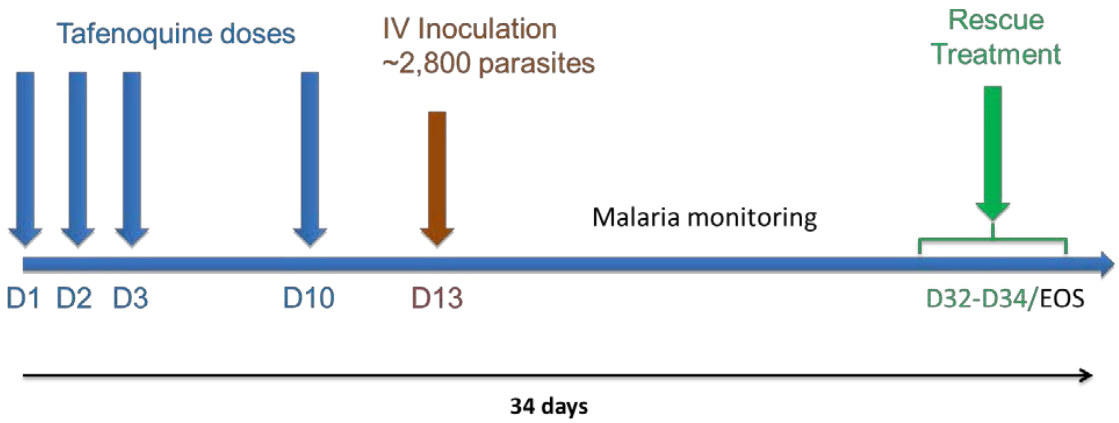

Figure 1. Study Scheme

While the primary endpoint was safety, the primary efficacy endpoints (exploratory) were malaria assessment by qPCR after challenge (qPCR parasitemia of >5,000 asexual blood stage estimated parasites/mL accompanied by a clinical symptom score of >6, or parasitemia of >5,000 asexual blood stage estimated parasites/mL and 2-fold increase within 48 hours), appearance of gametocytemia (pfs25 mRNA), and malaria clinical score.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

Inclusion criteria included, but were not limited to:

- Men or women aged 18 to 55 years, in good health
- Body weight ≥50 kg and a BMI 18 - 32 kg/m^2

Exclusion Criteria

Exclusion criteria included, but were not limited to:

- Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal cardiovascular, hepatic, psychiatric, neurologic, or allergic disease
- History of retinal abnormalities, visual field defects, hearing disorders
- History of malignancy within the past five years

8.5.2 Statistical Methodologies

Analysis Population

The following analysis populations were defined:

Intent-to-Treat (ITT) population (analyzed as treated): The ITT population consisted of all randomized participants who received at least one dose of study treatment, the BSPC inoculum and those who had at least one post-BSPC evaluation from Day 20 to Day 34. The ITT population was the primary population for analyses of TQ PK.

PP population (analyzed as treated): All participants who received study treatment

from Days 1-3 and again at Day 10, who had baseline evaluations conducted on Day 1 prior to investigational medicinal product administration, who received BSPC inoculum on Day 13 and completed all malaria monitoring visits from Day 17 to the End-of-Study visit (Day 34 ± 2 days) and who had no major protocol deviations. This was the primary population for the primary efficacy endpoint analysis.

Analysis Methods

Efficacy data (malaria assessment by qPCR and malaria clinical score) were presented for all participants. The proportion of participants experiencing malaria failure prior to the scheduled artemether/lumefantrine treatment period (on Day 32) was tabulated with 95% Clopper-Pearson exact CI and the two groups were compared using Fisher's exact test. PE with a 95% CI was determined. Mean (range) malaria scores at each time point were also tabulated. No formal interim analyses were performed.

8.5.3 Patient Disposition

The study was conducted between January 12 and March 31 2017 in Australia. All randomized subjects were included in the safety, ITT, and PP populations.

Table 25. Study TQ 2016-02: Patient Disposition

	Placebo	TQ	All
Randomized	4	12	16
Safety	4	12	16
ITT	4	12	16
PP	4	12	16

Demographic Characteristics

Demographic characteristics are presented in Table 26. The TQ group contained a higher proportion of female subjects, was slightly younger, and had lower body weight and BMI. Female subjects were between 20 and 40 years old. The majority of subjects were White (94%).

Table 26. Study TQ 2016-02: Demographic Characteristics

	Placebo (N=4)	TQ (N=12)	All (N=16)
Sex, n(%)			
Male	2 (50.0)	4 (33.3)	6 (37.5)
Female	2 (50.0)	8 (66.7)	10 (62.5)
Age	4	12	16
Mean (SD)	34.3 (8.66)	25.3 (3.05)	27.5 (6.16)
Median	36.0	25.5	26.0
Range	23 - 42	20 – 30	20 – 42
Body weight (kg)			
Mean (SD)	79.65 (11.112)	69.81 (11.238)	72.27 (11.691)
Median	78.00	68.35	69.70
Range	68.9 – 93.7	56.0 – 97.7	56.0 – 97.7
BMI (kg/m^2)			
Mean (SD)	26.50 (2.963)	23.23 (2.934)	24.05 (3.194)

	Placebo (N=4)	TQ (N=12)	All (N=16)
Median	23.50	26.90	23.95
Range	18.6 – 30.2	22.8 – 29.4	18.6 – 30.2
Race, n (%)			
Other	0 (0.0)	1 (25.0)	1 (6.3)
White	12 (100.0)	3 (75.0)	15 (93.8)

Exploratory Primary Efficacy Analysis

Table 27 shows cumulative malaria incidence by Day 34 after parasite inoculum on Day 13. The TQ treatment was successful in all 12 patients (100%) and there was a statistically significant difference in malaria incidence between the two groups (Fisher's exact test p-value=0.0005).

Table 27. Study TQ-2016-02: Malaria Cumulative Incidence by Day 34 after Parasite Challenge on Day 13 in the ITT Population

	Placebo (N=4)	TQ (N=12)
Malaria	4	0
95% CI for malaria	39.8%, 100%	0%, 26.5%
Fisher's exact test p-value		0.0005

Source: Table 7, Study Report

After parasite inoculum on Day 13, all subjects in the placebo group had detectable parasites starting on Day 17. All subjects on TQ had 0 parasite counts at all time visits. Table 28 contains the parasite counts for the placebo subjects.

Table 28. Study TQ-2016-02: Asexual Parasite Count (estimated parasites/mL) in the Placebo Group in the ITT Population

Visit	Subject			
		(b) (6)		
Day 17	29	33	27	66
Day 18	88	245	185	865
Day 19	94	150	69	72
Day 20	3662	3502	2286	18238
Day 21	5654	1603	15829	41216
Day 22	33053	70872	22195	3690
Day 23	758	1136	980	114
Day 24	40		41	
Day 27	5654	1603	15829	41216
Day 29		37		
Day 34 (End of Study)			37	

Malaria signs and symptoms occurred in 3 TQ subjects (3/12, 25%) with a maximum individual overall score of 2 (mild severity) (not meeting the study malaria definition), and in all placebo group subjects (4/4, 100%) (mild to moderate severity) with a maximum individual overall score of 4.

Findings in Special/Subgroup Populations or Additional Analyses Conducted on the

Individual Trial

As the incidence rates were 0 or 1 in the TQ and placebo groups, respectively, there were no subgroup analyses reported here.

Conclusion

Study TQ-2016-02 included 16 healthy, non-immune adult subjects. This challenge study demonstrated that subjects who received TQ prior to inoculation remained clear of blood stage parasites and showed a highly statistically significant treatment effect (incidence of malaria, TQ vs. placebo: 0/12 vs. 4/4, Fisher's exact p-value=0.0005).

9 Overall Efficacy Summary

9.1 Assessment of Efficacy Across Trials

The primary efficacy endpoint in the efficacy studies reviewed was parasitemia.

In studies 043 and 045, parasitemia during the 15 or 12 weeks of prophylaxis was the primary efficacy endpoint. The parasitemia proportions were comparable in Studies 043 and 045. Additionally, Study 030 showed similar results after re-reading of the slides. In Study TQ-2016-02, parasitemia by Day 34 after receiving blood-stage *P. falciparum* challenge inoculum on Day 13 was one of the primary efficacy endpoints. All four studies demonstrated a statistically significant treatment effect in terms of PE or the difference in incidence of parasitemia between treatment and placebo groups. See Table 29.

Table 29. Parasitemia in Placebo Controlled Trials (Discontinued subjects treated as parasitemic)

Study	Analysis Population	Treatment	Parasitemia	PE [Adjusted CI]*/ Difference in failure
043	ITT	Placebo	57/62 (91.9%)	PE: 73.3% [54.0%, 84.5%]
		TQ	15/61 (24.6%)	
045	Mitt	Placebo	88/94 (93.6%)	PE: 71.3% [55.8%, 81.4%]
		TQ	25/93 (26.9%)	
TQ-2016-02	ITT	Placebo	4/4 (100%)	
		TQ	0/12 (0%)†	
030 (unplanned, blinded re-reading of slides)	Mitt	Placebo	32/93 (34.4%)	PE: 94.1% [70.6%, 98.8%]
		TQ	2/99 (2%)	
		TQ	10/492 (3.9%)	

*Bonferroni's adjustment for multiple comparisons in a study. The adjusted confidence levels were 98.3% and 98.75% for the first two studies, respectively. †The difference was statistically significant with a p-value from Fisher's exact test of 0.0005.

The one active-controlled trial in a non-immune population, Study 033, had no cases of parasitemia during the prophylactic phase and five cases of parasitemia during the follow-up phase of the trial (0.8% vs. 0.6% for TQ and MQ, respectively).

Subpopulations

Studies 043, 045, and 030 were conducted in Africa in participants of a single race (Black). TQ-2016-02 and 033 mainly included White subjects (93.8% and 98.5%, respectively). The five studies included only one TQ 200 mg subject who was greater than 65 years old (Study 045). Therefore, the effect of TQ in populations aged >65 years is essentially unknown. There were large proportions of women in the three studies in Africa (39% in 043, 30% in 045, and 35% in 030), but Study 045 limited enrollment to post-menopausal women. Only 3.4% of subjects were women in Study 033, and 10 of 16 (62.5%) subjects were women in TQ-2016-02.

The limited demographic range of the study participants makes it difficult to generalize the efficacy findings of any particular study to a larger population. However, no concerning trends were seen across the studies regarding the different subgroups.

9.2 Summary and Conclusions of Efficacy

The five efficacy studies reviewed were randomized, double-blind, controlled, prophylactic studies in non-immune or semi-immune healthy subjects.

Study 033 evaluated the efficacy of 26-week TQ and MQ treatment in non-immune subjects. FDA analysis showed no observed cases of malaria during the prophylactic phase of the trial and prophylactic success proportions at Week 26 of 96.1% (473/492) for TQ and 96.9% (157/162) for MQ when subjects withdrawn or missing were considered as not having a prophylactic success; the difference between the groups was -0.78%, 95% CI [-2.39%, 3.94%]. Because it was not possible to justify a noninferiority margin due to unknown malaria attack rates, it was not possible to definitively conclude that TQ was non-inferior to MQ. However, the Applicant provided information suggesting that subjects were likely exposed to malaria during the study. There were five cases of *P. vivax* malaria during the relapse follow-up phase of the trial, with similar rates in the two treatment arms.

Studies 043 and 045 were conducted in semi-immune subjects with a treatment duration of 15 and 12 weeks, respectively. Compared with the placebo group, TQ demonstrated statistically significant protection against the incidence of parasitemia.

The blood-stage parasite challenge study TQ-2016-02 demonstrated a significant effect of TQ mg compared to placebo in preventing parasitemia in healthy, non-immune subjects (prophylactic success proportion: 100% (12/12) for TQ vs. 0% (0/4) for placebo, Fisher's exact test two-sided p-value 0.0005).

Study 030 evaluated the efficacy of 24 weeks of TQ compared with MQ in semi-immune subjects. Both TQ and MQ failed to demonstrate protective efficacy with the original parasite slide-reading results. Following suspected errors in slide reading and unplanned but blinded re-reading of the slides, the two treatment groups showed significant protection against malaria by Week 25. This study provided supportive evidence for the TQ efficacy in the prevention of malaria infection.

Although the treatment durations varied, and no study tested the proposed regimen strictly (the final dose after exiting the malarious area), TQ at the proposed dose did show statistically significant prophylactic effects in Studies 043, 045, and TQ-2016-02. Other two studies (033, 030) provided supportive evidence for the efficacy of TQ.

10 Evaluation of Safety

10.1 Safety Summary

TQ at the anticipated clinical regimen (TQ ACR) of 200 mg daily for 3 days, followed by 200 mg weekly appears to be reasonably safe for malaria prophylaxis in adults for up to 6 months.

Although there were 825 subjects exposed to the TQ ACR in the Extended Safety Set (five clinical studies that evaluated TQ ACR), only 529 subjects were exposed to the TQ ACR for greater than or equal to 23 weeks.

Key safety findings identified during the review include:

Ocular: TQ is associated with reversible vortex keratopathy. The risk of adverse effects on vision and the retina cannot be adequately ascertained with the data provided.

Cardiac: Based on the data submitted, no large mean increase (i.e., >20 ms) in the QTc interval is anticipated for TQ 400 mg, a higher dose than the TQ ACR.

Hematologic: TQ ACR is associated with decrease in hemoglobin (Hb) levels, hemolytic anemia, and methemoglobinemia. No dose or duration response was identified with respect to Hb changes or methemoglobinemia in the populations studied. Note that TQ was not evaluated in individuals with G6PD deficiency, where the risk of hemolytic anemia would be higher.

Neurologic: In the Extended Safety Set, the incidence of headache and lethargy was similar between the TQ ACR group (29% and 3%, respectively) and the MQ group (30% and 4%). The Treatment Emergent Adverse Event (TEAE) of dizziness was reported at a higher rate in the MQ group compared to the TQ group (6% vs. 3%). The TEAEs of vertigo/tinnitus also occurred at lower rate in the TQ group (5%) compared to the MQ group (7%).

In Study 033, the incidence of dizziness was similar between the TQ and MQ groups (1%), while headache, lethargy, vertigo and tinnitus were more frequent in the MQ group. In Study 057, the incidence of myalgia in the TQ ACR group was higher than the placebo group (7% vs. 0%), while fall/dizziness/lightheadedness, headache, fatigue, lethargy, and visual disturbance were numerically higher for placebo than TQ. A single case of tinnitus was reported in the TQ group and remained unresolved at the end of the study.

In studies 030, 043 and 045, the rate of headache in the TQ group was slightly higher (33%) than the placebo group (31%), while fall/dizziness/lightheadedness were higher than in the placebo group but lower than in the MQ group (5% TQ vs. 3% placebo vs. 10% MQ). Systematic monitoring for neurologic AEs was not conducted in these trials and, therefore, the reported AE rate may significantly underestimate the true incidence of these events in these trials. The safety of TQ in individuals with underlying neurologic conditions cannot be ascertained because these subjects were excluded from the TQ clinical trials.

Psychiatric: In the Extended Dosing Safety Set, psychiatric adverse reactions were reported in 3.9% (32/825) subjects receiving TQ ACR, 3.2% (10/309) subjects receiving MQ, and 0.8% (3/396) subjects receiving placebo.

In Study 033, the incidence of subjects experiencing sleep disturbances was similar in the TQ ACR (4%) and MQ groups (4%). Psychiatric adverse reactions leading to study discontinuation in the TQ ACR group included suicide attempt and depression, each occurred in 1 (0.1%) subject. Systematic monitoring for psychiatric AEs was not conducted in these trials and, therefore, the reported AE rate may significantly underestimate the true incidence of these events in these trials. The safety of TQ in individuals with underlying psychiatric conditions cannot be ascertained because these subjects were excluded from the TQ clinical trials.

Gastrointestinal: TQ ACR is associated with gastrointestinal adverse reactions, notably. abdominal pain, diarrhea, nausea, and vomiting. The safety profile of TQ when administered without food has not been assessed in the development program.

TQ ACR shares several safety issues with approved quinoline antimalarial drugs. Risk mitigation strategies include appropriate labeling and a Medication Guide. Postmarketing studies could evaluate ophthalmic, hematologic, neurologic, and psychiatric safety concerns further.

10.2 Methods

More than 20 clinical trials were included by the Applicant in the NDA submission. Comparative trials most relevant to the evaluation of clinical safety of the TQ ACR are summarized in Table 30. Studies 030, 033, 043, 045, and 057 (a Phase 1 study) constitute the Extended Dosing Safety Set. Four studies included a placebo arm (030, 043, 045, and 057), while two (030 and 033) had MQ as an active comparator.

A total of 825 subjects received TQ ACR and are included in the Extended Dosing Safety Set. Of the 825 subjects receiving TQ ACR, 677 subjects were enrolled in studies with a planned duration of exposure of 23 to 24 weeks (Studies 030, 033, and 057); 529 subjects were actually exposed to the TQ ACR for greater than or equal to 23 weeks. The actual duration of exposure for all TQ ACR exposed subjects ranged from less than 10 to 29 weeks.

Study 033 enrolled the most number of subjects with planned TQ treatment for >23 weeks (n=492), and hence is considered a key safety study. Study 033 enrolled Australian Defense Force (ADF) soldiers who were deployed on a peacekeeping mission to East Timor between October 2000 and April 2001.

Study 057 enrolled a significant number of healthy US and UK civilian and non-deployed military volunteers with a planned TQ prophylaxis for >23 weeks (n=81). The study was designed to evaluate renal and ocular safety of TQ and is considered a key supportive safety study.

Table 30. Key Studies used to Evaluate Clinical Safety

Study	Treatment Arms (*n*, safety population)	Planned Treatment Duration
030	**TQ 200 mg/d x 3 d, then 200 mg/wk (104)** MQ 250 mg/d x 3d, then 250 mg/wk (101) Placebo (101)	12 wks[1]
033	**TQ 200 mg/d x 3d, then 200 mg/wk (492)** MQ 250 mg/d x 3d, then 250 mg/wk (162)	26 wks
043	TQ 400 mg/d x 3d, then placebo/wk (60) **TQ 200 mg/d x 3d, then 200 mg/wk (55)** TQ 400 mg/d x 3d, then 400 mg/wk (59) Placebo (61)	15 wks
045	TQ 25 mg/d x3d, then 25 mg/week (93) TQ 50 mg/d x3d, then 50 mg/week (93) TQ 100 mg/d x3d, then 100 mg/week (94) **TQ 200 mg/d x3d, then 200 mg/week (93)** MQ 250 mg/day x3d, then 250 mg/week (46) Placebo (94)	12 wks
057	**TQ 200 mg/d x3, then 200 mg/week (81)** Placebo (39)	23 wks

TQ= tafenoquine, MQ=placebo, d=days, wks=weeks
[1]Although the planned duration of treatment for Study 030 was 24 weeks, most subjects were exposed to TQ for <12 weeks (72/104 [69%]).

Pooled analyses were used to detect potential low-frequency events observed in the Extended Dosing Safety Set, acknowledging inherent weakness in combining data from heterogeneous studies and cross-study comparisons. In general, all subjects receiving the TQ ACR (n=825), regardless of exposure duration were included in the pooled analyses. For submission-specific safety issues, pooled data, as well as individual study data, were reviewed and discussed as appropriate.

Incidence rates for TEAEs were analyzed using the Extended Dosing Safety Set. Multiple occurrences of the same event in the same patient were counted once.

10.3 Adverse Event Analysis

Summary of Adverse Events

A summary of subjects completing the studies in the Extended Dosing Safety Set, and subjects experiencing serious adverse events (SAEs) and TEAEs, is included in Table 31.

Table 31. Summary of Adverse Events

Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=396)	**Mefloquine 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Completed Study	656 (79.5%)	147 (38.9%)	205 (66.3%)
Deaths[1]	0	0	0
At least one SAE	47 (5.7%)	17 (4.3%)	11 (3.6%)
Withdrawn due to SAE	11 (1.3%)	1 (0.3%)	2 (0.6%)
At least one TEAE	692 (83.9%)	258 (65.2%)	249 (80.6%)
Withdrawn due to TEAE	34 (4.1%)	10 (2.5%)	5 (1.6%)

[1]There was one subject who received TQ 50 mg weekly and died due to suspected hepatocellular carcinoma.

Deaths

One death was recorded in the TQ program; a 53-year-old Ghanaian male randomized to receive TQ 50 mg weekly. This subject had been experiencing abdominal pain before study entry, which was not reported to investigators at enrollment. He was hospitalized for abdominal pain and dysentery at 75 days after initial TQ dose. A differential diagnosis of hepatocellular carcinoma, abdominal tuberculosis, and cirrhosis was made, and TQ was discontinued. At 131 days after the last TQ dose, the subject died. An autopsy was not performed. The investigator reported the death was due to suspected hepatocellular carcinoma, and as an SAE.

Serious Adverse Events

A total of 49 SAEs were reported among 47 (5.7%) subjects who received the TQ ACR. In general, SAEs in the TQ ACR arm were similar to that observed with placebo. Key SAEs reported in the TQ arm but not in the placebo or MQ group, include gastroenteritis (n=3 [0.4%]), keratopathy (n=5 [0.6]), retinal disorders (n=2 [0.2]), suicide attempt (n=1 [0.1%]), and hemolytic anemia (n=1 [0.1%]). Retinal disorder SAE was reported in 2 (0.2%) subject in TQ ACR compared to zero in the placebo and 1 (0.3%) in the MQ group.

Adverse Events Leading to Study Discontinuation

In the Extended Dosing Safety Set, TQ was discontinued due to a TEAE in 34/825 (4.1%) of patients, while the placebo and mefloquine were discontinued in 10/396 (2.5%) and 5/309 (1.6%) of patients, respectively. The most common TEAEs leading to study discontinuation in TQ ACR were increased ALT (6/825 [0.7%]), decreased Hb (3/825 [0.4%]), and decreased GFR (2/825 [0.2%]).

Treatment Emergent Adverse Events

Adverse reactions occurring in ≥2% of subjects in the TQ group in the Extended Dosing Safety Set are presented in Table 32.

Table 32. Selected Adverse Reactions Occurring in ≥2% of Patients Receiving TQ in Pooled Clinical Trials for the Prevention of Malaria

Dictionary Derived Term Number of subjects	Tafenoquine 200 mg daily x3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=396)[1]	Mefloquine 250 mg daily x3 days, then 250 mg weekly (n=309)[1]
Ear and labyrinth disorders			
Vertigo[2]	3%	0%	3%
Gastrointestinal disorders			
Abdominal pain[3]	8%	13%	13%
Diarrhea	12.7%	5.8%	10.7%
Nausea	6%	6%	6%
Vomiting	4%	2%	4%
Musculoskeletal and connective tissue disorders			
Arthralgia	7%	4%	10%
Musculoskeletal pain[4]	21%	14%	24%
Myalgia	3%	7%	5%
Nervous system disorders			
Dizziness	3%	6%	6%
Headache	22%	32%	30%
Lethargy	3%	0%	4%

[1]Not all pooled clinical trials had placebo or mefloquine as a comparator arm.
[2]Includes motion sickness, vertigo and vertigo positional.
[3]Includes abdominal pain and abdominal pain upper.
[4]Includes musculoskeletal pain, back pain and neck pain.

10.4 Adverse Reactions of Special Interest and Submission Specific Safety Issues

TQ is an 8-aminoquinoline drug. There are five other quinoline drugs approved for malaria prophylaxis and/or treatment in the US: PQ, CQ, hydroxychloroquine , quinine, and MQ. A focused safety review evaluated TQ for issues known to occur with exposure to any of these drugs.

10.4.1 Ophthalmic

Vortex keratopathy was reported in 21 to 93% of TQ subjects in the studies which included ophthalmic evaluations (study 033 and study 057 and study 058). The keratopathy resolved within one year after drug cessation. Retinal abnormalities were also noted in less than 1% of TQ subjects.

Corneal Disorders

The majority of the TQ trials did not perform the ophthalmic examinations necessary to evaluate for keratopathy. In the Extended Dosing Safety Set, 69 subjects reported a TEAE of keratopathy in the TQ ACR group, all in Study 033, where detailed ophthalmic assessments were performed in a subgroup of 98 study participants (77 TQ; 21 MQ). The vortex keratopathy seen with TQ in Study 033 was fully reversible by Month 12 of follow-up.

In Study 057, 120 healthy US/UK volunteers received either TQ ACR or placebo for 23 weeks. Ophthalmic assessments were conducted on treatment and up to 6 months of follow up. Treatment-emergent keratopathy developed in 21% (15/70) of subjects receiving TQ ACR compared to 13% (4/32) of subjects receiving placebo. Keratopathy in the placebo-treated subjects resolved by 6 weeks after onset compared to Week 48 in the TQ-treated subjects.

In Study 058, adult Thai subjects with *P. vivax* malaria received either TQ 400 mg/day for 3 days (Days 1 to 3), or CQ/PQ combination treatment. Ophthalmic examinations were performed at baseline and Days 28 and 90. Twelve of 46 (26.1%) subjects receiving TQ developed vortex keratopathy by Day 28, compared to none in the PQ/CQ group. By the Day 90 assessment, the corneal deposits resolved in 6/12 subjects. Two subjects were lost to follow-up. In 4 subjects, the corneal deposits were still present at the Day 90 assessment.

Retinal Disorders

In Study 033, the incidence of retinal disorders TEAEs were similar in the TQ group (1.4% [7/492]) and the MQ group (1.9% [3/162]). Baseline retinal photography was not performed. The presence of the retinal findings in the population under study (active duty military) indicates a potential problem with the quality of the fundoscopic examinations and/or their interpretation, or potential drug effect.

In Study 057, retinal abnormalities identified by digital photography were reported in one subject in each treatment group at the follow-up visit only (safety population: TQ n=70, placebo n=32).

In Study 058, retinal pigmentation was observed on Day 28 in 19.6% (9/46) TQ-treated subjects, and was still present in 8 subjects at Day 90. In contrast, only 4.2% (1/24) of CQ/PQ subjects developed retinal findings. In both groups, retinal findings were not associated with any change in vision.

10.4.2 Cardiac

Among subjects who received the TQ ACR, there were no cardiac SAEs and no study discontinuations due to cardiac TEAEs. Furthermore, no cardiac TEAEs occurred at an incidence ≥1% in subjects who received the TQ ACR.

ECG data submitted in the NDA were primarily from Study 014, a randomized, open-label, parallel group bioequivalence study. In this study, 58 healthy subjects were randomized to receive single 400 mg dose of TQ 200 mg capsule (existing formulation), 400 mg dose of TQ 200 mg Phase 3 capsule (novel formulation), and 400 mg dose of TQ 200 mg Phase 3 tablet (to-be-marketed formulation) on 3 consecutive days. Based on by-time analysis for bioequivalence, no large mean increase (i.e., >20 ms) in the QTc interval is anticipated for TQ 400 mg. The largest upper bounds of the 2-sided 90% CI

for the mean difference for TQ 400 mg was < 20 ms and the mean changes were <10 ms. Additionally, no significant relationship between TQ concentration and changes in the QTc interval was observed. These findings are further supported by the available preclinical information (hERG assay, isolated dog Purkinje fiber, dog CV safety studies) which revealed no QT liability. The Applicant did not conduct a thorough QT study.

10.4.3 Hematologic

Hematologic TEAEs leading to study discontinuation presented in Table 33 included decreased Hb and hemolytic anemia. Of note, all 3 withdrawals due to decreased Hb occurred in Study 045, where withdrawal criteria guided the investigator to discontinue subjects for minor changes in laboratory parameters. In all 3 cases, the decrease in Hb did not require treatment and resolved in 28 to 50 days.

Table 33. Summary of Hematologic Adverse Events: TQ ACR Group vs. Placebo and MQ – Extended Dosing Safety Set

Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=396)	**Mefloquine 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Hematologic TEAEs leading to discontinuation			
Hb decreased	3 (0.4%)	1 (0.3%)	-
Hemolytic anemia	2 (0.2%)	-	-
Hematologic SAEs			
Hemolytic anemia	1 (0.1%)	-	-
Hematologic TEAEs occurring ≥1% study subjects			
Anemia	10 (1.2%)	7 (1.8%)	1 (0.3%)
Leukocytosis	8 (1.0%)	5 (1.3%)	8 (2.6%)
Thrombocytopenia	10 (1.2%)	9 (2.3%)	4 (1.3%)

Two withdrawals due to hemolytic anemia occurred in Study 057. Neither subject required treatment and anemia resolved in both subjects within 1 month.

Three hematologic TEAEs occurred at incidences ≥1% in the TQ ACR group (anemia, leukocytosis, and thrombocytopenia); however, none had a higher incidence than in the placebo group.

The following TEAEs occurred at <1% in the TQ ACR group in the Extended Dosing Safety Set: Hb decreased, platelet count decreased, hematocrit increased, hematocrit abnormal, and hematocrit decreased.

The two subjects enrolled in Study 058, the *P. vivax* treatment study, experienced hemoglobinuria.

The percentage of subjects with any Hb decreases ≥0.66 g/dL was higher in the TQ ACR group (60.1%) than placebo (41.9%) or MQ (46.3%). See Table 34.

Table 34. Subjects with Hb change from Baseline - Extended Dosing Safety Set

Hb Change Decrease – Interval Categories Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)	**Mefloquine 250 mg daily for 3days, then 250 mg weekly** (n=309)	**Placebo** (n=396)
≥0.66 to < 1 g/dL decrease	120 (14.6%)	45 (14.6%)	62 (15.7%)
≥1 to < 2g/dL decrease	293 (35.5%)	80 (25.9%)	83 (21.0%)
≥2 to <3 g/dL decrease	64 (7.7%)	13 (4.2%)	18 (4.6%)
≥3 g/dL decrease	19 (2.3%)	5 (1.6%)	3 (0.8%)
Any Hb level decrease ≥0.66 g/dL	496 (60.1%)	143 (46.3%)	166 (42.0%)

Increase in methemoglobin levels relative to baseline were observed at a higher rate with TQ compared to both the placebo and MQ groups. Methemoglobin level changes from baseline are shown in Table 35.

Table 35. Change from baseline methemoglobin levels during study – Extended Dosing Safety Set

Methemoglobin Level – Increase from Baseline Interval Categories Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=396)	**Mefloquine 250 mg daily for 3 days, then 250 mg weekly** (n=309)
≥ 1% to <2%	58 (7.0%)	2 (0.5%)	0
≥2% to <3%	27 (3.3%)	1 (0.3%)	0
≥3% to <5%	12 (1.5%)	0	0
≥5% to <10%	8 (1.0%)	0	0
≥10%	1 (0.1%)	0	0
Any change ≥ 1%	106 (12.9%)	3 (0.8%)	0

10.4.4 Renal

Among renal TEAEs in the Extended Dosing Safety Set, GFR decreased led to study discontinuation in two (0.2%) subjects in the TQ ACR group, both in Study 057. In these subjects, serum creatinine remained within the normal range and the decreases in GFR were mild and transient. Five (0.6%) subjects in the TQ group and 2 (0.5%) in the placebo group experienced a TEAE of GFR decreased, all classified as an SAE. There were no subjects with GFR decreased TEAE in the MQ group. All subjects (TQ and placebo) with a TEAE of GFR decreased were enrolled in Study 057. TEAEs of creatinine increased or creatinine abnormal occurred in 3 (0.4%) subjects in the TQ group, 1 (0.3%) subject in the placebo group, and 3 (1%) subjects in the MQ group.

In Study 033, mean serum creatinine increases from baseline in both TQ and MQ groups were not clinically significant. A long-term renal follow-up study was conducted in a cohort of 183 (TQ, n=147; MQ, n=36) subjects with serum creatinine concentrations ≥ 0.23 mg/dL above baseline at the end of the prophylactic phase and/or at follow-up. Ten subjects were referred for renal follow-up due to elevated serum creatinine or abnormal urinalysis (TQ, n = 7; MQ, n = 3) and were confirmed by the nephrologist as having no evidence of renal injury.

The primary renal safety endpoint in Study 057 was the mean change in GFR from baseline to Week 24 (NI margin of -15% or 14.8 mL/min/1.73m^2). Only 53/81 (65.4%) TQ and 29/39 (74.4%) of placebo subjects completed the study. The renally evaluable population consisted of 50 subjects in the TQ group and 23 subjects in the placebo group. The adjusted mean change (mL/min) in GFR from baseline at Week 24 was 1.4 in the TQ group and 5.0 in the placebo group; the treatment difference -3.7, 95% CI (-10; 2.7).

Significant urinalysis finding as urine protein, blood, or glucose were identified in two (3.6%) TQ and three (11.5%) placebo subjects at Week 24.

10.4.5 Neurologic

Neurologic AEs with TQ were assessed in the Extended Dosing Safety Set. Note that systematic monitoring for neurologic symptoms during treatment, such as actively asking subjects about neurologic symptoms, was not performed in the five trials. This may result in an underestimation of the actual incidence of neurologic AEs.

There were no deaths due to a neurologic AE. Neurologic TEAEs leading to study discontinuation in the TQ ACR group included visual field defect and hyperesthesia, in one subject each:

- *(Study 057):* A 45-year-old female subject received TQ 200 mg once daily for three days, followed by TQ 200 mg weekly. Three weeks after starting treatment with TQ, the subject developed a mild reduction in visual field. A Humphreys visual field analyser showed a repeatable decrease in sensitivity of greater than 10 decibels from screening, at a given point in both eyes. No retinopathy was evident in both eyes. This case was assessed serious as defined by the protocol. Treatment with TQ was discontinued and the subject was withdrawn from the study. The subject received no treatment for this event. The event resolved six weeks after onset. The investigator reported the reduction in visual field as possibly related to TQ.

- *(Study 033):* A 26-year-old White male ADF soldier in the TQ group, hepatitis B carrier positive, reported moderate hyperesthesia on Study Day 12. Before experiencing hyperesthesia, study personnel documented at least 1 episode of heavy alcohol use in the subject, together with alcohol-associated malaise while on study (reported as AEs on Study Day 2). Hyperesthesia, considered possibly related to TQ, was treated using unspecified non-medicinal modalities and resolved after 130 days.

In the MQ group, no patient had a neurologic TEAE that led to study discontinuation or was considered serious.

No neurologic TEAEs led to study discontinuation in the TQ ACR group.

In the Extended Dosing Safety Set, the number of subjects with TEAEs within the Nervous System Disorders SOC was numerically lower in the TQ ACR (27.5% [227/825]) than in the MQ (36.6% [113/309]) or placebo (37.1% [147/396]) groups. The incidence of headache and lethargy was similar in the TQ ACR group (28.6% and 2.9%,

respectively) and the MQ group (29.8% and 3.6%). The incidence of dizziness in the TQ ACR group (2.7%) was lower than both the placebo (6.3%) and MQ (5.5%) groups.

In Study 033, the incidence of TEAEs within the Nervous System Disorders SOC was numerically lower in the TQ group compared to MQ (22.4% [110/492] vs. 27.2% [44/162], respectively). In Study 033, the incidence of dizziness was similar between the TQ and MQ groups, while headache, lethargy, vertigo and tinnitus were more frequent in the MQ group. See Table 36.

Table 36. Selected Neurologic Adverse Reactions in Study 033 – Safety Population

Adverse Reactions	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=492)	Mefloquine 250 mg daily for 3 days, then 250 mg weekly (n=162)
Headache[1]	72 (14.6%)	30 (18.5%)
Fatigue and lethargy	28 (5.7%)	11 (6.8%)
Vertigo[2] and tinnitus	24 (4.9%)	11 (6.8%)
Dizziness	7 (1.4%)	2 (1.2%)
Myalgia	3 (0.6%)	1 (0.6%)
Deafness	-	1 (0.6%)

[1]Includes headache, migraine, sinus headache and tension headache.
[2]Includes vertigo, vertigo positional and motion sickness.

In Study 057, myalgia occurred at a higher incidence in the TQ group 7.4% (6/81) vs. placebo 0% (0/39). Neurological AE rates for headache, fatigue, lethargy, fall/dizziness/lightheadedness, and visual disturbance were numerically higher for placebo than TQ. A single case of tinnitus was reported in the TQ ACR group and remained unresolved at the end of the study.

In a pooled analysis of studies (030, 043, 045) with similar duration of exposure (12 to 15 weeks), a dose-related increase in the incidence of headache and myalgia was observed. See Table 37. There is also an increased incidence of fall/dizziness/lightheadedness in the TQ and MQ groups compared to placebo.

Table 37. Selected Neurologic Adverse Event Reported in Studies 030, 043, and 045

Adverse Event	TQ 400 mg weekly N=59 n (%)	TQ 200 mg weekly N=252 n (%)	Placebo N=256 n (%)	Mefloquine N=147 n (%)[1]
Headache[2]	25 (42.4)	84 (33.3)	78 (30.5)	68 (46.3)
Myalgia	13 (22.0)	24 (9.5)	31 (12.1)	14 (9.5)
Fall, dizziness, lightheadedness	3 (5.1)	13 (5.2)	8 (3.1)	15 (10.2)
Fatigue and lethargy	0	1 (0.4)	1 (0.4)	1 (0.7)
Visual disturbance	0	1 (0.4)	0	1 (0.7)
Vertigo and tinnitus	0	0	0	2 (1.4)

[1]Study 043 did not have a mefloquine arm
[2]Includes headache, migraine, sinus headache and tension headache.

10.4.6 Psychiatric

Exclusion criteria for psychiatric conditions varied among the studies in the Extended Dosing Safety Set. See Table 38. In the studies with an MQ control arm, individuals with a history of psychiatric disorder were excluded, consistent with current labeling for mefloquine. Note that systematic monitoring for psychiatric symptoms during treatment, such as a rating scale for depression, anxiety, psychosis, insomnia, or suicidal ideation, was not performed in any of the trials. This may result in an underestimation of the actual incidence of psychiatric AEs.

Table 38. Psychiatric Exclusion Criteria – Extended Dosing Safety Set Studies

Study	Exclusion Criteria
030	History of a psychiatric disorder
033	History of a psychiatric disorder History of drug or alcohol abuse
043	None
045	Personal or family history of a frank psychiatric disorder
057	History of drug or alcohol abuse

There were no deaths due to a psychiatric AE. Psychiatric TEAEs leading to study discontinuation in the TQ ACR group included suicide attempt and depression, each of which occurred in 1 (0.1%) subject:

- *(Study 043):* A 24 year-old Kenyan male was found to be acutely intoxicated with ethanol eight days after TQ exposure (200 mg weekly). The family reported that the subject had marital problems and had threatened suicide. He had ethanol on his breath, was combative and disoriented on presentation to the drug center. The family reported that he had also taken poison for suicide. The subject was hospitalized and the event resolved 2 days later. The subject was withdrawn from the study because the investigators felt that he was not psychologically stable enough to continue in a controlled drug trial. Suicide attempt was reported as a SAE.

- *(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 TQ.

Psychiatric TEAEs leading to study discontinuation in the MQ group included severe anxiety in a single subject in Study 030 on Study Day 3. Cannabis use was suspected. Diazepam was administered and the event resolved after 4 days.

In the placebo group, no patient had a psychiatric TEAE that led to study discontinuation, or was considered severe or serious.

There were four subjects with psychiatric TEAEs considered serious or severe among the other TQ dose arms of Studies 043 and 045, and the remainder of the studies in the ISS. Three received TQ and one received placebo. Case narratives for these subjects follow.

TQ

- *(Study 014)*: A 23-year-old male experienced paranoid ideation and hallucinations 25 days after receiving tafenoquine 400 mg/day x 3 days. It was discovered that this subject had a past history of psychosis.

- *(Study 057):* A 22-year-old male received a single dose of TQ 350 mg and experienced an acute psychotic episode 3 weeks later. This subject had a history of 2 psychiatric hospitalizations.

- *(Study 050):* This was a 30-year-old male received a single dose of TQ 500 mg and experienced a psychotic episode one week later. It was discovered that he had a history of schizophrenia.

Placebo

- *(Study 006):* A 16-year-old female received placebo and had an unintended pregnancy. She took an overdose of chloroquine attempting to induce an abortion.

In the Extended Dosing Safety Set, the number of subjects with TEAEs within the Psychiatric Disorders SOC was similar in the TQ ACR 3.9% (32/825) and MQ 3.2% (10/309) groups, and both groups were higher than placebo 0.8% (3/396). Insomnia occurred at 1.2% (10/825) in the TQ ACR group compared to 0.8% (3/396) in the placebo and 0.3% (1/309) in the MQ groups.

In study 033, the incidence of TEAEs within the Psychiatric Disorders SOC was numerically higher in the TQ group compared to MQ (5.1% [25/492] vs. 4.3% [7/162], respectively). The incidence of sleep symptoms was similar between the TQ ACR and MQ groups (3.5% [17/492] vs. 3.7% [6/162]), respectively).

Table 39. Psychiatric Adverse Event Reporting Rates in Study 033 – Safety Population

Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=492)	**Mefloquine 250 mg daily for 3 days, then 250 mg weekly** (n=162)
Any subject with TEAE within Psychiatric Disorders SOC	25 (5.1%)	7 (4.3%)
Any sleep symptom[1]	17 (3.5%)	6 (3.7%)
Insomnia	8 (1.6%)	1 (0.6%)
Abnormal dreams[2]	7 (1.4%)	3 (1.9%)
Sleep disorder	2 (0.4%)	2 (1.2%)
Anxiety[3]	4 (0.8%)	-
Depression	1 (0.2%)	1 (0.6%)
Euphoric mood	2 (0.4%)	-
Agitation	2 (0.4%)	-
Somnambulism	-	1 (0.6%)

[1]Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.
[2]Includes abnormal dreams and nightmares.
[3]Includes anxiety disorder, panic attack, and stress.

10.4.7 Hepatobiliary

There were no hepatic SAEs reported in the TQ ACR group and no hepatic TEAEs occurred at a frequency ≥1% in the Extended Dosing Safety Set.

An SMQ for hepatic disorders revealed an overall lower incidence of TEAEs in the TQ ACR group (2.4% [20/825]) vs. the placebo (4.0% [16/396]) and mefloquine (4.2% [13/309]) groups. The TEAE incidence of alanine aminotransferase increased was similar in the TQ ACR, placebo, and MQ groups (1.5%, 1.5%, and 1.3%, respectively). An analysis of subjects enrolled in Study 033 revealed TEAEs only in the MQ group (1 subject each of liver function test abnormal and cytomegalovirus hepatitis), with zero TEAEs in the TQ and placebo groups.

There were no subjects who met the criteria for Hy's Law in the Clinical Use Studies and Extended Dosing Safety Set in any treatment group, including TQ-exposed subjects. In the entire TQ safety population of greater than 20 studies, a single subject with *P. vivax* malaria exposed to TQ met Hy's Law laboratory criteria.

10.4.8 Gastrointestinal

Discontinuations due to gastrointestinal (GI) TEAEs included one subject each with abdominal pain upper and irritable bowel syndrome in the TQ ACR group. GI SAEs in the TQ ACR group included one subject each with abdominal pain, diarrhea, upper abdominal pain, and irritable bowel syndrome.

In pooled analyses, selected GI TEAEs occurring at the incidence of ≥1% in the TQ ACR group included: abdominal pain, upper abdominal pain, constipation, diarrhea, dyspepsia, gastritis, nausea, and vomiting. Diarrhea (12.7%) and vomiting (3.8%) occurred at a higher incidence in the TQ ACR group than in the placebo group (5.8% and 1.5%) or MQ group (10.7% and 3.6%).

In Study 033, GI TEAEs ≥1% were numerically lower in the TQ compared to MQ group (diarrhea 18.1% vs. 19.8%; nausea 6.9% vs. 9.3%; vomiting 4.9% vs. 5.6%; and abdominal pain 4.9% vs. 7.4%; respectively).

11 Draft Points for Advisory Committee Discussion

- Evidence of the effectiveness of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing.
- Evidence of the safety of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing.

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Original article

Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis

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ABSTRACT

Background: Tafenoquine is a new prophylactic antimalarial drug. The current analysis presents an integrated safety assessment of the Tafenoquine Anticipated Clinical Regimen (Tafenoquine ACR) from 5 clinical trials, including 1 conducted in deployed military personnel and 4 in non-deployed residents, which also incorporated placebo and mefloquine comparator groups.

Methods: Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®, Version 15.0) and summarized. Among all subjects who had received the Tafenoquine ACR, safety findings were compared for subjects who were deployed military personnel from the Australian Defence Force (Deployed ADF) versus non-deployed residents (Resident Non-ADF).

Results: The incidence of at least one AE was 80.6%, 64.1%, 67.6% and 94.9% in the mefloquine, placebo, tafenoquine Resident Non-ADF and tafenoquine Deployed ADF groups, respectively. The latter group had a higher incidence of AEs related to military deployment. AEs that occurred at $\geq$ 1% incidence in both tafenoquine sub-groups and at a higher frequency than placebo included diarrhea, nausea, vomiting, gastroenteritis, nasopharyngeal tract infections, and back/neck pain.

Conclusions: Weekly administration of tafenoquine for up to six months increased the incidence of gastrointestinal AEs, certain infections, and back/neck pain, but not the overall incidence of AEs versus placebo.

Clinical Trial Registration Numbers/ClinicalTrials.gov Identifiers: NCT02491606; NCT02488980; NCT02488902.

1. Introduction

Malaria, a protozoan infection that targets human erythrocytes, is a potentially fatal illness that is transmitted by Plasmodium-infected mosquitoes. In the US, the overall trend of malaria cases has been increasing, with 84% of patients requiring hospitalization [1]. In spite of the considerable risks associated with malaria, over 90% of US patients who developed malaria in 2013 had not adhered to a medically-advised chemoprophylaxis drug regimen [1].

Historically, mefloquine was once a favored prophylactic antimalarial, due to its efficacy and convenient weekly dosing schedule [2]. However, mefloquine's association with adverse neuropsychiatric effects has prompted safety concerns [3] and has curtailed mefloquine's use by the US military [4]. As alternatives to mefloquine, doxycycline, atovaquone/proguanil, and primaquine all require daily dosing, which can decrease compliance, and all are associated with bothersome gastrointestinal side effects, among other safety problems [5–8]. Hence, due to the dosing inconvenience and safety drawbacks of existing prophylactic antimalarials, a safe and effective alternative drug has been sought.

Tafenoquine is a primaquine analog being developed for malaria prophylaxis in adults. Like primaquine, tafenoquine is an 8-aminoquinoline; however, its half-life of ~2 weeks is considerably longer, allowing for weekly dosing [8]. Tafenoquine is active against *Plasmodium* parasites *in vitro* and has been tested successfully

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against malaria in animal models [9]. In man, the anticipated clinical regimen (ACR) of tafenoquine for malaria prophylaxis is 200 mg orally (PO) daily for 3 consecutive days (the loading dose), followed by 200 mg PO once weekly. This regimen has proven effective for malaria prophylaxis in both non-immune [10] and semi-immune subjects [2].

For the Tafenoquine ACR, safety data comes from 5 clinical trials (Table 1), all previously published. These include: Study 033, a randomized, double-blind, active-controlled trial of tafenoquine vs. mefloquine in non-immune Australian Defence Force (ADF) soldiers deployed to East Timor (now Timor Leste) [11]; Studies 030, 043, and 45, all randomized, double-blind, placebo-controlled trials of tafenoquine in residents of malaria endemic regions of Africa [2,12,13]; and Study 057, a randomized, double-blind, placebo-controlled safety study of tafenoquine in healthy adult residents of the United States (US) or the United Kingdom (UK) [14]. Because tafenoquine like primaquine [15] can cause hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, these clinical trials have excluded G6PD-deficient subjects, as well as pregnant women. Of the 5 trials, only Study 033 lacked a placebo control group for ethical and operational reasons [10].

A goal of the present analysis was to present an integrated safety and tolerability assessment of the Tafenoquine ACR across the 5 studies in which it was utilized (Table 1). To assure a uniform approach to adverse event (AE) coding, this analysis employed a unified, updated, and consistent coding system for AEs. In addition, targeted analyses were performed to allow for safety comparisons between subgroups that were potentially impacted by disparate extrinsic factors, especially military deployment under warlike conditions.

2. Methods

2.1. Ethical approval and subject consent

Descriptions of the ethical approval process and subject consent procedures for each study are provided in the individual study publications. Briefly, study protocol and consent forms were reviewed and approved by one or more of the following scientific and ethical review boards: the Scientific Steering and Ethical Review Committee of the Kenya Medical Research Institute (Studies 030 and 043); the Ghanaian Ministry of Health (Study 045); the Australian Defence Medical Ethics Committee (Study 033); and the institutional review boards of the Walter Reed Army Institute for Research (Study 043) and the US Army (all studies). In trials conducted in Africa, local approval of the study was granted by traditional chiefs and community leaders. Tribal language consent forms were read by or to every prospective subject, and informed affirmation or informed consent was obtained from those residents wishing to participate. In studies 033 and 057, subjects provided informed consent based on study information provided in English.

2.2. Conduct of the studies

Detailed descriptions of the screening, randomization, drug administration, and clinical assessments employed in the 5 studies have been provided previously [2,11–14]. All 5 studies included healthy adults who were not G6PD deficient as determined by pre-study testing. All females were non-pregnant and non-lactating. Good health was verified by medical history, physical examination, and clinical laboratory testing [complete blood count (CBC), serum biochemistry, dipstick urinalysis]. For African studies where antimalarial pre-treatments were administered (Studies 030, 043, and 045), Giemsa-stained thick and thin blood smears were performed to confirm parasite clearance prior to initiating study medications. All study drugs were administered with a meal. Safety assessments included reports of AEs; abnormalities in CBC, methemoglobin levels, and serum biochemistry; and urinalysis. Also, based on sporadic reports of mild elevations of serum creatinine in Study 033, changes in glomerular filtration rate (GFR) by iothalamate clearance were assessed in all subjects in Study 057 [14]. In addition, targeted ophthalmologic assessments were

Table 1
Overview of Study design: Clinical Trials that Assessed the Safety and Tolerability of the Prophylactic Anticipated Clinical Regimen (ACR) of Tafenoquine.

	Study 030	Study 043[a]	Study 045[a]	Study 033	Study 057
Year(s) Conducted	2000	1997	1998	1999–2000	2003–2006
Study Design[b]	R, DB, PC, AC	R, DB, PC	R, DB, PC, AC	R, DB, AC	R, DB, PC
Parameters Assessed	Safety and Efficacy	Safety and Efficacy	Safety and Efficacy	Safety and Efficacy	Safety
Population Characteristics	Healthy adult residents of malaria-endemic area	Healthy adult residents of malaria-endemic area	Healthy adult residents of malaria-endemic area	Healthy non-immune Australian military population (ADF) deployed to malaria-endemic area	Healthy adult residents of US and UK
Study Location	Nyanza Province, Kenya	Nyanza Province, Kenya	Kassena Nankana District, Ghana	Bobonaro District and capitol (Dili) of East Timor (now Timor Leste)	Maryland, USA and Berkshire, UK
Pre-Treatments Administered[c]	Halofantrine 250 mg × 3 days	Halofantrine 250 mg × 3 days	Quinine 10 mg/kg tid x 4 days, then doxycycline 100 mg bid x 7 days and Primaquine 30 mg × 14 days	None	None
No. Subjects:					
TQ-ACR[d]	104	55	93	492	81
MQ[e]	101	0	46	162	0
Placebo	101	61	94	0	39
Duration of Study Drug Dosing	24 weeks	10-15 weeks	13 weeks	26 ± 4 weeks	24 weeks
Safety Follow-up after Study Drug Dosing	4 weeks	4 weeks	4 weeks	24 weeks	24 weeks

[a] Tafenoquine doses other than the Anticipated Clinical Regimen (ACR) were also administered in this study. Only information for the ACR group is reported here.
[b] R = Randomized, DB = Double-Blind, AC = Active Comparator (Mefloquine), PC=Placebo-Controlled.
[c] Pre-treatments were given to eradicate any pre-existing parasitemia in the African studies. Study drug administration commenced 4–5 days after pre-treatments ended.
[d] TQ-ACR = Tafenoquine Anticipated Clinical Regimen of 200 mg × 3 days, then 200 mg weekly.
[e] MQ = Mefloquine 250 mg × 3 days, then 250 mg weekly.

performed in a subpopulation of Study 033 [11] and in all subjects of Study 057 [14].

2.3. Conduct of the integrated safety analysis

For each study, safety data were double-entered and verified, and data files were locked before analysis. Safety analyses were conducted using the Safety Analysis Set of each study, defined as all patients who had been randomized and received at least one dose of study drug. Baseline was defined as the last non-missing assessment made on or prior to the first dose of study drug, while Study Day 1 was defined as the first day on which study drug was taken. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®, Version 15.0) and summarized by preferred term and body system. In studies where AEs had been originally coded according to the World Health Organization (WHO) Adverse Reaction Terminology (ART) dictionary, the AEs were re-coded according to the MedDRA terminology. AEs due to pregnancy were not included in the AE summaries, but were listed separately. AE relationship to study drug was defined conservatively – an AE was considered "related" to the study drug if it was assessed as unlikely, possibly, probably, or definitely related to the drug. Only AEs assessed as unrelated to the study drug comprised the "not related" category.

3. Results

3.1. Demographics

Subject demographics for the 5 Tafenoquine ACR studies are presented in Supplementary Table 1. Across the 5 studies, a total of 825 subjects received the Tafenoquine ACR (labeled the "Tafenoquine ACR Overall" group), while 309 received Mefloquine, and 295 received Placebo. Among the Tafenoquine ACR Overall group, the majority of subjects were members of the Deployed ADF subgroup (n = 492). These subjects were ADF personnel in Study 033 who were involved in peacekeeping activities in Timor Leste, including night patrols and militia encounters [10]. The second subgroup of the Tafenoquine ACR population was termed the "Resident Non-ADF" subgroup (n = 333), as these subjects were either residents of African villages (Studies 030, 043, and 045) or of municipalities in the USA or UK (Study 057) and were not involved in the types of military activities to which the Deployed ADF subgroup was exposed.

Among all 5 studies, subjects ranged in age from 17 to 69 years, with the majority being male (62.8–97.2%). The Tafenoquine ACR Overall group (n = 825) and Mefloquine comparator group (n = 309) were well matched with respect to age and sex. However, the Tafenoquine ACR Overall group included a higher percentage of Whites than the Mefloquine group (63.8% vs. 51.8%, respectively) and fewer African/Black subjects (33.7% vs. 47.6%). The Placebo group included a greater percentage of African/Black subjects (90.1%) than either the Tafenoquine ACR Overall or Mefloquine groups due to the African locations of Studies 030, 043, and 045.

With respect to the two Tafenoquine ACR subgroups, Deployed ADF versus Resident Non-ADF, the deployed subgroup was younger (mean age 25.4 years versus 35.4 years, respectively) and was comprised of a larger percentage of males (97.2% vs. 64.3%) reflective of the infantry battalion that took part in the study. In addition, the Deployed ADF group was almost exclusively of Caucasian race (98.4%), while the Resident Non-ADF population was largely African/Black (83.5%), reflecting the demographics of the African studies.

3.2. Extent of exposure

Extent of exposure to study drug (Supplementary Table 1) was longer in the Tafenoquine ACR Overall group (mean 21.2 weeks) than in either the Mefloquine group (18.9 weeks) or in the Placebo group (9.3 weeks). The abbreviated exposure time in the Placebo group reflected early withdrawals due to lack of efficacy (i.e., malaria) in the 3 African studies. Within the 2 subgroups of the Tafenoquine ACR Overall population, Deployed ADF troops received tafenoquine for a mean of 27 weeks, which was longer than the Resident Non-ADF group (mean 12.7 weeks). These different time periods reflected pre-planned trial duration rather than lack of efficacy.

3.3. Treatment discontinuations

No deaths occurred among subjects who received the Tafenoquine ACR. The number of treatment discontinuations due to AEs (Table 2) by-study were as follows: for Study 030, one (1.0%) of 104 subjects; for Study 033, twelve (2.4%) of 492 subjects; for Study 043, one (1.8%) of 55 subjects; for Study 045, ten (10.8%) of 93 subjects; and for Study 057, six (7.4%) of 81 subjects. The high withdrawal rate in Study 045 was driven by the study's nontraditional withdrawal criteria [12], which removed a subject from study participation if the subject's laboratory values drifted outside of those listed in the study's entry criteria. Consequently, even minor, non-serious, alterations in ALT (including some ALT values below 60 U/L) were grounds for withdrawal. Similarly, all 3 withdrawals due to decreased hemoglobin (decreases of 1.6–2.2 g/dL) in Study 045 were considered non-serious, and all resolved without treatment. With the exception of withdrawals due to generally mild laboratory abnormalities in Study 045, discontinuations in the 3 African studies (Studies 030, 043, and 045) were rare, involving only 1 subject per study (1.0%–1.8% of the study population).

Discontinuations for ophthalmic or renal AEs in the Tafenoquine ACR group of Study 057 reflected the fact that this trial was a targeted safety study, wherein specific variations in renal or ophthalmologic parameters would lead to protocol-directed withdrawals. Subjects discontinued due to changes in iothalamate clearance GFR showed no concurrent clinically significant changes in serum creatinine or urinalysis findings. Their mild GFR changes were attributed to variations in the GFR measuring techniques and were considered unlikely to be related to study drug. The co-occurrence of 3 ophthalmologic AEs (decreased visual acuity, night blindness, and visual field defect) in one subject in Study 057 led to that subject's discontinuation. Reports of these AEs were based on mild changes in the results of specialized eye tests at one study visit. On repeat evaluation, the subject's visual parameters were found to be normal.

In Study 033, multiple discontinuations occurred in the Tafenoquine ACR group due to injuries (5 subjects) or musculoskeletal pain (2 subjects), all of which were the result of military deployment and unrelated to tafenoquine. A single ADF subject was discontinued due to depression and a second due to hyperesthesia.

3.4. Analyses of adverse events

Analyses were performed to search for any effects related to protocol-based antimalarial pretreatments in the African studies. The findings indicated that these antimalarials had no impact on safety.

Table 3 presents an overview of safety findings in the 5 studies, including findings for the 2 sub-groups of the Tafenoquine ACR Overall population (Deployed ADF and Resident Non-ADF). In all studies, the majority of AEs were mild and considered "not related"

Table 2
Adverse events leading to study discontinuation: Subjects who received the tafenoquine anticipated clinical regimen.

	Study 030 (n = 104)	Study 043 (n = 55)	Study 045 (n = 93)	Study 033 (n = 492)	Study 057 (n = 81)
Subjects Discontinued, n (%)	1 (1.0%)	1 (1.8%)	10 (10.8%)	12 (2.4%)	6 (7.4%)
Adverse event (AE) cited as Reason for Treatment Discontinuation[a]					
ALT increased	0	0	6 (6.5%)	0	0
Hemoglobin decreased	0	0	3 (3.2%)	0	0
*GFR decreased	0	0	0	0	2 (2.5%)
*Cellulitis	0	0	1 (1.1%)	0	0
*Viral infection	0	0	0	1(0.2%)	0
*Fall	0	0	0	0	1 (1.2%)
*Injury	0	0	0	5 (1.0%)[b]	1 (1.2%)[c]
Abdominal pain, upper	0	0	0	1 (0.2%)	0
*Irritable bowel syndrome	0	0	0	1 (0.2%)	0
*Musculoskeletal pain	0	0	0	2 (0.4%)	0
Hyperesthesia	0	0	0	1 (0.2%)	0
Visual field defect	0	0	0	0	1 (1.2%)[d]
Depression	0	0	0	1 (0.2%)	0
*Intentional self injury	0	1 (1.8%)	0	0	0
Hemolytic anemia	1 (1.0%)	0	0	0	1 (1.2%).
Night blindness	0	0	0	0	1 (1.2%)[d]
Visual acuity reduced	0	0	0	0	1 (1.2%)[d]
Rash	0	0	0	0	1 (1.2%)
Hyperbilirubinemia	1 (1.0%)	0	0	0	0
Jaundice, cholestatic	1 (1.0%)	0	0	0	0
*Lactose intolerance	0	0	0	1 (0.2%)	0

*Indicates that all AEs of this type were considered either unrelated, or unlikely to be related to the study drug (tafenoquine).
[a] Some subjects had more than one AE leading to treatment discontinuation.
[b] Includes 1 gunshot wound: 1 joint injury (ankle); 1 injury of the meniscus; 1 soft tissue injury; 1 thermal burn.
[c] Upper limb fracture.
[d] One of 3 separate ophthalmologic AEs reported in a single subject.

to the study drugs. Placebo subjects and Resident Non-ADF subjects who received tafenoquine were similar in their overall incidence of AEs (64.1% vs. 67.6%, respectively) and AE relationship to study drug. Percentages of AEs that were considered “not related” to the study drug were higher in the Tafenoquine ACR Overall group (73.9%) and in the Mefloquine comparator group (77.1%) than in the Placebo group (55.6%). In the Tafenoquine ACR Overall group, the percentages of subjects with serious adverse events (SAEs) and subjects with treatment-related SAEs (5.7% and 2.7%, respectively) were higher than in either the Placebo group (3.4% and 1.0%, respectively) or in the Mefloquine comparator group (3.6% and 1.3%, respectively). Specific treatment-related SAEs that occurred in more than 1 subject within the Tafenoquine ACR Overall population were keratopathy (corneal deposits) (5 subjects or 0.6% of the

Table 3
Overview of adverse events.

	Tafenoquine Anticipated Clinical Regimen 200 mg × 3 days, then 200 mg weekly			Placebo (n = 295)	Mefloquine250 mg daily x 3 days, then 250 mg weekly (n = 309)
	Tafenoquine Anticipated Clinical Regimen Overall (n = 825)	Deployed Australian Defence Force (n = 492)	Resident Non-Australian Defence Force (n = 333)		
Studies Included	030, 033, 043, 045, 057	033	030, 043, 045, 057	030, 043, 045, 057	030, 033, 045
Total No AEs	3496	2204	1292	1045	1445[a]
AE Intensity					
Mild	3026	1864	1162	919	1311
Moderate	423	317	106	111	125
Severe	35	22	13	8	7
Missing	12	1	11	7	2
AE Relationship to Study Drug					
Not Related, n (%)	2584 (73.9%)	1899 (86.2%)	685 (53.0%)	581 (55.6%)	1114 (77.1%)
Related, n (%)	912 (26.1%)	305 (13.8%)	607 (46.0%)	464 (44.4%)	330 (22.8%)
Subjects with at Least One AE, n (%)	692 (83.9%)	467 (94.9%)	225 (67.6%)	189 (64.1%)	249 (80.6%)
Subjects with at least one AE not related to Study Drug, n (%)	352 (42.7%)	293 (59.6%)	59 (17.7%)	49 (16.6%)	123 (39.8%)
Subjects with at least one AE related to Study Drug, n (%)	340 (41.2%)	174 (35.4%)	166 (49.8%)	140 (47.5%)	126 (40.8%)
Subjects with SAEs, n (%)	47 (5.7%)	26 (5.3%)	21 (6.3%)	10 (3.4%)	11 (3.6%)
Subjects with Treatment-Related SAEs, n (%)	22 (2.7%)	11 (2.2%)	11 (3.3%)	3 (1.0%)	4 (1.3%)

[a] In the Mefloquine group, AE relationship to the study drug was not documented for 1 subject and AE intensity was missing for 2 subjects.

population), decreased GFR (5 subjects or 0.6%), and retinal disorder (2 subjects or 0.2%) (data not shown). Additional treatment-related SAEs that each affected only 1 subject in the Tafenoquine Overall group were pneumonia, gastroenteritis, helminthic infection, urinary tract infection, diarrhea, abdominal pain, abdominal pain upper, irritable bowel syndrome, headache, visual field defect, and haemolytic anemia. In comparison, treatment-related SAEs in the Mefloquine comparator group were retinal disorder, pneumonia, anxiety, and rash. Each of these was reported in one subject (0.3%) in the Mefloquine group. The keratopathy reports were in the first cohort in which this finding was detected (a new significant finding) and were not reported as SAEs after these initial reports. The keratopathy was not associated with any deficit in visual acuity and was fully resolved in all subjects by 1 year [11].

In the Tafenoquine ACR Overall population (Table 3), the percentage of subjects with AEs was markedly higher in the Deployed ADF subgroup (94.9%) than in the Resident Non-ADF subgroup (67.6%). In addition, a much higher percentage of AEs in the Deployed ADF subjects was considered to be “not related” to treatment (86.7%) than in the Resident Non-ADF group (53.0%). This suggested that the Deployed ADF subgroup had been exposed to extrinsic factors that influenced the safety findings of Study 033. To examine this issue, AEs were categorized for the Tafenoquine ACR Overall population and its two subgroups versus Placebo (Table 4). Compared to Resident Non-ADF subjects, Deployed ADF subjects had higher incidences of ear and labyrinth disorders (6.7% vs. 1.8%), eye disorders (17.1% vs. 10.2%), gastrointestinal disorders (36.2% vs. 30.9%), immune system disorders (4.9% vs. 0.3%), infections and infestations (68.7% vs. 42.9%), injuries, poisonings, and procedural complications (39.8% vs. 10.5%), musculoskeletal and connective tissue disorders (28.7% vs. 26.7%), psychiatric disorders (5.1% vs. 2.1%) and skin and subcutaneous tissue disorders (21.1% vs. 11.4%). Conversely, Resident Non-ADF subjects had higher incidences of blood and lymphatic system disorders (9.3% vs. 0.4%), general disorders and administration site conditions (12.0% vs. 3.7%), hepatobiliary disorders (1.5% vs. 0), investigations AEs (8.4% vs. 1.2%), metabolism and nutrition disorders (4.2% vs. 2.2%), nervous system disorders (35.1% vs. 22.4%), and reproductive system and breast disorders (3.9% vs. 1.6%).

Notably, for many of the AE categories in Table 4, the profile of the Resident Non-ADF group was similar to that of Placebo. This included ear and labyrinth disorders (Resident Non-ADF 1.8% vs. Placebo 1.7%), eye disorders (10.2% vs. 10.5%), gastrointestinal disorders (30.9% vs. 32.5%), infections and infestations (42.9% vs. 46.4%), musculoskeletal and connective tissue disorders (26.7% vs. 26.4%), nervous system disorders (35.1% vs. 34.2%), reproductive system and breast disorders (3.9% vs. 3.7%), and skin and subcutaneous tissue disorders (11.4% vs. 12.5%).

To further explore the safety profile of Deployed ADF subjects versus the Resident Non-ADF group, AEs that occurred at ≥1% incidence were compared for these populations (Supplementary Table 2). AEs that were reported in ≥1% of the Deployed ADF subgroup but in ≤1% of the Resident Non-ADF subgroup were keratopathy (13.8% in the Deployed ADF subgroup vs. 0% in the Resident Non-ADF subgroup; see explanation above for this new safety finding in Study 033), GERD (2.6% vs. 0.3%), seasonal allergy (3.9% vs. 0.3%), impetigo (1.6% vs. 0%), otitis externa (1.8% vs. 0.6%), tinea infection (1.4% vs. 0.6%), tinea pedis (4.9% vs. 0%), arthropod bite (2.4% vs. 0.6%), heat illness (2.2% vs. 0%), joint injury (3.7% vs. 0.9%), muscle strain (2.8% vs. 0.9%), soft tissue injury (12.2% vs. 0.6%), thermal burn (1.8% vs. 0.3%), lethargy (4.7% vs. 0.3%), insomnia (1.6% vs. 0.6%), heat rash (10.8% vs. 0%), and ingrowing nail (2.4% vs. 0%). Other AEs for which there was an incidence disparity of 10% or more between the Deployed ADF subgroup and the Resident Non-ADF subgroup included diarrhea (18.1% vs. 4.8%), gastroenteritis (37.2% vs. 7.8%), and nasopharyngitis (19.7% vs. 3.3%). Overall, these disparities in AE incidences were consistent with the fact that the Deployed AE subjects were de facto travelers in a foreign land, with an increased risk for gastroenteritis and diarrhea, as well as for other maladies related to deployment during a military operation

Table 4
Subjects with specific Categories of adverse events.

AE Category[a]	Tafenoquine Anticipated Clinical Regimen 200 mg × 3 days, then 200 mg weekly			Placebo (n = 295)
	Tafenoquine Anticipated Clinical Regimen Overall (n = 825)	Deployed Australian Defence Force (n = 492)	Resident Non-Australian Defence Force (n = 333)	
Blood and Lymphatic System Disorders	33 (4.0%)	2 (0.4%)	31 (9.3%)	26 (8.8%)
Ear and Labyrinth Disorders	39 (4.7%)	33 (6.7%)	6 (1.8%)	5 (1.7%)
Eye Disorders	118 (14.3%)	84 (17.1%)	34 (10.2%)	31 (10.5%)
Gastrointestinal Disorders	281 (34.1%)	178 (36.2%)	103 (30.9%)	96 (32.5%)
General Disorders and Administration Site Conditions	58 (7.0%)	18 (3.7%)	40 (12.0%)	26 (8.8%)
Hepatobiliary Disorders	5 (0.6%)	0	5 (1.5%)	0
Immune System Disorders	25 (3.0%)	24 (4.9%)	1 (0.3%)	0
Infections and Infestations	481 (58.3%)	338 (68.7%)	143 (42.9%)	137 (46.4%)
Injury Poisoning and Procedural Complications	231 (28.0%)	196 (39.8%)	35 (10.5%)	19 (6.4%)
Investigations	34 (4.1%)	6 (1.2%)	28 (8.4%)	21 (7.1%)
Metabolism and Nutrition Disorders	25 (3.0%)	11 (2.2%)	14 (4.2%)	6 (2.0%)
Musculoskeletal and Connective Tissue Disorders	230 (27.9%)	141 (28.7%)	89 (26.7%)	78 (26.4%)
Nervous System Disorders	227 (27.5%)	110 (22.4%)	117 (35.1%)	101 (34.2%)
Psychiatric Disorders	32 (3.9%)	25 (5.1%)	7 (2.1%)	3 (1.0%)
Renal and Urinary Disorders	7 (0.8%)	4 (0.8%)	3 (0.9%)	1 (0.3%)
Reproductive System and Breast Disorders	21 (2.5%)	8 (1.6%)	13 (3.9%)	11 (3.7%)
Respiratory Thoracic and Mediastinal Disorders	94 (11.4%)	23 (4.7%)	71 (21.3%)	49 (16.6%)
Skin and Subcutaneous Tissue Disorders	142 (17.2%)	104 (21.1%)	38 (11.4%)	37 (12.5%)
Vascular Disorders	4 (0.5%)	3 (0.6%)	1 (0.3%)	2 (0.7%)

[a] Not all AE categories are listed because adverse events within some of these categories were not observed.

(heat illness, heat rash, allergies, impetigo, otitis externa, arthropod bites, and tinea infections). Also, the ADF subjects were exposed to hostile conditions that often occurred during night patrols [10], increasing their risk for combat-related injuries (joint injury, muscle strain, soft tissue injury, and burns), insomnia, and (post-patrol) lethargy.

AEs that were reported in ≥1% of the Resident Non-ADF subgroup but in ≤1% of the Deployed ADF subgroup (Supplementary Table 2) were anaemia (incidence 3.0% vs. 0%, respectively), leukocytosis (2.4% vs. 0%), thrombocytopenia (3.0% vs. 0%), abdominal pain upper (3.6% vs. 0.8%), constipation (5.1% vs. 0.6%), dental caries (2.4% vs. 0.2%), dyspepsia (3.0% 0.6%), chest pain (5.1% vs. 0.2%), fatigue (3.3% vs. 0.8%), amoebiasis (2.7% vs. 0%), bronchitis (3.0% vs. 0.4%), cellulitis (1.8% vs. 1.0%), pharyngitis (1.2% vs. 0.8%), rhinitis (4.8% vs. 0.2%), urinary tract infection (3.0% vs. 0.4%), wound sepsis (2.4% vs. 0%), ALT increased (3.6% vs. 0%), decreased appetite (3.6% vs. 0.6%), myalgia (7.8% 0.2%), dysmenorrhoea (2.4% vs. 0.4%), nasal congestion (3.3% vs. 0.4%), cough (13.5% vs. 1.0%, and pruritis (5.1% vs. 0.4%). Other AEs for which there was an incidence disparity of ≥10% between the Resident Non-ADF subjects and the Deployed ADF subjects were URI (20.1% vs. 9.1%) and headache (31.8% vs. 14.6%). These disparities in AE incidences were consistent with the more mundane home-centered lifestyle of the Resident Non-ADF subgroup, with its associated risk of typical nasopharyngeal infections, coughs, constipation, and headaches. In some cases, (primarily in African studies) there was also a risk for endemic concurrent infections (e.g., amoebiasis and helminthic infections) and for suboptimal nutrition.

3.5. Common adverse events independent of extrinsic factors

AEs that occurred at an incidence ≥1% in both the Deployed ADF and Resident Non-ADF subgroups and also at a higher incidence than in the Placebo group (Table 5) were diarrhea, nausea, vomiting, body tinea, gastroenteritis, nasopharyngitis, sinusitis, tonsillitis, laceration, ligament sprain, back pain, neck pain, and rash. Among these, only gastroenteritis and back pain occurred in more than 5% of subjects in both subgroups.

Regarding AEs that are known to occur with mefloquine [16], comparative incidences for the Mefloquine Group versus the Tafenoquine ACR Overall group were as follows: dizziness (5.5% vs. 2.7%), myalgia (4.5% vs. 3.3%), nausea (5.8% vs. 6.1%), headache (29.8% vs. 21.6%), vomiting (3.6% vs. 3.8%), diarrhea (10.7% vs. 12.7%), skin rash (2.3% vs. 3.0%), abdominal pain (11.3% vs. 5.9%), loss of appetite (1.9% vs.1.8%) (data not shown). Overall, the Tafenoquine ACR was associated with lower risk for dizziness, myalgia, headache, and abdominal pain than mefloquine.

3.6. Psychiatric adverse events

To explore the potential impact of a hostile environment on psychiatric AEs among military personnel in the Deployed ADF group, the percentages of subjects with specific low-incidence (≤1%) psychiatric AEs were compared (Table 6) between the Tafenoquine ACR Overall group, the Deployed ADF subgroup, and the Resident Non-ADF subgroup. Among the 25 Deployed ADF subjects who experienced psychiatric disorders, the majority [18 (72%) of 25] developed problems related to sleep (insomnia, abnormal dreams, nightmares, sleep disorder). In comparison, among Resident Non-ADF subjects, sleep AEs affected 3 (42.9%) of 7 subjects.

Types of psychiatric AEs (Table 6) that occurred in a greater percentage of Deployed ADF subjects than in Resident Non-ADF subjects were the following: insomnia, abnormal dreams, nightmares, sleep disorder, agitation, anxiety disorder, euphoric mood, panic attack, and stress. Overall, the Deployed ADF military subjects of Study 033 experienced a higher incidence of psychiatric AEs and a greater variety of psychiatric AEs than did non-deployed Resident Non-ADF subjects. .

To potentially identify specific extrinsic factors in subjects who reported psychiatric AEs in the Deployed ADF subgroup versus the Resident Non-ADF subgroup, medical histories and non-psychiatric AEs were reviewed for subjects who reported insomnia or sleep disorder in these 2 subgroups (Table 7). 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 Resident Non-ADF 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 7).

4. Discussion

To date, Tafenoquine has been tested in more than 25 clinical trials, during which the drug was administered at different doses and dosing regimens for various malaria-related clinical indications. The goal of the present analysis was to provide an overview of the safety of tafenoquine when it is administered for antimalarial prophylaxis utilizing an anticipated clinical regimen (Tafenoquine ACR) of 200 mg PO daily loading dose for 3 consecutive days, followed by 200 mg once weekly. This regimen has been administered in 5 clinical trials, in which some 825 subjects received the Tafenoquine ACR, with 492 being deployed ADF military personnel (the Deployed ADF dataset) and 333 being residents of Africa, the US, or the UK (the Resident Non-ADF dataset). In Study 033 involving ADF personnel, Nasveld reported that the rates of some common AEs were similar for tafenoquine and mefloquine [11]. However, this study of necessity had no placebo group [10], and, until now, the contribution of the deployment environment to the AEs in Study 033 had not been assessed. The present analysis, which includes placebo groups from 4 other Tafenoquine ACR studies, helps put this issue into context.

As an analog of primaquine, tafenoquine might be expected to share some characteristics of primaquine's AE profile, including gastrointestinal side effects, dizziness, rash, pruritus, anemia, methemoglobinemia, leukopenia, cardiac arrhythmia, prolongation of the QT interval, and hemolytic anemia (in individuals with G6PD deficiency) [15]. With respect to this list, some previous publications for trials that have utilized tafenoquine at higher exposures than the Tafenoquine ACR have reported the adverse effects of gastrointestinal distress, and reversible asymptomatic methaemoglobinemia, together with hemolytic anemia in rare individuals with G6PD deficiency who were admitted to the trials in error [2]. The decision to utilize a 200 mg daily dose in the Tafenoquine ACR was informed not only by its satisfactory efficacy results for malaria prophylaxis, but also by safety findings indicating fewer gastrointestinal problems, among other side effects, as compared to higher daily doses [13,17]. In the present integrated analysis of 5 trials, the tafenoquine dosing regimen utilized (Tafenoquine ACR) was safe and well tolerated. In the majority of trials, only 1.0%–2.4% of subjects discontinued tafenoquine due to adverse events. The exceptions were selected subjects in Studies 045 and Study 057, where protocol-mandated withdrawals occurred due to what were typically mild, transient changes in laboratory parameters or reversible eye test abnormalities.

In all studies, the majority of AEs were mild and considered

Table 5
Selected adverse events occurring in ≥1% of subjects in both the deployed Australian Defence Force (deployed ADF) group and the Resident Non-Australian Defence Force (resident Non-ADF) group.

	Number (%) of Subjects			
	Tafenoquine Anticipated Clinical Regimen Overall (N = 825)	Deployed Australian Defence Force (n = 492)	Resident Non-Australian Defence Force (n = 333)	Placebo (n = 295)
Included Studies	030, 033, 043, 045, 057	033	030, 043, 045, 057	030, 043, 045, 057
Ear pain	11 (1.3%)	6 (1.2%)	5 (1.5%)	4 (1.4%)
Conjunctivitis	24 (2.9%)	7 (1.4%)	17 (5.1%)	18 (6.1%)
Abdominal Pain	49 (5.9%)	20 (4.1%)	29 (8.7%)	33 (11.2%)
Diarrhoea	105 (12.7%)	89 (18.1%)	16 (4.8%)	9 (3.1%)
Gastritis	13 (1.6%)	6 (1.2%)	7 (2.1%)	8 (2.7%)
Nausea	50 (6.1%)	34 (6.9%)	16 (4.8%)	6 (2.0%)
Vomiting	31 (3.8%)	24 (4.9%)	7 (2.1%)	5 (1.7%)
Body tinea	17 (2.1%)	12 (2.4%)	5 (1.5%)	4 (1.4%)
Cellulitis	11 (1.3%)	5 (1.0%)	6 (1.8%)	6 (2.0%)
Furuncle	10 (1.2%)	6 (1.2%)	4 (1.2%)	5 (1.7%)
Gastroenteritis	209 (25.3%)	183 (37.2%)	26 (7.8%)	17 (5.8%)
Nasopharyngitis	108 (13.1%)	97 (19.7%)	11 (3.3%)	7 (2.4%)
Sinusitis	17 (2.1%)	12 (2.4%)	5 (1.5%)	2 (0.7%)
Tonsillitis	27 (3.3%)	16 (3.3%)	11 (3.3%)	2 (0.7%)
URI	112 (13.6%)	45 (9.1%)	67 (20.1%)	56 (19.0%)
Viral Infection	48 (5.8%)	40 (8.1%)	8 (2.4%)	6 (2.0%)
Laceration	37 (4.5%)	29 (5.9%)	8 (2.4%)	6 (2.0%)
Ligament sprain	10 (1.2%)	6 (1.2%)	4 (1.2%)	0
Arthralgia	61 (7.4%)	47 (9.6%)	14 (4.2%)	14 (4.7%)
Back Pain	116 (14.1%)	69 (14.0%)	47 (14.1%)	25 (8.5%)
Musculoskeletal Pain	38 (4.6%)	12 (2.4%)	26 (7.8%)	24 (8.1%)
Neck pain	17 (2.1%)	12 (2.4%)	5 (1.5%)	3 (1.0%)
Dizziness	22 (2.7%)	7 (1.4%)	15 (4.5%)	8 (2.7%)
Headache	178 (21.6%)	72 (14.6%)	106 (31.8%)	94 (31.9%)
Cough	50 (6.1%)	5 (1.0%)	45 (13.5%)	35 (11.9%)
Oropharyngeal pain	30 (3.6%)	12 (2.4%)	18 (5.4%)	8 (2.7%)
Rash	25 (3.0%)	20 (4.1%)	5 (1.5%)	2 (0.7%)

Table 6
Subjects with psychiatric adverse events in tafenoquine anticipated clinical regimen populations: Deployed Military (Australian Defence Force) subjects in study 033 vs. Resident Non-Australian Defence Force subjects (studies 030, 043, 045, and 057).

	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (Anticipated Clinical Regimen)		
	All Subjects (n = 825)	Deployed Australian Defence Force Subjects (n = 492)	Resident Non-Australian Defence Force Subjects (n = 333)
Studies Included	030, 033, 043, 045, 057	033	030, 043, 045, 057
Any AE	692 (83.9%)	467 (94.9%)	225 (67.6%)
Injury, Poisoning, and Procedural Complications	231 (28.0%)	196 (39.8%)	35 (10.5%)
Psychiatric Disorders	32 (3.9%)	25 (5.1%)	7 (2.1%)
Psychiatric Disorders Affecting Sleep	21 (2.5%)	18 (3.7%)	3 (0.9%)
Insomnia	10 (1.2%)	8 (1.6%)	2 (0.6%)
Abnormal dreams	5 (0.6%)	5 (1.0%)	0
Nightmares	3 (0.4%)	3 (0.6%)	0
Sleep Disorder	3 (0.4%)	2 (0.4%)	1 (0.3%)
Agitation	2 (0.2%)	2 (0.4%)	0
Anxiety disorder	2 (0.2%)	2 (0.4%)	0
Depression	2 (0.2%)	1 (0.2%)	1 (0.3%)
Euphoric mood	2 (0.2%)	2 (0.4%)	0
Bipolar disorder	1 (0.1%)	0	1 (0.3%)
Depressed mood	1 (0.1%)	0	1 (0.3%)
Neurosis	1 (0.1%)	0	1 (0.3%)
Panic attack	1 (0.1%)	1 (0.2%)	0
Stress	1 (0.1%)	1 (0.2%)	0
Suicide attempt	1 (0.1%)	0	1 (0.3%)

unrelated to the study drugs. Among the Tafenoquine ACR Overall population (Table 3), the Resident Non-ADF subgroup was similar to Placebo subjects in overall incidence of AEs (67.6% vs. 64.1%, respectively), AE relationship to study drug, and AE profile (Table 4). These findings were consistent with those of previous reports [12–14]. In contrast, the percentage of subjects with AEs

Table 7
Concurrent illness or injury among subjects with adverse events of insomnia or sleep disorder: Tafenoquine anticipated clinical regimen.

Subgroup	Subjects with Insomnia or Sleep Disorder, n (%)	No. Subjects with Concurrent Illness/Injury, n (%)[a]			
		Gastrointestinal	Active Pain[b]	Upper Respiratory	None
Deployed Australian Defence Force (n = 492)	10 (2.0%)	5 (1.0%)[c]	6 (1.2%)	2 (0.4%)[d]	2 (0.4%)
Resident Non-Australian Defence Force (n = 333)	3 (0.9%)	0	2 (0.6%)	0	1 (0.3%)
Tafenoquine Anticipated Clinical Regimen Overall (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 hayfever.

was markedly higher in the Deployed ADF subgroup (94.9%) than in the Resident Non-ADF subgroup (67.6%) (Table 3). In addition, a much higher percentage of AEs in the Deployed ADF subjects were considered to be unrelated to treatment (86.7%) than in the Resident Non-ADF group (53.0%). This suggested that the Deployed ADF subgroup had been exposed to extrinsic factors, unrelated to drug intake, which influenced their safety findings. It also demonstrated that the ADF subjects were forthright in sharing their AE experiences with medical personnel during Study 033 and did not discriminate against any class of AE (i.e. neuropsychiatric events).

All members of the Deployed ADF subgroup participated in Study 033 [10,11] in which the study population was comprised entirely of ADF soldiers deployed on United Nations peacekeeping duties in East Timor (October 2000–April 2001). All were healthy adults, ages 18–55, G6PD normal, with no history of psychiatric disorders or seizures. This specific "peacekeeping" operation has in fact been described as "warlike" [18], where the use of force was authorized and where casualties were expected [19]. Consistent with this violent milieu, traumatic exposures reported by ADF personnel included the danger of being killed or injured (71% of soldiers reporting); seeing dead bodies (49%); fear of exposure to a toxic agent, contagious disease, or injury (31%); and having a friend/associate killed or injured (30%) [18]. With these stressors as likely contributing factors, 7.2% of ADF personnel deployed to East Timor have reported symptoms of post-traumatic stress disorder (PTSD), while 6.9% report long-term high levels of psychological stress [18].

Compounding these psychological threats were the physical threats and trauma which the Deployed ADF subgroup experienced, as evidenced by a high rate of injuries (39.8%) that was roughly 4 times that of the Resident Non-ADF subgroup (10.5%) (Table 4). Furthermore, compared to Resident Non-ADF subjects, Deployed ADF subjects had a higher incidence of gastroenteritis, diarrhea, and maladies related to military deployment (heat illness, heat rash, allergies, impetigo, otitis externa, arthropod bites, and tinea infections). Overall, these findings suggest that multiple extrinsic factors to which the Deployed ADF subgroup was exposed negatively impacted the perceived safety profile of tafenoquine in that population. This finding is consistent with similar observations made for studies conducted in military populations with prophylactic mefloquine [20] or doxycycline [21].

Regarding psychiatric AEs, it has been recommended that investigators consider the physiological and psychological stressors associated with military activities whenever they monitor a drug's tolerability under military operational conditions [21]. For prophylactic antimalarial drugs in particular, support for this recommendation comes from studies showing that incidences of neuropsychiatric AEs (e.g., adjustment disorder, insomnia, anxiety disorder) are higher in deployed vs. non-deployed military populations, especially when deployment occurs under combat conditions [21,22]. Under these circumstances, an increased level of risk is evident even for FDA approved antimalarials that have no known neuropsychiatric AE profile (e.g., doxycycline, atovaquone/proguanil) [21,22]. Consistent with this increased risk, a review of psychiatric data in the present analysis revealed that the Deployed ADF subgroup reported a higher incidence of psychiatric AEs and a greater variety of psychiatric AEs than did non-deployed Resident Non-ADF subjects. This suggests that deployed military subjects who received the Tafenoquine ACR during peacekeeping operations were in fact exposed to deployment-related extrinsic factors, including unique physical and psychological stressors, which placed them at a higher risk for psychiatric AEs than their Resident Non-ADF counterparts living at home.

Notably, among the 25 Deployed ADF subjects who reported psychiatric disorders, the majority [18 (72%) of 25] developed problems related to sleep (insomnia, abnormal dreams, nightmares, sleep disorder). This underscores the potentially dramatic effect that deployment can have on sleep in military populations [23]. Sleep problems, particularly insomnia, are highly prevalent during military deployments [24,25] and insomnia is often reported not only during actual combat operations but also post-deployment after combat ends [26–28]. 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 [23]. 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.

Given differences in the incidences of some AEs in the Deployed ADF subgroup compared to the Resident Non-ADF subgroup, what represents an appropriate safety profile of AEs associated with the Tafenoquine ACR for the population most likely to use malaria prophylaxis (i.e., non-military travelers to endemic regions)? Common AEs that were reported in 5% of both subgroups included only gastroenteritis, upper respiratory tract infection (URI), back pain, and headache, many of which likely occurred independent of tafenoquine exposure, especially given the longer-term (12-month) durations of Studies 033 and 057. This underscores the safety and acceptable tolerance of the dosing regimen. Furthermore, in comparison to mefloquine, the Tafenoquine ACR (n = 825) showed a more benign safety profile, being associated with lower risks for dizziness, myalgia, headache, and abdominal pain.

Limitations of the current analysis include the fact that the majority of subjects in all trials were young adults, and that fewer females than males were included. In addition, safety analyses were not performed by race.

A further limitation relates to the inclusion of targeted eye assessments for ophthalmological AEs (keratopathy and retinal changes) in Studies 033 and 057, but not in the 3 studies that were conducted earlier (African Studies 030, 043, or 045). Notably, whenever ophthalmological AEs were identified in Studies 033 or 057, any observed changes to the cornea or retina were mild, fully reversible, and had no impact on visual acuity. Although targeted

ophthalmological assessments were not performed in the early African studies, there was similarly no safety signal in these trials indicating that vision was affected.

Following the completion of the Phase III study which ended in 2001, the development of tafenoquine was paused due to altered commercial priorities and safety concerns. The latter involved the ophthalmologic AEs referred to above together with the increased serum creatinine observed in the Phase III study [11]. These issues were subsequently resolved in healthy volunteers [14]. Overall, the present analysis reaffirms that tafenoquine, when administered according to the anticipated prophylactic clinical regimen, is a safe, effective, and convenient prophylactic antimalarial drug in adults. Although the drug's safety profile may be altered in some respects when it is administered in deployed military populations, any differences are more likely to reflect the rigors and hazards of military deployment rather than side effects intrinsic to tafenoquine.

Conflict of interest declaration

Geoffrey Dow is the CEO and Bryan Smith is the CMO of 60 Degrees Pharmaceuticals, the US Army's licensee for tafenoquine for malaria prophylaxis. Lisa Read is a Project Manager involved with Tafenoquine development by the US Army. Anne Novitt-Moreno and Janet Ransom are employed by Fast-Track Drugs & Biologics, LLC, which is under contract with the U.S. Army to aid in Tafenoquine development. Stephen Toovey has been compensated for consulting on antimalarials by a number of marketing authorization holders and developers, including 60 Degrees Pharmaceuticals.

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Disclaimer

The views expressed herein by the authors are their own and do not necessarily reflect the view of the United States Army or the United States Department of Defense.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tmaid.2017.05.008.

References

[1] Cullen KA, Mace KE, Arguin PM. No. SS-2. Malaria surveillance — United States, 2013. MMWR surveill summ, vol. 65; 2016. p. 1–22. http://dx.doi.org/10.15585/mmwr.ss6502a1.
[2] Dow GS, Liu J, Lin G, Hetzell B, Thieling S, McCarthy WF, et al. Summary of anti-malarial prophylactic efficacy of tafenoquine from three placebo-controlled studies of residents of malaria-endemic countries. Malar J 2015;14:473. http://dx.doi.org/10.1186/s12936-015-0991-x.
[3] Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. 2013. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362232.pdf [accessed 17.01.19].
[4] Department of Defense (USA). Office of the assistant secretary of Defense. Memorandum: guidance on medications for prophylaxis of malaria. April 2013 (Document Identification # 13–002). Date: 15.
[5] GlaxoSmithKline LLC. Malarone (atovaquone and proguanil hydrochloride tablets, film coated) Highlights of Prescribing Information. 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fc22e8d8-3bfb-4f70-a599-dd81262a4887 [accessed 17.03.27].
[6] Tan KR, Magill AJ, Parise ME, Arguin PM. Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC expert meeting on malaria chemoprophylaxis. Am J Trop Med Hyg 2011;84:517–31.
[7] Leslie T, Rab MA, Ahmadzai H, Durrani N, Fayaz M, Kolaczinski J, et al. Compliance with 14-day primaquine therapy for radical cure of vivax malaria—a randomized placebo controlled trial comparing unsupervised with supervised treatment. Trans R Soc Trop Med Hyg 2004;98:168–73.
[8] Fernando D, Rodrigo C, Rajapakse S. Primaquine in vivax malaria: an update and review on management issues. Malar J 2011;10:351. http://dx.doi.org/10.1186/1475-2875-10-351.
[9] Peters W. The evolution of tafenoquine—antimalarial for a new millennium? J R Soc Med 1999;92:345.
[10] Dow GS, McCarthy WF, Reid M, Smith B, Tang D, Shanks GD. A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic antimalarials in non-immune individuals. Malar J 2014;13:49. http://dx.doi.org/10.1186/1475-2875-13-49.
[11] Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother 2010;54:792–8.
[12] Hale BR, Owusu-Agyei S, Fryauff DJ, Koram KA, Adjuik M, Oduro AR, et al. A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against Plasmodium falciparum. Clin Infect Dis 2003;36:541–9.
[13] Shanks GD, Oloo AJ, Aleman GM, Ohrt C, Klotz FW, Braitman D, et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. Clin Infect Dis 2001;33:1968–74.
[14] Leary KJ, Riel MA, Roy MJ, Cantilena LR, Bi D, Brater DC, et al. A randomized, double-blind, safety and tolerability study to assess the ophthalmic and renal effects of tafenoquine 200 mg weekly versus placebo for 6 months in healthy volunteers. Am J Trop Med Hyg 2009;81:356–62.
[15] Sanofi-Aventis USLLC. Primaquine phosphate (tablet, film coated) drug label information. 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1BFBF4AE-81B8-4160-A00D-6322AADD4B59 [accessed 16.10.31].
[16] FDA. Medication Guides. Roche lariam (mefloquine hydrochloride) tablets. Nda 19–951/S028. 2009. https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088616.pdf [accessed 17.05.03].
[17] Elmes NJ, Nasveld PE, Kitchener SJ, Kocisko DA, Edstein MD. The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of Plasmodium vivax malaria in the Southwest Pacific. Trans R Soc Trop Med Hyg 2008;102:1095–101.
[18] Waller M, Treloar SA, Sim MR, McFarlane AC, McGuire AC, Bleier J, et al. Traumatic events, other operational stressors and physical and mental health reported by Australian Defence Force personnel following peacekeeping and war-like deployments. BMC Psychiatry 2012;12:1.
[19] Kirk KM, McGuire A, Nielsen L, Cosgrove T, McClintock C, Nasveld PE, et al. Self-reported tinnitus and ototoxic exposures among deployed Australian Defence Force personnel. Mil Med 2011;176:461–7.
[20] Croft A, Garner P. Mefloquine Prev Malar a Syst Rev trials BMJ 1997;315:1412.
[21] Kitchener SJ, Nasveld PE, Gregory RM, Edstein MD. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. Med J Aust 2005;182:168–71.
[22] Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL. Neuropsychiatric outcomes after mefloquine exposure among US military service members. Am J Trop Med Hyg 2017;96:159–66.
[23] Troxel WM, Shih RA, Pedersen ER, Geyer L, Fisher MP, Griffin BA, et al. Sleep in the military: promoting healthy sleep among U.S. servicemembers. Santa Monica, CA: RAND Corporation; 2015. http://www.rand.org/pubs/research_reports/RR739.html [accessed 17.03.28].
[24] Seelig AD, Jacobson IG, Donoho CJ, Trone DW, Crum-Cianflone NF, Balkin TJ. Sleep and health resilience metrics in a large military cohort. Sleep 2016;39:1111–20.
[25] Mental Health Advisory Team 9 (MHAT-9), Operation Enduring Freedom (OEF) 2013 Afghanistan, Washington, D.C.: Office of the Surgeon General, U.S. Army Medical Command; Office of the Command Surgeon, Headquarters, U.S. Central Command; and Office of the Command Surgeon, U.S. Forces Afghanistan. http://armymedicine.mil/Documents/MHAT_9_OEF_Report.pdf; 2013 [accessed 17.03.28].
[26] McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of posttraumatic stress disorder in U.S. service members returning from military deployments. Mil Med 2010;175:759–62.
[27] Nissen LR, Stoltenberg C, Vedtofte MS, Neilson AB, Marrott JL, Gyntelberg F, et al. Increased postdeployment use of medication for common mental disorders in Danish Gulf War veterans. Mil Med 2017;182(3):e1677–83.
[28] Plumb TR, Peachey JT, Zelman DC. Sleep disturbance is common among servicemembers and veterans of Operations Enduring Freedom and Iraqi Freedom. Psychol Serv 2014;11:209–19.

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Original article

Tafenoquine is not neurotoxic following supertherapeutic dosing in rats

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ABSTRACT

Background: Tafenoquine is a new drug for malaria prevention. The goal of the present work was to conduct a specific neurobehavioral study in rats with histopathological assessment of the brain.
Methods: The clinical, hematological, behavioral, motor activity, and neurohistopathologic changes induced by different dose levels of tafenoquine were evaluated following single super-therapeutic dose administration. Toxicokinetic data were generated to allow extrapolation to clinical exposures.
Results: At the highest dose (500 mg/kg), two animals (of 12) died. Surviving animals showed clinical signs of toxicity and had reduced body weight 7–8 days after dosing. Decreases in motor activity were observed on more than one occasion at doses > 9-fold higher than the clinical exposure. No statistically significant changes were observed for other behavioral endpoints. No neurohistopathological changes were noted. Changes in hematological and clinical pathology endpoints were observed at the lowest dose level (125 mg/kg). For context, the human dosing regimen is a 10 mg/kg load followed by 3.3 mg/kg weekly (in a 60 kg person).
Conclusions: As in humans, adverse events other than neurotoxicity were dose-limiting for tafenoquine in rats. This raises the prospect that a new weekly prophylactic, without neurologic liability, may become available in the near future.

1. Introduction

Tafenoquine is an 8-aminoquinoline analog of primaquine in late stage development for various malaria indications by GlaxoSmithKline, Medicines for Malaria Venture, the U.S. Army and 60 Degrees Pharmaceuticals (60P). The conferment of breakthrough therapy designation by the U.S. Food and Drug Administration [1] suggests that substantial public health benefits may accrue if tafenoquine is approved by regulators.

The long half-life of tafenoquine allows for more convenient dosing regimens. The anticipated clinical dose of tafenoquine will be 200 mg/day for three days (total of 10 mg/kg over three days in a 60 kg person) followed by 200 mg maintenance doses thereafter (3.3 mg/kg weekly in a 60 kg person [2]). In the context of travel medicine, tafenoquine would become the only available once weekly regimen useful for malaria prevention in areas of the world with chloroquine or mefloquine-resistant malaria. It would also provide travel medicine practitioners the option of being able to prescribe a chemoprophylactic agent with a weekly dosing regimen, but without the neuropsychiatric adverse event profile associated with mefloquine [3]. In some jurisdictions, concerns regarding the neuropsychiatric effects of mefloquine have resulted in very restrictive prescribing rules and there is concern that in the future this drug may not be available for special populations [4].

Dow et al. [5] reported that mefloquine, the weekly prophylactic antimalarial for which tafenoquine could be an alternative, induced degeneration of brain stem nuclei and neurobehavioral changes at threshold doses with exposure levels relevant to human dosing in female rats. The general methodology employed in that study is

List of abbreviations: 60P, 60 Degrees Pharmaceuticals; Alb, Albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Chol, cholesterol; CNS, Clinical Network Services; EDTA, ethylenediaminetetra acetic acid; F, female; FOB, Functional observation battery; G6PD, Glucose-6-phosphate dehydrogenase; H&E, Haematoxylin and Eosin stain; HCT, haematocrit; HGB, haemoglobin; LUC, large unstained cell; Lymph, lymphocyte; M, male; Mono, monocyte; Neut, neutrophil; No., number; PLT, platelet count; RBC, red blood cell; Retic, reticulocyte; SD, Sprague Dawley; TP, total protein; USAMMDA, US Army Medical Materiel Development Activity.

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required by regulators as a component of the core non-clinical safety battery included in regulatory filings [6]. Recently, 60P, as one of the commercial sponsors of tafenoquine, updated its non-clinical dossier by conducting a specific neurobehavioral study in rats with histopathological assessment of the brain. The results of this work is reported herein.

2. Materials and methods

2.1. MTD rat study

With the goal of identifying the maximum tolerated dose, groups of 5 male and 5 female Sprague Dawley (SD) rats were administered a single oral dose of 0 (vehicle), 125, 250, 400 or 700 mg/kg tafenoquine succinate (dose expressed as free base) in 1%/0.4% methylcellulose/Tween 80 in water, at a dose volume of 10 mL/kg [Note the 400 mg/kg dose group was administered an actual dose of 506 mg/kg due to a higher concentration dose formulation being prepared whereas all other groups were within 12% of nominal dose]. The day of dosing was designated Day 1. Animals were observed for 7 days following dosing.

Animal viability checks and physical observations were made daily, body weights were recorded pre-dose and twice during the study, and clinical pathology parameters were assessed on Day 7. Following Day 7 assessments animals were euthanized without further examination, although any animals dying earlier than the scheduled end of study were grossly examined at necropsy. The dose formulation for each group was analyzed to confirm the absence (control) or actual concentration of tafenoquine.

2.2. Neurobehavioral, histopathologic and toxicokinetic study

Based on the rat maximum tolerated dose study results, three groups of 12 male and 12 female SD rats were dosed once orally with 125, 250 or 500 mg/kg tafenoquine succinate (dose expressed as free base). The highest dose was anticipated to be the maximum tolerated dose. The lower doses were selected because they exceed therapeutic doses, were well tolerated in the maximum tolerated dose study, and allowed dose response to be explored. A group of 9 male and 9 female SD rats were dosed concurrently with vehicle i.e. 1%/0.4% methylcellulose/Tween 80 in distilled water.

Six rats of each sex in the control and tafenoquine-treated groups were used to assess neurobehavioral effects following dosing while the remaining 3/sex in the control group and 6/sex in the tafenoquine-treated groups were included in the toxicokinetic investigations. Blood samples (~0.5 mL) were collected from tafenoquine-treated toxicokinetic group animals (3/sex/group/time point) at 1, 3, 5, 8, 24, 48, 72 and 168 h after dosing. Blood was collected 8 h post dosing in control animals. Blood was placed in to K_2EDTA anticoagulant tubes and stored on wet ice prior to plasma separation by centrifugation. Plasma was stored frozen at approximately −80 °C (±10 °C) within 2 h of collection until analysis. Plasma was analyzed by high performance liquid chromatography with mass spectrometric detection.

All dose formulations were analysed to confirm absence (control) or concentration of tafenoquine and the homogeneity of mixtures. Daily viability checks were performed morning and evening along with general clinical observations prior to dosing and at least twice following dosing on all animals along with body weights pre-dose and on the day of necropsy. A functional observation battery (FOB) [7] was performed on neurobehavioral group animals by trained observers with no prior knowledge of treatment, pre-dosing (Day −1) and at 0.5, 3, 6, 24 and 48 h after dosing. After the FOB, pretest and at 6, 24 and 48 h post dosing, horizontal and vertical motor activity was monitored for 60 min (divided in to 12, 5 min intervals) using an automated motor monitor system.

Animals from the neurobehavioral groups were necropsied on Day 4 and 8 (3/sex/time point), i.e. 72 h and 168 h after dosing, respectively. Animals were deeply anesthetized with sodium pentobarbital before whole body perfusion via the ascending aorta with ~100 mL of saline followed by ~500 mL of 0.1 M phosphate buffer (pH 7.4 ± 0.1) containing 4% paraformaldehyde. The brain remained in situ and the carcass was refrigerated for 3–6 h, then the heads removed and post-fixed for 24–48 h with neutral buffered formalin before removal of the brain from the skull and storage in the same fixative as needed until processing.

All fixed brain tissues were processed to paraffin blocks. Rat brains were gross-trimmed according to the guide provided in Bolon *et al* for the 'best practice' approach to neuropathologic assessment in developmental neurotoxicity [8]. Since the gracile and cuneate (and potentially other brainstem) nuclei were targets for mefloquine [5], depending on the amount of tissue after the 8th slice as depicted in the Bolon *et al* recommendation, a 9th slice was taken caudal to the 8th slice and placed face down in the block. Two sections were taken from the blocks at each of levels 1 to 7 and stained with Haematoxylin and Eosin (H&E) and Bielschowsky's silver stain. The 8th and 9th (if present) blocks were step sectioned, first taking 4 serial sections on separate slides (2 stained with H&E and Bielschowsky's stain, the remaining 2 as spares) and then microtoming 50 μm deeper to take another 2 sections for H&E and Bielschowsky's staining.

H&E and silver-stained sections from control and high-dose rats were evaluated by a board certified pathologist with knowledge of dose groups. The study protocol called for blinded examination of all tissues in all dose groups if differences were noted between the high and vehicle-dosed groups.

3. Results

3.1. Maximum tolerated dose study

The dose formulation analysis confirmed the actual dose concentrations were within 12% of target concentration except for the 400 mg/kg dose group, where the formulation was 126% higher than the nominal solution concentration of 40 mg/mL thus achieving a dose of 506 mg/kg as opposed to 400 mg/kg (Note the results for this group are referred to by the nominal dose of 400 mg/kg). This was not considered to have adversely affected the aim of the study.

Clinical and physiological changes following single dose administration of tafenoquine are summarized in Table 1. One male died on Day 6 following the single oral administration of 700 mg/kg on Day 1. Clinical signs following the single administration of tafenoquine were whole body pallor (all animals at ≥400 mg/kg), dark or dull bilateral eyes at ≥400 mg/kg and thin appearance (2 females), staining on head (abnormal red color, in 1 female) and rales (1 female) at 700 mg/kg. No clinical signs were noted at 125 or 250 mg/kg. Dose related statistically significant decreases in body weight was seen at all doses in males, and at 700 mg/kg in females. Food consumption was decreased at 400 and 700 mg/kg in males and females compared to pretest baseline values. One male rat dosed with 700 mg/kg was found dead on Day 6 and had gross pathology of enlarged liver, small right testis and thymus with dark areas.

The main clinical pathology changes included decreases in red blood cell (RBC) parameters, increase in neutrophils as well as increases in liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The decreases in red blood cell mass (hemoglobin, hematocrit, and RBC count) at all doses in females were associated with a regenerative response (increased

Table 1
Changes in clinical, hematological and clinical chemistry endpoints in rats administered a single oral dose of 125, 250, 400 or 700 mg/kg tafenoquine.

Parameter	0 mg/kg		125 mg/kg		250 mg/kg		400 mg/kg		700 mg/kg	
Gender	M	F	M	F	M	F	M	F	M	F
No./sex/group	5	5	5	5	5	5	5	5	5	5
Clinical observations Day 6–7 (no. affected)										
Unscheduled death	0	0	0	0	0	0	0	0	1[a]	0
rales	0	0	0	0	0	0	0	0	0	1
Thin	0	0	0	0	0	0	0	0	0	2
Dark eyes	0	0	0	0	0	0	0	0	1	1
Dull eyes	0	0	0	0	0	0	5	5	0	0
Skin -pallor	0	0	0	0	0	0	5	5	4	5
Staining on head	0	0	0	0	0	0	0	0	0	1
Mean Body weight change (g)										
Day 1–6	14	3	−7**	−3	−14**	−2	−35**	−6*	−34**	−24**
Mean Food consumption (g/animal/day)										
Pre-dose	10	11	8	5	6	7	28	19	28	18
Day 1–3	25	23	18	12	16	12	19	12	19	9
Day 3–6	24	22	20	15	15	14	9	12	12	9
Haematology (Day 7)										
HGB g/dL	16.8	16.4	16.2	14.5**	15.8	14.1**	16.0	13.5**	17.0	13.7**
HCT %	52.1	49.1	50.1	43.2**	47.9	41.5**	49.0	40.2**	51.0	40.2**
RBC $x10^6/\mu L$	8.85	8.47	8.61	7.47**	8.47	7.46**	8.79	7.16**	9.14	7.08**
PLT	974	1002	1060	946	990	1011	1058	1258*	1131	1248*
Retic $x10^9/L$	202.2	180.4	277.8*	284.8	282.9*	398.5**	209.8	431.5**	130.9	324.9**
Neut $x10^3/\mu L$	2.34	0.93	3.65	2.44**	5.03**	4.64**	7.37**	4.38**	7.19**	9.35**
Lymph $x10^3/\mu L$	10.26	8.00	11.21	9.52	8.80	7.33	5.65**	6.70	5.74**	3.99**
Mono $x10^3/\mu L$	0.46	0.22	0.60	0.29	0.49	0.33	0.55	0.34	0.88**	0.18
LUC $x10^3/\mu L$	0.19	0.14	0.32	0.15	0.32	0.20	0.48*	0.24	0.49*	0.10
AST u/L	155	109	147	108	185	217	1659**	516**	1285**	3649**
ALT U/L	45	43	46	36	50	47	233*	73	582*	389**
BUN mg/dL	14	16	16	17	16	17	17	16	20**	21**
Chol mg/dL	78	88	84	70	60	77	55	69	50*	90
TP g/dL	7.0	7.6	6.9	6.8*	6.6	6.9*	6.1**	7.1*	6.3**	6.8*
Alb g/dL	4.1	4.7	4.1	4.2*	4.0	4.2*	3.6**	4.4*	3.7**	4.0**

Key: * = $p < 0.05$ ** = $p < 0.01$.
Abbreviations: Alb, Albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Chol, cholesterol; F, female; HCT, haematocrit; HGB, haemoglobin; LUC, large unstained cell; Lymph, lymphocyte; M, male; Mono, monocyte; Neut, neutrophil; No., number; PLT, platelet count; RBC, red blood cell count; Retic, reticulocyte; TP, total protein.
[a] One male died Day 6.

reticulocytes). The increases in AST and ALT activities at ≥ 400 mg/kg were considered adverse due to their larger magnitudes of change. The majority of other changes were noted at the higher doses of 400 and 700 mg/kg and included decreased lymphocytes in males at 400 and 700 mg/kg and females at 700 mg/kg, increased large unstained cells in males at 400 and 700 mg/kg, increased monocytes in males at 700 mg/kg, increased blood urea nitrogen in both sexes at 700 mg/kg, decreased cholesterol in males at 700 mg/kg, and decreased total protein and albumin. Other than the liver enzyme changes, all changes, were considered non-adverse due to their relatively small magnitudes.

In summary, the nominal dose of 400 mg/kg (achieved 506 mg/kg) was associated with moderate toxicities. At 700 mg/kg, similar clinical signs were noted as in the 400 mg/kg group with additional findings of change in breathing pattern, thin appearance and dark/dull eyes as well as death in one of 5 males on Day 6. The dose of 700 mg/kg was considered to exceed the maximum tolerated dose. At single doses of 125 and 250 mg/kg, there were no adverse clinical signs, minimal effects on body weight, and small changes on red blood cell parameters.

3.2. Functional observational battery, motor activity, histology and toxicokinetic assessments

All dose formulations were homogeneous mixtures and within ±8% of the nominal concentrations of 12.5, 25 and 50 mg/mL. The control formulation showed absence of tafenoquine.

Two animals (one male TK animal and one female main study animal) were found dead on Day 7 or 8 following dosing with 500 mg/kg and showed no gross tissue pathology at necropsy. Clinical signs following a single administration of tafenoquine at 500 mg/kg were piloerection, decreased fecal pellets, hunched appearance, irregular breathing, and red staining on head on Days 7 and/or 8. At 500 mg/kg, there were decreases in body weights in males (−18%) and females (−16%) at termination on Day 8 when compared to the control group. The FOB performed pretest, 0.5, 3, 6, 24 and 48 h post-dose showed no significant tafenoquine-related findings relative to control rats of either gender. This is illustrated in Table 2 where the main FOB parameters are summarized for male rats at pretest, 24 and 48 h time points. The earlier time points and female rats showed similar results (data are not presented).

Motor activity was reduced at 24 h after dosing, for at least one 5 min interval during the 1 h observation period, in males dosed with 500 mg/kg and females dosed with 250 or 500 mg/kg, although changes only reached statistical significance in females (data not shown). At 48 h after dosing, motor activity was decreased in males at all doses and females dosed with 250 or 500 mg/kg (Figs. 1 and 2). The effect was more pronounced at 48 h at 500 mg/kg and in male animals with a greater number of observation intervals showing a significant change (Figs. 1 and 2).

Table 2
Functional observational battery assessments in male rats following a single oral dose of tafenoquine.

Observation	Time point relative to dosing											
Time point	Pre-test				24 h				48 h			
Dose mg/kg	0	125	250	500	0	125	250	500	0	125	250	500
No. animals/sex/group	6	6	6	6	6	6	6	6	6	6	6	6
Home cage observation												
Posture:												
Sitting or standing Normally	5	6	3	4	1	4	3	3	4	5	2	3
Asleep- lying on side or curled up	1	0	3	2	5	2	3	3	2	1	4	3
Palpabrel closure:												
Eyelid open	5	5	3	4	1	2	2	3	4	5	2	3
Eyelid half closed	0	1	0	0	0	2	1	0	0	0	0	0
Eyelid closed	1	0	3	2	5	2	3	3	2	1	4	3
Vocalisation:												
None	6	6	6	6	6	6	6	6	6	6	6	6
Motor activity [a]												
Normal	6	6	6	6	6	6	6	6	6	6	6	6
Handling evaluations												
Ease of removal/handling												
Very easy	5	5	5	5	6	6	6	6	6	6	6	6
Easy	1	1	1	1	0	0	0	0	0	0	0	0
Chromodacryorrhea												
Not present	6	6	6	6	6	6	6	6	6	6	6	6
Lacrimation												
Not present	6	6	6	6	6	6	6	6	6	6	6	6
Salivation												
Not present	6	6	6	6	6	6	6	6	6	6	6	6
Coat												
Normal	6	6	6	6	6	6	6	6	6	6	6	6
Open field observations												
Gait and posture [b]												
Normal	6	6	6	6	5	6	6	6	6	5[c]	6	6
Body drags/flattened	0	0	0	0	1	0	0	0	0	0	0	0
Locomotion												
Not impaired	6	6	6	6	6	6	6	6	6	6	6	6
Arousal												
Alert	6	6	6	6	1	2	0	3	1	1	0	2
Slightly low/sluggish	0	0	0	0	3	2	4	3	2	4	5	3
Moderately low/slight stupor	0	0	0	0	2	2	2	0	3	1	1	1
Piloerection												
None	6	6	6	6	6	6	6	6	6	6	6	6
Exophthalmia												
None	6	6	6	6	6	6	6	6	6	6	6	6
Motor movements												
Fasiculations/tremors/convulsions	6	6	6	6	6	6	6	6	6	6	6	6
Not present												
Reflex Assessments												
Visual approach												
slowly, sniffs and turns away	6	6	6	6	4	4	2	5	3	5	3	4
Freezes or slightly pulls away	0	0	0	0	2	2	3	1	3	1	3	2
No reaction	0	0	0	0	0	0	1	0	0	0	0	0
Hearing												
Flinches and flicks ears	5	6	6	6	6	6	6	6	6	6	6	6
Exaggerated; jumps, flips, bites	1	0	0	0	0	0	0	0	0	0	0	0
Proprioception												
Returns leg to original position	6	6	6	6	6	6	6	6	6	6	6	6
Pain												
Turns or walks forward or vocalizes with Little or no movement	6	6	6	6	6	6	6	6	6	6	6	6
Pupil response												
Pupil constricts	6	6	6	6	6	6	6	6	6	6	6	6
Righting Reflex												
Normal: Lands on 4 feet	6	6	6	6	6	6	6	6	6	6	6	6

[a] Includes examination for the presence of tremors, vasiculations, convulsions, stereotypical behavior.
[b] Includes examination for presence of ataxia, hindlimb and/or forelimbs splayed or dragged, walking on tiptoes, hunched, body drag or flattened.
[c] One animal limping on left forelimb.

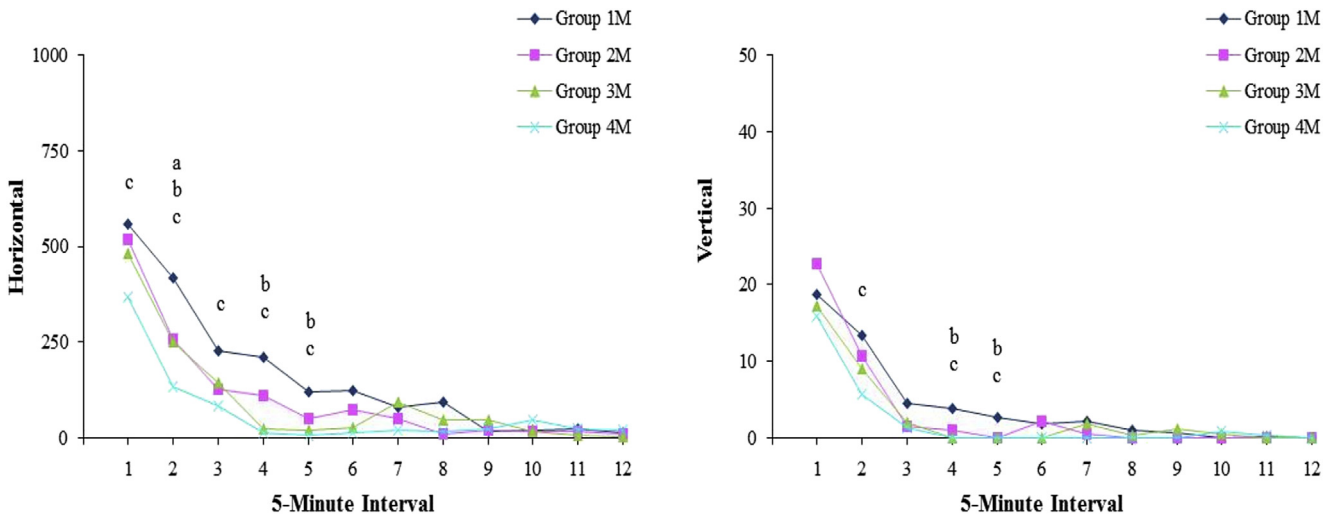

Fig. 1. Motor activity (number of beam breaks) 48 h after administration of a single dose of 125, 250 or 250 mg/kg tafenoquine to male rats. Dose groups 1 M, control group; 2 M, 125 mg/kg; 3 M, 250 mg/kg; 4 M, 500 mg/kg. An a, b, or c on the graphs indicates the mean value of the 125, 250 or 500 mg/kg is statistically different from the mean value of the vehicle control group.

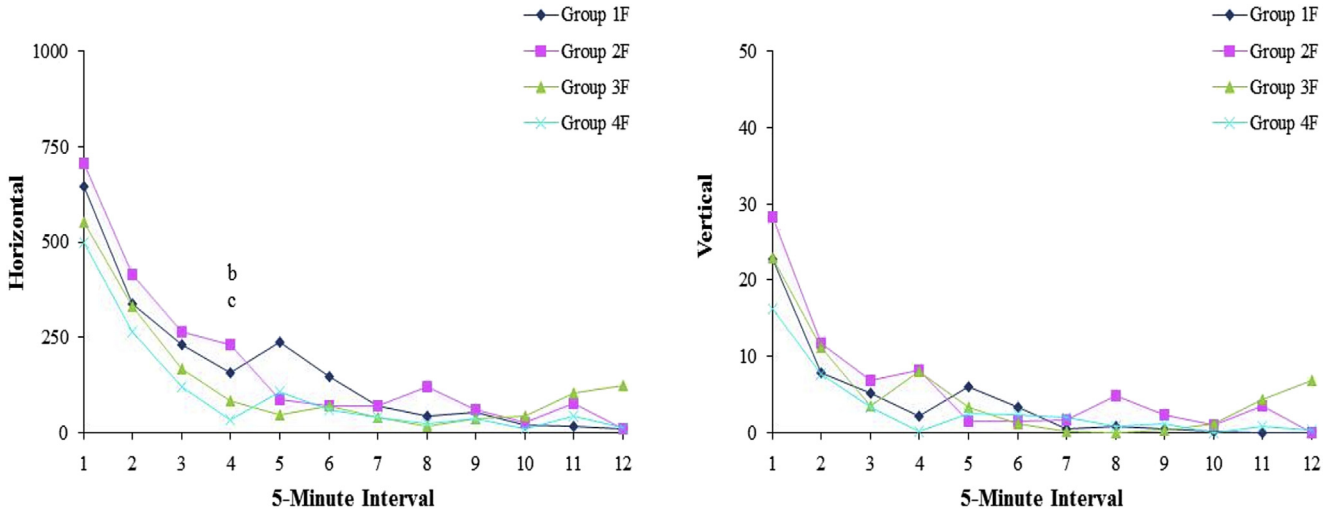

Fig. 2. Motor activity (number of beam breaks) 48 h after administration of a single dose of 125, 250 or 250 mg/kg tafenoquine to female rats. Caption: Dose groups 1F, control group; 2F, 125 mg/kg; 3F, 250 mg/kg; 4F, 500 mg/kg. An a, b, or c on the graphs indicates the mean value of the 125, 250 or 500 mg/kg is statistically different from the mean value of the vehicle control group.

There were no drug-related findings in the brain sections of animals dosed with 500 mg/kg tafenoquine compared to control rats. H&E sections showed no evidence of neurodegeneration or other morphological abnormalities, and axon morphology as demonstrated by Bielschowsky silver stain was comparable between tafenoquine-treated and control animals. The gracile nucleus, cited by Dow et al. [5] as a potential target for toxicity, was identified in at least one sectioned level from all animals and showed no abnormalities.

Tafenoquine was measurable in all the plasma samples collected from tafenoquine dosed animals but in none of the control animal samples (Cmax data summarised in Table 3).

4. Discussion

Here we report that tafenoquine at doses up to the minimum lethal dose (500 mg/kg single dose) in adult rats did not exhibit any dose-related histopathological changes in the brain. A Good Manufacturing Practice batch of tafenoquine, synthesized using the intended commercial process, was utilized in the studies. Both studies were conducted at a global toxicology house and the neurobehavioral study was conducted under Good Laboratory Practice conditions. The methodology used was broadly similar to that used previously to demonstrate histopathological changes due to mefloquine in the central nervous systems of rats, and was consistent with regulatory guidance's for conducting such studies. Our data suggest that tafenoquine does not cause histopathological changes in the central nervous system of the rat.

In adult rats, there were no statistically significant changes in any functional endpoints other than on motor activity. There was a general dose-related decrease in motor activity at later (24 and 48 h) time points. A dose-related decrease in weight loss was also observed in the behavioral study and the maximum tolerated dose study. In fact, the main adverse effects noted in the maximum tolerated dose study were dose-related reductions in red blood cell parameters, and increases in liver enzymes with threshold doses as

Table 3
Mean Cmax data in rats following oral administration and compared to human exposure.

Study Type	Dose (mg/kg)	Cmax (ng/mL)		Animal:Human Margin
Neurobehavioural study		Male	Female	
Single dose				
	125	3010	2240	5.6–7.5
	250	3820	3920	9.5–9.8
	500	5640	3840	9.6–14
Human PK study[a]	600 mg	401	–	n/a

n/a not applicable.
[a] Estimated human Cmax of 401 ng/mL following a single dose of 600 mg to 4 male volunteers [11].

low as 125 mg/kg. Collectively, these data suggest that clinical pathology-related adverse events should be dose-limiting upon translation into man.

The adverse events commonly seen in clinical trials involving tafenoquine have predominantly related to gastrointestinal disturbances, reversible vortex keratopathy (corneal deposits; secondary to phospholipidosis), and hematologic changes particularly in glucose-6-phosphate dehydrogenase (G6PD) deficiency [2,9,10]. Gastrointestinal disturbance is the dose-limiting toxicity in individuals who are G6PD-normal while hemolytic toxicity is the dose-limiting toxicity in G6PD deficiency [2,9,10]. Keratopathy had no effect on vision acuity and fully resolved within 6–12 months [2].

In summary, our data suggest that in rats, super-therapeutic doses of tafenoquine appear to be free of neurologic toxicity, in contrast to some other antimalarials, including mefloquine. Furthermore, as with clinical studies, adverse events other than neurologic toxicity are dose limiting in rats dosed with tafenoquine.

Ethics approval

The studies reviewed in this manuscript were performed by a global CRO laboratory. All were performed under the ethical and regulatory guidance relevant to that organization and country at the time.

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Authors' contributions

TB reviewed the study reports in preparation of this article and was one of the major contributors to the writing of this manuscript along with GD. All authors contributed to the conception of the study or drafting of the manuscript, and read approved the final manuscript.

Competing interests

TB and MR have no financial interest in the registration of Tafenoquine. TB and MR are employees of Clinical Network Services (CNS) Pty Ltd and have acted as paid consultants to 60P and the US Army Medical Materiel Development Activity (USAMMDA). MR was the former study coordinator of the 033 clinical study (Nasveld et al., 2010) and a former uniformed, serving member of the Australian Defence Force.

BS was a former Product Manager for Antimalarial Drugs in the USAMMDA as well as having held a number of positions with Walter Reed Army Institute of Research and Armed Forces Research Institute of Medical Sciences. BS is the CMO of 60 Degrees Pharmaceuticals, the US Army's licensee for Tafenoquine for malaria prophylaxis and a paid consultant for Clinical Network Services (CNS) Pty Ltd.

GD is the CEO and CSO of 60P and has a financial interest in the registration of Tafenoquine.

ST has been compensated for consulting on antimalarials by a number of marketing authorization holders and developers, including 60P.

These statements are made in the interest of full disclosure and not because the authors consider this to be a conflict of interest.

Consent for publication

The US Army and 60 Degrees Pharmaceuticals consented to publication of the material contained herein. The views expressed are the authors' own and do not necessarily reflect the views of the US Army or US Department of Defence.

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References

[1] Medicines for Malaria Venture. Breakthrough Therapy designation for potential new anti-relapse medicine for malaria. 2013. http://www.mmv.org/newsroom/press-releases/breakthrough-therapy-designation-potential-new-anti-relapse-medicine-malaria.
[2] Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother 2010;54(2):792–8. http://dx.doi.org/10.1128/AAC.00354-09.
[3] Toovey S. Mefloquine neurotoxicity: a literature review. Travel Med Infect Dis 2009;7(1):2–6. http://dx.doi.org/10.1016/j.tmaid.2008.12.004.
[4] Schlagenhauf P, Hatz C, Behrens R, Visser L, Funk M, Holzer B, et al. Mefloquine at the crossroads? Implications for malaria chemoprophylaxis in Europe. Travel Med Infect Dis 2015;13(2):192–6. http://dx.doi.org/10.1016/j.tmaid.2015.03.010.
[5] Dow G, Bauman R, Caridha D, Cabezas M, Du F, Gomez-Lobo R, et al. Mefloquine induces dose-related neurological effects in a rat model. Antimicrob Agents Chemother 2006;50(3):1045–53. http://dx.doi.org/10.1128/AAC.50.3.1045-1053.2006.
[6] International Conference on Harmonization. Safety pharmacology studies for human pharmaceuticals, Safety Pharmacology Studies for Human Pharmaceuticals S7A. 2000. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S7A/Step4/S7.
[7] Moser VC. Screening approaches to neurotoxicity: a functional observational battery. Int J Toxicol 1989;8(1):85–93. http://dx.doi.org/10.3109/10915818909009095.
[8] Bolon B, Garman R, Jensen K, Krinke G, Stuart BA. “best practices” approach to neuropathologic assessment in developmental neurotoxicity testing–for

today. Toxicol Pathol 2006;34:296–313. http://dx.doi.org/10.1080/01926230600713269.

[9] Shanks GD, Oloo AJ, Aleman GM, Ohrt C, Klotz FW, Braitman D, et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. Clin Infect Dis 2001;33(12):1968–74. http://dx.doi.org/10.1086/324081.

[10] Elmes NJ, Nasveld PE, Kitchener SJ, Kocisko DA, Edstein MD. The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of Plasmodium vivax malaria in the Southwest Pacific. Trans R Soc Trop Med Hyg 2008;102:1095–101. http://dx.doi.org/10.1016/j.trstmh.2008.04.024.

[11] Brueckner RP, Coster T, Wesche DL, Shmuklarsky M, Schuster BG. Prophylaxis of Plasmodium falciparum infection in a human challenge model with WR 238605, a new 8-aminoquinoline antimalarial. Antimicrob Agents Chemother 1998;42(5):1293–4.

Tafenoquine for Prevention of Malaria

July 26, 2018

60 Degrees Pharmaceuticals, LLC

Antimicrobial Drugs Advisory Committee Meeting

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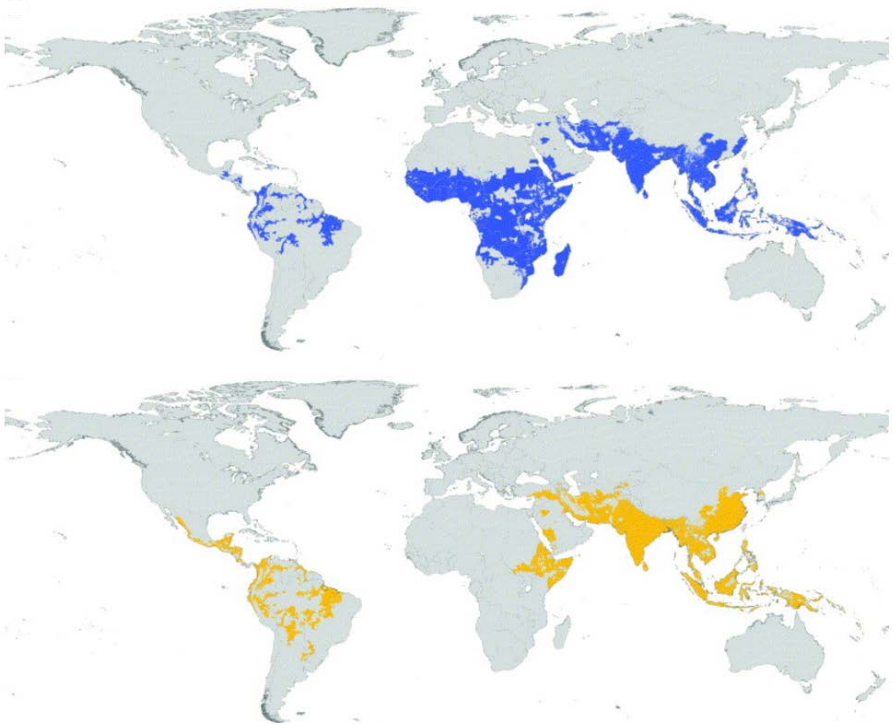
Overview

Geoffrey Dow, PhD

Chief Scientific Officer & CEO

60 Degrees Pharmaceuticals, LLC

Global Burden of Malaria



P. falciparum
216,000,000 cases annually

P. vivax
8,550,000 cases annually

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Tatem (2017). *Malaria Impact and Burden*
WHO (2017). *World Malaria Report*

Current Approaches to Malaria Elimination Fall Short

	Number of cases						
	2010	2011	2012	2013	2014	2015	2016
Lower 95% CI	218,000,000	207,000,000	199,000,000	191,000,000	191,000,000	192,000,000	196,000,000
Estimated total	237,000,000	225,000,000	217,000,000	210,000,000	210,000,000	211,000,000	216,000,000
Upper 95% CI	278,000,000	267,000,000	262,000,000	256,000,000	256,000,000	257,000,000	263,000,000

New Therapeutics With Different Labeling Required?

- Multiple dosing
- Longer duration of dosing
- Asymptomatic & non-immune subjects

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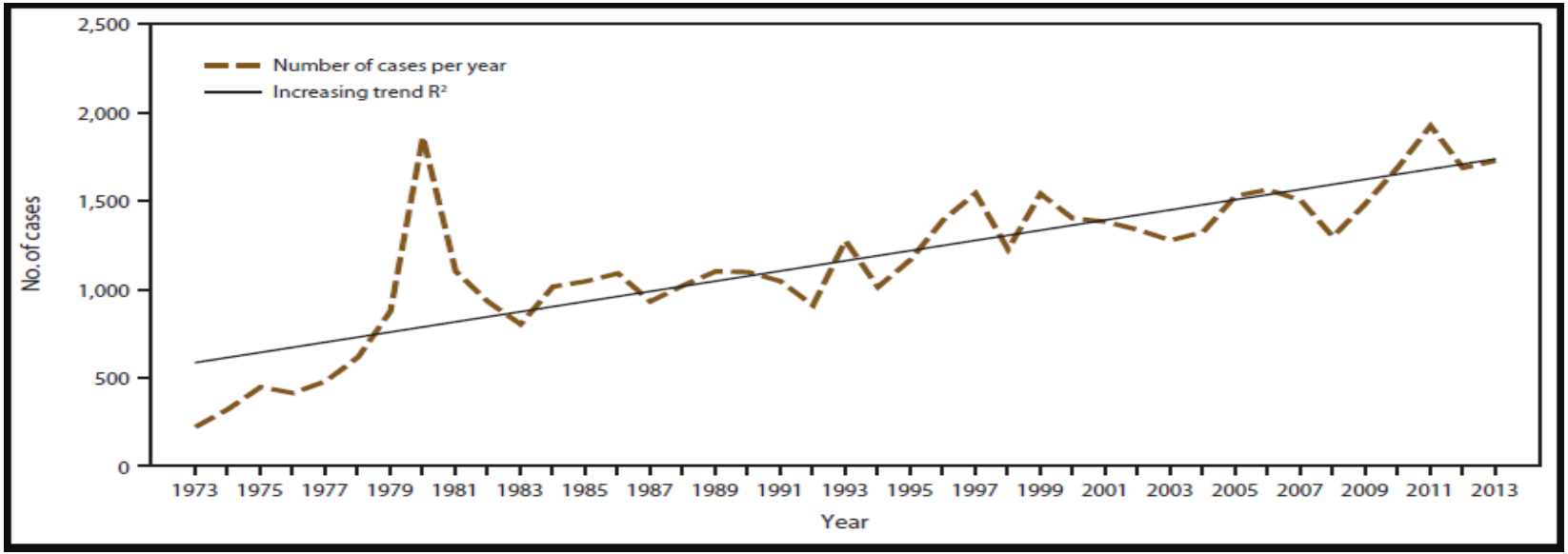
WHO (2017). *World Malaria Report*

US Malaria Burden 1973-2013



Cullen KA, Mace KE, Arguin PM. Malaria Surveillance — United States, 2013. MMWR Surveill Summ 2016;65(No. SS-2)(No. SS-2):1–22. DOI: http://dx.doi.org/10.15585/mmwr.ss6502a1

96% of malaria cases due to failure to comply with malaria chemoprophylaxis

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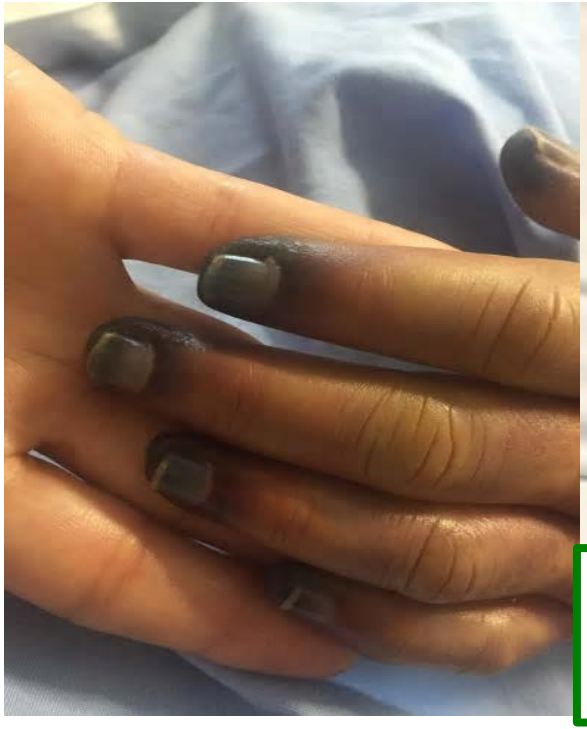
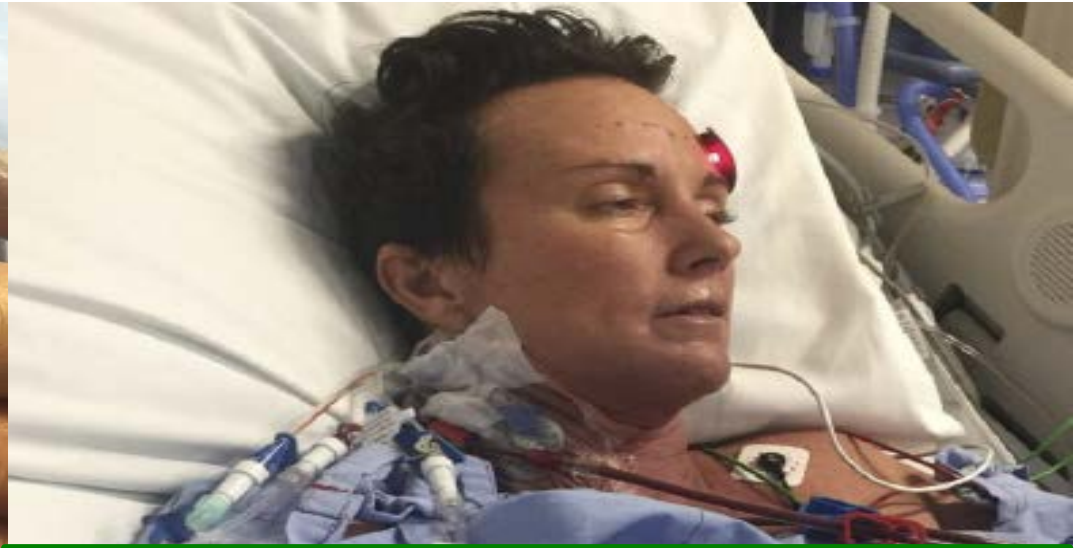
This just isn't good enough!





Severe malaria is entirely preventable

Vision: Malaria Prevention with ARAKODA

0

pediatric deaths from falciparum malaria

0

malaria cases amongst deployed U.S. service members

0

malaria cases in U.S. returning travelers

0

outbreaks in elimination regions

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ARAKODA – Target Label Claims

Description & Target Label Claims	
Attribute	**Description**
API Name	• Tafenoquine succinate
Presentation	• 100 mg tablets
Indication	• Prevention of malaria in adults for up to six months dosing
Dosing	• Loading dose: 200 mg once per day for 3 days within one week of travel • During travel: 200 mg once per week • Following travel: 200 mg once within 1 week of return from travel
Efficacy	• During travel: Protective efficacy (95% CI) = 100% (93-100%) • Post exposure: Protective efficacy equivalent to primaquine (30 mg x 14 days)
Common AEs	• GI distress, back pain, certain infections
Contraindications	• Severe G6PD deficiency • Pregnancy - G6PD status of fetus cannot be determined

“All parasites, everywhere, with a safe, simple dosing regimen”

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ARAKODA Compared to Standard of Care

Drug	Dosing	Kills all Pf and Pv stages	Global use	Single Dose Post-Exposure	# Tabs for 1 MO trip*	Neurologic Liability	G6PD Test Required
	Daily	No	Yes	No	72	No	No
	Weekly	No	No	No	25	Yes	No
	Daily	No	Yes	No	51	No	No
ARAKODA	**Weekly**	**Yes**	**Yes**	**Yes**	**16**	**No**	Yes

** Includes loading or pre-travel doses, post-travel doses, and 14 days of post-exposure primaquine (the latter only for Malarone®, Doxycycline, and Lariam®)*

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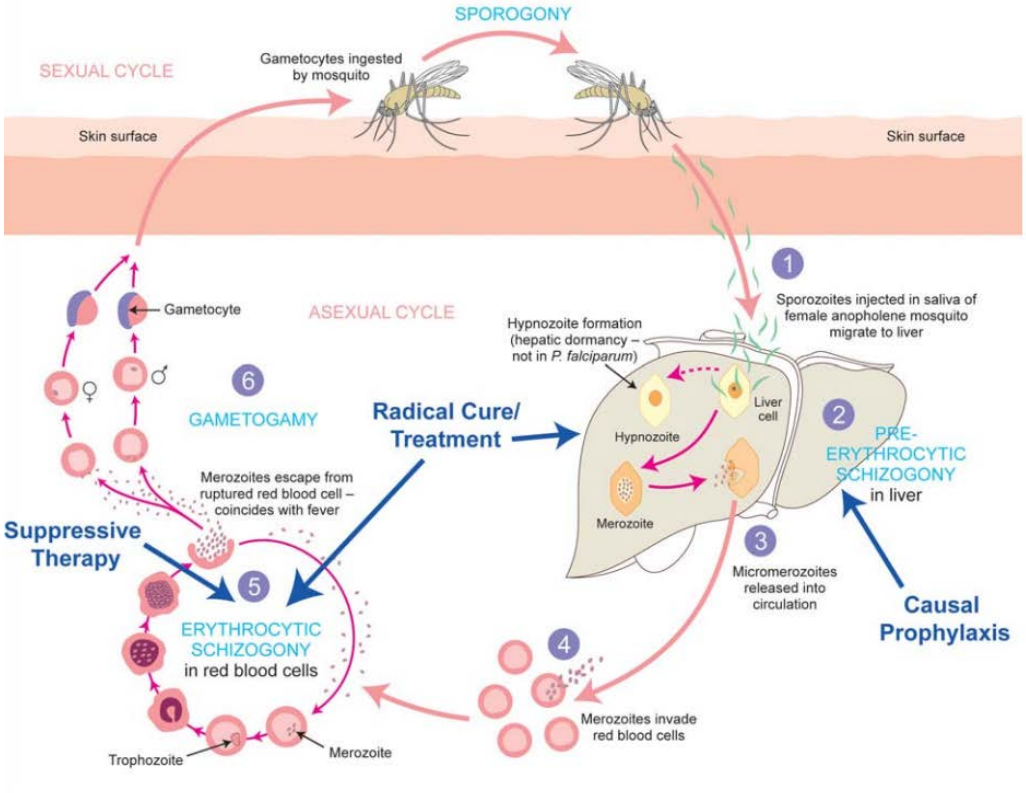
Malaria Lifecycle



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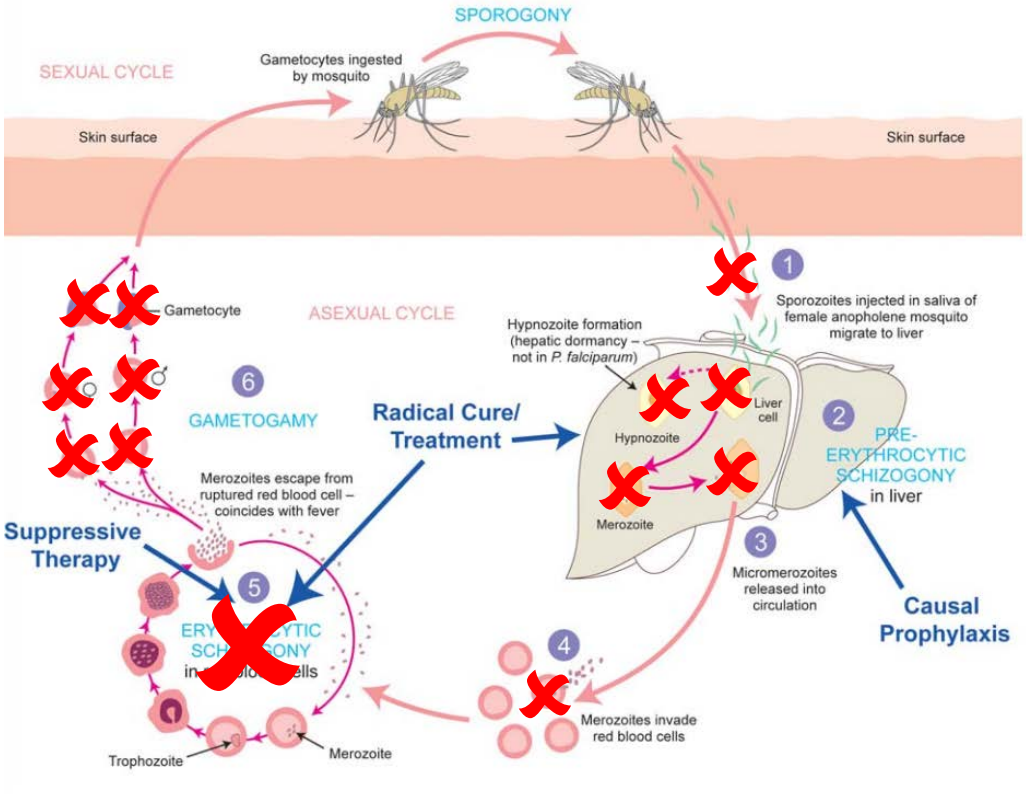
Malaria Lifecycle & Mode of Action of ARAKODA



ARAKODA is active against all the mammalian stages of malaria

- Exact mechanism of action is not known

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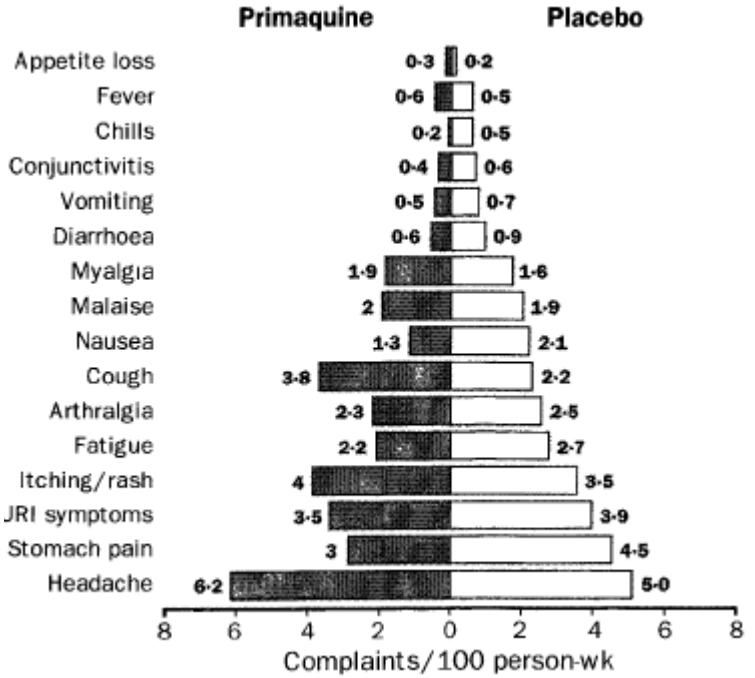
Tolerability of Primaquine for Malaria Prophylaxis

Adverse event	Primaquine No. of events	Primaquine Incidence density	Placebo No. of events	Placebo Incidence density	RR	95% CI	*P*
Headache	34	1.01	74	1.63	0.62	0.41–0.93	.02
Abdominal pain	34	1.01	33	0.73	1.39	0.86–2.23	.18
Cough	31	0.92	84	1.85	0.50	0.33–0.74	<.001
Nausea	20	0.59	34	0.75	0.79	0.46–1.38	.41
Dizziness	19	0.56	19	0.42	1.35	0.72–2.53	.36
Neck/back pain	18	0.53	19	0.42	1.28	0.67–2.42	.46
Cold/flu	18	0.53	30	0.66	0.81	0.45–1.45	.47
Pruritis	15	0.45	30	0.66	0.67	0.36–1.25	.21
Myalgia	15	0.45	22	0.49	0.92	0.47–1.78	.80
Fever	14	0.42	29	0.64	0.65	0.35–1.23	.18
Malaise	12	0.33	14	0.31	1.15	0.54–2.48	.72
Arthralgia	12	0.36	21	0.46	0.77	0.38–1.56	.47
Diarrhea	9	0.27	13	0.29	0.93	0.39–2.20	.87
Vomiting	9	0.27	8	0.18	1.51	0.59–3.89	.39
Chills	7	0.21	5	0.11	1.88	0.61–5.82	.27
Chest pain	6	0.18	6	0.13	1.35	0.44–4.14	.61
Sore throat	6	0.18	24	0.53	0.34	0.14–0.79	.01
Respiratory difficulty	5	0.15	15	0.33	0.45	0.17–1.20	.11
Anorexia	4	0.12	2	0.04	2.69	0.53–13.7	.23
Insomnia	5	0.15	3	0.07	2.24	0.56–9.0	.26

6 MO Baird (1992)



12 MO Fryauff (1995)

- **Primaquine and placebo equally well tolerated following daily administration up to 12MO**

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Adverse Event Labeling for Primaquine Prophylaxis

Adverse drug reactions. Most common mild/moderate adverse drug reactions (ADRs): abdominal pain, nausea, vomiting.

Severe hemolysis in persons with G6PD deficiency. Met-hemoglobinemia occurs, but is not reported to be clinically significant at dosages used for prophylaxis. In studies, 0-2% of persons have reported a severe reaction and 0-2% have discontinued prophylaxis because of ADRs.

No specific warnings for neuropsychiatric events

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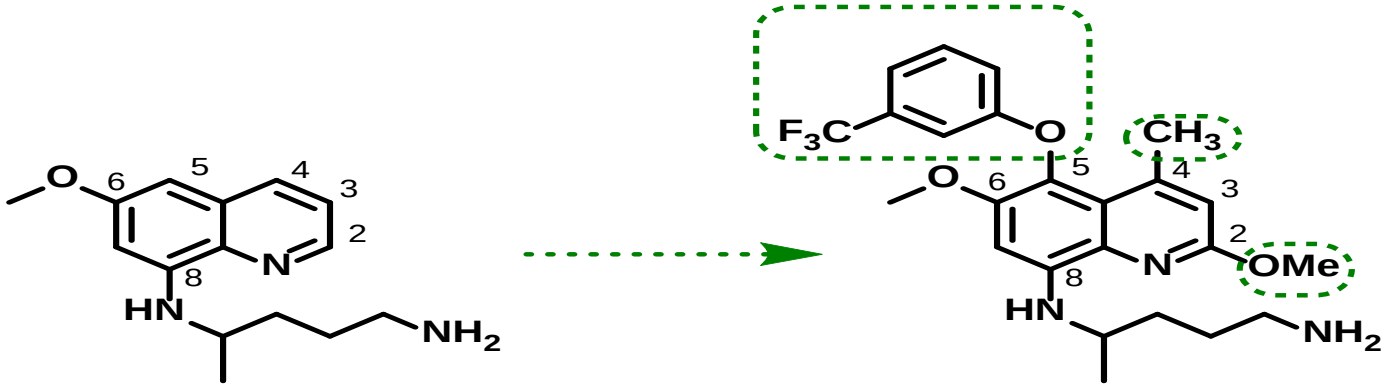
Hill (2006)

ARAKODA is an Improved Primaquine Analog



PRIMAQUINE

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

ARAKODA

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

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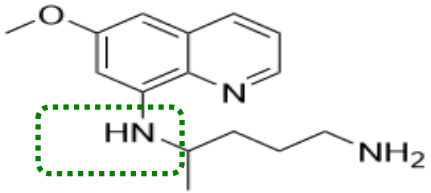
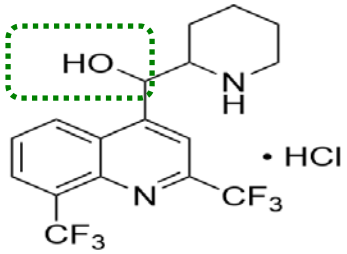
Primaquine and Mefloquine Act Differently



Primaquine

Defining Structural Feature



Mefloquine

Activation in vivo

ACTIVE OXIDATIVE SPECIES

DIRECT ACTION

PRIMAQUINE (8-AMINOQUINOLINE)

- Kills parasites following activation
- Kills hepatic stages
- Weak activity against blood stages
- No evidence of neurologic liability from clinical literature

MEFLOQUINE (4-QUINOLINE METHANOL)

- Direct antiparasitic effect
- No effect on hepatic stages
- Potent blood schizonticide
- Increases frequency of neuropsychiatric events relative to standard of care

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Important Clinical Studies of ARAKODA

Study	030	043	045	033	057	60PH02	60PH04
Year(s) Conducted	2000	1997	1998	1999-2000	2003-2006	2017	Ongoing
Study Design*	PC, MQ	MQ	PC, MQ	MQ	PC	PC	PC
Parameters Assessed	Safety & Efficacy	Safety & Efficacy	Safety & Efficacy	Safety & Efficacy	Safety	Efficacy & Safety	Safety
Population Characteristics (all Healthy Adults)	Residents of malaria-endemic area	Residents of malaria-endemic area	Residents of malaria-endemic area	Non-immune military population (deployed to malaria-endemic area)	Residents of US and UK	Residents of Australia	Residents of Australia
Study Location	Nyanza Province, Kenya	Nyanza Province, Kenya	Kassena Nankana District, Ghana	Bobonaro District and capitol (Dili) of East Timor (now Timor Leste)	Maryland, USA and Berkshire, UK	Brisbane, Queensland	Multiple sites in Australia and US
Number of Subjects (ARAKODA; Mefloquine (M); Placebo (P))	104 ARAKODA 101 MQ 101 PC	55 ARAKODA 0 MQ 61 PC	93 ARAKODA 46 MQ 94 PC	492 ARAKODA 162 MQ 0 PC	81 ARAKODA 0 MQ 39 PC	12 ARAKODA 0 MQ 4 PC	300 ARAKODA** 0 MQ 300 PC
Duration of Study Drug Dosing	24 weeks	10-15 weeks	13 weeks	26±4 weeks	24 weeks	10 days	52 weeks
Safety Follow-up after Study Drug Dosing	4 weeks	4 weeks	4 weeks	24 weeks	24 weeks	21 days	12 weeks

*All studies were randomized and double blinded, comparators were PC = placebo or MQ = mefloquine
**Size of Safety Database at filing: 825; Size of Safety Database at 60PH04 Completion: 1125

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Deployment is a Risk Factor for Neuropsychiatric Events

Psychologically-attributed war-related illnesses have included (Hyams (1996), Jones (2002)):

- **"nostalgia" (US Civil War);**
- **shell shock or trench neurosis (World War I);**
- **battle fatigue, combat exhaustion, or operational fatigue (World War II and the Korean Conflict);**
- **post-traumatic stress disorder (PTSD) (Vietnam War and Persian Gulf War)**

Diagnoses of mental illnesses, especially PTSD and depression, increased substantially among returned US military personnel who had been deployed to Iraq or Afghanistan (Seal (2009), Plumb (2014), McGlinchey (2017), Nissen (2017), Primack (2017), Qi (2016)).

In almost all studies of war-related illnesses, a suitable control population is unavailable, and the single unifying theme is that a unique (military) population is intensely scrutinized after experiencing an exceptional, life-threatening set of exposures (Hyams (1996)).

In the rare studies that do report on comparisons deployed and non-deployed personnel, or comparisons between pre- and post-deployment mental health status, these studies support a negative effect of deployment on mental health (Hermes (2014), Hom (2017), Jaksic (2017)).

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Timor Deployment Considered "Warlike" by Australian Government - Waller (2012)

- **Psychologically-attributed Study 033 – ADF deployed to East Timor (2000-2001), a "warlike" military operation. Australian government: "Warlike operations" = military activities where force is authorized and casualties are expected**
- **Specific traumatic exposures reported by ADF deployed to East Timor:**
  - **danger of being injured or killed (71% of ADF reported this);**
  - **witness to human degradation and misery on a large scale (58%);**
  - **saw dead bodies (49%) or handled dead bodies (28%);**
  - **feared 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%);**
  - **present when a close friend or co-worker was injured or killed (13%).**
  - **Other stressors: threat of danger (67%) and health concerns (52%).**
- **Among all ADF personnel deployed to East Timor: 7.2% developed PTSD and 6.9% had a long-term high level of psychological stress at 7-9 years after deployment**

Burden of Diagnosed Neuropsychiatric Illness Following Mefloquine and Malarone Administration in US Military Personnel

Antimalarial	Mefloquine		Malarone	
Deployment Status	**Not Deployed**	**Deployed**	**Not Deployed**	**Deployed**
Total Incidence of Neuropsychiatric Adverse Reactions per 1000 Person Years/Number of Personnel*	**58.59/ 10,847**	**98.27/ 25,691**	**57.92/ 10,261**	**98.46/ 2,620**
Increase Associated With Deployment (%)	**68%**		**70%**	

Individual Neuropsychiatric Endpoints:

- No statistical difference amongst deployed individuals
- Incidence of PTSD higher amongst non-deployed individuals administered mefloquine relative to Malarone

*Excluding tinnitus

Eick-Cost (2017)

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Important Nonclinical Studies of ARAKODA

Key Findings:

- **Comprehensive nonclinical safety package. All available information submitted to FDA and TGA for review.**
- **In the 35 *in vivo* acute and chronic dose toxicology studies (with mice – 2 years; rats – 2 years; dogs – 1 year) as well as 15 pharmacology studies (mice, rats, dogs, and monkeys), no neurotoxicity observed**
- **Major organ risk is lung (phospholipodosis, dog only), liver (centrilobular inflammation, apoptosis and fatty change, increased plasma transaminases) and kidney (tubular nephrosis, necrosis, and dilation [rat only, 13 wks])**
- **ARAKODA:**
  - **has no safety pharmacology risk for lung and brain. No clinical risk to the heart from QT prolongation.**
  - **is not mutagenic**
  - **has a low risk of carcinogenicity to humans**
  - **is not teratogenic**

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Sponsor's Post-Marketing Requirements for ARAKODA

- **Long-Term Safety Study:**
  - Evaluate safety and tolerability of ARAKODA versus placebo for 12 months (300:300)
  - Primary endpoint: Ophthalmologic safety
  - Psychiatric (MINI, LESQ, DHI, C-SSRS) and hematology assessments are secondary endpoints
  - Enrollment initiated October 2017
- **Health Database Outcomes Study:**
  - Document rates of diagnosed neuropsychiatric events in travelers (e.g. through Tricare)
  - Local standard of care as comparator
  - Conduct analysis once first 10,000 ARAKODA prescriptions have been recorded
- **Pediatric Study:**
  - Age and weight de-escalation study in a malaria endemic country
  - Placebo versus ARAKODA for up to 6 months
  - Pediatric subjects 0-18 years of age

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Malaria and Neurotoxicity

Parameter	Malaria Patients With No Pre-Existing Neurologic Condition	Malaria Patients With Pre-Existing Neurologic Conditions
N	40,799	105
Number of neurologic adverse events within 30 days of malaria	17	6
Incidence	0.04%	5.7%
Approximate Relative Risk Pre-existing v No Pre-Existing Condition	~140	

Ric Price et al – unpublished data

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Tafenoquine Indications

Details	Radical Cure of *Pv* Malaria	Prevention of *Pf/Pv* Malaria
Sponsor	GlaxoSmithKline	60 Degrees Pharmaceuticals LLC
Tablet Strength	150 mg	100 mg
Dose	300 mg	600 mg at steady state for six months
Comedication	Chloroquine	None
Symptomatic Malaria	Yes	No
Warning Language Required for Psychiatric AEs	Yes?	No?

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Sponsor's Agenda

The Sponsor Will Address the Following Issues:

- **Unmet Medical Need for ARAKODA - Military and Civilian Travelers**
  - Dr. Stephen Toovey
  - Mark Reid
- **Efficacy**
  - Dr. Jonathan Berman
- **Safety**
  - Dr. Bryan Smith
- **Neuropsychiatric Safety**
  - Dr. Geoffrey Dow
- **Benefit/Risk**
  - Dr. Stephen Toovey

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Unmet Medical Need

Stephen Toovey, MD, PhD

Infectious and Tropical Disease Physician

Mark Reid, MBA

ADF Veteran

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Malaria Disease in Non-Immunes

- ***Pf*** **a progressive disease in non-immunes**
- ***Pv*** **is an increasingly important threat**
- **US travelers are predominantly non-immune**
- **More recent arrivals to US suffer waning immunity and may be at risk when returning to countries of origin to visit friends and relatives – known as 'VFR' travellers**
- **Prevention including chemoprophylaxis has a positive Benefit:Risk ratio**

Chemoprophylaxis Prescribing Considerations

- **Malaria risk and destination**
- **Efficacy in clinical studies and effectiveness in the field i.e. outside of trial settings**
- **Age, gender, duration, activities and accommodation, pregnancy, comorbidities, comedication, itinerary**
- **Absolute and relative contraindications**
- **Adherence**
  - Safety & tolerability
  - Dosing frequency
  - Duration of post exposure use
  - Total tablet/pill burden
  - Persistence of prophylactic blood levels allows a patient to be “late” with a dose

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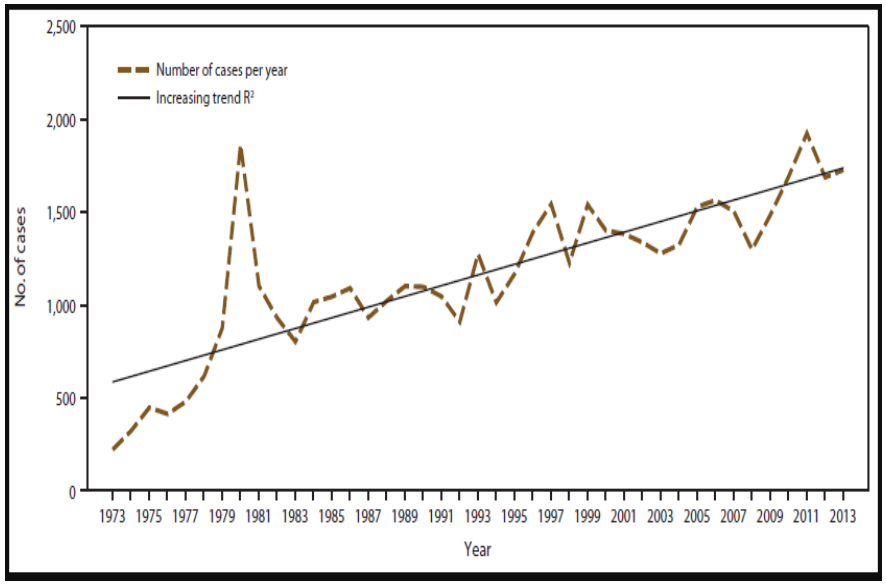
US Malaria Burden in Civilian Travelers



- 96% of cases are due to poor adherence
- Analysis of Cullen et al data
- <u>Burden is civilian dominated and increasing</u>
- Demonstrates importance of adherence
- Supports need to make adherence easier and missed dosing more forgiving i.e. use of long half-life agents

Cullen (2013), MMWR Surveill Summ (2016), CDC Yellow Book (2018)

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No Ideal Chemoprophylactic Agent

Summary of Considerations for Choosing a Drug for Malaria Prophylaxis (CDC) in Regions where Chloroquine-resistant *P. falciparum* Exists. Currently licensed agents (CDC).

Drug	Prophylactic Efficacy	Resistance May Diminish Efficacy	Requires Daily Dosing	Continued dosing after travel	Notable side effects	Contraindications or issues with pre-existing illnesses
Malarone	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

Weekly vs Daily Regimen Preferences

- **Favoring weekly**
  - Phillips 1996 - civilians
  - Shamiss 1996 - military
  - Hoebe 1997 - civilian
  - Lobel 2001 - civilian
  - Sanchez 2003 - military
  - Somnez 2005 - military
  - Tan 2011 (CDC expert meeting report on doxycycline)
  - Saunders 2015 - military
  - CDC 2018 on PK grounds
- **Weekly vs daily not important**
  - Stoney 2016 - civilian

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The Chemoprophylactic Armamentarium

- **Currently there are issues with all drugs and regimens**
- **There is no 'one size fits all' solution**
- **What do clinicians, travelers, and the health care system need?**
- **Need for new options**
  - Regimens with reduced dosing frequency and pill burden
  - Regimens with reduced post-exposure duration
  - Different safety profile especially improved neuropsychiatric profile

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Statement of Unmet Medical Need

- **No existing drugs/regimens have all of the following characteristics:**
  - Simple dosing regimen before and after travel
  - Efficacious everywhere for all major species of malaria
  - Acceptable safety profile

ARAKODA is Needed to Prevent Malaria

Anaesth Intensive Care 2001; 29: 426-434

Severe Falciparum Malaria in Five Soldiers from East Timor: a Case Series and Literature Review

P. G. BLUM*, D. STEPHENS†
Intensive Care Unit, Royal Darwin Hospital, Darwin, Northern Territory

SUMMARY

Despite chemoprophylaxis, malaria remains a serious threat for large numbers of non-immune soldiers deployed in endemic areas. Five adult cases of severe falciparum malaria are reported. Three cases were complicated by multi-organ failure and one of these patients died from cerebral malaria. These cases serve to highlight issues, in an

Mil Med. 2003 Jun;168(6):457-9.

An outbreak of malaria in a forward battalion on active service in East Timor.

Kitchener S[1], Nasveld P, Russell B, Elmes N.

Abstract

An outbreak of **malaria** first developed within Second Battalion Royal Australian Regiment, a forward (Australian) Battalion of the International Force in **East Timor** in October 1999. Before the Battalion redeployed to Australia, 17 **cases** had occurred and in the 12 months following return to Australia another 89 **cases** have occurred, including 18 single recurrences and 2 second recurrences. The overall attack rate for this deployment of 4 months, mostly including the wet season of **Timor**, has been 13.5%. The attack rate for the Battalion (5/7 Royal Austarlian Regimen) subsequently occupying this ground (for approximately 4 months and including the 12 months following redeployment) was 5.2%. Investigation of the initial outbreak and comparisons with the subsequent Battalion suggest major risk factors for contracting **malaria** were side effects from doxycycline, involvement in night operations, lack of preventive medicine support, and the location of platoon positions.

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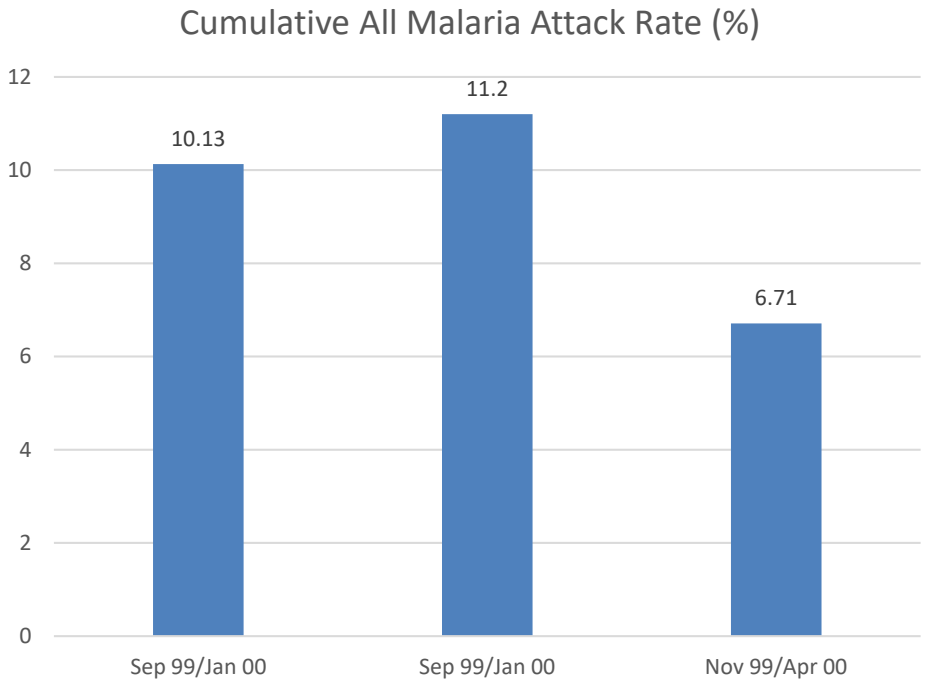
ARAKODA Use in Military Population

Key Findings:

- First time Australian Army completely stopped malaria (in country) in Infantry unit was Study 033
- **Indonesian TNI battalion opposing Aust. 1 Bn on the border had soldiers die from *Pf* (using unobs. Fansidar®)**
- Requested use of Tafenoquine from the PI during border meeting
- Weekly medication has military advantages (esp. with long half life, if doses are missed during high intensity ops and irregular meal/sleep timings the soldier can still be protected)



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Efficacy

Jonathan Berman, MD, PhD

Senior Vice President for Clinical Affairs

Fast-Track Drugs & Biologics, LLC

Derivation of the Recommended Prophylactic Regimen

- **Loading: 200 mg/day x 3 days**
- **Maintenance: 200 mg once weekly**
  - While in the endemic region and for 1 week thereafter
- **This recommendation covers the 2 periods over which prophylaxis is needed**
  - While in the endemic region
  - Post-exposure prophylaxis

Derivation of the Recommended Prophylactic Regimen: Exposure Levels Needed for Efficacy

- **Concentrations when non-immune/mixed-immunes failed:**
  - **48, 20, 38, 21, 20 ng/mL**
- **Concentration when no failure in mixed immune study**
  - **>55 ng/mL**
- **Precautionary concentration for successful prophylaxis**
  - **Trough concentration > 80 ng/mL**

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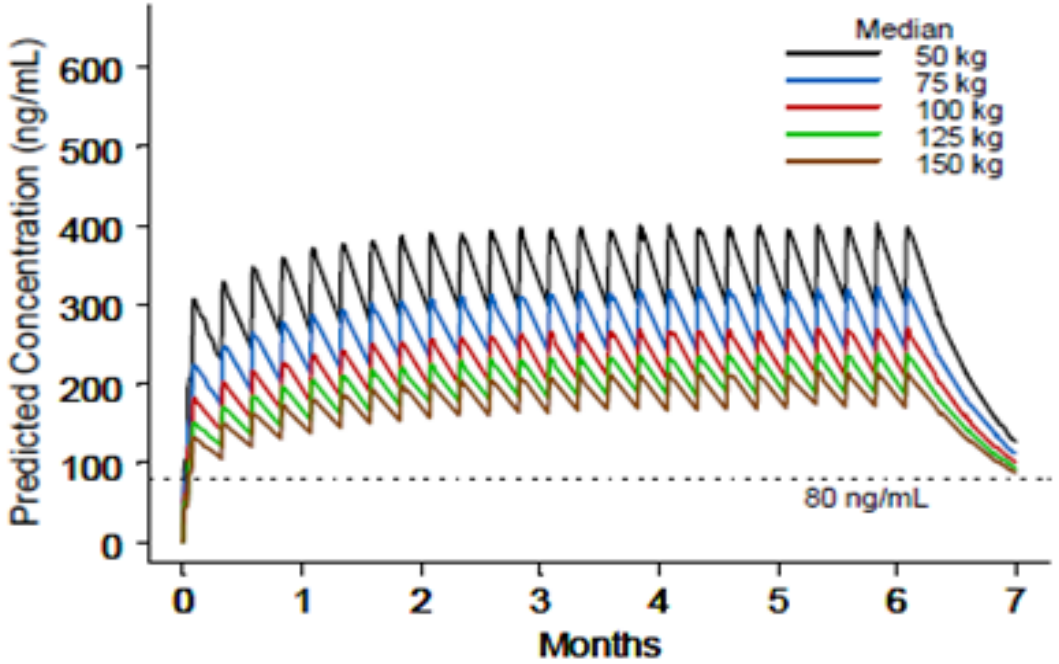
Derivation of the Recommended Prophylactic Regimen: 200 mg Dose Level

- **Study 043**
  - **200 mg per dose: PE = 88%**
  - **400 mg per dose: PE = 90%**
- **200 mg regimen better tolerated than the 400 mg regimen**
- **200 mg regimen chosen since it was the highest dose level that was well tolerated**

Pharmacokinetics of ARAKODA at Different Weights

Predicted ARAKODA Concentrations versus Time after 3 × 200 mg Once-Daily Loading Doses Followed by 200 mg Once-Weekly for Approximately 6 Months



Malaria Prophylactic Study: Ideal

- **ARAKODA vs positive comparator vs placebo in a large non-immune population**
- **Essentially impossible to conduct ideal study**
  - For a rapidly mortal disease in non-immunes, a placebo-group in a field trial is ethically questionable

Malaria Drug Guidance 2007

3 Alternative Study Designs

- **Comparator-controlled study in non-immunes**
  - Interpretation difficult because of the need to use “historic” rate of placebo infection
- **Placebo-controlled trial in malaria endemic communities**
  - Interpretation difficult because of the unknown contribution of immunity to drug effect
- **Placebo-controlled Challenge Study in non-immunes**
  - Interpretation difficult because of unknown relationship of the 1 parasite to the multiplicity of parasites in the field
- **[Treatment studies also suggested]**

Prevention of Malaria while in the Endemic Region: at Least One Study with Each Mentioned Design

- **Study 033: Active comparator-controlled prophylactic trial in non-immunes**
  - ARAKODA vs mefloquine for the prophylaxis of *Pf* and *Pv* malaria in non-immune Australian soldiers deployed to Timor Leste
  - Good estimate of placebo control rate
- **Study 043: Placebo-controlled prophylactic trial in semi-immunes**
  - Placebo-controlled comparison of ARAKODA for semi-immunes in Kenya
- **Study 045: Placebo-controlled prophylactic trial in semi-immunes**
  - Placebo-controlled evaluation of ARAKODA compared to mefloquine for chemoprophylaxis of *Pf* in northern Ghana
- **[Study 058: *Pv* treatment]**
  - Naturally infected semi-immune Thais
- **[Study TQ-2016-02: *Pf* Treatment]**
  - Non-immunes in a human challenge model

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FDA Efficacy Summary

- **Studies 043 and 045**
  - "were conducted in semi-immune subjects ...
  - Compared with the placebo group, ARAKODA demonstrated statistically significant protection against the incidence of parasitemia"
- **Study 033 (ARAKODA vs Mefloquine in non-immune subjects)**
  - "FDA analysis showed no observed cases of malaria during the prophylactic phase of the trial…
  - "The Applicant references literature that documents the incidence of malaria in East Timor. It states that though this is not conclusive evidence of exposure to malaria in Study 033,
    - It does show that there is a high likelihood that subjects in Study 033 were exposed to both *P. falciparum* and *P. vivax*
    - The FDA agrees with this assessment"

Study 045 Design/Demographics

- **Treating existing parasitemia with quinine / doxycycline / primaquine during the "radical cure phase"**
- **Randomized to ARAKODA (200 mg), Mefloquine (250 mg), Placebo**
  - For each group: 3 days loading dose then weekly for 12 weeks
- **Primary analytic population**
  - Completed radical cure, completed the loading period, received at least one dose of weekly prophylactic medication, had at least one efficacy assessment
- **ARAKODA group**
  - Mean 38 yrs; Weight 45 (F)-54 (M) (35-72) kg; Male 71%; African 100%

Study 045 Results

ARAKODA has a Protective Efficacy (PE) of 86%

Group	N	Failures (%)	PE
Placebo	94	86 (92%)	--
ARAKODA (200 mg)	91	12 (13%)	86%
Mefloquine	46	6 (13%)	86%

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Study 045: ARAKODA Non-inferior to Mefloquine

- **Failure rates**
  - ARAKODA: 12/91 --- 13.1 %
  - Mefloquine: 6/46 --- 13.0 %
  - Difference (ARAKODA – Mefloquine): 0.1% [95% CI (-11%, 14%)]
  - Placebo : 86/94 --- 92%
- **Efficacy margin = [Placebo failure rate – Mefloquine failure rate] = [92%-13%] = 79%**
- **If we assume that the non-inferiority margin is 25% of the efficacy margin of 79%, the non-inferiority margin would be 19.75%**
- **The upper limit of the 95% CI of the difference between ARAKODA and mefloquine is 14%, which is below the non-inferiority margin**
- **Conclude that ARAKODA is non-inferior to mefloquine**

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Study 033: Design/Demographics

- **ARAKODA vs Mefloquine for prophylaxis of both *Pf* and *Pv* in non-immune Australian soldiers deployed to Timor Leste**
- **Prophylactic Phase (26 weeks) followed by Relapse Follow-up Phase (24 weeks)**
  - During deployment (Prophylactic Phase) subjects received either ARAKODA 200 mg or Mefloquine 250 mg
  - On return to Australia (Relapse Follow-up Phase), Mefloquine group received 14 days of Primaquine (15 mg bid) while ARAKODA group received placebo
- **Prospectively defined primary analytic population**
  - Per protocol population
- **Primary endpoint: Failure ("prophylactic failure")**
  - A microscopically-confirmed positive smear (any species)
  - Concurrent clinical signs and symptoms consistent with malaria infection
- **ARAKODA group**
  - Mean age 25 yrs; Weight = 81 (50-135) kg; 97% Male; 99% White

Study 033 Results

All subjects were prophylactic successes during the prophylactic phase

Group	N	Deployment/Proph	Relapse	
		# Fail (%)	# Fail (%)	Week
ARAKODA	462	0 (0)	4 (0.9)	12-20
MQ/PQ	153	0 (0)	1 (0.7)	13
"Placebo" Controls (Historic Values)		*Pv*: 4.06% to 6.88% *Pf:Pv ratio:* 0.15:0.74 *Pf* + *Pv*: 4.6% to 12%	3 (0.6%)	7-12M

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Study 033 Prophylactic Phase: ARAKODA non-inferior to Mefloquine

- **Failure rates**
  - ARAKODA: 0/462 = 0% [95% CI (0%, 1%)]
  - Mefloquine: 0/153 = 0% [95% CI (0%, 2.4%)]
  - Difference (ARAKODA – Mefloquine): 0% [95% CI (-2%, 1%)]
- **Historical control: failure rate = 4.6% to 12%**
- **Efficacy margin = [“Placebo” failure rate – MQ failure rate] = [4.6%/12% - 0%] = 4.6% to 12%**
- **The upper limit of the 95% CI of the difference between ARAKODA and mefloquine is 1%, which is a small fraction of all efficacy margins**
- **Conclude that ARAKODA is non-inferior to mefloquine**

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In Country Prophylaxis: Summary

- **Study 033 for *Pv* and *Pf* in non-immunes**
  - ARAKODA had efficacy identical to that of the standard mefloquine comparator: no subject had parasitemia in either group over 6 months of prophylaxis
  - Historic "placebo" control data indicate that subjects would have become infected with *Pv* and *Pf*
- **Study 045 for *Pf* in semi-immunes**
  - PE compared to placebo was 86% for ARAKODA and 86% for mefloquine

In both studies: ARAKODA was non-inferior to mefloquine

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Post-Exposure Prophylaxis Summary

- **Requirements**
  - Dormant liver forms (hypnozoites)
    - ARAKODA effective in Study 033, Study 049, and Detective/GSK reports
  - Initial liver and blood stages [if parasite challenge in week prior to exit]
    - Extend protection by 1 week with 1 dose post-endemic region
- **Post-Exposure: 1 ARAKODA dose compares favorably to:**
  - Mefloquine x 4 weeks, plus Primaquine (14d)
  - Malarone x 1 week, plus Primaquine (14d)

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Safety

Bryan Smith, MD

Chief Medical Officer

60 Degrees Pharmaceuticals, LLC

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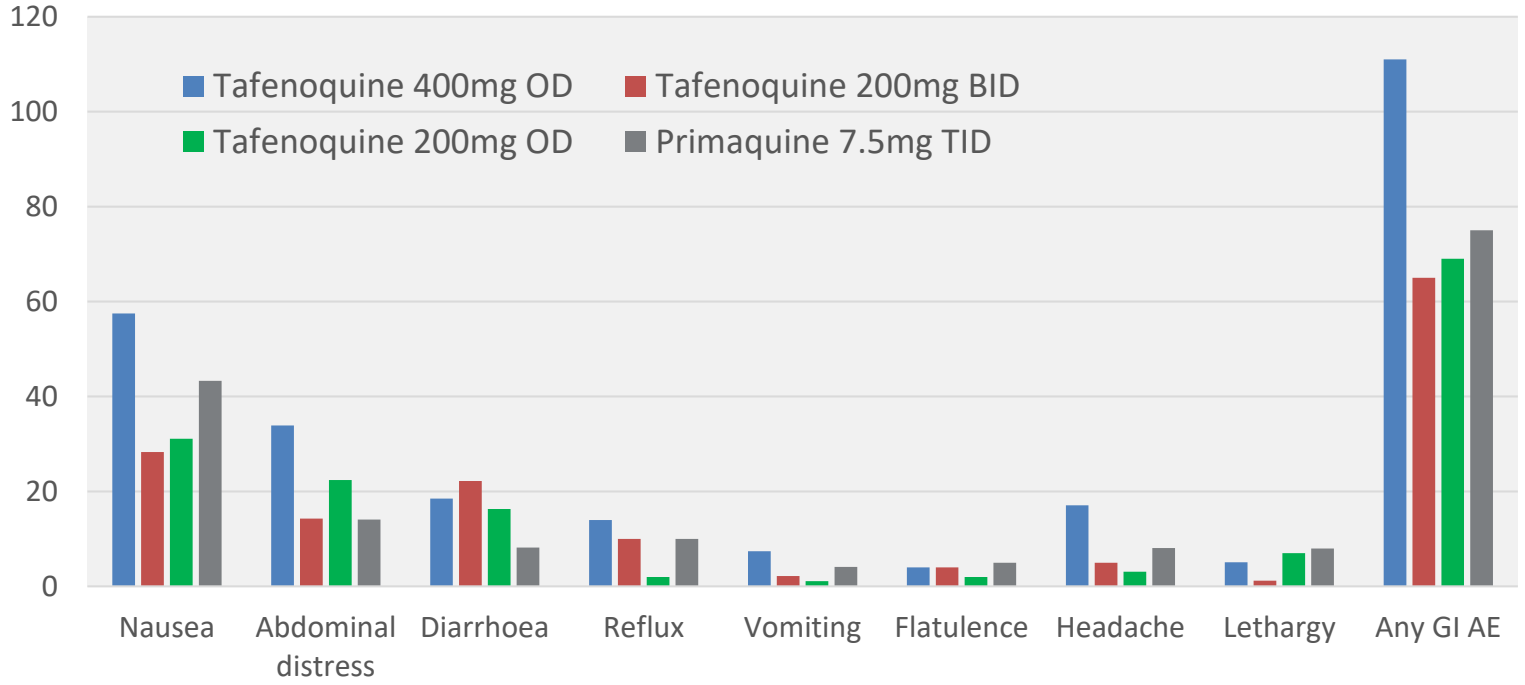
Dose Selection Based on Tolerability

Comparison of the rates of AE (%) between healthy subjects administered **3d courses of ARAKODA** and a **14d course of primaquine plus doxycycline** for post-exposure *P. vivax* malaria prophylaxis



Elmes (2008)

Safety Database, Populations, Assessments

- **Total of 3184 subjects** were exposed to ARAKODA
- Recommended Prophylactic Regimen was administered to **825 subjects** (mostly healthy volunteers)

	ARAKODA			Mefloquine	Placebo
	All Studies	Deployed Military	Non-Deployed Residents		
Studies	030, 033, 043, 045, 057	033	030, 043, 045, 057	030, 033, 045	030, 043, 044, 045, 057
n	825	492	333	309	396

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Exposure to the ARAKODA Recommended Prophylactic Regimen

In ARAKODA Subjects:

- **Mean duration of exposure was 21.2 weeks; more than 57% of subjects received exposure ≥24 weeks**
- **Maximum duration of exposure was 29.6 weeks**
- **Mean number of study doses was 23.8**

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No Treatment-Related Deaths

ARAKODA Program Overall - Only one unrelated death (Study 045)

Summary: 53-year-old Black male (study group: ARAKODA 50 mg weekly) was hospitalized for abdominal pain at 75 days after his first ARAKODA dose. Pain had been present prior to study entry, but this was not disclosed to investigators. In the Ghanaian hospital, no tests were carried out, and the subject was discharged with the presumed diagnosis of hepatocellular carcinoma (recorded as an SAE). ARAKODA was stopped, and the subject was withdrawn from the study. At 131 days after his last ARAKODA dose, the subject expired; no autopsy was performed.

The investigator reported the death as due to suspected hepatocellular carcinoma, unrelated to ARAKODA.

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Treatment-Related AEs Leading to Discontinuation

ARAKODA vs Placebo

- **Among the 34 withdrawn subjects who received the ARAKODA recommended prophylactic regimen (n=825), only 16 (1.9%) were discontinued due to AEs that were considered "possibly" or "probably" related to ARAKODA**
  - No discontinuations were considered "definitely" related to ARAKODA
  - Six subjects were discontinued due to "ALT increased" > 41 U/L (upper limit of normal)
    These were removed per-protocol in Study 045 with peak ALTs of 47 U/L, 51 U/L, 61 U/L, 68 U/L, 82 U/L, and 145 U/L.
  - Minus the 6 subjects discontinued for increased ALT, discontinuations drop to 10 (1.2%)
- **In comparison, 4 (1.0%) of Placebo subjects (n=396) were discontinued due to AEs considered possibly, probably, or definitely related to study drug**

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Overview of AEs: ARAKODA vs Placebo

	ARAKODA (200 mg x 3 days, then 200 mg weekly)			Placebo
	ARAKODA Overall (n=825)	Deployed ADF (n=492)	Non-Deployed Residents (n=333)	(n=396)
Total Number of AEs	3496	2204	1292	1298
Mild, n (%)	3026 (86.6%)	1864 (84.6%)	1162 (89.9%)	924 (71.2%)
Moderate, n (%)	423 (12.1%)	317 (14.4%)	106 (8.2%)	112 (8.6%)
Severe, n (%)	35 (1.0%)	22 (1.0%)	13 (1.0%)	19 (1.5%)
Not Graded, n (%)	12 (0.3%)	1 (0.05%)	11 (0.9%)	243 (18.7%)
Subjects with at Least One AE, n (%)	692 (83.9%)	467 (94.9%)	225 (67.6%)	258 (65.2%)
Subjects with SAEs, n (%)	47 (5.7%)	26 (5.3%)	21 (6.3%)	17 (4.3%)
Treatment-Related SAEs, n (%)	22 (2.7%)	11 (2.2%)	11 (3.3%)	9 (2.3%)

AEs Occurring in ≥1% of Subjects

The table presents AEs occurring in ≥1% of subjects in the ARAKODA group and with an incidence numerically greater than in the Placebo group.

Adverse Reaction	ARAKODA Total Population (N=825)	ARAKODA Non-Deployed 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%)

*Early reports of corneal deposits thought to be secondary to phospholipidosis 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.

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AEs Occurring in ≥1% of Subjects (continued)

Adverse Reaction	ARAKODA Total Population (N=825)	ARAKODA Non-Deployed Subjects (N=333)	Placebo (N=396)
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%)

AEs Occurring in ≥1% of Subjects (continued)

Adverse Reaction	ARAKODA Total Population (N=825)	ARAKODA Non-Deployed Subjects (N=333)	Placebo (N=396)
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%)
Impetigo	8 (1.0%)	0	0
Tinea infection	9 (1.1%)	2 (0.6%)	0

GI Adverse Events of 8AQs Are Locally Mediated

- **GI effects of primaquine ameliorated if taken with food, despite greater bioavailability** Hill (2006)
- **GI effects of ARAKODA less frequent with food following a single dose of 400 mg (Study 003)**
- **GI inflammation observed at necropsy following administration of 12 mg/kg x 4 days to Rhesus monkeys**

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GI Symptoms: No Evidence for Prodromal Link to Psychiatric AEs

- **Among 825 subjects who received the ARAKODA prophylactic regimen, only 4 of the 32 subjects with a Psychiatric AE also had nausea or vomiting**
- **Only 1 of 825 subjects had nausea or vomiting that preceded their reported psychiatric AE**

Study	No. Subjects with Any Psychiatric AE	No. Subjects with Any Psychiatric AE and also Nausea or Vomiting	No. Subjects where Nausea or Vomiting Preceded the Psychiatric AE
030	1	0	--
033	25	3	0
043	2	0	--
045	0	0	--
057	4	1	1
Total	32	4	1

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Ophthalmologic Disorders

	Number (%) of Subjects	
	ARAKODA 200 mg daily x 3 days, then 200 mg weekly (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
Number (%) of Subjects with Ophthalmologic SAEs	7 (0.8%)	1 (0.3%)
Keratopathy (corneal deposits)	5 (0.6%)	0
Retinal disorder	2 (0.2%)	0
Metamorphopsia	0	1 (0.3%)
Ophthalmologic AEs Occurring in ≥ of Study Subjects		
Conjunctivitis	24 (2.9%)	18 (4.5%)
Keratopathy (corneal deposits)	68 (8.2%)[a]	0

[a]All reports are from Study 033

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Keratopathy and Retinal Changes: Fully Reversible with No Impact on Vision

- **Early Short-Term Dosing Trials – Keratopathy (benign, reversible) seen at ARAKODA supratherapeutic doses >400 mg**
- **Study 033 (ARAKODA) – Detailed eye exams showed fully reversible vortex keratopathy with no effect on vision; 2 cases of retinal disorders were mild granularity/pigmentation of retinal pigment epithelium, hard drusen with no effect on vision**
- **Study 057 (Eye Safety Study): ARAKODA vs Placebo for 6 months**
  - Objectives: Specifically assess night vision effects – assessments included
  - Forward light scatter (FLS), low contrast visual acuity (LCVA), mesopic contrast threshold (MCT), and scotopic contrast threshold (SCT)
  - Results:
    - New-onset corneal deposits: 15 (21.4%) of ARAKODA subjects vs 4 (12.5%) of Placebo
    - No FLS test failures in either treatment group
    - LCVA, MCT, and SCT: Similar findings for ARAKODA and Placebo
    - Resolution of keratopathy: 95% of cases by Week 12; 100% by Week 48

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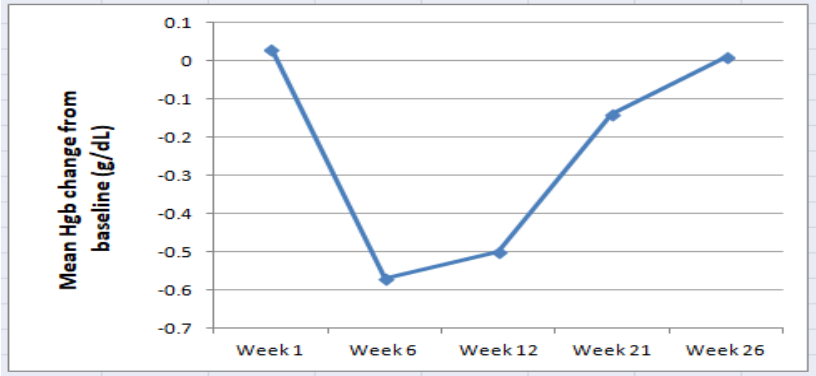
Hematologic Changes

Adverse Reaction	ARAKODA 200 mg daily x 3 days, then 200 mg weekly (n=825)	Placebo (N=396)
Hemoglobin Decreased ≥0.66 g/dL	496 (60.1%)	166 (41.9%)
Hemolytic anemia*	2 (0.2%)	0
Methemoglobin ≥1%	115 (13.9%)	3 (6.0%)
Methemoglobin ≥10%	0	0

*≥15% decrease from baseline in Hgb or Hct, together with a ≥50% decrease from baseline in haptoglobin.

Study 033 ARAKODA GROUP
Change in Hemoglobin Over Time



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Primaquine in G6PD Deficiency: Risk for Hemolysis

Hemolysis depends on primaquine dose and G6PD deficiency Variant – WHO (2016)

- Mild hemolysis for A- variant (Class III = Moderate)
- Severe for Mediterranean (Class II = Severe)

Dose Regimen	Cumulative Dose	G6PD Deficiency Variant	Variant Class*	Outcome
0.25 mg/kg once	0.25 mg/kg	Any variant	Any	Usually well tolerated
0.25-0.50 mg/kg x 14 days	3.5 -7.0 mg/kg	A-	III	Hemolysis evident after 1-2 days. If drug is continued, hemolysis lessens and Hgb rises as reticulocyes enter circulation.
		Mediterranean	II	Hemolysis evident after 1-2 days. If drug is continued, hemolysis continues and may cause life-threatening anemia.

*Class II = Severe (enzyme activity <10% of normal); Class III = Moderate (enzyme activity 10-60% of normal)

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ARAKODA in G6PD Deficiency: Risk for Hemolysis

Hemolytic Effects with ARAKODA (n=13, all females) were Similar to Primaquine

- Low doses = Asymptomatic with no hemolysis or limited hemoglobin (Hgb) decrease
- Cumulative Doses > 1200 mg = More severe anemia
- Even Class II G6PD-deficient patients were asymptomatic at low doses of ARAKODA

Dose Regimen	Cumulative Dose	G6PD Deficiency Variant	Variant Class	Outcome
≤8 mg once	≤8 mg (n=6)	A- Intentional enrollment in Study 001	III	Asymptomatic. No hemolysis
300 mg once	300 mg	Mahidol	III	Asymptomatic. No hemolysis
300 mg once	300 mg	Vanua Lava	II	Asymptomatic Hgb decrease of 2.1 g/dL
600 mg once	600 mg	A-	III	Asymptomatic Hgb decrease of 1.9 g/dL
450 mg x 2 days	900 mg	A-	III	Asymptomatic Hgb decrease of 3.0 g/dL
450 mg x 2 days	900 mg	Santa Maria	II	Asymptomatic Hgb decrease of 2.8 g/dL
400 mg x 3 days	1200 mg	A-	III	Anemia (Hgb of 9.1 g/dL). Treated with OTC iron and folic acid. Resolved in 2 months.
400 mg x 3 days	1200 mg	A-	III	Hemolytic anemia, hospitalized, transfused, recovered

Psychiatric AEs by ARAKODA Sub-Group

	Placebo	ARAKODA 200 mg daily x 3 days, then 200 mg weekly		
		All Subjects	Deployed ADF Military (ADF) Subjects	Non-Deployed Subjects
	(n=396)	(n=825)	(n=492)	(n=333)
Number (%) of Subjects with Injury, Poisoning, and Procedural Complications	23 (5.8%)	231 (28%)	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*	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%)

*"Related" includes unlikely, possibly, probably, or definitely related

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Neuropsychiatric Safety

Geoffrey Dow, PhD

Chief Scientific Officer & CEO

60 Degrees Pharmaceuticals, LLC

Advocacy Community Believes Tafenoquine is Neurotoxic

"Quinism Foundation is a new 501(c)(3) nonprofit organization established to support education and research on chronic quinoline encephalopathy and other medical conditions caused by poisoning, or intoxication, by mefloquine and related quinoline drugs, including tafenoquine — a new quinoline drug, even more neurotoxic than mefloquine — now under review by international drug regulators."

www.quinism.org

Concerns of Advocacy Community

- **Mefloquine is neurotoxic in rats and tafenoquine has a lower EC50 *in vitro* against rat neurons:**
  - Agaboruche et al 2009 FASEB Journal 23 (Meeting Abstract Supplement): 529.3.
  - Dow et al 2006;50:1045-53
- **Some 8-aminoquinolines found to be neurotoxic in humans and Rhesus monkeys in the 1940s:**
  - Schmidt & Schmidt J Neuropathol Exp Neurol. 1948;7:368-398
  - Schmidt & Schmidt J Comp Neurol. 1949;91:337-67
  - Schmidt & Schmidt J Neuropath Exp Neurol 1951;10:231-256
  - Craige et al J Clin Invest 1947;27:17-24
  - Loken Am J Trop Med Hyg 1949;29:341-52.
- **Adverse events reported to TGA by veterans' groups 16+ years following completion of clinical trials**
- **GI distress alleged to be centrally mediated (and thus prodromal for neurotoxicity)**

Neurotoxicity of Mefloquine, a 4-Quinoline Methanol

Mefloquine Induces Dose-Related Neurological Effects in a Rat Model

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Mefloquine is one of the drugs approved by the FDA for malaria chemoprophylaxis. Mefloquine is also approved for the treatment of malaria and is widely used for this purpose in combination with artesunate. However, the clinical utility of the compound has been compromised by reports of adverse neurological effects in some patients. In the present study, the potential neurological effects of mefloquine were investigated with six 7-week-old female rats given a single oral dose of the compound. Potential mefloquine-induced neurological effects were monitored using a standard functional observational battery, automated open field tests, automated spontaneous activity monitoring, a beam traverse task, and histopathology. Plasma mefloquine concentrations were determined 72 h after dosing by using liquid chromatography-mass spectrometry. Mefloquine induced dose-related changes in endpoints associated with spontaneous activity and impairment of motor function and caused degeneration of specific brain stem nuclei (nucleus gracilis). Increased spontaneous motor activity was observed only during the rats' normal sleeping phase, suggesting a correlate to mefloquine-induced sleep disorders. The threshold dose for many of these effects was 187 mg/kg of body weight. This dose yielded plasma mefloquine concentrations after 72 h that are similar to those observed in humans after the treatment dose. Collectively, these data suggest that there may be a biological basis for some of the clinical neurological effects associated with mefloquine.

Behavioral and permanent histopathological changes following single dose mefloquine administration in rats

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Neurotoxicity of Selected 8-Aminoquinolines

8AQ	TI* Monkeys	TI Humans	Clinical Signs Related to Brain Lesions	Onset of Clinical Signs Relative To Dosing (Days)
Plasmocid (PC)	0.19	~ 1	Nystagmus, loss of pupillary reflexes, motor coordination and equilibrium, death	≤ 2
Pentaquine (PT)	≤ 3.7	2	Syncope, persistent hypotension without other cause, erectile dysfunction, death	Humans < 28 Monkeys < 12
Pamaquine (PM)	9	8	Paralyzed palate, death	≤ 7
Primaquine	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**	NA

Therapeutic Index
***Hill (2006), Clayman (1952)*

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Sensitivity of Nonclinical Species to Plasmocid

Species	Minimum Lethal Daily Dose (mg/kg/day)/ Minimum Cumulative Dose (mg/kg) Causing Neurologic Signs or Lesions*	Human Equivalent Dose (mg/kg)**
Rhesus monkeys	4.5/3	1.4/0.96
Cynomolgus monkeys	< 3/6	< 0.96/1.9
Mangabey monkeys	24/72	7.7/23
Dogs	3/9	1.7/5.4
Rats	24/196	4/33
Mice	72/144	5.9/12

**From Schmidt (1948)*

***Calculated by dividing non-neurotoxic dose by the appropriate scaling factor from CDER (2005) Guidance for Industry: Estimating the maximum safe starting dose initial clinical trials in healthy adult volunteers. U.S. Department of Health & Human Services.*

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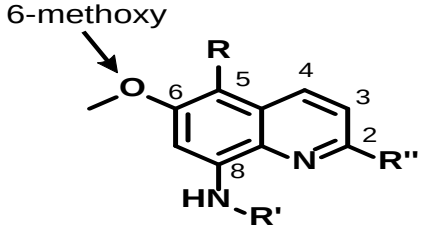
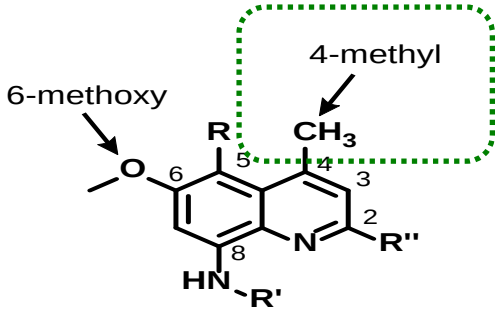
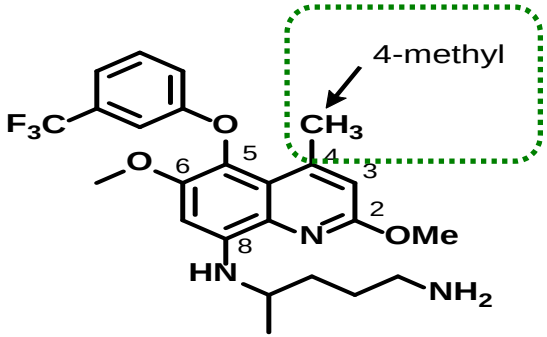
Structural Features Suggest ARAKODA Should Not be Neurotoxic in Rhesus Monkeys







In 6 pairs of matched 6 methoxy, 8-aminoquinolines, installation of a 4 position methyl group abolished neurotoxicity in Rhesus monkeys (data from Schmidt 1983, AAC 24:615-652)

ARAKODA is 4-methyl substituted and would not be expected to be neurotoxic in Rhesus monkeys or humans

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ARAKODA is Not Neurotoxic in Rats

Tafenoquine is not neurotoxic following supertherapeutic dosing in rats

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ABSTRACT

Background: Tafenoquine is a new drug for malaria prevention. The goal of the present work was to conduct a specific neurobehavioral study in rats with histopathological assessment of the brain.
Methods: The clinical, hematological, behavioral, motor activity, and neurohistopathologic changes induced by different dose levels of tafenoquine were evaluated following single super-therapeutic dose administration. Toxicokinetic data were generated to allow extrapolation to clinical exposures.
Results: At the highest dose (500 mg/kg), two animals (of 12) died. Surviving animals showed clinical signs of toxicity and had reduced body weight 7–8 days after dosing. Decreases in motor activity were observed on more than one occasion at doses > 9-fold higher than the clinical exposure. No statistically significant changes were observed for other behavioral endpoints. No neurohistopathological changes were noted. Changes in hematological and clinical pathology endpoints were observed at the lowest dose level (125 mg/kg). For context, the human dosing regimen is a 10 mg/kg load followed by 3.3 mg/kg weekly (in a 60 kg person).
Conclusions: As in humans, adverse events other than neurotoxicity were dose-limiting for tafenoquine in rats. This raises the prospect that a new weekly prophylactic, without neurologic liability, may become available in the near future.

GLP study employing modern staining techniques and ICH-approved behavioral endpoints

No evidence of brain lesions at 9x therapeutic exposures following single, maximum tolerated dose of tafenoquine

Changes in hematological endpoints observed at the lowest dose tested

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ARAKODA is Not Neurotoxic in Rhesus Monkeys

Total Cumulative Dose (mg/kg)*	N	Cmax (ng/ml)	Ratio of Cmax to Cmax of Therapeutic Dose***	Source	Clinical Signs****
1.8**	35	50	1	Dow (2011)	None
12	3	124	2.5	NDA 210607	None
24	3	284	5.5	NDA 210607	One animal vomited. No neurologic signs reported. Methemoglobin elevated
48 (non-lethal)	2	333	6.7	NDA 210607	Methemoglobin elevated
48 (lethal)	2	581	11	NDA 210607	Clinical signs included listlessness, vomiting, depression and poor appetite in two animals. Two animals died. Methemoglobin elevated. No specific neurologic signs observed. Hepatotoxicity observed at autopsy. The brain of one animal was examined post mortem – No abnormal findings were reported
7-22	45	No data	NA	Puri (2003), Dow (2011), Ditusa (2014)	No specific neurologic signs reported. Dow and Ditusa studies overseen by board-certified veterinarian

**Cumulative dose over 3-4 days. **Dose curing 95% of P. cynomolgi infections in combination with blood schizontocidal drugs. ***Calculated by dividing Cmax at dose of interest by Cmax at CD95. ****Monkeys in toxicokinetic observed closely for 4h following each of the 4 daily doses received.*

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ARAKODA is Not Neurotoxic Following Long-Term Exposure in Plasmocid-Sensitive Toxicological Species

Species	Longest Duration/ Maximum Daily Dose (mg/kg/day)/ Total Dose Administered (mg/kg)	CNS a Target Organ	Target Organs
Dogs	1 year/4/1460	NO	Lung, spleen, kidney, bone marrow, lymphoid tissue, liver
Rats	2 years/2/1460	NO	Lung, spleen, liver, bone marrow, kidney, liver, adrenal glands
Mice	2 years/1/730	NO	Blood, kidney, lung

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ARAKODA Does Not Exhibit Plasmocid-Like Neurotoxicity

Clinical Neurologic Signs Associated With Pentaquine, Pamaquine, and Plasmocid in Animals and Humans	ARAKODA Dose Number/%				Placebo Number/(%) N=396
	Phase 1 (4-600 mg) N=45	200 mg x 3 N=491	400 mg x 3 N=713	Recommended Dose N=825	
Nystagmus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coordination abnormal	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)[a]	0 (0.0)
Balance disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pupillary reflex impaired	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)[b]	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Erectile dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)
Areflexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]*Both subjects reported abnormal coordination at the beginning of the study (Day 0), suggesting pre-existing factors were at play. One subject had a history of spinal surgery, while the other had been using loratadine for 7 years.*
[b]*In both cases, there was a single episodes of syncope that was considered mild and unrelated to* ARAKODA.

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Psychiatric SAEs, Discontinuations, and Severe Adverse Events are Rare

Tafenoquine Dose	Subject	AE	Severity	SAE ?	Drug Withdrawn	Related to TQ	Mitigating Circumstances
Tafenoquine 200 mg loading then weekly	24 yo/ M/	Suicide attempt	Severe	Yes	Yes	No	Self injury ("took poison") while acutely intoxicated with alcohol and despondent over marital problems
Tafenoquine 350 mg x 3 days	22 yo/ M/	Acute psychosis	Severe	Yes	Yes	Possibly	History of 2 hospitalizations for psychiatric illness (not disclosed at screening). Acute psychotic episode reported as "possibly" related to study drug. However, described in CSR as "more likely to represent a manifestation of concomitant illness".
Tafenoquine 500 mg x 3 days	30 yo/ M/	Psychotic disorder	Severe	Yes	Yes	Unlikely	History of schizophrenia not disclosed at screening.
Tafenoquine 200 mg loading then weekly	28 yo/ M	Depression	Moderate	No	Yes	Possibly	History of intracranial head injury (closed head injury) that occurred 3 years prior to study entry.
Tafenoquine 400 mg x 3 days (loading)	23 yo/ M	Psychotic disorder	Moderate	Yes	Yes	Unlikely	After AE occurred, subject's psychiatrist informed investigators that subject had symptoms of psychosis prior to study entry. At screening, the subject did not report his history of psychosis.

Safety Database = 3,184 subjects

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15 Tafenoquine Studies (total n=1985) had No Psychiatric Exclusion: Studies 003, 006, 014, 015, 022, 040, 043, 047, 049, 050, 051, 052, 053, 057, 058

	Studies That Employed This Tafenoquine Dose						
Dosing Duration	≤200 mg Short Term	200 mg BID Short Term	Other >200 mg Short Term	200 mg x 3 days, then weekly	>200 once weekly	400 mg x 3 days, then weekly	No. of Subjects in Studies at this Duration
1 Day	022, 050, 052		003, 047, 050, 052, 053				166
3 Days	006, 049	049	014, 043, 049, 058				1509
3-Day DDI			015				28
1 Week			047				63
10 Weeks					051		24
10-25 Weeks				043		043	114
23 Weeks				057			81
Total No. Subjects in Studies at this Dose	811	161	794	136	24	59	1985

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Treatment-Related Psychiatric Adverse Events in 15 ARAKODA Studies with No Psychiatric Exclusion

Study	TQ Dose	AE/ Intensity	Relatedness	Other information
049	200 mg BID x 3 d	Insomnia/ Mild	Possible	
049	200 mg BID x 3 d	Insomnia/ Mild	Possible	
047	600 mg x 3 d	Insomnia/ Moderate	Possible	
043	400 mg x 3 d, then 400 mg weekly x 12 weeks	Insomnia/ Mild	Possible	
040	400 mg x 3 d	Disinhibition/ Mild	Possible	Drug cocktail study*
040	400 mg x 3 d	Euphoria/ Mild	Possible	Drug cocktail study*
043	200 mg x 3 d, then 200 mg weekly x 12 weeks	Neurosis/ Mild	Possible	Subject became anxious about having blood drawn
050	350 mg x 3 d	Psychotic Episode/ Severe	Possible	Undisclosed history of 2 hospitalizations for mental illness. AE onset (Day 24) when TQ levels low/ absent. ” investigator felt this was only remotely related to study drug and basically represented a concomitant illness”

*ARAKODA given following dosing with midazolam, flurbiprofen, and caffeine

Total Number of Subjects = 1,985

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ARAKODA in Study Subjects Taking Psychiatric Medications at Baseline

- In ARAKODA trials that had no psychiatric exclusions, 3 Subjects were enrolled while taking psychiatric medications at baseline
- None reported psychiatric AEs that were considered related to ARAKODA

Study	ARAKODA Dose	Subject	Psychiatric History	Psychiatric Medication at Baseline	Neuropsychiatric Outcome
001	TQ 8 mg, single dose	44 y.o. female	None known	Self-medicating with Diazepam, Promethazine, and Tramadol, (undisclosed to study personnel)	Moderate nervousness/irritability, duration <1 day. Not treated. "Not related" to study drug.
044	TQ 400 mg x 3d, then 400 mg monthly	21 y.o. male	Undocumented	Lorazepam	Subject discontinued Lorazepam during the study and reported no psychiatric AEs
045	TQ 25 mg x 3d then 25mg weekly	44 y.o. male	Anxiety	Diazepam	Subject discontinued Diazepam before starting ARAKODA and reported no psychiatric AEs

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Psychiatric Events Following Administration of ARAKODA Are Not Dose or Schedule Dependent

Psychiatric Adverse Events*	ARAKODA Dose** Number/%					Placebo Number/(%)	Mefloquine Number/(%)
	200 mg		400-600 mg	400 mg			
AE Start Day	1 - ≤3 Days	> 3 Days	Loading Only – 1 - ≤3 Days	Weekly > 3 Days	Monthly > 3 Days	1- ≤ 3 Days	1 - ≤3 Days
	N=340		N=778	N=62	N=104	N=528	N=149
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
Disinhibition	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Euphoric Mood	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	3 (0.4)	1 (1.6)	1 (1.0)	1 (0.2)	0 (0.0)
Neurosis	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sleep Disorder	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TOTAL	1 (0.3)	1 (0.3)	5 (0.6)	1 (1.6)	1 (1.0)	1 (0.2)	2 (1.3)

*Events considered possibly, probably, or definitely related to study medication

**Study 033 participants were excluded

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Summary of Adverse Events Reported to TGA

- **17 neuropsychiatric adverse events were reported to the TGA between February 18-23, 2017**
  - Reports made by or on behalf of ADF veterans who believe exposure to tafenoquine in clinical trials 16+ years earlier caused their neuropsychiatric events
- **4 of the more detailed cases were summarized in an INDSR report by GSK**
  - Case information allowed cross-referencing to study records for 049 and 033
- **12 of the remaining 13 cases had sufficient information to cross match to safety database:**
  - 8 of these cases were matched to study records for 033

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GSK INDSR Cases

Case	Study/ ARAKODA Dose	Weekly Doses Taken	Neuropsychiatric Events Reported to TGA	Adverse Events in Sponsor Database	Contributing Factors
1	049/400 mg x 3	NA	Encephalopathy onset not specified	None	NA
2	033/200 mg	27	Multiple neurologic disorders commencing 2007	None	NA
3	033/200 mg	26	Anger, anxiety, PTSD, panic attack, nightmare contemporaneous with dosing	None	NA
4	033/200 mg	27	Anger, mental disorder contemporaneous with dosing	Insomnia suspected related to treatment	Pre-existing, persistent shoulder injury treated with ibuprofen/diclofenac

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Sponsor Information on Other 8 Cases

- **No treatment-related neuropsychiatric adverse events recorded in Sponsor database for 7 of 8 cases where corresponding subject ID could be determined**

- **Neuropsychiatric events were captured in Sponsor database for one subject**
  - This subject reported 15 days of lethargy/somnolence that began 4 days after he received his final ARAKODA 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 ARAKODA dosing.

Future ARAKODA Use

Stephen Toovey, MD, PhD

Infectious and Tropical Disease Physician

ARAKODA for Prevention: Benefits & Risks

Balance of Benefit-Risk Favors Use for the Prevention of Malaria

Benefits

- **Not teratogenic/mutagenic**
- **Neurotoxicity not observed**
- **Causal prophylactic**
- **Active against all species**
- **No geographic limitations**
- **Prevent malaria fatalities**
- **Prevent severe disease**
- **Prevent malaria sequelae**
- **Adherence (weekly dosing)**
- **Single dose only post exposure**
- **Reduced pill burden**
- **Forgiving PK for missed doses**
- **Low drug-drug interaction risk**
- **Without QT concern**
- **Without neuropsychiatric liability of other antimalarials – suitable for sensitive activities in-country**
- **Overall acceptable safety and tolerability**

Risks

- G6PD induced hemolysis (risk can be managed)
- Adverse reactions (generally not disabling; reversible)

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Future ARAKODA Use

- **Likely frontline role in protecting travelers with increased adherence**
  - Private travelers
    - Short notice
    - Adequate notice
  - Business/frequent travelers
  - Long-term travelers/expatriates
  - Deployed military
- **Private short-notice travelers main group unlikely to use ARAKODA unless G6PD status known**
- **Military and business/frequent travelers would have induction G6PD testing**
- **Long-term travelers/expats would have G6PD test as part of pre-departure travel health preparation**
- **Global efficacy (*Pf* and *Pv*) will simplify selection by clinician**

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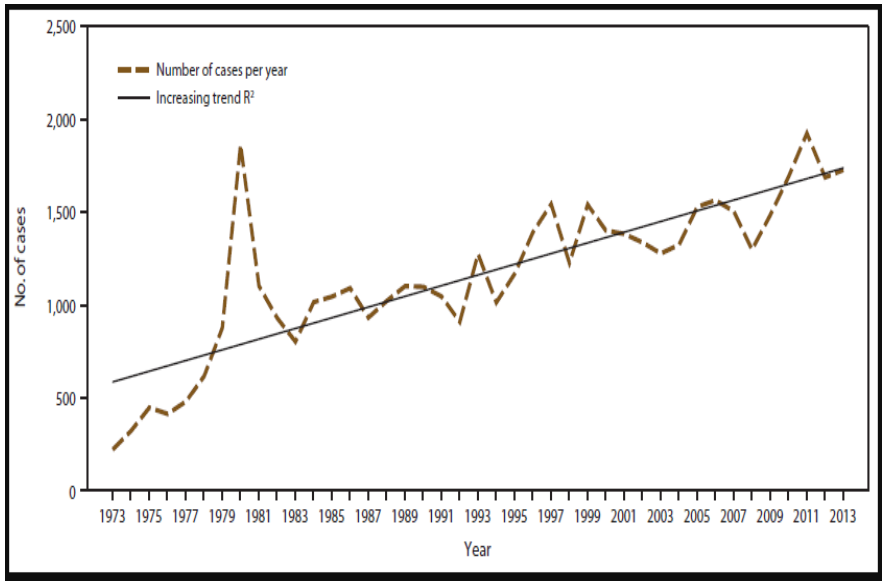
Reduce the Malaria Burden in US Travelers



Cullen (2013), MMWR Surveill Summ (2016), CDC Yellow Book (2018)

For the traveler:

- Adherence a key issue with all travelers
- Civilian regimens especially need to be simple and 'forgiving'
- But, even military populations prefer simple weekly regimen *(Saunders 2015)*
- Friendly to frequent and business travelers

For the prescriber:

- Ideally should simplify prescriber decision making
- Need for drug that 'works everywhere'
- Need for more prophylactic antimalarials
- Need for well tolerated agents
- Need for simple 'forgiving' regimen

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Backup Slides Shown

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Immune System Disorders (Hypersensitivity) at Any Tafenoquine Dose

Dose	AE Description	Intensity/ SAE	Treatment	AE Duration	Tafenoquine Withdrawn	Related to Tafenoquine
Tafenoquine 200 mg x 3 days, then weekly	Day 165 - Conjunctivitis, sinusitis, and rhinitis	Mild/ No	Promethazine HCl	<1 day	No	No
Tafenoquine 200 mg x 3 days, then weekly	Day 183 -Allergic reaction, body as a whole general	Moderate/ No	Loratadine	<1 day	No	No
Tafenoquine 400 mg x 3 days, then 400 mg monthly	Day 112 - Allergic dermatitis at neck, edema both eyes	Moderate/ No	Unspecified symptomatic therapy	5 days	No	No

Immune System Disorders (Hypersensitivity) with Krintafel at Any Dose

Dose	AE Description	SAE	Treatment	Resolved/ AE Duration	Krintafel Withdrawn	Related to Krintafel
Krintafel 300 mg	Day 17 - Lip swelling, itching, diffuse hives, and difficulty breathing	Yes	Diphenhydramine and Corticosteroids	Yes/ Not stated	N/A (single dose)	Possibly
Krintafel 600 mg	Day 18 - Difficulty swallowing, swelling of the throat, some swelling of the hands and feet, and hives	Yes	Diphenhydramine and Corticosteroids	Yes/ Not stated	N/A (single dose)	Possibly

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Psychiatric AEs in Non-Deployed Considered Related to Study Drug

Study Identifier	Relatedness	Adverse Event
Study 057	unlikely	**Bipolar/Depression**
Study 057	possibly	**Sleep Disorder**
Study 057	unlikely	**Neurosis**

Psychiatric AEs Considered Related to Study Drug in Study 033 Comparing ARAKODA to MQ

Adverse Event	ARAKODA	Mefloquine
Abnormal dreams	1 (0.2%)	1 (0.6%)
Agitation	2 (0.4%)	0
Anxiety	0	2 (1.2%)
Depression	1 (0.2%)	1 (0.6%)
Insomnia	4 (0.8%)	1 (0.6%)
Nightmares	2 (0.4%)	1 (0.6%)
Sleep disorder	0	2 (1.2%)

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Context of Adverse Event Reporting to TGA

The advocacy community has alleged that tafenoquine and primaquine cause permanent neurologic injury, and that the conduct of Studies 033 and 049 was unethical. These concerns have been proven to be unfounded in independent Australian government inquiries:

A Report from the Australian Defence Force Officer of the Inspector General determined that:

"Participants in the 1 RAR tafenoquine/mefloquine anti-malarial drug trial undertook a comprehensive three phase medical briefing process culminating in a witnessed consent form being signed before a medical officer. This process ensured that participants were aware of the potential side effects of both drags and that the trial was a voluntary trial, without detriment to deployment, and they could withdraw at any time."

www.defence.gov.au/publications/coi/Docs/COI-AntiMalarialTrials.pdf

The Repatriation Medical Authority reviewed the scientific literature and determined that:

"Having carried out the investigation as notified, the Authority declares that it does not propose to make a Statement of Principles concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine, for the purposes of subsection 196B(2) or (3) of the Act. The Authority is of the view that there is insufficient sound medical-scientific evidence that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury. Further, there is insufficient sound medical-scientific evidence that there is a characteristic and persisting pattern of signs and symptoms following exposure to mefloquine, tafenoquine or primaquine that could be determined to be a particular kind of disease of, or injury to, the brain."

http://www.rma.gov.au/assets/Other/RMA-Statement-of-reasons-chemically-acquired-brain-injury-29-August-2017.pdf

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Prodromal Symptoms of Mefloquine

Mefloquine Label

"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."

Teva Pharmaceuticals USA, Inc. updated December 29, 2017

Clinical Evidence for Prodromal Symptoms of Mefloquine During Short Term Travel

2017 Cochrane Review - **Mefloquine for preventing malaria during travel to endemic areas:**

20 RCTs (11,470 participants); 35 cohort studies (198,493 participants); and four retrospective analyses of health records (800,652 participants

Neuropsychiatric Adverse Event for Which Incidence is Different From Standard of Care	Comparative Incidence Per 100 Subjects		Comparative Incidence Per 100 Subjects	
	Mefloquine	Doxycycline	Mefloquine	Atovaquone Proguanil
Abnormal dreams	31%	3%	14%	7%
Insomnia	12%	3%	13%	3%
Depression	11%	1%	6%	1%
Anxiety	18%	1%	6%	1%
TOTAL	82%	8%	39%	12%

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Treatment Related* Prodromal Psychiatric Adverse Events at the Recommended Dose of ARAKODA

Prodromal Neuropsychiatric Events	N/(%)		
	ARAKODA Deployed (N=492)	ARAKODA Resident (N=333)	Placebo (n=396)
Abnormal dreams or nightmares	7/1.4%	0/0.0%	0/0.0%
Insomnia or sleep disorder	4/0.8%	1/0.3%	1/0.3%
Depression or depressed mood	1/0.2%	0/0.0%	0/0.0%
Anxiety or anxiety disorder	0/0.0%	0/0.0%	0/0.0%
TOTAL	12/2.4%	1/0.3%	1/0.3%

**Possibly, probably and definitely related to drug treatment*

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TQ 2016-02: Challenge Study Design

- **Aim: Blood schizonticidal activity of ARAKODA against challenge with blood stage *Pf* in healthy, non-immunes**
- **Volunteers were randomized to receive ARAKODA or placebo in a 6:2 ratio**
  - For a sufficient amount of time to reach steady state (in the ARAKODA™ group) comparable to CR
- **Then 3,000 blood stage parasites administered**
- **Monitored for parasitemia by quantitative polymerase chain reaction (qPCR)**

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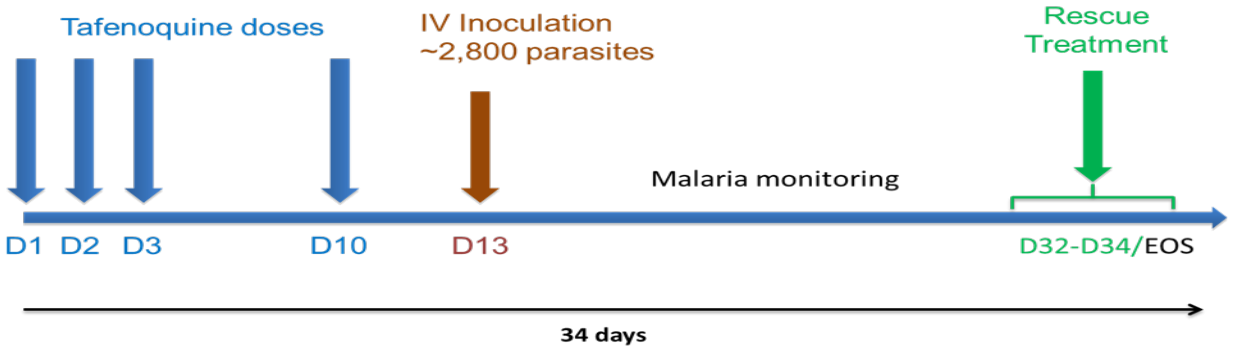
TQ 2016-02: Challenge study Design



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TQ 2016-02: Results

ARAKODA was completely effective against *Pf* blood stage parasites inoculated into non-immune normal volunteers

Group	N	Fail	[95% CI]	PE
Placebo	4	4 (100%)	[40-100%]	--
ARAKODA	12	0 (0%)	[0-27%]	100%

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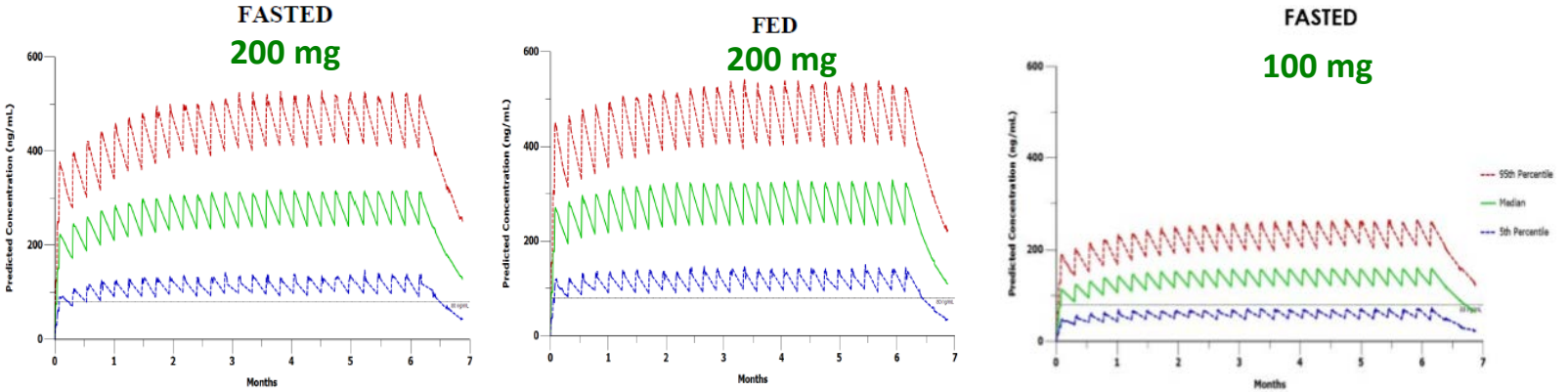
Steady State Pharmacokinetics of ARAKODA™ Doses

Predicted Tafenoquine Concentrations versus Time after 3 × 100 mg or 200 mg Once-Daily Loading Doses Followed by 100 or 200 mg Once-Weekly for Approximately 6 Months



Modeling was performed with data from 10 Phase 1/2/3 studies (866 subjects)
Apparent clearance (CL/F) of tafenoquine is a function of body weight and age (contributing to 2.9% intersubject variability): Mean CL/F of 25 year old with lowest body weight (43 kg) is 0.97 of mean CL/F overall; mean CL/F in highest body weight (135 kg) is 1.03-fold the mean CL/F overall; Mean CL/F in older age category (60 years) is 0.84-fold mean CL/F overall.

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Krintafel (tafenoquine succinate tablets)

FDA Advisory Committee Briefing Document

July 12, 2018

US Regulatory Affairs
GlaxoSmithKline Research & Development Limited
1250 S. Collegeville Road
Upper Providence, PA 19426
June 11, 2018

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ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
AP	All Primary studies in the radical cure program: 582 Part 1, 582 Part 2, 564
AST	Aspartate Aminotransferase
AUC	Area under the concentration time curve
CI	Confidence Interval
CQ	Chloroquine
CSR	Clinical Study Report
CYP	Cytochrome P450
DRM	Drug-related material
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
G6PD	Glucose-6-Phosphate Dehydrogenase
GI	Gastrointestinal
GSK	GlaxoSmithKline
Hb	Hemoglobin
ICH	International Council on Harmonization
ITT	Intent-to-Treat
IU	International Units
MATE1	Multidrug and toxic compound extrusion protein-1
MATE2-K	Multidrug and toxic compound extrusion protein-2K
mITT	Microbiologic Intent-to-Treat
OCT2	Organic cation transporter-2
PC	Placebo-controlled studies in the radical cure program: 582 Part 1, 582 Part 2
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PQ	Primaquine
P. falciparum	Plasmodium falciparum
P. vivax	Plasmodium vivax
QTc	Corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
QWBA	Quantitative whole-body autoradiography
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SD	Single dose
StdD	Standard Deviation
SOC	System Organ Class
TQ	Tafenoquine
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

1. EXECUTIVE SUMMARY

GlaxoSmithKline (GSK) is seeking Food and Drug Administration (FDA) approval for 300 mg single dose tafenoquine (TQ) and upon approval would make TQ available to treat patients with *Plasmodium vivax (P. vivax)* malaria in the US. Based on the small numbers of *P. vivax* patients in the US, TQ has Orphan Drug Designation. TQ was granted Breakthrough Therapy status in 2013 due to the potential substantial treatment benefit in a serious infectious disease.

GSK has been developing 300mg single dose TQ together with the not for profit organization Medicines for Malaria Venture (MMV) as part of GSK's Global Health program aimed at improving healthcare for underprivileged populations. In addition to providing a treatment option to US patients, FDA review and approval of the NDA would be informative to other regulatory agencies and subsequent World Health Organization (WHO) prequalification to support future TQ use in malaria-endemic countries where there is significant unmet medical need for effective therapies. Furthermore, GSK and MMV's global development of tafenoquine to treat P. vivax malaria aligns with USAID and US Government initiatives on the global fight to treat and eradicate this disease.

1.1. Disease and Therapeutic Background

1.1.1. *P. vivax* infection can be severe, and is associated with a significant global disease burden

The global disease burden of malaria due to *P. vivax* is significant and *P. vivax* has the largest geographic distribution of human malarias [Gething, 2012]. The WHO World Malaria Report estimated 8.5 million (uncertainty range 6.6 to 10.8 million) cases in 2015 [WHO, 2016].

The clinical features of *P. vivax* malaria include fever, chills, vomiting, malaise, headache and myalgia. *P. falciparum* is generally considered to be responsible for most malaria-associated deaths and severe disease; however, in endemic areas, *P. vivax* is a common cause of severe malaria: 16% of all cases of severe malaria in Papua are due to *P. vivax;* in Thailand and Indonesia, almost 30% of patients hospitalized for malaria have *P. vivax* infection [Price, 2007]. In another review, the risk of a fatal outcome in patients with severe malaria was indistinguishable between those with *P. falciparum* versus *P. vivax* malaria [Barcus, 2007].

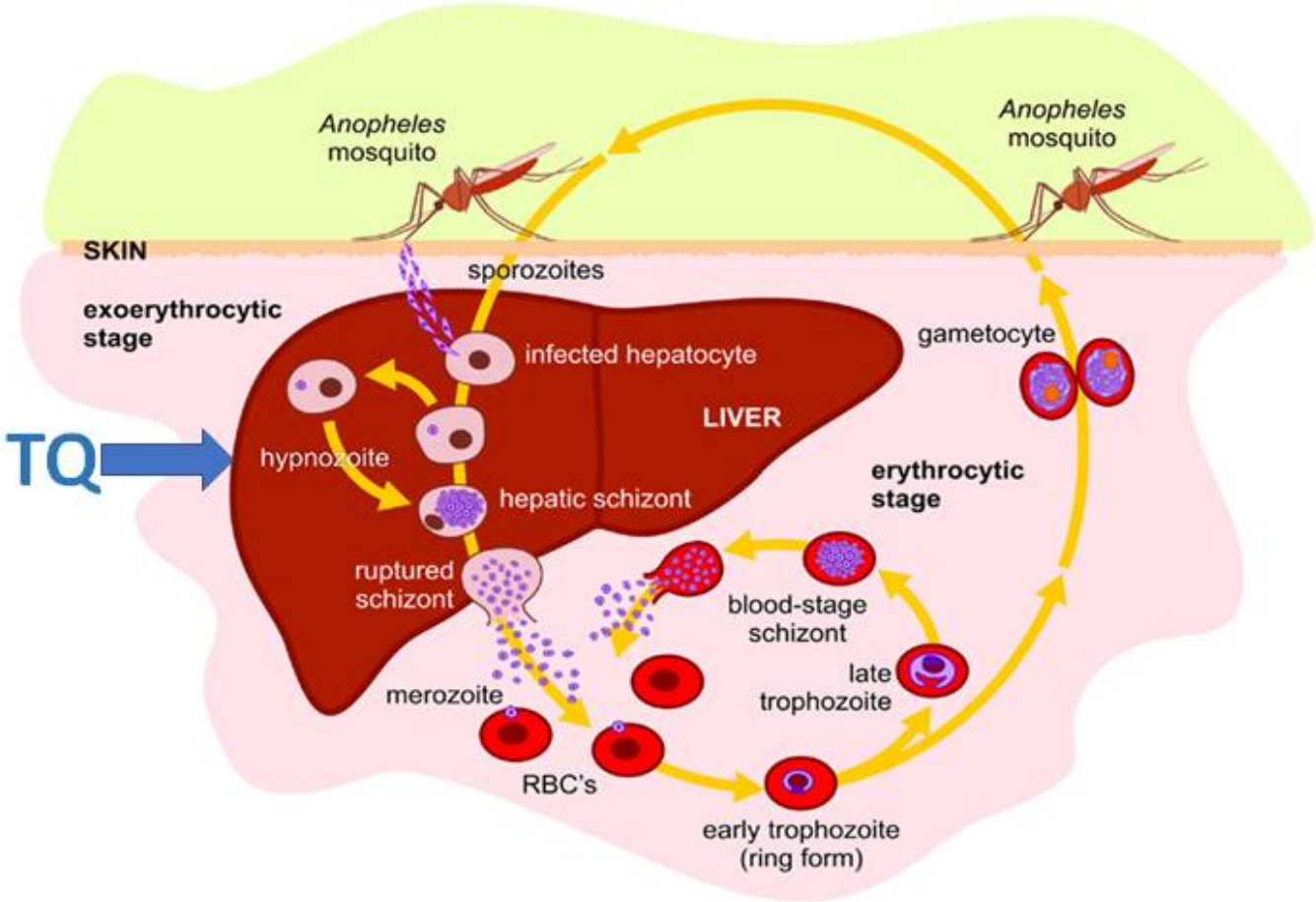
In countries that have eliminated malaria, the majority of cases reported are in returning travelers [Mace, 2017; Queensland Health, 2015]. In 2014, there were 230 cases of imported *P. vivax* reported to the US CDC. Of these, India, Pakistan and Ethiopia contributed the largest number of cases [Mace, 2017]. A review of >12,000 cases of *P. vivax* in returning US travelers found that 0.09% of cases resulted in death and 1.3% were classified as severe, including cerebral malaria, acute respiratory distress syndrome and/or renal failure (29.4%) [Hwang, 2014].

The persistence of mosquito vectors capable of transmitting malaria can make countries that have previously eradicated malaria susceptible to outbreaks of imported malaria (which could be due to relapse in a traveler who arrived some months previously, see below) [Filler, 2006; European Centre, 2017; Queensland Health, 2015; Wells, 2010].

1.1.2. Parasite life cycle

P. vivax infection in humans consists of both blood (erythrocytic) and liver (exo-erythrocytic) stages. Treatment of the blood stage infection (with medicines such as quinine, chloroquine or artemisinin-based combination therapies [ACTs]) does not clear the latent liver stage (hypnozoites). Activation of the hypnozoite can subsequently cause a relapse of malaria weeks, months or years later, without another infected mosquito bite. Patients may suffer from several relapses, and relapsing malaria can be a substantial proportion of the clinical cases in an area.

Figure 1 *P. vivax* Parasite Life Cycle in Humans



a. [Lima, 2016]

1.1.3. Current Therapies

Effective therapy requires not only treatment of the symptom-causing blood stage infection, but also of the hypnozoite burden in the liver, which will otherwise remain a source of recurrent infection. Of the many available antimalarial drugs, chloroquine is currently the most widely used for the treatment of the acute *P. vivax* blood stage infection. Liver hypnozoites are much less susceptible to treatment than the blood stage parasite, and currently, only the 8-aminoquinoline class of drugs, of which primaquine (PQ) is the only FDA approved 8-aminoquinoline, have shown efficacy. Using a drug to target the hypnozoite, in combination with standard anti-malarial drugs (such as chloroquine or ACTs) is called 'radical cure', since both the blood and liver stages of *P. vivax* are eliminated. Whilst a current focus of research, *in vitro* and *in vivo* models of *P. vivax* relapse are poorly developed and thus currently the precise mechanism of action for PQ and TQ anti-hypnozoite activity is unknown.

1.1.3.1. PQ is current standard of care for radical cure, but compliance is often poor

PQ was approved in the US in 1952 for the treatment of malaria, and remains the only FDA-approved drug that can eliminate all liver stages of *P. vivax* [Wells, 2010]. Without radical cure, relapses do occur in US patients and can lead to death. According to 2015 data collected by the Centers of Disease Control and Prevention (CDC) approximately 40% of US patients received primaquine treatment for P. vivax infection. [Mace, 2018].

PQ is administered as a once daily oral dose for 14 days, but in real world use this regimen is associated with poor compliance, resulting in lower efficacy than that reported by carefully-conducted clinical trials. Although data in the US are lacking, it has been estimated that the observed PQ efficacy in a population is reduced 3- to 4- fold when used in an unsupervised or semi-supervised manner [Abreha, 2017, Takeuchi, 2010; Douglas, 2017]. This can occur when as few as 3 doses out of 14 are omitted [Abreha, 2017].

In fact, compliance with unsupervised PQ treatment is reported to be as low as 30% in some settings [Abreha, 2017, Khantikul, 2009]. Fever and other malaria symptoms disappear when the blood stage infection is cleared. However, patients are required to continue taking PQ for several more days, in the absence of symptoms, to appropriately treat the liver hypnozoites. In one study patients with *P. vivax* were randomized to receive PQ by directly observed therapy (DOT) or self-administered therapy (SAT). DOT patients were approximately 6 times less likely than SAT patients to have *P. vivax* reappearance within the 90-day follow-up period. One of the factors related to the reappearance of vivax malaria was inadequate total PQ dosage [Takeuchi, 2010].

PQ DOT improves effectiveness, but requires a corresponding increase in health resource utilization [Takeuchi, 2010]. Current guidelines do not mandate DOT [WHO, 2015].

There are no International Council on Harmonisation (ICH) regions for which systematically collected data on real-world PQ compliance are available; however, it is known that compliance with short-course anti-infectives can be poor. An Australian

study of antibiotic compliance in a general practice showed that 27% of patients failed to complete at least 80% of a prescribed antibiotic course [Cockburn, 1987]. Data from one US center showed that 49% of patients failed to complete a short course of antibiotics following discharge from the Emergency Department [Suffoletto, 2012]. It is therefore reasonable to expect that a similar situation for PQ compliance could exist in the ICH regions as well.

There is thus evidence of poor compliance to PQ in the real world, which is associated with poor efficacy. This limits the benefit derived by the patients, which has important global public health consequences. In many countries, malaria elimination efforts are challenged by the capacity of *P. vivax* to relapse, and new tools are urgently needed.

1.1.3.2. TQ to address the unmet medical need

Given the reported poor compliance to PQ treatment and reduced effectiveness of the current 14-day standard of care regimen of PQ, there is a clear unmet medical need for a well-tolerated and effective therapy that targets the liver hypnozoite, and that can be administered as a shorter treatment duration.

TQ, administered as a single dose in conjunction with the standard 3-day treatment with chloroquine (CQ), is a simple dosing regimen that is anticipated to provide high treatment compliance even in the real-world setting, resulting in improved individual and public health outcomes.

1.1.3.3. Indication for 300 mg single dose Tafenoquine for *P. vivax* malaria

The proposed therapeutic indication for 300 mg single dose TQ is for the radical cure (prevention of relapse) of *P. vivax* malaria in patients 16 years and older.

Radical cure requires the elimination of the dormant (hypnozoite) liver stage of the parasite. Radical cure cannot be achieved by drugs used to treat the acute blood stage infection, such as chloroquine or ACTs, but requires in addition an 8-aminoquinoline, such as primaquine (PQ) or TQ, a derivative of PQ.

TQ is to be coadministered with CQ on the first or second day of CQ treatment.

1.1.3.4. 8-aminoquinolines and G6PD deficiency

PQ and TQ, as 8-aminoquinolines, can cause hemolysis in individuals with a deficiency in glucose-6-phosphate dehydrogenase (G6PD) enzyme activity, a hereditary X-linked condition [Cappellini, 2008]. The key factors determining the severity of drug-induced hemolysis are dose and the degree of G6PD enzyme activity.

Males, having one copy of the G6PD gene (one X-chromosome), have either normal or deficient enzyme activity. Females carry two copies of the gene, and can therefore be heterozygous for G6PD deficiency, and may have intermediate enzyme activity levels.

To manage this hemolysis risk, patients must be tested, and G6PD-deficient patients then excluded from treatment with TQ or PQ. The prescribing information for PQ contains a contraindication for patients with G6PD deficiency, and G6PD testing is performed routinely in the US before prescribing PQ. In the TQ Phase 2b/3 clinical program all subjects were tested for G6PD deficiency. Including only patients with levels that were ≥70% of the site median proved effective in avoiding any cases of clinically significant hemolysis.

Access to G6PD testing remains a barrier to effective treatment of *P. vivax* malaria in many endemic countries. GSK and MMV are collaborating with PATH on the parallel development of a robust, portable, quantitative G6PD diagnostic suitable for use in resource-poor settings. This may also prove to be an important innovation in addressing the global disease burden of *P. vivax* malaria.

1.2. Clinical Development Program

The clinical development program for TQ in the radical cure of *P. vivax* was designed in consultation with regulatory authorities in the US and Australia and in consultation with the World Health Organization (WHO) Global Malaria Program.

Three primary studies (Table 1) have established that 300 mg TQ is an effective single-dose treatment for the radical cure of *P. vivax*:

- 300 mg was selected as the lowest efficacious dose from a placebo-controlled dose-ranging study: 582 Part 1 (Phase 2b)
- Efficacy of the selected 300 mg dose was confirmed, showing a 70% reduction in the risk of recurrence vs. CQ alone, in a pivotal placebo-controlled study: 582 Part 2 (Phase 3)
- An acceptable safety profile has been demonstrated for the selected 300 mg dose, when given together with CQ, throughout the 6-month follow-up: 582 Parts 1& 2, 564 (Phase 3)
- Efficacy and safety were observed to be similar to that of PQ, given together with CQ, the current standard of care: Studies 582 Parts 1& 2, Study 564.

The primary studies enrolled patients ≥16 years of age with a diagnosis of acute *P. vivax* malaria (parasite count 100-100,000 parasites/μL), and with G6PD enzyme activity ≥70% of normal. While the phase 2b/3 studies were conducted in malaria-endemic countries, i.e. at sites outside the US (See Appendix Sections 9.1, 9.2, 9.4), there is no reason to expect differing responses to treatment between US patients who acquired *P. vivax* due to travel, and patients in endemic regions with *P. vivax* disease.

Safety data from across the whole TQ development program include 33 studies in healthy volunteers and patients, which were used to inform the type and frequency of uncommon and rare events observed with TQ. Across the TQ development program, more than 4000 subjects have been exposed to TQ, including >800 subjects exposed to a 300 mg total dose, of which >700 received a single dose (Table 28).

In addition to the safety data from the primary studies, specific safety results from 2 key individual studies in healthy volunteers, the study assessing ophthalmic safety (TAF201807) and the definitive study of cardiac safety (TAF114582), provide clinically important safety observations.

Table 1 Overview of Key Studies Contributing Efficacy and Safety Data for 300 mg Single Dose TQ

	Primary Studies in *P. vivax*-infected Subjects			Specific Safety in Healthy Volunteers	
	Placebo-controlled Studies		Study TAF116564	Ophthalmic	QTc
	Study TAF112582 Part 1	Study TAF112582 Part 2		Study 201807	Study TAF114582
Study design	Randomized, double-blind, placebo- and active-controlled, double-dummy, parallel-group	Randomized, double-blind, placebo and active-controlled, double-dummy, parallel-group	Randomized, double-blind, active-controlled, double-dummy, parallel-group	Randomized, single-blind, placebo-controlled, parallel-group	Randomized, single-blind, placebo-controlled, parallel-group
Phase	Phase 2b	Phase 3	Phase 3	Phase 1	Phase 1
Study population	Subjects ≥16 yrs; confirmed *P. vivax* infection; ≥70% normal G6PD levels[b] stratified by baseline parasite count (≤7500/μL, >7500/μL)	Subjects ≥16 yrs[a]; confirmed *P. vivax* infection; ≥70% normal G6PD levels[b]	Subjects ≥16 yrs[a], confirmed *P. vivax* infection; males with ≥70% normal G6PD levels[b] and females with ≥40% normal G6PD levels[b]	Healthy subjects; 18 to 45 yrs (inclusive)	Healthy subjects; 18 to 65 yrs (inclusive)
Treatment groups (n)	CQ for 3 days plus: TQ 50 mg SD (n=55) TQ 100 mg SD (n=57) TQ 300 mg SD (n=57) TQ 600 mg SD (n=56) PQ 15 mg once daily for 14 days (n=50) Placebo (i.e., CQ alone) (n=54)	CQ for 3 days plus: TQ 300 mg SD (n=260) PQ 15 mg once daily for 14 days: (n=129) Placebo (i.e., CQ alone) (n=133)	CQ for 3 days plus: TQ 300 mg SD (n=166) PQ 15 mg once daily for 14 days (n=85)	TQ 300 mg (n=332) Placebo (n=168)	TQ 300 mg (n=52) TQ 600 mg (n=52) TQ 1200 mg (n=52) Moxifloxacin (n=52) Placebo (n=52)
Primary objective	Efficacy	Efficacy	Occurrence of clinically relevant hemolysis	Retinal effects (CFB)	QTcF effects (CFB)

Abbreviations: CFB=change from baseline; CSR=clinical study report; QTc=corrected QT interval; SD=single dose

a. In Ethiopia, ≥18 years

b. ≥70% of site median of G6PD normal males

1.3. Efficacy

1.3.1. Primary Endpoint

The primary endpoint for efficacy was the recurrence of *P. vivax* malaria over a 6-month duration of follow up, and the primary objective was to compare the efficacy of TQ +CQ

versus CQ alone. Studies were conducted in malaria-endemic areas, and therefore there was a continuous risk of re-infection throughout the follow-up period. For *P. vivax* recurrences, it is not possible to completely distinguish true relapses from new infections, even using parasite genotyping.

The observed efficacy in the Phase 2b/3 studies thus demonstrates the overall benefit of TQ in preventing recurrence, even in the presence of likely re-infection over the 6-month period of follow-up.

All three Phase 2b/3 studies included a PQ+CQ treatment arm as a benchmark treatment, but were not designed to have sufficient power to make formal comparisons of efficacy (e.g., non-inferiority) of single dose TQ to PQ for 14 days when co-administered with standard doses of CQ. Treatment comparisons were made to the CQ alone group in the placebo-controlled studies. Efficacy for 300 mg single dose TQ was similar to that observed for compliant treatment with PQ for 14 days.

- 300mg single dose TQ, when given with CQ, resulted in a clinically and statistically significant reduction in the risk of recurrence over 6 months by 70.1% (95% confidence interval [CI]: 59.6%, 77.8%; p<0.001) compared with CQ alone, based on a Cox proportional hazards model (Study 582 Part 2) (Table 2). The Kaplan Meier estimates of recurrence-free efficacy at 6 months were 27.7% (95% CI: 19.6%,36.3%) in the CQ alone group and 62.4% (95% CI: 54.9%, 69.0%) in the TQ+CQ group.
- Treatment with PQ+CQ resulted in a reduction in the risk of recurrence at any time over 6 months by 73.8% (95% CI: 61.3%, 82.2%; p<0.001) compared with CQ alone. The estimate of recurrence-free efficacy at 6 months was 69.6% (95% CI: 60.2%,77.1%) in the PQ+CQ group.

Table 2 6-Month Recurrence-free Efficacy by Cox Proportional Hazards Analysis in 582 Part 2 (mITT Population)

	CQ alone N=133	TQ+CQ N=260	PQ+CQ N=129
Recurrences over 6 months, n (%)	88 (66)	85 (33)	36 (28)
Hazard Ratio vs CQ alone (95% CI)	--	0.299 (0.222,0.404)	0.262 (0.178,0.387)
p-value	--	<0.001	<0.001

An alternative logistic regression analysis (where subjects who were not confirmed recurrence-free at 6 months were assumed treatment failures) was consistent with the survival analyses (Table 3). There was a 75.9% reduction in the odds of recurrence (95% CI: 61.8%, 84.8%; p<0.001) in TQ+CQ treatment compared with CQ alone.

Table 3 Logistic Regression Analysis of 6-Month Recurrence-free Efficacy in 582 Part 2 (mITT Population)

	CQ alone N=133	TQ+CQ N=260	PQ+CQ N=129
Missing, n (%)	10 (8)	20 (8)	10 (8)
Recurrences over 6 months, n (%)	98 (74)	105 (40)	46 (36)
Odds Ratio for Recurrence vs CQ alone (95% CI)	--	0.241 (0.152,0.382)	0.198 (0.117,0.335)
p-value	--	<0.001	<0.001

The two other primary studies (582 Part 1 and 564) provided consistent and supportive evidence of efficacy for the 300 mg single dose TQ+CQ treatment:

- The dose range finding study, 582 Part 1 (Table 49), showed a statistically significant difference in efficacy between TQ+CQ compared to CQ alone. The estimates of recurrence-free efficacy at 6 months were 37.5% (95% CI: 23%, 52%) in the CQ alone group, 89.2% (95% CI: 77%, 95%) in the 300 mg TQ+CQ group, and 77.3% (95% CI: 63%,87%) in the PQ+CQ group.
- In Study 564 (Table 60) the estimates of recurrence-free efficacy at 6 months were 72.7% (95% CI: 64.8%, 79.2 %) in the TQ+CQ group, and 75.1% (95% CI: 64.2%, 83.2%) in the PQ+CQ group.

The results of all pre-specified sensitivity analyses of the primary endpoint were consistent with the primary analyses for the Phase 3 studies.

In the pivotal and supportive efficacy studies, demographic characteristics were well-balanced across the treatment groups and the baseline disease characteristics were similar across treatment groups. In all 3 efficacy studies, the study completion rate was ≥94% in all treatment groups and there were no adverse events (AEs) leading to withdrawal from the studies.

In the Phase 3 studies, study sites were able to achieve very high (≥96%) compliance with all study medications based on reinforced, targeted efforts; hence almost all of the PQ+CQ group received the full 14-day treatment course of PQ. However, outpatient compliance with PQ in TAF112582 Part 1, was lower in comparison with the other studies.

1.3.2. Secondary Endpoints

It was anticipated that the majority of relapses would occur within the first 4 months of follow up (as shown in the Kaplan-Meier analysis of the time to recurrence in the CQ only arm), and that there would be a background risk of re-infection throughout the duration of the study. Hence efficacy was also evaluated at the 4-month time period, in order to attempt to minimize the confounding effect of re-infection (which cannot be

assessed by any genotypic evaluation, as discussed above), and this is a key secondary endpoint. This endpoint was derived using the follow up data up to 4 months.

1.3.2.1. Recurrence at 4 months

In Study 582 Part 2, TQ, when given with CQ, resulted in a reduction in the risk of recurrence at any time over 4 months by 72.9% (95% CI: 62.4%, 80.5%; p<0.001) compared with CQ alone. The estimates of recurrence-free efficacy at 4 months were 36.0% (95% CI 26.8%,45.4%) in the CQ alone group and 73.0% (95% CI: 66.0%,78.9%) in the TQ+CQ group.

Supportive efficacy studies showed similar results at 4 months:

- Study 582 Part 1 (Table 50) showed a statistically significant difference in efficacy between TQ+CQ compared to CQ alone. The estimates of the recurrence-free efficacy at 4 months were 46.5% (95% CI: 32%, 60%) in the CQ alone group and 89.4% (95% CI: 75%, 96%) in the 300 mg TQ+CQ group.
- In Study 564 (Table 62) the estimate of recurrence-free efficacy at 4 months was 82.3% (95% CI: 74.9%,87.7%) in the TQ+CQ group

1.3.2.2. Other secondary endpoints

Additional secondary endpoints evaluated the initial parasitological and symptomatic response of the presenting episode of *P. vivax* malaria. Endpoints included: number of patients who did not clear their initial infection by Day 33, time to fever clearance, time to parasite clearance, and the incidence of *P. falciparum* infection. Very few subjects failed to clear the initial infection, and there were very few secondary *P. falciparum* infections, and no differences were observed in these and other secondary endpoints between treatment groups across the studies.

1.4. Safety

The safety profile of TQ at the recommended 300 mg single dose supports its use for radical cure. In Phase 2b/3 studies the safety profile of TQ was similar to that of PQ 15 mg daily for 14 days.

Across the TQ development program with all dosing regimens, more than 4000 subjects have been exposed to TQ, including >800 subjects exposed to a 300 mg total dose. The Phase 2b/3 studies outlined above provide the primary evidence of an appropriate safety profile for the TQ 300 mg single dose in the radical cure of *P. vivax* malaria, when given with CQ, and are discussed in detail in this document. Altogether, a total of 483 subjects with P. vivax malaria have been exposed to TQ+CQ in the 3 primary studies. This dataset of 483 patients with acute *P. vivax* malaria who received TQ+CQ enables comparison both with patients who received CQ alone (TQ+CQ: N 317; CQ alone: N 187) across the placebo-controlled studies (PC grouping), and who received PQ+CQ (TQ+CQ: N 483; PQ+CQ: N 264) across the three Phase 2b/3 studies (all primary, AP grouping).

1.4.1. Adverse events

Overall, the AE profiles for treatment groups in the PC grouping were similar (Table 4).

Table 4 AEs at 5% or More in Any Treatment Group in the PC Grouping (Safety Population)

Preferred term	CQ alone N=187	TQ+CQ N=317	PQ+CQ N=179
Any event	**127 (68)**	**202 (64)**	**108 (60)**
Pruritus	27 (14)	42 (13)	17 (9)
Headache	39 (21)	37 (12)	24 (13)
Dizziness	16 (9)	30 (9)	14 (8)
Nausea	15 (8)	26 (8)	13 (7)
Vomiting	9 (5)	24 (8)	16 (9)
Viral upper respiratory tract infection	9 (5)	19 (6)	12 (7)
Diarrhoea	10 (5)	18 (6)	9 (5)
Myalgia	22 (12)	16 (5)	12 (7)
Abdominal pain upper	18 (10)	17 (5)	14 (8)
Pharyngitis	7 (4)	15 (5)	11 (6)
Back pain	4 (2)	17 (5)	5 (3)
Haemoglobin decreased	3 (2)	15 (5)	3 (2)
Pyrexia	23 (12)	14 (4)	16 (9)
Urinary tract infection	9 (5)	12 (4)	7 (4)
Blood creatine phosphokinase increased	10 (5)	11 (3)	7 (4)
Alanine aminotransferase increased	9 (5)	10 (3)	7 (4)
Abdominal pain	9 (5)	8 (3)	7 (4)
Chills	20 (11)	6 (2)	12 (7)

The incidence of relapse was higher in the CQ only group; this may account for the higher incidence of AEs that might be associated with a *P. vivax* malaria recurrence, and/or re-treatment with CQ and PQ. Therefore, in order to account for this confounding effect, AEs occurring within the first 29 days (prior to the first documented *P. vivax* recurrence on any study arm) were also analyzed (Table 5).

Within the first 29 days, pruritus was the most common AE in all 3 treatment groups in the PC grouping, which is consistent with the known effects of CQ. The majority of subjects with AEs had events that were mild or moderate in severity and few severe AEs (Grade ≥3) were reported.

Dizziness and hemoglobin decrease were more frequently reported in the TQ+CQ group compared with CQ alone. These findings are discussed under hematologic safety and CNS effects, below.

Table 5 AEs With Onset On Or Prior to Study Day 29 Reported in at Least 5% of Subjects in Any Treatment Group by Preferred Term (PC Safety Population)

Preferred Term	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)
Any event	**90 (48)**	**160 (50)**	**88 (49)**
Pruritus	24 (13)	37 (12)	17 (9)
Dizziness	6 (3)	25 (8)	10 (6)
Nausea	12 (6)	20 (6)	8 (4)
Hemoglobin decreased	3 (2)	15 (5)	3 (2)
Headache	12 (6)	15 (5)	9 (5)
Vomiting	7 (4)	17 (5)	10 (6)
Abdominal pain upper	14 (7)	13 (4)	12 (7)

1.4.2. Serious Adverse Events

There were no deaths in the 3 primary studies, 582 Part 1 and Part 2, and 564, or in the radical cure program studies.

Decreased hemoglobin was the most common serious AE (SAE), and the only SAE reported in >1 subject in the TQ+CQ group, based on the placebo-controlled studies (PC) grouping, and occurred in 4% of TQ+CQ patients, compared with 2% in the CQ alone, and 2% in the PQ+CQ groups.

As hematologic safety was of special interest (discussed further, below), decreased hemoglobin (Hb) was pre-defined as an SAE in the protocols (Hb decreases of ≥30% or >30 g/L from baseline; or, an overall drop in Hb below 60 g/L in the first 15 days of the study). Events in the studies that met these criteria, and hence were counted as SAEs, did not, in any instance, otherwise fulfill the criteria for 'serious', such as life-threatening or requiring hospitalization. In fact, none of these events required any specific intervention and no patient had a Hb below 60 g/L.

1.4.3. Laboratory evaluations

No clinically significant hepatobiliary or renal effects were observed.

Transient, sporadic increases in liver transaminases have been observed, but no clinically significant hepatobiliary effects were observed across the clinical program. All hepatobiliary AEs were mild or moderate in intensity and no subjects discontinued study treatment or withdrew from any of the 3 primary studies due to hepatobiliary AEs.

No renal toxicity signal was observed across the TQ development program. The proposed 300 mg single dose TQ was associated with small reversible increases in creatinine, which were consistent with the known renal transporter inhibition effect.

1.4.4. AEs of Special Interest

Given the known safety profile of TQ and that of other currently used anti-malarials, particular aspects of the safety profile for TQ were evaluated further (QT prolongation, ophthalmic safety, hematologic safety, CNS effects), either through the conduct of targeted studies, or through additional analyses. These potential safety issues are discussed below.

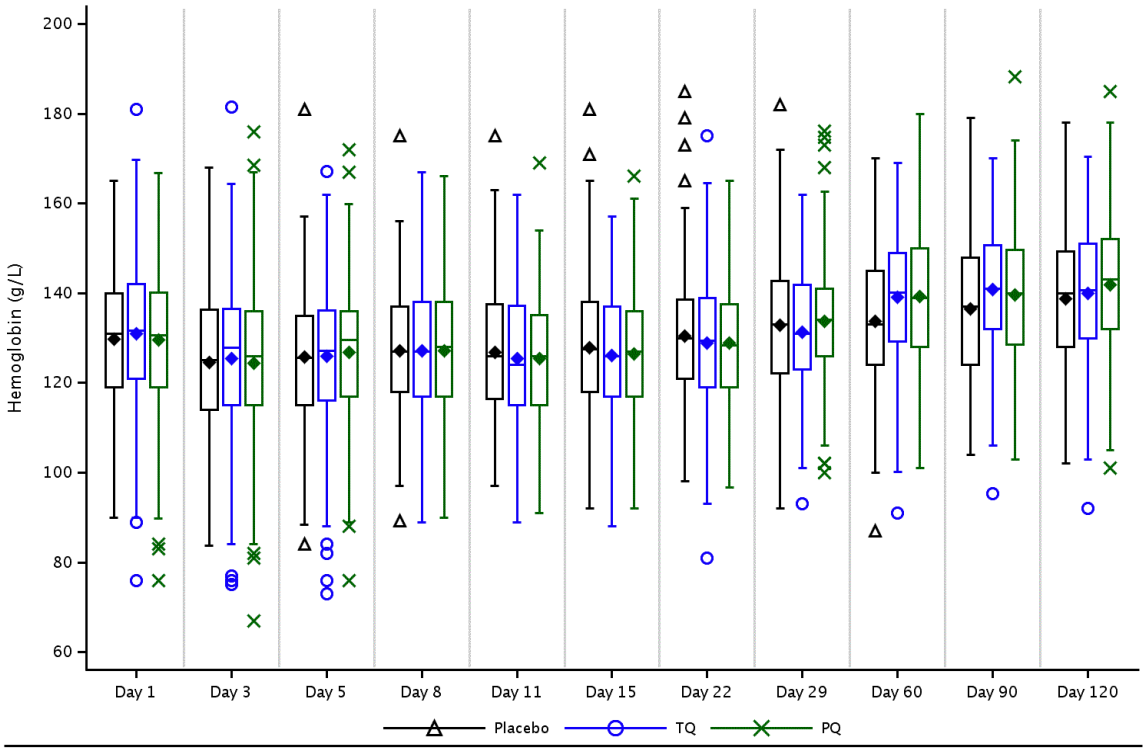
1.4.4.1. Hematologic safety

The hematologic safety profile for TQ 300mg single dose has been well-characterized, and the TQ development program has established that excluding patients with G6PD activity <70%, which was the cut-off in the clinical trials, is effective at preventing clinically significant drug-induced hemolysis in patients with *P. vivax* malaria.

The main safety concern for 8-aminoquinolines such as PQ and TQ, is drug-induced hemolysis in patients with G6PD enzyme deficiency. Patients with G6PD deficiency (<70% normal enzyme activity) were therefore excluded from the studies, and our proposed labeling for TQ currently under review by the FDA includes a contraindication in G6PD deficiency (G6PD enzyme levels <70% of normal). This contraindication would be consistent with labelling, and WHO guidelines, on the use of 8-aminoquinolines. In the US and other ICH regions, quantitative laboratory diagnostics are readily available for use prior to administration of 8-aminoquinolines [Trinity Biotech, 2012].

In G6PD normal patients, overall trends in Hb changes over time were similar across the treatment groups in the PC grouping (Figure 2), consistent with the hematologic effects of, and recovery from an acute episode of malaria. None of these changes were regarded as clinically significant.

Figure 2 Hb Values by Visit (PC Safety Population)



Subjects											
Placebo	187	187	186	185	184	186	184	183	181	181	132
TQ	317	315	313	312	310	310	308	309	309	308	251
PQ	179	179	177	175	173	173	173	172	173	168	123

Placebo = CQ alone; TQ = TQ+CQ; PQ = PQ+CQ

1.4.4.2. Ophthalmic safety

Ophthalmic assessments in the Phase 3 studies, and in a healthy volunteer study (201807) which used more detailed and sensitive ophthalmic techniques, did not identify any signal for retinal toxicity with use of a 300 mg single dose TQ.

In common with other cationic amphiphilic drugs, TQ has the potential to cause phospholipid accumulation in the cornea, a benign and reversible keratopathy; this finding has been observed in studies where higher doses and longer durations of TQ treatment were used. CQ (in high cumulative doses) is associated with retinopathy; retinal toxicity has also been associated with use of quinine and quinidine. Ophthalmic safety was therefore of special interest in the TQ studies.

Ophthalmic evaluations were included for a subset of patients enrolled in the primary studies, according to capabilities at individual study sites. Across the primary studies there was no evidence of retinal toxicity or corneal changes associated with vision changes for the proposed 300 mg TQ single dose. AEs associated with ocular changes were infrequent and similar across the treatment groups in the PC and AP groupings, and

all events were mild or moderate in severity. No clinically significant changes to ophthalmic safety parameters were observed, based on visual acuity measurements, anterior segment examination with evaluation for vortex keratopathy, posterior segment examination including fundus photographs, color perception assessment, and Humphrey visual field perimetry.

Given the limited capacity for Phase 3 clinical trial sites to conduct detailed ophthalmic safety assessments, a specific placebo-controlled safety study, Study 201807, was conducted in healthy US volunteers using highly sensitive ophthalmic techniques (Spectral Domain Optical Coherence Tomography, and Fundus Autofluorescence) to establish whether there is a risk of retinopathy with the proposed 300 mg single dose of TQ. This study did not identify any signal for retinal toxicity with use of a single 300 mg dose of TQ.

1.4.4.3. Cardiac safety

In a definitive cardiac safety study at 2 US sites (Study TAF114582) there was no indication of a QT effect at clinically relevant doses of TQ (300 mg and 600 mg) compared with placebo. The maximum effect on QTcF at the supratherapeutic dose of 1200 mg compared to placebo was <10 msec and within the FDA E14 guidelines for lack of effect.

Data from other clinical studies did not show an additional effect of TQ 300mg single-dose on the corrected QT interval (QTcF) duration to that recognized for CQ or ACTs such as dihydroartemisinin/piperaquine (DHA/PQP).

1.4.4.4. Central Nervous System effects

CNS effects in P. vivax patients treated with 300 mg single dose TQ

No serious CNS AEs were reported in the PC and AP groupings from the phase 2b and 3 studies; all neurologic and psychiatric AEs were mild to moderate in severity, and self-limiting.

In the PC and AP groupings, headache and dizziness were the most commonly reported neurologic events (Table 35). A higher incidence of headache in the CQ only arm (likely to be associated with the higher incidence of *P. vivax* relapse) was observed. This prompted a review of CNS events occurring within the first 29 days, before any documented malaria recurrence (Table 6). This analysis of neurologic and psychiatric AEs showed that dizziness was more frequently reported in the TQ+CQ group, compared with CQ alone, which is consistent with what was reported in healthy volunteers treated with TQ, in the absence of malaria.

Insomnia and anxiety were the only psychiatric AEs reported at any time by patients receiving TQ+CQ across the entire 6-month follow-up, and were reported at similar rates in the PQ+CQ group.

Table 6 Central Nervous System AEs with Onset On or Prior to Day 29 by System Organ Class and Preferred Term (PC and AP Safety Populations)

	PC Grouping			AP Grouping	
System Organ Class Preferred Term	**CQ alone (N=187) n (%)**	**TQ+CQ (N=317) n (%)**	**PQ+CQ (N=179) n (%)**	**TQ+CQ (N=483) n (%)**	**PQ+CQ (N=264) n (%)**
Nervous System Disorders, any event	**19 (10)**	**36 (11)**	**18 (10)**	**75 (16)**	**35 (13)**
Dizziness	6 (3)	25 (8)	10 (6)	52 (11)	23 (9)
Headache	12 (6)	15 (5)	9 (5)	34 (7)	19 (7)
Syncope	0	2 (<1)	0	2 (<1)	0
Tremor	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Dysaesthesia	0	0	1 (<1)	0	1 (<1)
Migraine	1 (<1)	0	0	0	0
Somnolence	0	1 (<1)	0	1 (<1)	0
Psychiatric Disorders, any event	**5 (3)**	**12 (4)**	**8 (4)**	**14 (3)**	**9 (3)**
Insomnia	5 (3)	12 (4)	8 (4)	14 (3)	8 (3)
Anxiety	0	2 (<1)	0	2 (<1)	1 (<1)

CNS events in studies evaluating other TQ dosing regimens

Central nervous system (CNS) events i.e. nervous system and psychiatric disorders, are recognized for some anti-malarials, including CQ and quinine, and most noticeably with the 4-quinolinemethanol, mefloquine, but are typically reversible and rarely persist long term. In 2016 we first received spontaneous reports of possible long-term CNS effects from soldiers who had participated in studies conducted by GSK over 15 years ago with the Australian Defense force (discussed below). This prompted a thorough evaluation of all available clinical trial data and relevant literature.

Following this review, terms relating to mild or moderate, self-limiting CNS effects with 300 mg SD TQ have been included in proposed labeling subject to FDA review. Additionally, a conservative position is being taken with regard to patients with a history of serious psychiatric disorders, which to date have only been observed at doses higher than the proposed 300 mg single dose. Precautionary language has been added to the proposed label that is currently under FDA review (See Section 6.5, CNS Events).

A limited number of serious psychiatric events have been reported in individuals who have received a total dose of TQ ≥350 mg. These were mainly in individuals with a history of significant psychiatric disorders. Amongst the clinical trial database of > 4000 subjects who have been exposed to TQ, including all healthy volunteer and prophylaxis studies, a total of 9 individuals receiving TQ single or multiple doses reported severe or serious psychiatric disorders (n 7), or otherwise considered medically important for the purposes of this evaluation (n 2) (Table 36).

Four of the 9 were reported in patients and healthy volunteers who received a single dose of TQ. They received doses ranging from 350 mg to 600 mg: 2 reports (1 healthy volunteer, 1 *P. vivax*-infected subject) of depressed mood and 2 reports (both healthy

volunteers) of psychosis. One of the subjects with depressed mood had a history of depression. Both of the subjects with psychosis had a history of psychosis that was not disclosed at study entry. In the subject with no relevant past medical history, the depressed mood was mild, lasted for 3 days, and resolved without intervention, suggesting that patients without a history of serious psychiatric disorders may be at a lower risk. All of the serious events resolved fully during follow-up with treatment.

The remaining 5 were reported in individuals who received repeat doses of TQ (cumulative doses up to 5200 mg) in prophylaxis or other healthy volunteer studies. Two individuals, with no previous relevant history, developed mild depression/bipolar depression, of which one resolved without intervention, and one occurred 2 months after the last dose of TQ, but was subsequently lost to follow-up. One individual, with a history of closed head injury, developed moderate depression, and one individual with a relevant past history developed suicidal behavior in association with alcohol intoxication. One individual, with an undisclosed history of psychosis, reported an episode of psychosis.

While a causal role for TQ has not been established, a current or prior history of psychiatric disorder may be a risk factor for these events.

Reports from subjects in previous TQ studies

Starting in 2016, reports of psychiatric disorders have been received from a total of 18 subjects out of the >1500 individuals who received TQ in studies (mostly for prophylaxis) conducted with the Australian Defense Force (ADF) (Study SB252263/033, Study SB252263/046, and Study SB252263/049), which were conducted >15 years ago.

The self-reported medical histories contained in these more recent reports from former ADF study participants describe more CNS events than were reported at the time of the study, including anger outbursts, confusional state, and hallucinations. These reports provided only limited medical information, and were not medically confirmed. The majority of soldiers making reports were exposed to triggers for post-traumatic stress syndrome, the symptoms of which are similar to those included in the reports. These aspects taken together make evaluation more challenging and mean that a firm conclusion cannot be drawn although a role for tafenoquine cannot be excluded.

While there may be reasons why symptoms were under-reported at the time, the rate for CNS effects was nonetheless higher in the ADF study SB252263/033 compared to study SB252263/057, which studied the same TQ dosing regimen (200mg x 3 loading dose, then 200mg weekly for 6 months) but in healthy volunteers including non-deployed military personnel. The absence of an untreated control group in Study SB252263/033 poses difficulties in interpretation of this data compared to background rates of CNS events in a military population. Literature suggest that there is a substantial background rate of depression (~12%, Brignone, 2017; Fanning, 2013; Ilgen, 2010 O'Toole, 2015; Ramsawh, 2014) and anxiety disorders (~10%, Brignone, 2017; Fanning, 2013; Ilgen, 2010; McFarlane, 2011; O'Toole, 2015) in military populations.

To date, due to limitations in the data available and the inability to perform an accurate and non-confounded retrospective analysis, e.g. recruitment/selection and recall bias, it has not been possible to make a connection between mild to moderate side effects reported during Study SB252263/033, and any permanent serious long- term effects with onset after completion of the study. It is therefore possible that the deployed ADF soldiers represented a higher risk population.

Preclinical evaluation of CNS Effects

Tafenoquine does not induce neurotoxicity in single and repeat dose toxicology studies in mice, rats and dogs, or specific neurobehavioral studies in rats at exposures that are comparable to or in excess of those seen at the recommended treatment dose for patients (Section 3).

CNS Safety Conclusion

In the >800 subjects who have received a total dose of 300mg TQ, no serious CNS events have been reported and the observed events have been mild to moderate and self-limiting. Therefore, the single 300 mg TQ dose + CQ for radical cure of *P. vivax* malaria is anticipated to have a low risk of significant CNS effects in patients without an active or past history of serious psychiatric disorders.

Adopting a conservative approach and given the totality of both clinical data and the scientific literature, the proposed labeling for 300 mg single dose TQ currently under review by the FDA indicates that caution is advised when administering TQ to patients with a current or past history of serious psychiatric disorder. The intention is for the safety of tafenoquine to be monitored carefully post-registration (see Benefit:Risk Section 7)

1.5. Benefit : Risk

P. vivax malaria is responsible globally for a very significant burden of illness, despite being rare in the US. Relapse from the dormant liver stages, which has been reported in US patients [Mace, 2017; Mace, 2018], undoubtedly contributes to this burden of disease in the individual patient, and also to the onward transmission of the infection. Patient compliance with a full (14 day) course of PQ, as the current standard of care, is typically incomplete, and this is associated with significantly diminished effectiveness, and hence persistent infection. There is a clear unmet need for a simple regimen that provides radical cure and offers US prescribers a viable alternative to PQ.

The Phase 2b/3 program has demonstrated high efficacy for TQ, even in the face of likely re-infections during the 6-month follow-up. These studies demonstrated an appropriate safety profile throughout the 6-month follow-up, that supports use in this indication, and the risks of hemolysis in G6PD deficiency can be safely managed by testing prior to treatment. Identified potential risks are described in proposed labeling subject to FDA review, and methods for active surveillance (enhanced pharmacovigilance) for the US and in endemic countries, are currently being developed, under consultation with the FDA and the WHO ‘Smart Safety Surveillance’ initiative.

Based on the data from studies of 300 mg single dose TQ, the benefit:risk for the radical cure of *P. vivax* malaria in adults and adolescents ≥16 years of age with G6PD levels ≥70% of normal is favorable.

1.6. Conclusion

TQ would provide a new treatment option for the radical cure of *P. vivax* malaria. The safety profile of TQ 300 mg single dose is acceptable and broadly similar to that of PQ 15 mg for 14 days. Coupled with high efficacy, and a very simple and convenient dosing regimen, TQ would be an important and significant new tool in the treatment of *P. vivax* malaria for US patients, as well as addressing the high global burden of this disease.

2. INTRODUCTION AND BACKGROUND

2.1. Current Therapies for Treatment of *P. vivax* malaria

Historically, a variety of drugs of diverse structures and mechanisms of action have been utilized in the treatment of malaria species (Table 7), including treatments for both active infection and prophylaxis.

Table 7 Chemical Classification of Antimalarial Drugs

Class	Drugs
4-Aminoquinolines	Chloroquine, amodiaquine, hydroxychloroquine
8-Aminoquinoline	Primaquine, tafenoquine, pamaquine, pentaquine
Quinoline-containing cinchona alkaloids	Quinine, quinidine
4-quinolinemethanols	Mefloquine
Phenanthrene methanol	Halofantrine, lumefantrine
Biguanides	Proguanil, chlorproguanil
Diaminopyrimidines	Pyrimethamine
Sulfonamides	Sulfalene, sulfadoxine, dapsone
Antibiotics	Tetracycline, doxycycline, arithromycin
Hydroxynaphthoquinones	Atovaquone
Artemisinin derivatives	Artemisin, artesunate, artemether, arteether

Source: [Bitta, 2017; Nqoro, 2017; Staines, 2012]

Any effective *P. vivax* treatment regimen needs to not only treat the blood stage infection causing symptoms, but also to remove the hypnozoite burden in the liver. Currently, only the 8-aminoquinolines, like PQ and TQ, can accomplish this (Figure 3). Using these drugs in combination with standard anti-malarial drugs (such as CQ or ACT) is called 'radical cure', since both the blood and liver stages of *P. vivax* are then eliminated.

Figure 3 P. vivax Malaria Treatment Options Adapted from CDC

Option	Blood Stage Treatment	Liver Stage Treatment
1st	**Chloroquine (x 3 days)**	**Primaquine phosphate (x 14 days)**
2nd	Atovaquone-proguanil **or** artemether-lumefantrine	
3rd	Quinine sulfate combinations (+ doxycycline, tetracycline, or clindamycin)	
4th	Mefloquine	

TQ and PQ are both 8-aminoquinolines with a potential to cause drug-induced hemolysis in patients with a deficiency in G6PD enzyme activity, a condition which is sex-linked. Patients with G6PD deficiency must therefore be excluded from taking TQ or PQ. The estimated prevalence of G6PD deficiency in the US population is 4-7% [Nkhoma, 2009]. The prevalence of G6PD deficiency is higher in many malaria endemic areas, because this genetic defect appears to offer some protection against malaria infection [Howes, 2013]. The co-incidence of malaria and this enzyme deficiency is therefore common and highly relevant clinically.

The distribution of G6PD enzyme activity in males is bimodal and individuals are either normal or deficient, since they carry only one copy of the G6PD gene. Females carry two copies of the gene, and can therefore be heterozygous for G6PD deficiency.

There are more than >180 known G6PD gene alleles [Luzzatto, 2016], and as a consequence genetic testing to identify G6PD-deficient subjects is at present not routinely performed. Instead, males hemizygous for G6PD deficiency and females homozygous for G6PD deficiency are readily identified by qualitative enzymatic tests such as the fluorescent spot test, and therefore readily excluded from treatment with drugs that cause hemolysis.

Females who are heterozygous for G6PD deficiency have varying levels of X-chromosome inactivation, resulting in a spectrum of G6PD enzyme activity ranging from fully deficient to, intermediate levels of deficiency through to normal levels of enzyme activity. The difference in G6PD activity is at a cellular level, with individual cells being either deficient or normal [Shah, 2012]. Qualitative tests such as the fluorescent spot test are unable to reliably identify heterozygous females with intermediate levels of G6PD deficiency [Baird, 2015]. In the US high quality quantitative laboratory testing for G6PD deficiency is readily available.

The long half-life of TQ (about 15 days compared with 4 9 hours for PQ) means that treatment once administered cannot be withdrawn, making it imperative that patients with G6PD deficiency are not prescribed TQ [Rajapakse, 2015]. However, the shorter half-life of PQ does not improve the benefit-risk calculation as much as one might assume,

because with drug-induced hemolysis secondary to PQ, Hb continues to decline for 3 to 4 days after withdrawal of PQ [Hodgkinson, 1961; George, 1967; Charoenlarp, 1972].

2.2. Clinical Development Program and Key Studies Contributing Efficacy and Safety Data

The primary studies were based on ex-US sites for recruitment and observation of relapse because there is no endemic malaria in the US, and the generally shorter time to relapse in tropical regions. However, there is no reason to expect *P. vivax* disease in endemic region patients to differ from US patients who contract malaria due to travel or occupational exposure. More than 400 healthy volunteers have been dosed with TQ in clinical pharmacology studies at study sites in the US and no clinically relevant differences in systemic exposure (AUC) have been observed for TQ in US subjects compared to those enrolled in the Phase 2b/3 program.

GSK and FDA agreed a subset of 13 studies that directly supported the *P. vivax* radical cure program (Table 8). Overall, 33 clinical studies of TQ have been completed. Clinical studies include Phase 1, 2, and 3 studies, single and multiple oral dose studies, studies in fasted and non-fasted subjects, bioavailability studies for different TQ formulations, drug-drug interaction studies, malaria challenge studies, malaria prophylaxis studies, and *P. vivax* malaria treatment studies (i.e., for radical cure, defined as prevention of relapse) (Appendix Section 9.7).

Table 8 Studies Directly Supporting TQ in the *P. vivax* Radical Cure Program

Study	Description of Study
TAF112582 Part 1	Phase IIb dose finding study in patients with *P. vivax* malaria
TAF112582 Part 2	Pivotal Phase III efficacy study in patients with *P. vivax* malaria
TAF116564	Phase III safety study in patients with *P. vivax* malaria
SB252263/022	Phase I Food effect study in healthy volunteers
TAF114582	Phase I Thorough QT study in healthy volunteers
201807	Phase I Ophthalmic safety study in healthy volunteers
SB252263/015	Phase I Drug-drug interaction study with desipramine in healthy volunteers
SB252263/040	Phase I Drug-drug interaction study with midazolam, flubiprofen and caffeine in healthy volunteers
TAF106491	Phase I Drug-drug interaction study with chloroquine in healthy volunteers
200951	Phase I Drug-drug interaction study with artemether-lumefantrine, and dihydroartemisinin-piperaquine tetraphosphate in healthy volunteers
TAF110027	Phase I dose escalation study in healthy volunteers and G6PD deficient healthy volunteers
201780	Phase I study in healthy volunteers to determine the effects of tablet aging (dissolution profiles) on the PK of TQ
TAF115226	Non-interventional study in healthy volunteers to establish site level normal ranges for G6PD enzyme activity

The primary evidence for the clinical efficacy and safety of 300 mg single dose TQ for radical cure of *P. vivax* malaria is provided by 3 randomized, double-blind studies (hereafter referred to as the primary studies) (Table 1): 582 Part 1 (Phase 2b), 582 Part 2 (pivotal Phase 3), and 564 (Phase 3). In all 3 primary studies, 300 mg single dose TQ was co-administered with CQ (Days 1 to 3) (TQ+CQ) and subjects treated with PQ 15 mg once daily for 14 days also received CQ (Days 1 to 3) (PQ+CQ). Altogether, a total of 483 subjects with *P. vivax* malaria have been exposed to TQ+CQ in the 3 primary studies.

In addition to the safety data from the primary studies, specific safety results from 2 individual studies in healthy volunteers, the study assessing ophthalmic safety and the definitive study of cardiac safety, provide clinically important safety observations to the regulatory submission under review:

- **Study 201807:** Ophthalmic safety data were collected across several studies prior to the launch of the primary studies in *P. vivax* subjects (SB252263/033, SB252263/057, SB252263/058 and TAF106491), as well as in the Phase 2b and Phase 3 studies. Study 201807 was a definitive ophthalmic safety study based on regulatory agency guidance.
- **Study TAF114582:** Similarly, while electrocardiogram (ECG) data were evaluated across multiple studies, including the primary studies, Study TAF114582 is considered the definitive study of cardiac safety. The primary endpoint was QT duration corrected for heart rate by Fridericia's formula (QTcF).

Safety data from the 3 primary studies of TQ for the radical cure of *P. vivax* malaria were pooled, as agreed with US FDA, to address the primary objectives (Table 9). The principal pooled data for assessing TQ+CQ compared with CQ alone includes Parts 1 and 2 of TAF112582 (PC grouping). The grouping that includes all 3 primary studies provides further evidence for TQ+CQ in *P. vivax* malaria compared with the current standard of care, PQ+CQ (AP grouping). In addition, a comprehensive evaluation of safety across the diverse TQ development program is supported by pooled safety data from different dosing regimens and populations, including an All Studies grouping with an All TQ group.

Table 9 Pooled Groupings for Analysis of Safety Data

Grouping label	Studies included	Subjects
All Studies	26 completed studies with available safety datasets[a]	All treated
All Primary Studies (AP)	582 Part 2, 582 Part 1 (CQ alone, 300 mg TQ), 564	*P. vivax*-infected
Placebo-controlled Studies (PC)	582 Part 2, 582 Part 1 (CQ alone, 300 mg TQ)	*P. vivax*-infected

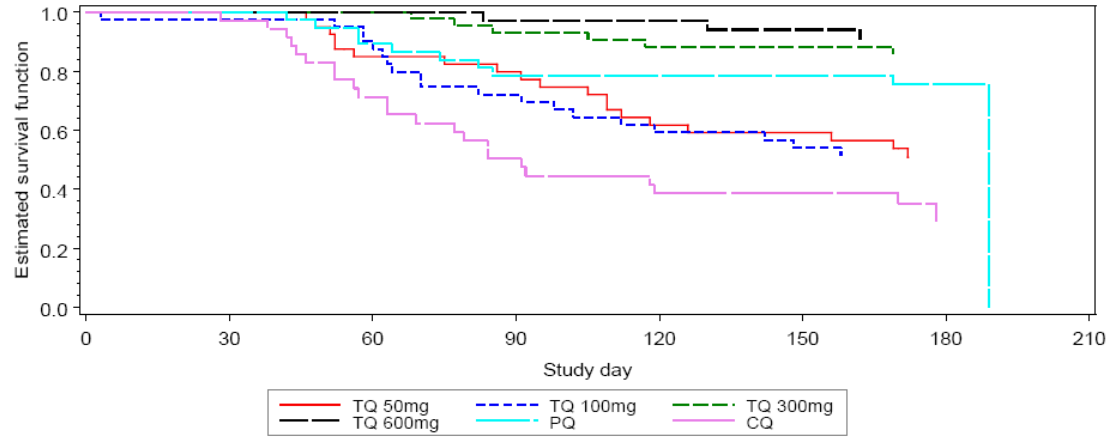
a. Data from studies SB252263/003, 036, 050, 051, 052, 053 and 054 have been excluded from the pooled groupings; Interim data from Study 201807 included.

2.3. Rationale for 300 mg Single Dose TQ Treatment

TQ 300 mg is an effective single-dose treatment for the radical cure of *P. vivax*. The simple dosing regimen is anticipated to provide high treatment compliance, even in the real-world setting, resulting in improved individual and public health outcomes.

Study 582 Part 1 was a Phase 2b dose-ranging study used to define the optimal dose for Phase 3. Doses ranging from 50 mg to 600 mg were chosen for Study 582 Part 1 in order to minimize risk to G6PD-deficient individuals with moderate deficiency, while optimizing the chance of identifying an efficacious dose. Of the 4 TQ doses studied in Part 1, 300 mg and 600 mg TQ+CQ met the efficacy criteria for selection to Part 2 (statistically significant difference compared to CQ alone ($p \leq 0.05$).

Figure 4 Survival Curves for Time to P. vivax Relapse in TAF112582 Part 1 (ITT Population)



Number of subjects at risk during the interval

TQ 50mg	40	33	31	24	22	6
TQ 100mg	39	36	28	23	21	5
TQ 300mg	43	43	40	37	37	15
TQ 600mg	36	36	33	32	30	9
PQ	37	33	28	28	28	10
CQ	34	24	17	13	13	5

A categorical and regression tree (CART) analysis identified TQ exposure (AUC) of 56.4 µg.hr/mL as a breakpoint exposure threshold that was a significant predictor of relapse outcome. The initial population PK model predicted that 93% of subjects were predicted to have an AUC value exceeding the CART-derived breakpoint of 56.4 µg.h/mL with the 300 mg TQ dose (Section 4.5.3).

Criteria for an acceptable safety profile were applied considering all safety data. No new safety concerns were identified at any of the TQ dose levels in Study 582 Part 1. However, based on the lack of evidence of any increase in efficacy between 300 mg and 600 mg TQ, the 300 mg dose was selected for evaluation in the Phase 3 studies.

In addition, the TQ development program has established that excluding patients with G6PD activity <70% is effective at preventing clinically significant drug-induced

hemolysis, and the safety of TQ dosing is supported by a well-defined G6PD enzyme activity cut-off. In ICH regions, existing quantitative laboratory diagnostics already have this capability [Trinity Biotech, 2012].

3. SUMMARY OF NON-CLINICAL STUDIES

Mechanism of Action

TQ is being developed for radical cure of *P. vivax* malaria infections, however, the exact antimalarial mechanism of action of TQ has not been identified. Several possible mechanisms of action have been postulated for TQ and other related 8-aminoquinolines in relation to their activity against the parasite liver stage hypnozoite. The 4-amino-1-methylbutyl side chain has been shown to generate superoxides, which may contribute to the activity of this drug class against exoerythrocytic parasites. TQ has been reported to inhibit hematin polymerization, which may contribute to its schizonticidal activity, although this effect has not been demonstrated for PQ. Sporogony of *P. berghei* was shown to be interrupted by TQ with inhibition of oocyst production and development, and decreased sporozoite release and invasion of mosquito salivary glands. Finally, treatment with the 8-aminoquinolines may result in mitochondrial dysfunction and alteration of intracellular membrane structures in both erythrocytic and exoerythrocytic stages of this parasite [Crockett, 2007]. To date, no molecular target has been identified as responsible for TQ activity. Co-administration with another blood schizonticide (initially CQ) will be required for treatment of *P. vivax* malaria since the combination targets with high efficacy both blood and liver stages of infection.

Resistance

The probability of pre-existing resistance to TQ is low. Multi-drug resistant strains of *P. falciparum* were susceptible to TQ in vitro. TQ exhibited equivalent activity to primaquine against CQ-susceptible strains; however, CQ-resistant and other multi-drug (mefloquine, pyrimethamine) resistant strains were more susceptible to TQ. In primate models, blood stages of CQ-resistant *P. vivax* were successfully treated with TQ [Vennerstrom, 1999].

There is no indication of *in vitro* or *in vivo* resistance of *Plasmodium* liver stages to TQ. However, some observations have been reported in the literature with respect to resistance development to TQ by human malaria parasite blood stages [Kaewpruk, 2016; Manzano, 2011; Peters, 2003]. However, as variations in measured IC50s were <2-fold and because acquisition of resistance can largely be suppressed by combination of CQ, any clinical resistance is unlikely to occur.

However, *in vitro* and *in vivo* models of *P. vivax* relapse are poorly developed, limiting the definition of mechanism of action and study of hypnozoite resistance.

Safety Pharmacology

There were no findings in safety pharmacology studies on respiratory, cardiovascular or neurobehavioral function (including motor activity) that would indicate an unacceptable risk for single dose oral administration of TQ.

Toxicology

Repeat Exposure

TQ has been evaluated in repeat dose toxicity studies of up to 13, 26 and 52-week in duration in mice, rats and dogs and a 4-day PK study in monkeys. Principal findings, following repeat dosing, were mortality and morbidity, hematological (e.g., decreased Hb, increased methemoglobin), pulmonary (e.g., increased numbers of foamy macrophages and the presence of eosinophilic material in alveoli), hepatic (e.g., increased liver weight, subacute inflammation), and renal toxicity (e.g., renal tubular lesions). The majority of the hematologic, hepatic, pulmonary and renal affects were both dose- and duration-dependent, and reversible upon cessation of treatment.

Nervous System

A series of studies to assess the potential CNS effects of TQ in nonclinical species have been conducted including; histopathological assessments in numerous single and repeat dose studies (mice, rats and dogs), investigation of the tissue/organ distribution of TQ in rats, and detailed assessments of both neurobehavioral function and neurohistopathology in both single and repeat dose studies in rats.

There was no evidence that TQ administration was associated with changes in brain weight, gross macroscopic abnormalities of the brain or abnormal microscopic histopathological changes in the brain in the repeat dose toxicology studies conducted with mice, rats and dogs of up to 13, 26, and 52 weeks in duration, respectively, and no evidence of any abnormal non-neoplastic microscopic histopathological changes in the brain in the carcinogenicity studies in mice and rats.

The distribution of TQ was investigated in male rats in studies following a single oral dose of [^{14}C]-TQ up to 25 mg/kg, and in male and female rats as part of a quantitative whole-body autoradiography (QWBA) study following a single oral dose of [^{14}C]-TQ at 0.5 mg/kg.

Although TQ drug-related material (DRM) penetrates the blood-brain barrier in rats, brain concentrations of radiolabelled DRM were low, both in term of absolute levels (<1% dose), and levels relative to concentrations in other body tissues/organs. In rat tissue, plasma concentration ratio for TQ levels in the brain was amongst the lowest among all body tissues assessed with QWBA.

In a rat, single dose neurobehavioral and CNS-pathology study no test article related CNS-pathological effects were observed. There was no effect on functional observation battery, the only observation was a test article related attenuation in spontaneous locomotor activity. Following consultation with the FDA, neurobehavioral evaluations were included in the repeat dose juvenile rat toxicology study. In this repeat dose study,

no test article related neurobehavioral or CNS-pathological effects were observed in juvenile rats.

Neurobehavioral alterations and /or CNS-pathology with certain quinoline anti-malarials have been variously observed in mice, rats, dogs and/or rhesus monkeys [Dow 2006, Lee 1981, Korte 1979, Korte 1982, Schmidt 1948, Schmidt 1949, Schmidt 1950, Schmidt 1951]. TQ has been tested in species (mice, rats and dogs) that have been shown to be sensitive for these changes; the effect of TQ on the CNS of the monkey has not been examined in a toxicology study.

In summary, TQ does not induce neurotoxicity in single and repeat dose toxicology studies in mice, rats and dogs, or specific neurobehavioral studies in rats at exposures that are comparable to or in excess of those seen at the recommended treatment dose for patients.

Carcinogenicity
TQ was not genotoxic in a standard battery of vitro or in vivo assays. TQ was not carcinogenic in mice but was carcinogenic in rats (following exposure for 2 years) inducing an increase in the incidence of renal cell tumors and hyperplasia in males.

Teratogenicity
In a rat fertility study in the presence of toxicity, there was reduced fertility in female rats. No developmental toxicity was seen in rats or rabbits. In a pre- and postnatal development study in rats, in the presence of toxicity, decreased offspring body weight gain (not observed at maturity) was associated with a delay in eye opening and decrease in motor activity.

4. OVERVIEW OF CLINICAL PHARMACOLOGY

4.1. Clinical Pharmacology Summary

Overall, the PK, PD, PK/PD relationships in patient populations, and drug interaction profiles support 300 mg single dose TQ therapy for the radical cure of *P. vivax*.

4.1.1. Pharmacokinetics

- TQ is slowly absorbed following oral administration to humans with maximum concentrations reached approximately 12-15 h post dose.
- TQ should be administered with food in order to improve systemic absorption and minimize GI side effects.
- PK is linear with dose proportional increase in systemic exposures up to 1200 mg.
- TQ exhibits a biphasic concentration-time profile with high volume of distribution and long elimination half-life of 15 days on average.
- Whole blood TQ levels are higher than plasma concentrations reflecting the preferential partitioning of drug in erythrocytes.

- No dose adjustment needed based on age or race.
- Dose adjustments in patients with hepatic or renal impairment are unlikely to be required based on the available nonclinical and clinical data, and as TQ is administered as a single dose.

4.1.2. Drug-Drug Interactions

- TQ does not have any clinically relevant impact on cytochrome P450 (CYP) 2D6, CYP3A4, CYP2C8, CYP2C9, CYP1A2 substrates.
- TQ can be administered without dose adjustment with other commonly prescribed anti-malarial drugs such as CQ and ACTs, namely dihydroartemisinin/piperaquine (DHA/PQP) or artemether/lumefantrine (AL).
- TQ inhibited the *in vitro* transport of [^{14}C]-metformin via human organic cation transporter (OCT)2, multidrug and toxic compound extrusion protein (MATE)1 and MATE2-K. There may be a small risk of lactic acidosis in patients due to increased metformin exposure secondary to blockade of these transporters. Therefore, TQ should be used with caution with metformin.
- Drugs with small therapeutic index that are substrates of the renal transporters OCT2 and MATEs should not be co-administered regardless of renal function.

4.1.3. Pharmacodynamics

- TQ has no clinically significant effect on QT at clinically relevant doses of 300 and 600 mg compared to placebo. The maximum effect on QTcF prolongation with the supratherapeutic dose of TQ 1200 mg compared to placebo was within the safety margin of 10 msec set out in the regulatory guidelines.
- TQ demonstrates dose-dependent Hb declines in heterozygous G6PD deficient subjects with increasing doses of TQ. The highest median Hb declines observed in G6PD heterozygous females with intermediate levels of deficiency (G6PD activity >40% <70%) at the TQ 300mg dose was comparable to PQ (15mg daily for 14 days).
- No clinically significant Hb declines have been reported in subjects with G6PD ≥70% normal.

4.1.4. PK/PD Relationships

The exposure-response analysis identified a systemic exposure threshold AUC (56.4 μg.h/mL) above which the recurrence-free rate at the end of 6 months was 89% as compared to when AUC <56.4 μg.h/mL with a recurrence-free rate of 48%.

The 300 mg dose is expected to achieve systemic exposures higher than this threshold in the majority of the patients.

4.2. Absorption, Distribution, Metabolism, and Excretion

4.2.1. Absorption and Distribution

TQ is slowly absorbed in humans following oral administration with median t_{max} of 12-15 hours. The slow absorption is consistent with nonclinical data where t_{max} was generally >6 hours after single or repeat oral dosing in rat, dog and monkey. Systemic exposure generally increased proportionately with dose and substantial accumulation of TQ is observed (up to 10x) on repeat dosing consistent with its long half-life.

Dosing TQ with food leads to increased exposure with average increases of 41% and 31% in AUC and Cmax respectively. Administering with food leads to better tolerability and fewer incidences of GI disturbances. TQ is recommended to be taken with food to increase systemic absorption and minimize GI side effects consistent with the approach employed in all patient studies. TQ exhibits linear PK with approximate dose proportional increases in exposure between 36 mg to 1200 mg oral doses.

TQ exhibits very high plasma protein binding in nonclinical species and humans (>99.5%) with higher blood concentrations as compared to plasma levels. This reflects preferential partitioning of the drug in the erythrocytes. TQ has moderate absorptive membrane permeability *in vitro* and is widely distributed in both nonclinical species and human with a large apparent oral volume of distribution (>1500 L) as identified from the population PK analysis.

Following dosing of [^{14}C]-TQ to rats, concentrations of radioactivity peaked between 12 and 24 h with the highest concentrations observed in the GI tract, adrenal cortex, pituitary, ovary, liver, lungs, Harderian gland, spleen and small intestine mucosa. In contrast, the lowest levels of radioactivity were associated with the central nervous system (including brain), white fat and blood. Tissue levels of radioactivity declined slowly and at 240 h after dosing, most tissues still contained quantifiable levels of radioactivity.

4.2.2. Metabolism

Negligible metabolism of TQ was evident in multiple *in vitro* incubations performed (nonclinical and /or human hepatocytes, microsomes or recombinant drug metabolizing enzymes [CYPs and monoamine oxidases (MAOs)]. All drug-related components observed were detected in sample and control incubations, and definitive investigations highlighted that the DRM present, other than TQ, was generated via visible light instability and not directly formed via metabolism. In humans (including both G6PD normal and G6PD deficient females), following administration of 300 mg single oral doses of TQ, DRM identified in blood and plasma was almost exclusively in the form of unchanged TQ. All other circulating components observed were minor, the most notable being a carboxylic acid metabolite, which represented ≤6% of the parent concentration. Drug-related components were excreted very slowly in human urine, primarily as products of O-demethylation, oxidation, O-dearylation and glucuronide conjugation all of which had been previously seen in both rat and dog. It was noted that within in vivo

studies it was not possible to determine whether several of the observed drug-related components were formed by ex vivo degradation and/or in vivo metabolism.

4.2.3. Excretion

Definitive elimination data in humans has not been generated. The slow absorption and long elimination half-life makes an ADME study infeasible in clinic. Therefore, no clinical ADME study has been conducted with [^{14}C]-TQ. Nonetheless, some data has been obtained showing very slow excretion via the urine (as determined over a 6-day collection period) and renal elimination of unchanged TQ in humans was a very minor route. Overall, TQ is slowly eliminated with an average terminal half-life of approximately 15 days. The population PK analysis also identified a low apparent oral clearance of approximately 3 L/hr.

In nonclinical species following administration of [^{14}C] TQ to rats, dogs and monkeys, feces was the predominant route of elimination accounting for between 35% and 67% of the administered dose, consisting primarily of unabsorbed TQ. Biliary secretion in the rat and dog was low and accounted for approximately 5% and 20% of the administered oral dose, respectively (absorbed drug being eliminated as metabolites and unchanged TQ). Urinary excretion was responsible for the elimination of up to 21% of the administered radiolabelled dose in non-cannulated rats, dogs and monkeys and was largely in the form of drug-related components (in vivo metabolites and/or ex vivo degradants). Slow protracted excretion of radioactivity was noted beyond 10-days post dose in these studies (in tissues/carcass where measured).

4.3. PK Analysis of TQ Exposure

4.3.1. Summary of TQ PK parameters

The PK of TQ can be characterized adequately based on dense serial PK sampling in clinical studies with healthy subjects (Table 10).

Table 10 PK Parameters from Healthy Volunteer Studies

Population	Dose	Formulation	Data Source	Cmax (ng/mL)	$AUC_{0\text{-}inf}$ (ug.hr/mL)	Mean $T_{1/2}$ (days)
Healthy	200 mg (fasted)	Capsule	SB252263/022	113	46.5	15.4
	200 mg (fed)	Capsule	SB252263/022	152	66.5	15.5
	300 mg (fed)	Tablet	200951	200	97.2	15.8
	300 mg (fed)	Tablet	201780	224	97.1	15.1

Note: TQ administered alone as a single dose regimen
AUC and Cmax – geometric means; 201780 - geometric LS means
All studies were conducted in the US or EU.

The single dose radical cure for *P. vivax* clinical studies employed sparse PK sampling (Table 11). The exposure in these patient populations was primarily characterized with a

population PK analysis. The PK data show similar PK profiles for healthy volunteers, including subjects from the US, and *P. vivax*-infected subjects from endemic regions.

Table 11 PK Parameters in the Patient Population from Population PK Analysis

Population	Dose	Study/Data Source	Formulation	Cmax (ng/mL)	$AUC_{0\text{-}60days}$ (ug.hr/mL)
Patients with *P vivax* malaria infection	300 mg	TAF112582 Part 1	Capsule	335 (188 – 549)	93.6 (62.3 – 152)
	300 mg	TAF112582 Part 2	Tablet	330 (193 – 505)	104 (61.1 – 152)
	300 mg	TAF116564	Tablet	302 (179 – 428)	96 (62.3 – 135)

Note: Based on the final population PK model post hoc estimates; AUC and Cmax - Median (90% prediction intervals)

4.3.2. PK in Special Populations

The PK of TQ in subjects with G6PD deficiency was assessed in a safety study (TAF110027). The study characterized TQ exposure in 24 G6PD-normal and 27 G6PD-genetically heterozygous females administered single doses ranging from 100 to 300 mg. There was no difference in exposure across subjects with or without G6PD deficiency.

TQ has not been studied in patients with hepatic impairment. Dose adjustments in patients with hepatic impairment are unlikely to be required as TQ is administered as a single dose.

Similarly, TQ has not been studied in patients with renal impairment. Dose adjustments in patients with renal impairment are unlikely to be required as TQ is administered as a single dose.

4.3.3. Population PK

Population PK analysis was conducted using TQ exposure data pooled from multiple studies ranging from Phase 1 with healthy volunteers through Phase 3 with *P. vivax*-infected subjects. The analysis demonstrated a lack of clinically relevant impact of age, gender, ethnicity or disease status on TQ PK. No dose adjustment is deemed necessary based on any of these factors.

4.4. Drug-Drug Interaction

4.4.1. Effect of TQ on the PK of Other Agents

In vitro, in human liver microsomes, TQ inhibited CYP1A2, CYP2A6, CYP2C8, CYP2C9 and CYP3A4 enzymes with Ki values ranging from 2 to 10 μM, with no evidence of metabolism dependent inhibition. Nonetheless, subsequent clinical drug-drug interaction studies demonstrated no clinically relevant inhibition of these CYP enzymes. No clinically significant changes were observed in concentrations of desipramine (CYP2D6 substrate), midazolam (CYP3A4 substrate), or flurbiprofen

(CYP2C9 substrate) when these drugs were either co-administered with TQ or administered alone.

The *in vivo* data from studies evaluating the impact of TQ on co-administration with other anti-malarial pharmacotherapy such as CQ and ACTs, i.e. DHA/PQP or AL (Table 12) demonstrated that no dose adjustment is deemed necessary for CQ or ACTs, as TQ has no clinically relevant impact on their systemic exposure [Miller, 2013; Green, 2016].

TQ inhibited the *in vitro* transport of [14C]-metformin via human OCT2 and MATE. This may be potentially correlated to the mild and transient serum creatinine increases observed in clinical studies across a range of doses and regimens due to inhibition of tubular transport. Risk assessments based on systemic concentrations (unbound Cmax) of TQ at therapeutic doses, compared with the in vitro IC50 values indicated a potential, but low, drug interaction risk with OCT2 and MATE substrates.

There may be a small risk of lactic acidosis in patients due to increased metformin exposure secondary to blockade of these transporters. Therefore, language indicating TQ should be used with caution with metformin is included in proposed labeling subject to FDA review. Drugs with narrow therapeutic index that are substrates of the renal transporters OCT2 and MATEs should not be co-administered regardless of renal function (e.g. phenformin, buformin, dofetilide, procainamide and pilsicainide).

The risk of clinically relevant drug interactions with other drug transporter substrates is considered limited based on the single dose regimen of TQ. Inhibition of PgP, BCRP, and OATP has not been studied.

Table 12 Effect of TQ on Concomitant Medications

Concomitant Drug	Concom Drug Dose (mg)[a]	TQ Dose (mg)	N[d]	Geometric Mean Ratio (90% CI) Co-ad drug+TQ/co-ad drug alone		Study	Conclusion
				AUC[c]	Cmax		
Desipramine	100	400 (x 3 day)	34	0.94 (0.89, 1.00[e])	1.04 (0.98, 1.10)	SB252263/015	No dose adjustment for CYP2D6 substrates
Midazolam	5	400	N_{Cmax} =25 N_{AUC} = 22	0.88 (0.83, 0.94)	0.97 (0.83, 1.13)	SB252263/040	No dose adjustment for CYP3A4 substrates
Flurbiprofen	50	400	24	1.13 (1.09, 1.16)	0.98 (0.91, 1.04)	SB252263/040	No dose adjustment for CYP2C9 substrates
Caffeine	200	400	24	1.01 (0.98, 1.05)	0.95 (0.89, 1.01)	SB252263/040	No dose adjustment for CYP1A2 substrates
Chloroquine[b]	1500	900	18	1.00 (0.84, 1.18)	Day2 – 0.89 (0.74, 1.08) Day3 – 1.04 (0.86, 1.25)	TAF106491	No CQ dose adjustment
Dihydroartemisinin (DHA)[b]	320/40 for 3 days	300	$N_{DHA/PQP}$=23 $N_{DHA/PQP+Taf}$=24	1.00 (0.82, 1.24)	0.95 (0.75, 1.20)	200951	No DHA/PQP dose adjustment
Piperaquine (PQP)[b]	320/40 for 3 days	300	N_{AL}=22 N_{AL+Taf}=24	0.94 (0.81, 1.08)	0.91 (0.76, 1.08)	200951	
Artemether (A)[b]	120/20 at 0,8,24,36,48 and 60 hrs	300	N_{AL}=22 N_{AL+Taf}=24	1.03 (0.52, 2.04)	1.03 (0.71, 1.49)	200951	No AL dose adjustment
Lumefantrine (L)[b]	120/20 at 0,8,24,36,48 and 60 hrs	300	22	1.13 (0.87, 1.45)	1.08 (0.86, 1.36)	200951	

a. Unit dose given for DHA-PQP and AL; total dose given for CQ.
b. refer to individual study reports for all study design details including dosing and PK sampling schedule
c. reflects AUC0-inf, AUC0-tau or AUC0-t as appropriate. Refer to individual study reports
d. all studies are parallel-design

4.4.2. Effect of Other Agents on the PK of TQ and Dose Recommendations

In vitro hepatocyte or microsomal studies demonstrated no metabolic turnover of TQ. Furthermore, the potential for TQ to be a victim of drug interactions is considered low due to its very slow *in vivo* metabolism, extended excretion and the single dose regimen.

Although the P-glycoprotein (Pgp) substrate status of TQ could not be reliably determined, if it were assumed TQ was a Pgp substrate, there exists some potential for an interaction at the level of the GI tract which could, potentially, increase TQ systemic exposure if co-administered with strong Pgp inhibitor(s). The OATP substrate status of TQ has not been studied, but based on the rat QWBA data and the principles outlined in Mikkaichi et al [Mikkaichi, 2015] TQ is not considered to be an OATP substrate. Nonetheless, TQ has been safely administered at doses of 600 mg single dose and 1200 mg (administered as 400 mg once daily for 3 days) which is 2-4 times higher than the currently recommended 300 mg single dose for *P. vivax* radical cure. Collectively, the risk of any clinically significant drug transporter mediated interaction is considered to be very low.

Further clinical drug interaction studies demonstrated a minor increase in TQ C_{max} when TQ was co-administered with CQ with no significant effect on the overall exposure. Similarly, there was an increase in TQ C_{max} on co-administration with the DHA/PQP (Table 13). These changes in TQ exposure are not considered to be clinically relevant. There was no change in TQ exposure on co-administration with AL. TQ can be co-administered with other anti-malarial drugs such as CQ or ACTs without any dose adjustment.

Table 13 Effect of Concomitant Medications on TQ and Dose Recommendations

Concomitant Drug	Concom Drug Dose (mg)[a]	TAF Dose (mg)	N[d]	Geometric Mean Ratio (90% CI) Co-ad drug+TAF/co-ad drug alone		Study	TQ Dose Recommendation
				AUC[c]	Cmax		
Chloroquine[b]	1500	900	N_{Taf}=20 $N_{DTaf+Chloroq}$=18	0.98 (0.84, 1.14)	Day2 – 1.38 (1.17, 1.64) Day3 – 1.13 (0.96, 1.34)	TAF106491	No dose adjustment
Dihydroartemisinin/Piperaquine (DHA/PQP)[b]	320/40 for 3 days	300	24	1.12 (1.01, 1.26)	1.38 (1.25, 1.52)	200951	No dose adjustment
Artemether/Lumefantrine(AL)[b]	120/20 at 0,8,24,36, 48 and 60 hrs	300	24	1.05 (0.93, 1.20)	1.04 (0.95, 1.15)	200951	No dose adjustment

a. Unit dose given for DHA-PQP and AL; total dose given for CQ.
b. refer to individual study reports for all study design details including dosing and PK sampling schedule
c. reflects AUC0-inf
d. all studies are parallel-design

4.5. PD, PK-PD and Dosing Recommendations

4.5.1. Effect on Cardiac Repolarization

In a randomized, single blind, placebo controlled parallel-group study (TAF114582), 260 subjects received oral administration of either placebo, 400 mg moxifloxacin (active control), 300 mg, 600 mg or supratherapeutic 1200 mg doses of TQ. All doses were administered as single doses except the supratherapeutic TQ dose of 1200 mg administered as 400 mg once daily for three days. The clinically relevant 300 mg and 600 mg TQ doses demonstrated a lack of effect on QTcF prolongation. The maximum effect on QTcF at the supratherapeutic dose of 1200 mg compared to placebo was <10 msec and within the FDA E14 guidelines for lack of effect. The largest effects in this 1200 mg dose group were observed at 36 hours post final dose (mean 6.39 msec, 90% CI: 2.86, 9.92) and at 72 hours post final dose (mean 6.39 msec, 90% CI; 2.85, 9.94).

Co-administration of TQ with other antimalarial drugs such as CQ or ACTs such as DHA/PQ or AL did not show an additional effect from TQ on the QTcF interval prolongation as evidenced in clinical studies TAF106491 and 200951.

4.5.2. Hemolytic potential in G6PD Deficiency

In an open label, single dose, dose-escalation study (TAF110027), TQ (100, 200 and 300 mg doses) was administered to female healthy volunteers genetically normal or heterozygous for a mutation conferring G6PD deficiency (40 60% G6PD activity). The study also evaluated PQ 15 mg once daily × 14 days as a positive control.

In contrast to the G6PD normal subjects, there was a dose dependent decline in Hb in heterozygous G6PD-deficient subjects with intermediate levels of G6PD activity with increasing doses of TQ, although the PK for the 2 groups was similar (Section 4.3.2). The highest median Hb declines were observed in G6PD deficient females in the TQ 300 mg and PQ group. No subjects reported any major clinical symptoms relating to their observed Hb decline.

Similar median Hb decreases were observed in subjects heterozygous for a G6PD gene mutation and with >60% G6PD activity, compared to control subjects without the mutation, leading to a recommended cut-off of ≥70% G6PD activity for 300 mg single dose TQ treatment [Rueangweerayut, 2017].

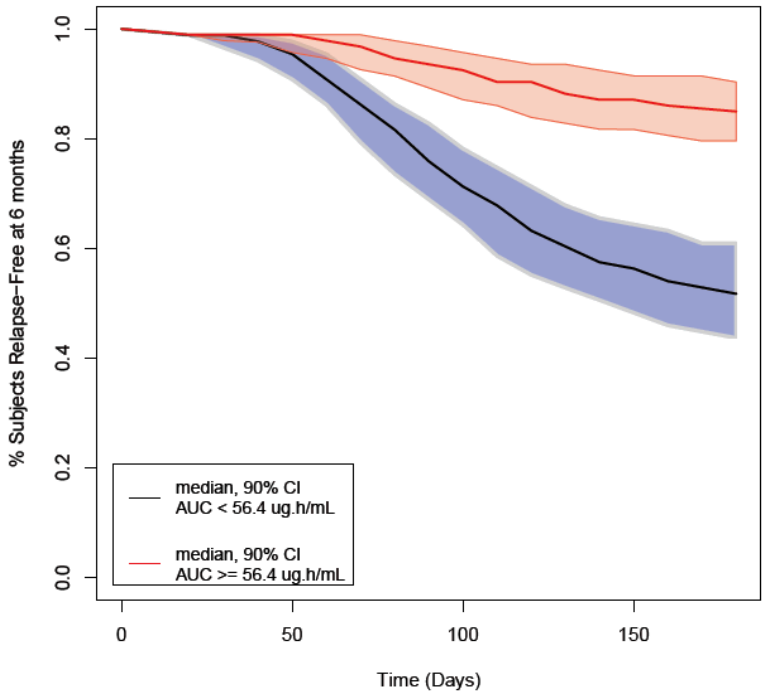
4.5.3. PK/PD relationship

TQ PK/PD relationship was conducted based on the TQ exposure (PK) and *P. vivax* malaria recurrence at the end of 6 months response (PD) data obtained from the dose ranging Phase 2b trial 582 Part 1. A categorical and regression tree (CART) analysis identified TQ exposure (AUC) of 56.4 µg.hr/mL as a breakpoint exposure threshold that was a significant predictor of relapse outcome. When AUC was ≥56.4 µg.h/mL, 89%

were recurrence-free at 6 months (72 success, 9 failure), whereas when AUC was <56.4 µg.h/mL, only 48% were recurrence-free at 6 months (40 success, 43 failure) (χ^2 test: p <0.001). Based on the time-to-relapse model simulations (Figure 5), the probability of being relapse-free at 6 months for subjects with an AUC above and below 56.4 µg.h/mL are:

- 85% (95% CI: 80% to 90%) in subjects with an AUC ≥56.4 µg.h/mL; and
- 52% (95% CI: 44% to 61%) in subjects with an AUC <56.4 µg.h/mL.

Figure 5 Probability of being Relapse-Free Below and Above the CART Analysis TQ Exposure Breakpoint



Dose based on PK/PD relationship

The initial population PK model predicted that 93% of subjects were predicted to have an AUC value exceeding the CART-derived breakpoint of 56.4 µg.h/mL with a 300 mg TQ dose, the dose which was evaluated in Phase 3 studies.

The 5th percentile of AUC across the two Phase 3 studies in the final population PK model is greater than the previously identified CART breakpoint exposure of 56.4 ug.hr/mL, providing most (>95%) subjects with exposures that have high likelihood of being relapse-free (Table 14). TQ efficacy has been clearly established in these Phase 3 studies. These data collectively support 300 mg single dose TQ for the radical cure of *P. vivax* malaria.

Table 14 Summary of TQ Exposures Obtained Using the Population PK Model

Dose	Study	Formulation	Cmax (ng/mL)	$AUC_{0\text{-}60days}$ (ug.hr/mL)
300mg	TAF112582 Part 2	Tablet	330 (193 – 505)	104 (61.1 – 152)
300mg	TAF116564	Tablet	302 (179 – 428)	96 (62.3 – 135)

Note: Based on the final population PK model post hoc estimates
AUC and Cmax - Median (90% prediction intervals)

5. OVERVIEW OF EFFICACY

The primary evidence for the clinical efficacy of TQ for the radical cure of *P. vivax* malaria is provided by one fully powered Phase 2b (582 Part 1) to confirm dose selection, and two Phase 3 studies (582 Part 2 and 564). The pivotal efficacy study was Study 582 Part 2 and supportive efficacy data came from Study 582 Part 1 and Study 564.

Based on the results from Study 582 Part 1, the 300 mg dose was selected for Phase 3. No clinically relevant additional benefit was seen with the 600 mg dose, and the hemolytic potential of the 300 mg dose was comparable to that of PQ 15 mg daily × 14 days + CQ treatment in G6PD-normal subjects.

Treatment with 300 mg single dose TQ, when co-administered with standard doses of CQ, resulted in a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 6 months relative to treatment with CQ alone in Study 582 Part 2. Similarly in the alternative logistic regression analysis, a larger proportion of subjects treated with TQ+CQ were recurrence-free during the first 6 months compared with CQ treatment alone and there was a clinically and statistically significant reduction in the odds of recurrence.

Analysis at 4 months follow-up, which reduced the complication of re-infections, also showed a higher recurrence-free rate for 300 mg single dose TQ+CQ compared to CQ alone.

Recurrence-free efficacy results at 6 months and at 4 months from Studies 582 Part 1 and 564 supported the results of the pivotal efficacy study.

Table 15 Recurrence-free Efficacy Results from the Primary Studies (mITT Population)

	582 Part 2			582 Part 1			TAF116564	
	CQ N=133	TQ+CQ N=260	PQ+CQ N=129	CQ N=54	TQ+CQ[e] N=57	PQ+CQ N=50	TQ+CQ N=166	PQ+CQ N=85
6 M Recurrence-free, n (%)	35 (26)	155 (60)	83 (64)	21 (39)	48 (84)	34 (68)	112 (67)	60 (71)
Estimate[c] at 6 M (95% CI)	27.7 (19.6,36.3)	62.4 (54.9,69.0)	69.6 (60.2,77.1)	37.5 (23,52)	89.2 (77,95)	77.3 (63,87)	72.7 (64.8,79.2)	75.1 (64.2,83.2)
6 M HR for recurrence (95% CI)	--	0.30 (0.22,0.40)	0.26 (0.18,0.39)	ND	ND	ND	0.98 (0.58,1.68)[b]	--
Missing=failure OR for 6 M recurrence (95% CI)	--	0.24 (0.15,0.38)[a]	0.20 (0.12,0.34)[a]	ND	ND	ND	1.14 (0.64,2.03[b]	--
4 M Recurrence-free[d], n (%)	47 (35)	177 (68)	90 (70)	24 (44)	51 (89)	34 (68)	127 (77)	63 (74)
Estimate[c] at 4 M (95% CI)	36.0 (26.8,45.4)	73.0 (66.0,78.9)	74.7 (65.7,81.6)	46.5 (32,60)	89.4 (75,96)	78.4 (64,88)	82.3 (74.9,87.7)	79.7 (68.9,87.1)

a. Compared to CQ alone
b. Compared to PQ+CQ
c. Kaplan-Meier estimate for recurrence-free efficacy rate
d. Based on 4 months FU
e. Results from the 300 mg TQ group

5.1. Study TAF112582 Part 2

5.1.1. Study Design for Study TAF112582 Part 2

The pivotal study in the TQ development program was Study 582 Part 2, a multi-center, double-blind, double-dummy, parallel-group, randomized, active- and placebo-controlled study with sites in Brazil, Peru, Ethiopia, Thailand, Cambodia and the Philippines.

In 582 Part 2, the null hypothesis for the primary endpoint was that the 6-month relapse-free efficacy rate was not different between the CQ+TQ and CQ alone treatment groups. A two-sided hypothesis test was performed at the 5% level.

Of note, it had initially been planned that TAF112582 Part 2 would comprise of two replicate and independently powered Phase 3 studies. After all the subjects were enrolled, centres were to be allocated to one of the two studies, based on the number of subjects. However, following the statistically significant TAF112582 Part 1 result, in consultation with the FDA, this plan was changed and all data in TAF112582 Part 2 was to be analysed together.

The primary comparison was made using a Cox's Proportional Hazards Model, adjusting for region, and utilized the microbiological intent-to-treat (mITT) population. The sample size assumptions for 582 Part 2 remained the same as in Part 1 (Section 5.2.1), resulting in >99% power for the primary comparison, based on a planned sample size of 300 subjects on TQ+CQ, and 150 on CQ. The larger sample size was required in order to ensure a sufficiently large safety database for the TQ *P. vivax* development program.

The PQ+CQ treatment arm was included as a benchmark, to help further interpret the TQ+CQ results. No formal comparison between the TQ+CQ and PQ+CQ treatment groups was planned.

Eligible subjects had a positive blood smear for *P. vivax* at entry with G6PD assay value of ≥70% of the site median. There was no stratification for baseline parasite count in Study 582 Part 2 (See Appendix Section 9.1). At least 600 subjects were planned to be randomized to 1 of 3 treatment groups, in a 1:2:1 ratio. Due to slow recruitment and in agreement with regulatory agencies, the target number of subjects recruited to the study was reduced from 600 subjects to 522 subjects, including 260 subjects in the TQ+CQ group.

All subjects were treated with CQ on Days 1 to 3 to treat the blood stage malaria infection, followed by their randomized treatment (300 mg single dose TQ, PQ for 14 days, or placebo [i.e., CQ only regimen]) (Table 16). All subjects received the same number of tablets/capsules for 15 days, according to the double-dummy study design.

Table 16 Treatment Groups in Study 582 Part 2

Treatment Groups		N
1	CQ only regimen (Days 1 to 3)	133
2	CQ (600 mg on Days 1 to 3) + TQ 300 mg single dose (Day 1 or 2)	260
3	CQ (600 mg on Days 1 to 3) + PQ 15 mg once daily for 14 days (Days 2 to 15)	129

It should be noted that although the endpoint measure was described as 'relapse' in the study protocols, it was in fact a composite of relapse (i.e., re-appearance of the parasite arising from untreated hypnozoite infection), and new infection. For *P. vivax* infections, it is not possible to distinguish relapses from new infections, even using genotyping; therefore, the term 'recurrence' was used throughout the Phase 3 clinical study reports (CSRs) to more accurately reflect the efficacy assessments reported in the studies.

The key efficacy studies were performed in regions endemic for *P. vivax* malaria. There was, therefore, a continuous risk of infection throughout the follow-up period of the studies and an expectation that re-infection would be similar in the treatment groups. Study sites were selected on the basis of historical evidence that time to relapse was short (approximately 3 to 6 weeks) [Battle, 2014]. Given the inability to distinguish relapse from new infection, a key secondary endpoint in Study 582 Part 2 and Study 564 was recurrence-free efficacy over 4-months post-dosing at which point there would have been

less opportunity for new infection to occur. The data up to and including the 4-month follow up visit were used in this analysis.

The primary objective of Study 582 Part 2 (pivotal Phase 3 efficacy study) was to determine the efficacy of TQ as a radical cure for *P. vivax* malaria, relative to a CQ-only control (a placebo-like arm, because CQ has no effect on radical cure). The primary comparison was the difference in recurrence-free efficacy between 300 mg TQ+CQ and CQ alone over 6 months using the mITT population. The 6-month primary endpoint was agreed between GSK and the US FDA at a Type C meeting in March 2010.

The primary survival analysis and alternative logistic regression analysis were performed on this endpoint and the conclusions from both analyses of the data were consistent:

- **Survival analysis** (Kaplan-Meier and Cox proportional hazards) using time to recurrence as defined in the WHO Protocol on Assessment and Monitoring of Antimalarial Drug Efficacy [WHO, 2003]. This was defined as the primary analysis in the Reporting and Analysis Plan (RAP).
- **Categorical analysis** using proportions (logistic regression) after imputation of treatment failure for those who were not confirmed recurrence-free at the end of the 6-month follow up or who took an anti-malarial medication other than study medication. This analysis was implemented for Study 582 Part 2 following discussion with the US FDA at the End of Phase 2 meeting in 2013, and is not available for Study 582 Part 1.

Safety assessments included monitoring of AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. Additional ophthalmic assessments were performed at selected sites. Key safety endpoints of interest were as follows:

- Clinically relevant hemolysis leading to decreases in Hb/hematocrit or complications thereof (required transfusions, acute renal failure)
- Changes in methemoglobin
- GI tolerability - incidence of abdominal pain, heartburn, diarrhea, constipation, nausea, and vomiting
- Ophthalmic safety - incidence of corneal deposits and retinal and visual field abnormalities.

5.1.2. Study Population Results in 582 Part 2

Although *P. vivax*-infected US subjects were not included in the studies, US patients would be most likely to acquire the infections from travel to, or occupational exposure in, endemic areas, and the disease would be expected to have similar characteristics in those patients.

5.1.2.1. Demographic Characteristics

In the pivotal efficacy study, demographic characteristics were well-balanced across the treatment groups. A higher percentage of males than females were enrolled, which represents the epidemiology of the disease.

Table 17 Demographic Characteristics in Study 582 Part 2 (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Age (years)				
Mean	35.3	35.0	34.7	35.0
Standard deviation	14.23	14.39	14.26	14.29
Sex, n (%)				
Male	97 (73)	196 (75)	99 (77)	392 (75)
Female	36 (27)	64 (25)	30 (23)	130 (25)
Race[a], n (%)				
Multiple	47 (35)	97 (37)	47 (36)	191 (37)
American Indian or Alaska native	43 (32)	81 (31)	41 (32)	165 (32)
Asian - Southeast Asian heritage	26 (20)	50 (19)	26 (20)	102 (20)
Black or African American	14 (11)	28 (11)	13 (10)	55 (11)
White	3 (2)	4 (2)	2 (2)	9 (2)
Ethnicity, n (%)				
Hispanic or Latino	93 (70)	182 (70)	89 (69)	364 (70)
Not Hispanic or Latino	40 (30)	78 (30)	40 (31)	158 (30)
Body mass index (kg/m²)				
n	133	260	128	521
Median	23.70	23.35	23.80	23.50
Minimum	14.9	15.9	15.7	14.9
Maximum	39.8	47.0	38.8	47.0
G6PD enzyme activity (IU/g Hb)				
Median	8.24	8.26	8.48	8.35
Minimum	5.8	5.6	5.4	5.4
Maximum	12.0	15.5	12.5	15.5
G6PD enzyme activity (as % of site median)				
Median	99.67	100.38	103.54	101.50
Minimum	72.6	70.2	70.4	70.2
Maximum	155.3	188.9	153.9	188.9

a. Subjects were categorized based on standard racial groupings, even though all subjects were ex-US.

5.1.2.2. Baseline Disease Characteristics

In the pivotal efficacy study, the baseline disease characteristics were similar across treatment groups (Table 18). The most common symptoms were headache, chills and rigors, and dizziness, consistent with a diagnosis of malaria. The majority of subjects reported a previous episode of malaria and there were no clinically meaningful

differences between treatment groups at baseline in *P. vivax* asexual parasite or gametocyte counts (Table 19).

Table 18 Malarial Signs and Symptoms in Study 582 Part 2 (mITT Population)

Symptom Severity	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Chills and rigors, n (%)				
Absent	8 (6)	18 (7)	8 (6)	34 (7)
Mild	47 (35)	88 (34)	35 (27)	170 (33)
Moderate	37 (28)	66 (25)	38 (29)	141 (27)
Severe	41 (31)	88 (34)	48 (37)	177 (34)
Headache, n (%)				
Absent	6 (5)	7 (3)	4 (3)	17 (3)
Mild	36 (27)	79 (30)	39 (30)	154 (30)
Moderate	29 (22)	74 (28)	37 (29)	140 (27)
Severe	62 (47)	100 (38)	48 (37)	210 (40)
Unknown	0	0	1 (<1)	1 (<1)
Dizziness, n (%)				
Absent	50 (38)	92 (35)	47 (36)	189 (36)
Mild	60 (45)	125 (48)	61 (47)	246 (47)
Moderate	19 (14)	38 (15)	16 (12)	73 (14)
Severe	4 (3)	5 (2)	5 (4)	14 (3)
Abdominal pain, n (%)				
Absent	94 (71)	158 (61)	88 (68)	340 (65)
Mild	32 (24)	85 (33)	36 (28)	153 (29)
Moderate	7 (5)	16 (6)	5 (4)	28 (5)
Severe	0	1 (<1)	0	1 (<1)
Anorexia, n (%)				
Absent	61 (46)	114 (44)	60 (47)	235 (45)
Mild	54 (41)	105 (40)	48 (37)	207 (40)
Moderate	18 (14)	36 (14)	16 (12)	70 (13)
Severe	0	5 (2)	5 (4)	10 (2)
Nausea, n (%)				
Absent	55 (41)	120 (46)	60 (47)	235 (45)
Mild	53 (40)	85 (33)	45 (35)	183 (35)
Moderate	24 (18)	51 (20)	24 (19)	99 (19)
Severe	1 (<1)	4 (2)	0	5 (<1)
Vomiting, n (%)				
Absent	93 (70)	190 (73)	93 (72)	376 (72)
Mild	32 (24)	51 (20)	28 (22)	111 (21)
Moderate	8 (6)	19 (7)	8 (6)	35 (7)
Severe	0	0	0	0
Diarrhea, n (%)				
Absent	127 (95)	241 (93)	120 (93)	488 (93)
Mild	4 (3)	17 (7)	7 (5)	28 (5)
Moderate	2 (2)	2 (<1)	1 (<1)	5 (<1)

Symptom Severity	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Severe	0	0	1 (<1)	1 (<1)
Pruritus/itching, n (%)				
Absent	118 (89)	214 (82)	111 (86)	443 (85)
Mild	12 (9)	29 (11)	11 (9)	52 (10)
Moderate	2 (2)	17 (7)	7 (5)	26 (5)
Severe	1 (<1)	0	0	1 (<1)
Coughing, n (%)				
Absent	109 (82)	221 (85)	103 (80)	433 (83)
Mild	22 (17)	39 (15)	22 (17)	83 (16)
Moderate	2 (2)	0	4 (3)	6 (1)
Severe	0	0	0	0

Note: Additional signs and symptoms were reported for some symptoms as 'Other'.

Table 19 Previous Malarial Episodes in Study 582 Part 2 (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Previous malarial episode, n (%)				
Yes	106 (80)	219 (84)	109 (84)	434 (83)
No	26 (20)	41 (16)	18 (14)	85 (16)
Unknown	1 (<1)	0	2 (2)	3 (<1)

a. Day 1 Assessment 1 values were used as Baseline.

5.1.2.3. Subject disposition and compliance

In the pivotal efficacy study, the completion rate was high (≥95%) across all treatment groups (Table 20). The most common reasons for withdrawal from the study overall were lost to follow-up (2%) or withdrawal by the subject (2%). There were no AEs that resulted in withdrawal from the study.

Table 20 Subject Disposition in Study 582 Part 2 (mITT population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Completion status, n (%)				
Completed	129 (97)	250 (96)	123 (95)	502 (96)
Withdrawn	4 (3)	10 (4)	6 (5)	20 (4)
Primary reason for withdrawal from study, n (%)				
AE	0	0	0	0
Protocol deviation	0	0	0	0
Subject reached protocol-defined stopping criteria	0	0	0	0
Study closed/terminated	0	0	0	0
Lost to follow-up	2 (2)	4 (2)	2 (2)	8 (2)
Physician decision	1 (<1)	1 (<1)	0	2 (<1)[a]
Withdrawal by subject	1 (<1)	5 (2)	4 (3)	10 (2)[a]

a. Reasons for withdrawal due to physician decision or withdrawal by subject were primarily related to logistical issues or personal decisions. None of the withdrawals were due to AEs.

In the pivotal efficacy study, all subjects received their scheduled in-clinic dose of TQ/TQ placebo, according to randomization. Compliance with CQ study medication was ≥97% in all treatment groups. Compliance with PQ study medication in the PQ+CQ group was high (97%; assessed by returned tablet counts), which was confirmed in the applicable subjects using PK analysis of PQ and carboxy-PQ plasma concentrations at Day 8 and Day 15 (defined as PQ detectable concentration at either time point).

Table 21 Study Medication Compliance and Exposure in 582 Part 2 (Safety Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Number of compliant doses of CQ, n (%)				
1	0	1 (<1)	0	1 (<1)
2	3 (2)	6 (2)	1 (<1)	10 (2)
3	130 (98)	253 (97)	128 (>99)	511 (98)
Subject compliance with TQ/TQ-PBO treatment, n (%)				
Yes	133 (100)	260 (100)	129 (100)	522 (100)
Total number of PQ/PQ-PBO doses[a], n (%)				
<12	7 (5)	12 (5)	1 (<1)	20 (4)
≥12	125 (94)	239 (92)	124 (96)	488 (93)
Missing	1 (<1)	9 (3)	4 (3)	14 (3)
Subjects with detectable PQ concentrations at Day 8 or Day 15, n (%)				
n[b]	NA	NA	125	NA
Subjects who met criteria	NA	NA	122 (98)	NA
Subjects with PQ count ≥12 AND detectable PQ concentrations at Day 8 or Day 15, n (%)				
n[c]	NA	NA	124	NA
Subject who met criteria	NA	NA	120 (97)	NA

a. 14 tablets taken was perfect compliance. The calculation of tablets was dependent on the number of tablets returned, not administration that was directly observed.
b. Number of subjects with a PQ PK assessment on Day 8 or Day 15.
c. Number of subjects with a PQ pill count AND a PQ PK assessment on Day 8 or Day 15.

5.1.3. Efficacy Results for Study 582 Part 2

Treatment with 300 mg single dose TQ, when co-administered with standard doses of CQ, resulted in a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 6 months relative to treatment with CQ alone in the primary efficacy study.

There was also a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 4 months relative to treatment with CQ alone in Study 582 Part 2.

5.1.3.1. 6 Month Recurrence-free Efficacy

5.1.3.1.1. *Survival analysis*

In Study 582 Part 2, treatment with TQ+CQ resulted in a clinically and statistically significant reduction in the risk of recurrence over 6 months by 70.1% (95% CI: 59.6%, 77.8%; p<0.001) compared with CQ alone based on a Cox proportional hazards model. The Kaplan Meier estimates of recurrence-free efficacy at 6 months were 27.7% (95%

CI: 19.6%,36.3%) in the CQ alone group and 62.4% (95% CI: 54.9%, 69.0%) in the TQ+CQ group. (Table 22; Figure 6).

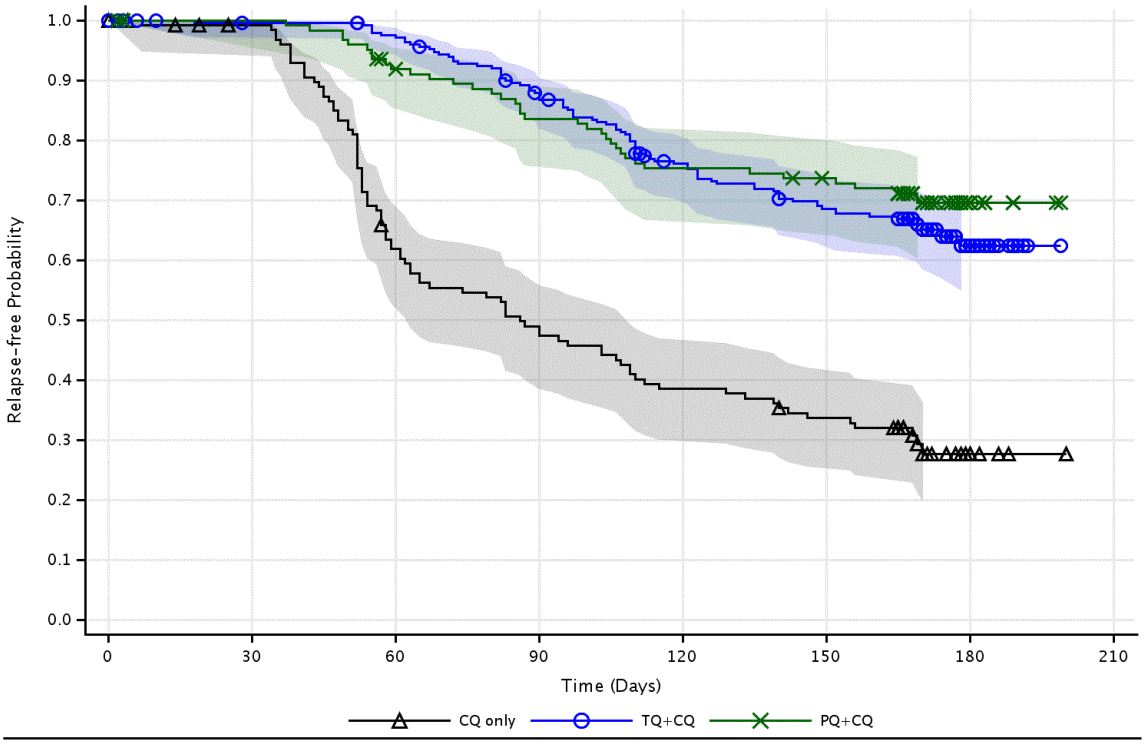
Supervised treatment with 15 mg PQ for 14 days, when co-administered with standard doses of CQ, also resulted in a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 6 months relative to treatment with CQ alone in the pivotal efficacy study (Table 22).

Table 22 Recurrence-Free Efficacy over 6 Months in 582 Part 2 (Kaplan Meier Analysis) (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)
Number of subjects, n (%)			
Recurrence-free at 6 months	35 (26)	155 (60)	83 (64)
Recurrence prior to or at 6 months	88 (66)	85 (33)	36 (28)
Censored, prior to 6 month assessment	10 (8)	20 (8)	10 (8)
Recurrence-free efficacy rate at 6 months			
Estimate (95% CI)	27.7 (19.6,36.3)	62.4 (54.9,69.0)	69.6 (60.2,77.1)
Number Needed to Treat (95%CI)[a]	--	2.9 (2.2,4.2)	2.4 (1.9,3.3)
Hazard Ratio of risk of recurrence vs CQ alone[b]			
Estimate (95% CI)		0.299 (0.222,0.404)	0.262 (0.178,0.387)
p-value		<0.001	<0.001

a. Number needed to treat to prevent one recurrence over 6 months compared to CQ alone.
b. A hazard ratio <1 indicates a lower chance of recurrence compared with CQ alone.

Figure 6 Survival Curves for Recurrence-Free Efficacy over 6 months in 582 Part 2 (mITT Population)



Subjects at Risk:								
CQ only	133	125	77	61	48	41	7	0
TQ+CQ	260	251	244	217	183	163	27	0
PQ+CQ	129	124	112	101	91	87	10	0

5.1.3.1.2. *Alternative logistic regression analysis*

In the Missing Failure logistic regression analysis for Study 582 Part 2, a larger proportion of subjects treated with TQ+CQ were recurrence-free during the first 6 months compared with CQ treatment alone and a clinically and statistically significant reduction in the odds of recurrence (75.9%, 95% CI: 61.8%, 84.8%; p<0.001) was observed for TQ+CQ treatment compared with CQ alone (Table 23).

The results for highly compliant PQ+CQ treatment were similar to those for TQ+CQ. A larger proportion of subjects treated with PQ+CQ were recurrence-free during the first 6 months compared with CQ treatment alone and a clinically and statistically significant reduction in the odds of recurrence (80.2%, 95% CI: 66.5%, 88.3%; p<0.001) was observed for PQ+CQ treatment compared with CQ alone.

Table 23 Recurrence-Free Efficacy at 6 Months in 582 Part 2 with Missing=Failure (Logistic Regression) (mITT Population)

Logistic regression analysis at 6 months[a]			
	CQ alone	TQ+CQ	PQ+CQ
Recurrence-free, n (%)	35 (26)	155 (60)	83 (64)
Subjects with a recurrence, n (%)	98 (74)	105 (40)	46 (36)
Odds ratio of recurrence (95% CI)[b]		0.241 (0.152,0.382)	0.198 (0.117,0.335)
p-value		<0.001	<0.001

a. Subjects with missing data were analyzed as failures.
b. Odds ratios <1 indicate a smaller chance of recurrence compared with CQ alone.

5.1.3.2. Sensitivity analyses

The results of all pre-specified sensitivity analyses of the primary endpoint were consistent with the primary analyses for Study 582 Part 2. Sensitivity analyses included using the Per Protocol Population, censoring homologous and heterologous relapses, and analyzing by CQ supply date. Together, these analyses show the robustness of the efficacy results.

5.1.3.3. Secondary Endpoint Results

5.1.3.3.1. *Recurrence-free efficacy at 4 months*

The key efficacy studies were performed in regions endemic for *P. vivax* malaria, and therefore there was a continuous risk of re-infection throughout the follow-up period of the study. Sites were selected on the basis of historical evidence that time to relapse was short [Battle, 2014]. Given the inability to distinguish relapse from new infection, recurrence-free efficacy over 4 months post-dosing was included as a secondary endpoint in Study 582 Part 2 and Study 564 because at that point there would have been less opportunity for new infection to occur. The analyses of the 4-month endpoint were based on the follow-up to the end of a 4-month window.

Survival analysis

In Study 582 Part 2, the reduction in the risk of recurrence at any time over 4 months was 72.9% (95% CI: 62.4%, 80.5%; p<0.001) compared with CQ treatment alone corresponding to a HR of 0.271 (0.195,0.376) (Table 24). The recurrence-free efficacy rate in the TQ+CQ group was approximately 10% higher at 4 months (73.0%) compared with results at 6 months (62.4%), and similar results were seen in the CQ alone group (36.0% at 4 months vs. 27.7% at 6 months) as would be expected with increases in new infections over time.

In the placebo arm (the CQ-only arm), the majority of recurrences occurred early in follow-up (Figure 6). The Kaplan-Meier curves are roughly parallel after the 4-month

mark, which is consistent with the expectation that the re-infection rate should be similar across all arms. This is consistent with the hypothesis that the majority of the events that occurred late in the follow-up period are in fact re-infections and not relapses, as none of the treatment regimens administered would have been expected to prevent these late re-infections.

The reduction in the risk of recurrence in the PQ+CQ group compared with the CQ alone group was consistent with the primary endpoint results at 6 months based on a Cox proportional hazards model. Treatment with PQ+CQ resulted in a clinically and statistically significant reduction in the risk of recurrence by 74.5% (95% CI: 61.0%, 83.3%; p<0.001) compared with CQ alone.

Table 24 Recurrence-Free Efficacy at 4 Months in 582 Part 2 (Kaplan Meier Analysis) (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)
Number of subjects, n (%)			
Recurrence-free at 4 months	47 (35)	177 (68)	90 (70)
Recurrence prior to or at 4 months	78 (59)	67 (26)	30 (23)
Censored, prior to 4 month assessment	8 (6)	16 (6)	9 (7)
Recurrence-free efficacy rate at 4 months			
Estimate (95% CI)	36.0 (26.8,45.4)	73.0 (66.0,78.9)	74.7 (65.7,81.6)
Hazard ratio of risk of recurrence vs CQ alone[a]			
Estimate (95% CI)		0.271 (0.195,0.376)	0.255 (0.167,0.390)
p-value		<0.001	<0.001

a. A hazard ratio <1 indicates a lower chance of recurrence compared with CQ alone.

Alternative logistic regression analysis (sensitivity analysis)

In the Missing Failure logistic regression analysis for Study 582 Part 2, a clinically meaningful and statistically significant reduction in the odds of recurrence (74.4%, 95% CI: 60.2%, 83.5%; p<0.001) was shown for TQ+CQ treatment compared with CQ alone (OR 0.256, 95% CI:0.165,0.398) (Table 25). Similar results were obtained for PQ+CQ treatment compared with CQ alone (OR 0.237, 95% CI:0.141,0.397; p<0.001).

Table 25 Recurrence-Free Efficacy at 4 Months in 582 Part 2 with Missing = Failure (Logistic Regression) (mITT Population)

				Comparison with CQ Alone		
Treatment	**N**	**Recurrence-Free, n (%)**	**Subjects with Recurrence, n (%)**	**Odds Ratio of Recurrence[a]**	**95% CI**	**P-Value**
CQ alone	133	47 (35)	86 (65)			
TQ+CQ	260	177 (68)	83 (32)	0.256	(0.165,0.398)	<0.001
PQ+CQ	129	90 (70)	39 (30)	0.237	(0.141,0.397)	<0.001

a. Odds ratios <1 suggest a smaller chance of recurrence compared with CQ alone.

The odds of recurrence at 4 months in the TQ+CQ group were similar to those in the PQ+CQ group (Table 25). As for the 6-month analysis, subjects who took an anti-malarial or not confirmed recurrence-free at 4 months were as assumed to be recurrences. The odds ratio was close to 1, suggesting that the odds of recurrence in the TQ+CQ and PQ+CQ groups are similar. These results are consistent with the survival analysis of recurrence-free efficacy over 4 months, and both analyses at 4-months were consistent with the analyses at 6-months.

5.1.3.3.2. *Early response to treatment*

Parasite clearance times were similar across treatment groups as expected due to CQ treatment (Table 26). Median parasite counts were rapidly reduced to zero by Day 3 in all 3 treatment groups. Gametocyte clearance times were also similar across treatment groups (Table 26). Median gametocyte counts were reduced to zero by Day 2 Assessment 2 in all treatment groups.

Fever clearance times were similar across treatment groups (Table 26). Of note, the use of paracetamol in the study was high (87%) and well-balanced across all 3 treatment groups.

Table 26 Analysis of Time to Parasite, Fever, and Gametocyte Clearance in 582 Part 2 (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)
Parasite Clearance, n (%)			
Parasite clearance achieved	129 (97)	254 (98)	127 (98)
Censored, parasite clearance not achieved	4 (3)	6 (2)	2 (2)
Time to parasite clearance (hours)			
Median (95% CI)	43 (41,48)	45 (42,47)	42 (39,45)
Fever Clearance, n (%)			
Fever clearance achieved	48 (36)	102 (39)	47 (36)
Censored, at Baseline	85 (64)	158 (61)	82 (64)
Censored, fever clearance not achieved	0 (0)	0 (0)	0 (0)
Time to fever clearance (hours)			
Median (95% CI)	7 (5,14)	7 (5,12)	8 (6,18)
Gametocyte Clearance, n (%)			
Gametocyte clearance achieved	85 (64)	168 (65)	79 (61)
Censored, at Baseline	47 (35)	92 (35)	49 (38)
Censored, gametocyte clearance not achieved	1 (<1)	0 (0)	1 (<1)
Time to gametocyte clearance (hours)			
Median (95% CI)	38 (32,40)	39 (37,41)	36 (24,41)

5.1.3.3.3. *Early Failures and Recrudescence*

Early failures were defined as subjects who did not demonstrate initial clearance of *P. vivax* parasitemia OR demonstrated initial clearance and had a subsequent non-zero genetically homologous *P. vivax* parasite count on or before Day 32 (recrudescence). Three subjects in the TQ+CQ group (1.2%) and 2 subjects in the CQ alone group (1.5%) were considered early failures. Three of these 5 subjects (2 TQ+CQ and 1 CQ) withdrew from the study prior to Day 5; therefore, data were not available to demonstrate initial clearance of parasitemia and the subjects were classified as early failures based on the above definition.

Only 1 subject, who was in the CQ alone group (0.8%), had recrudescence prior to Day 33. One additional subject in the TQ+CQ treatment group had a heterologous infection, which did not meet the criteria for recrudescence.

5.2. Study 582 Part 1

5.2.1. Study Design for Study 582 Part 1

Part 1 of Study 582 was a Phase 2b, multi-center, double-blind, double-dummy, parallel group, randomized, active- and placebo-controlled, dose-selection study with sites in

Brazil, Peru, Thailand, and India. The purpose of the study was to select an optimal Phase 3 dose based on efficacy, safety, and PK data [Llanos-Cuentas, 2014].

In TAF112582 Part 1, the null hypothesis for the primary endpoint was that the 6-month relapse-free efficacy rate was not different between the CQ+TQ and CQ treatment groups. A two-sided hypothesis test was to be performed at the 5% level.

The primary comparison was made using a log rank test for the difference in relapse-free survival rates over 6 months, and utilized the intent-to-treat (ITT) population. The sample size calculations assumed a 60% relapse-free efficacy rate for the CQ treatment group, and a 90% rate for the TQ+CQ rate (30% difference). Assuming a 10% attrition rate, 54 subjects per treatment group provided >90% power.

To allow for multiple testing while preserving the overall Type I error rate at 5%, a step-down testing approach was employed, starting with the comparison of the highest TQ dose vs CQ

The PQ+CQ treatment arm was included as a benchmark, to help further interpret the TQ+CQ results. No formal comparison between the TQ+CQ and PQ+CQ treatment groups was planned.

Eligible subjects had a positive blood smear for *P. vivax* at entry (parasite density >100/μL and <100,000/μL). Subjects with G6PD deficiency were excluded, defined as G6PD values of <70% of the site median for males and <70% for females with a screening Hb ≥100 g/L; females with Hb concentration of ≥70 g/L and <100 g/L were excluded if their enzyme level was not >90% of the site median. Subjects were randomized to 1 of 6 treatment groups, stratified by baseline parasite count (≤7500/μL, >7500/μL). All subjects were treated with CQ on Days 1 to 3 to treat the blood stage malaria infection, followed by either a single dose of TQ (50 mg, 100 mg, 300 mg, or 600 mg), or PQ 15 mg for 14 days, or CQ alone (i.e., placebo) (Table 27). All subjects received the same number of tablets/capsules for 15 days to maintain the double-dummy study design.

Table 27 Randomized Treatment Groups in Study 582 Part 1

Treatment Groups		N
1	CQ (600 mg on Days 1 to 3) (i.e., CQ only regimen)	54
2	CQ (600 mg on Days 1 to 3) + TQ 50 mg single dose (Days 1 or 2)	55
3	CQ (600 mg on Days 1 to 3) + TQ 100 mg single dose (Days 1 or 2)	57
4	CQ (600 mg on Days 1 to 3) + TQ 300 mg single dose (Days 1 or 2)	57
5	CQ (600 mg on Days 1 to 3) + TQ 600 mg single dose (Days 1 or 2)	56
6	CQ (600 mg on Days 1 to 3) + PQ 15 mg once daily for 14 days (Days 2 to 15)	50

The primary objective was to determine the efficacy of TQ as a radical cure for *P. vivax* malaria, relative to a CQ control. Secondary objectives were safety, population PK, and potential PK/PD relationships of TQ in subjects with *P. vivax* malaria. Planned

enrolment for Part 1 was at least 324 subjects, randomized equally (54 subjects per group).

Safety assessments included monitoring of AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. Additional ophthalmic assessments were performed at selected sites. Key safety endpoints of interest were as follows:

- Clinically relevant hemolysis leading to decreases in Hb/hematocrit or complications thereof (required transfusions, acute renal failure)
- Changes in methemoglobin
- GI tolerability - incidence of abdominal pain, heartburn, diarrhea, constipation, nausea, and vomiting
- Ophthalmic safety - incidence of corneal deposits and retinal and visual field abnormalities.

The results of Study 582 Part 1 indicated that the 300 mg dose of TQ was optimal in terms of both safety and efficacy, as described in the clinical study report (Table 49).

5.2.2. Study Population Results for Study 582 Part 1

In Study 582 Part 1, the demographic characteristics were well-balanced across the treatment groups and a higher percentage of males than females were enrolled, similarly to Study 582 Part 2 (Table 45).

The baseline disease characteristics were also balanced across the treatment groups and were similar to Study 582 Part 2 (Table 46, Table 47). There were no clinically meaningful differences between treatment groups at baseline.

Similar to Study 582 Part 2, the study completion rate was ≥94% in all treatment groups and there were no AEs leading to withdrawal from the studies (Table 43).

In Study 582 Part 1, compliance with TQ and CQ was measured using pill counts (Table 48) whereas in Study 582 Part 2 it was measured using both pill count and TQ PK. In Study 582 Part 1, ≥96% of subjects in the 300 mg TQ, PQ+CQ and CQ treatment groups received their scheduled dose of TQ/TQ placebo, and compliance with CQ was 100% in these groups.

Outpatient compliance with PQ, based on a count of returned tablets, was lower with 26% of subjects in the PQ + CQ treatment group returning the number of tablets suggestive of taking all 12 (±1) doses and 42% taking 14 or more doses, while 32% took 10 or fewer doses.

5.2.3. Efficacy Results for Study 582 Part 1

5.2.3.1. 6-month recurrence-free efficacy

Recurrence-free efficacy at 6 months in the 300 mg TQ group in Study 582 Part 1 was consistent with that of Study 582 Part 2.

In Study 582 Part 1, there was a statistically significant difference in efficacy between TQ+CQ compared to CQ alone. The estimates of recurrence-free efficacy at 6 months were 37.5% (95% CI: 23%, 52%) in the CQ alone group and 89.2% (95% CI: 77%, 95%) in the 300 mg TQ+CQ group.

Similar Kaplan-Meier curves were obtained from the results for the TQ+CQ and PQ+CQ groups (Figure 4).

5.2.3.2. Secondary endpoint results

4-month recurrence-free efficacy

Recurrence-free efficacy at 4 months in the 300 mg TQ group in Study 582 Part 1 was consistent with the results of the pivotal efficacy study (Table 50).

In Study 582 Part 1, the recurrence-free efficacy for TQ+CQ and CQ alone were statistically significant ($p<0.0001$) from the two-sided log-rank test (Table 50). The estimates of the recurrence-free efficacy at 4 months were 46.5% (95% CI: 32%, 60%) in the CQ alone group and 89.4% (95% CI: 75%, 96%) in the 300mg TQ+CQ group which were slightly higher than at 6 months.

The recurrence-free efficacy at 4 months in the PQ+CQ group was comparable to that over 6 months.

Other secondary efficacy endpoints

The other secondary efficacy endpoints in Study 582 Part 1 were consistent with, and supported, the primary endpoint (Table 51, Table 52, Table 53). The results were similar to the secondary endpoints in the pivotal Study 582 Part 2.

5.3. Study 564

5.3.1. Design for Study 564

The design of Study 564 was similar to the pivotal Phase 3 study, 582 Part 2, but without the CQ alone control arm. This was a randomized, double-blind, active-controlled, double-dummy, parallel-group study with sites in Brazil, Peru, Colombia, Thailand, and Vietnam.

The primary objective in Study 564 was to compare the incidence of hemolysis from treatment by TQ+CQ vs. PQ+CQ. Study 564 also provided supportive efficacy data on recurrence-free efficacy.

Study 564 was primarily a supporting safety study. There was no hypothesis tested in the study. The planned sample size of 200 TQ+CQ subjects and 100 PQ+CQ subjects was based on the regulatory requirement to obtain an appropriate total safety database in subjects treated with TQ+CQ within the TQ *P. vivax* program, and was not based on statistical considerations. The total sample size of 300 subjects included a subgroup of 50 female subjects (randomized 2:1 to TQ+CQ:PQ+CQ) with moderate (40-70%) G6PD deficiency. As for the total sample size, this was not based on statistical considerations.

The primary endpoint was the occurrence of clinically relevant hemolysis in all subjects; defined as a decrease in Hb of ≥30% or >30g/L from baseline; or, an overall drop in Hb below 60 g/L. The proportion of subjects and 95% CIs within each treatment group, for all subjects, and for the subset of females with moderate G6PD deficiency, were to be derived, using the safety population. Assuming event rates of 50% in the subgroup of females with moderate G6PD deficiency, and 0% in the rest of the subjects, the total sample size of 300 provided 95% confidence intervals with precision of 4% for TQ+CQ and 5% for PQ+CQ.

Efficacy was assessed as secondary objective. There was no formal comparison of TQ vs PQ with respect to efficacy.

Eligible subjects had a positive blood smear for *P. vivax* at entry. The study planned to enroll subjects with a minimum G6PD assay value of ≥70% of the site median and only female subjects with G6PD values of ≥40% to <70% of the site median.

As described above, the study planned to enroll at least 50 female subjects who displayed moderate G6PD deficiency (≥40% to <70% of the site median G6PD value); however, only 1 female subject meeting this criterion was enrolled. With agreement from regulatory agencies, recruitment of subjects into the G6PD-deficient female cohort was halted after 6 additional months of recruitment, during which follow-up on the G6PD-normal subjects was being conducted. Consequently, the study recruited a total of 251 subjects (166 subjects in the TQ+CQ group and 85 subjects in the PQ+CQ group).

All subjects were treated with CQ on Days 1 to 3 to treat the blood stage malaria infection, followed by their randomized treatment (300 mg single dose TQ or 15 mg PQ once daily for 14 days) and matching placebo.

In addition to the assessment of hemolysis, safety assessments also included AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. Additional ophthalmic assessments were performed at a selected site.

5.3.2. Study Population Results for Study 564

In Study 564, the demographic characteristics were well-balanced across the treatment groups and a higher percentage of males than females were enrolled (Table 56), similar to Study 582 Part 2.

The baseline disease characteristics were also balanced across the treatment groups (Table 57, Table 58) and were similar to Study 582 Part 2. There were no clinically meaningful differences between treatment groups at baseline.

Similar to Study 582 Part 2, the completion rate was ≥94% in all treatment groups and there were no AEs leading to withdrawal from the study (Table 54).

In Study 564, compliance was ≥96% for all study medications in both treatment groups (Table 59). The high compliance observed in the PQ+CQ group based on tablet counts (98%) was confirmed by PK analysis of PQ and 7-carboxy-PQ plasma concentrations at Day 8 and Day 15.

5.3.3. Efficacy Results for Study 564

5.3.3.1. 6-month recurrence-free efficacy

In Study 564, the estimates of recurrence-free efficacy at 6 months were 72.7% (95% CI: 64.8%, 79.2 %) in the TQ+CQ group and 75.1% (95%CI: 64.2%,83.2%) in the PQ+CQ group using Kaplan-Meier methodology (Table 60).

The efficacy in the TQ+CQ and PQ+CQ groups appear similar over 6-months follow up, although the study was not powered to make formal comparisons of the treatment groups (Figure 9).

For the recurrence-free efficacy using missing failure analysis for Study 564, the odds of recurrence at 6 months in the TQ+CQ group were similar to those in the PQ+CQ group. The odds ratio was close to 1, suggesting that efficacy in the two groups were similar (Table 61). These results are consistent with the survival analysis of recurrence-free efficacy over 6 months.

5.3.3.2. Secondary endpoint results

4-month recurrence-free efficacy

Recurrence-free efficacy results at 4 months from Study 564 (Table 62) supported the results of the pivotal efficacy study for both the TQ+CQ and PQ+CQ treatments.

Results of analyses of recurrence-free efficacy over 4 months were similar to those over 6 months (Table 63), and to the 4-month results for Study 582 Part 2. The risk of recurrence over 4 months was comparable between treatment groups.

Other secondary efficacy endpoints

The other secondary efficacy endpoints in Study 564 were consistent with, and supported, the primary endpoint (Table 64). The results were similar to the secondary endpoints in the pivotal Study 582 Part 2.

5.4. Subgroup Analyses

The results of analyses of the major subgroups of age, race and gender are generally consistent with the overall results from the mITT and safety populations in Study 582 (Part 2) and Study 564 studies. For smaller subgroups, subject numbers do not allow for a meaningful comparison with the overall results from the mITT and Safety populations in the 582 (Part 2) and 564 studies.

In the major age subgroup of 18-64 years of age, the recurrence-free efficacy results were similar to the mITT Population results. The proportion of TQ subjects who were recurrence-free was much greater than in the placebo group, and the proportions in the TQ and PQ groups were similar.

In the gender subgroups, the recurrence-free efficacy results were generally similar to the mITT Population results, particularly for the CQ only and PQ treatment groups. The proportions of TQ subjects who were recurrence-free were much greater than in the placebo groups in both groups.

In the largest race subgroups of Multiple Races and American Indian/Alaska Native (predominantly Brazilian and Peruvian subjects, respectively), the recurrence-free efficacy results were similar to the mITT Population results. The proportion of TQ subjects who were recurrence-free was much greater than in the placebo group, and the proportions in the TQ and PQ groups were similar.

5.5. Efficacy Conclusions

The selection of the 300 mg single dose of TQ was based on both efficacy and safety considerations. No additional efficacy benefit was seen with the 600 mg dose in Study 582 Part 1, and the hemolytic potential of 300 mg single dose TQ was comparable to that of PQ 15 mg daily for 14 days in TAF110027.

In the pivotal efficacy study, Study 582 Part 2, treatment with 300 mg single-dose TQ, when co-administered with standard doses of CQ, resulted in a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 6 months by 70.1% compared with CQ alone ($p<0.001$). The alternative missing failure logistic regression analysis and all other sensitivity analyses supported the results of the primary analysis in the pivotal efficacy study. The number needed to treat was 2.8, i.e., over a six-month period, one malaria recurrence was prevented in one out of about every three patients treated with 300 mg single dose TQ compared to placebo.

The observed rates of recurrence were slightly higher in all arms (including the CQ alone/placebo arm) in Phase 3 compared to Phase 2b. The potential reasons for this are multiple. Firstly, it is not possible to distinguish between relapse and re-infection: the epidemiology of *P. vivax* varies from year to year, even at the same site; changes in the re-infection rate would therefore manifest as changes in the rate of recurrence year-on-year. A second reason for the higher rate of recurrence in Phase 3 may therefore be due to improvements in microscopy as sites became more experienced in the technique, resulting in a greater detection of low-level asymptomatic parasitemia. Despite this variability across studies, TQ efficacy was consistently demonstrated in all studies.

The PQ compliance (assessed by pill counts) seen in Study 582 Part 1 (Phase 2b) was only 68%, while that for TQ was 96% (recurrence-free efficacy [95%CI]: TQ 89.2 [77,95]; PQ 77.3 [63,87]). In Study 582 Part 2, the compliance rates were both TQ and PQ were high (TQ: 100%; PQ: 96%). This may explain some of the variation in results between Phase 2b and Phase 3. The apparent improvement in PQ compliance from Part 1 to Part 2 was due to a greater emphasis by sites on encouraging compliance through regular visits and pill counts during the treatment period. This high degree of compliance with PQ treatment is not seen in real world settings. The single dose regimen of TQ facilitates treatment compliance and ensures consistent real-world use.

In conclusion, 300 mg single dose TQ, co-administered with CQ, clinically and statistically significantly reduced the risk of *P. vivax* recurrence compared to CQ alone. The single dose regimen of TQ, if licensed, would facilitate treatment compliance and could ensure consistent real-world efficacy as seen as in our clinical studies.

6. OVERVIEW OF SAFETY

Safety data from across all clinical studies of TQ (includes 33 completed studies in healthy volunteers and patients) were used to inform the type and frequency of uncommon and rare events observed with TQ. These studies cover a range of TQ doses and durations, including higher doses and/or longer durations than the recommended 300 mg single dose regimen.

The primary evidence for the clinical safety of 300 mg single dose TQ for radical cure of *P. vivax* malaria is provided by 3 randomized, double-blind studies: TAF112582 Part 1 (Phase 2b), TAF112582 Part 2 (pivotal Phase 3), and TAF116564 (Phase 3) (Table 1). The overall safety profile of TQ at the recommended 300 mg single dose is appropriate to support use as radical cure, and similar to that of PQ 15 mg daily for 14 days.

In addition, safety results from 2 individual studies in healthy volunteers provide clinically important safety observations to this regulatory submission. Study 201807 specifically assessed ophthalmic safety, and the cardiac safety study, TAF114582, was a definitive QTc study.

The safety data from the phase 2b and phase 3 radical cure studies (Studies 582 part1, 582 part 2 and 564) were pooled in the placebo-controlled and/or all primary studies to

better characterize the safety of 300 mg single dose TQ in subjects with *P. vivax* malaria (Table 28). Additionally, the pooled groupings provided exposure and key safety information from multiple studies within the TQ development program, including those utilizing different dosing regimens, and in different indications and populations.

6.1. Extent of Exposure

Across the TQ development program, >4000 subjects have been exposed to TQ, including >800 subjects exposed to a 300 mg total dose (Table 67). A total of 483 *P. vivax*-infected subjects have been treated with 300 mg single dose TQ+CQ in the All Primary (AP) studies grouping (Table 28). As noted in the footnote to Table 67, an additional 220 healthy US volunteers have received the 300mg single dose in study 807; this data was not available for the data integration, but all safety data from these subjects has been reviewed, and is discussed where relevant.

Table 28 Exposure Across the TQ Development Program, by Grouping

Grouping	Subjects	Total TQ Dose	N
All Studies	**All treated**	**Any**	**4129**
		<300 mg	392
		300 mg	810[a,c]
		>300 mg	2927[b]
All Primary Studies (AP)	***P. vivax*-infected**	**300 mg**	**483**
Placebo-controlled Studies (PC)	*P. vivax*-infected	300 mg	317
Supportive Studies	***P. vivax*-infected**	**Any**	**303**
		<300 mg	112
		>300 mg	191
Clinical Pharmacology Studies	**Healthy volunteers**	**Any**	**720[c]**
		<300 mg	82
		300 mg	243[d]
		>300 mg	395
Malaria Prophylaxis Studies	**All Treated**	**Any**	**2703**
		<300 mg	198
		300 mg	83
		>300 mg	2422

Note: Data from studies SB252263/003, 036, 050, 051, 052, 053 and 054 have been excluded from the pooled groupings.

a. One subject in the Supportive Studies took 300 mg TQ instead of the planned >300 mg dose.
b. There were 81 subjects in Study SB252262/057 who received >300 mg TQ and were included in both the Malaria Prophylaxis Studies and in the Clinical Pharmacology Studies, but they were only counted once in the overall total.
c. Total includes >400 subjects enrolled at US sites.
d. The final data for the ophthalmic safety study 201807 include an additional 220 healthy volunteer subjects (all from US sites) in the 300 mg TQ group.

6.2. Analysis of AEs

Overall, the safety profiles for treatment groups in the PC and AP groupings were similar (Table 29).

Table 29 AE Overview (PC and AP Safety Populations)

	PC Grouping			AP Grouping	
	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)	TQ+CQ (N=483) n (%)	PQ+CQ (N=264) n (%)
Any AE	127 (68)	202 (64)	108 (60)	321 (66)	172 (65)
Any SAE	10 (5)	23 (7)	11 (6)	29 (6)	12 (5)
Any fatal AE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any AE leading to study withdrawal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any AE leading to discontinuation of study treatment	6 (3)	12 (4)	1 (<1)	13 (3)	2 (<1)
Any drug-related AE	29 (16)	31 (10)	26 (15)	45 (9)	37 (14)

6.2.1. Common AEs

Due to the AEs associated with recurrence and CQ/PQ retreatment, the summary of common AEs in this section focuses on events reported during the first 29 days of the study. Disease-related events of pyrexia, chills, rigor, and headache were to be reported separately from other AEs if the subject had a positive slide for *P. vivax* at the time of the event; however, this information was inconsistently reported by investigators, and the most common AEs were complicated by symptoms of malaria.

Within the first 29 days, pruritus was the most common AE in all 3 treatment groups in the PC grouping, which is consistent with the known effects of CQ (See Table 5, section 1.4.1) [Chloroquine US PI, 2013]. The AE profile in the TQ+CQ group based on the AP grouping was consistent with that observed in the TQ+CQ group for the PC grouping.

The majority of subjects with AEs had events that were mild or moderate in severity and few severe AEs (Grade ≥3) were reported.

6.2.2. SAEs and Deaths

There were no deaths in the 3 primary studies, or in the radical cure program studies.

Decreased Hb was the most common SAE, and the only SAE reported in >1 subject in the TQ+CQ group, based on the PC grouping (Table 30). Decreased Hb was a protocol-defined SAE (Hb decreases of ≥30% or >30 g/L from baseline; or, an overall drop in Hb below 60 g/L in the first 15 days of the study) and did not, in any instance, otherwise fulfill the criteria for 'serious'. The SAE profile observed for the TQ+CQ group based on the AP grouping was consistent with that observed in TQ+CQ group for the PC grouping.

Table 30 Non-Fatal SAEs by Preferred Term (PC Safety Population)

Preferred Term	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)
Any event	**10 (5)**	**23 (7)**	**11 (6)**
Haemoglobin decreased	3 (2)	14 (4)	3 (2)
ECG QT prolonged	5 (3)	1 (<1)	4 (2)
Abscess limb	0	1 (<1)	0
Hepatitis E	0	1 (<1)	0
Urinary tract infection	0	1 (<1)	0
Diarrhoea	0	1 (<1)	1 (<1)
Anaemia	0	1 (<1)	0
Drug-induced liver injury	0	1 (<1)	0
Abortion spontaneous	0	1 (<1)	0
Menorrhagia	0	1 (<1)	0
Alanine aminotransferase increased	1 (<1)	0	0
Gastroenteritis	1 (<1)	0	0
Nausea	0	0	1 (<1)
Vomiting	0	0	1 (<1)
Methaemoglobinaemia	0	0	1 (<1)
Hepatitis acute	0	0	1 (<1)
Dehydration	0	0	1 (<1)

6.2.3. AEs Leading to Withdrawal from the Study or Discontinuation of Study Treatment

No subject had an AE leading to withdrawal in the PC or AP groupings. The majority of AEs that led to the discontinuation of study treatment in the TQ+CQ group were protocol-defined SAEs of Hb decreased, which occurred in a higher proportion of subjects in the TQ+CQ group (3%) compared with the CQ alone (1%) or PQ+CQ groups (none) in the PC grouping (Table 31). The profile for AEs leading to discontinuation of study treatment in the TQ+CQ group based on the AP grouping was consistent with those observed in the TQ+CQ group for the PC grouping.

Table 31 AEs Leading to Discontinuation of Study Treatment by Preferred Term (PC Safety Population)

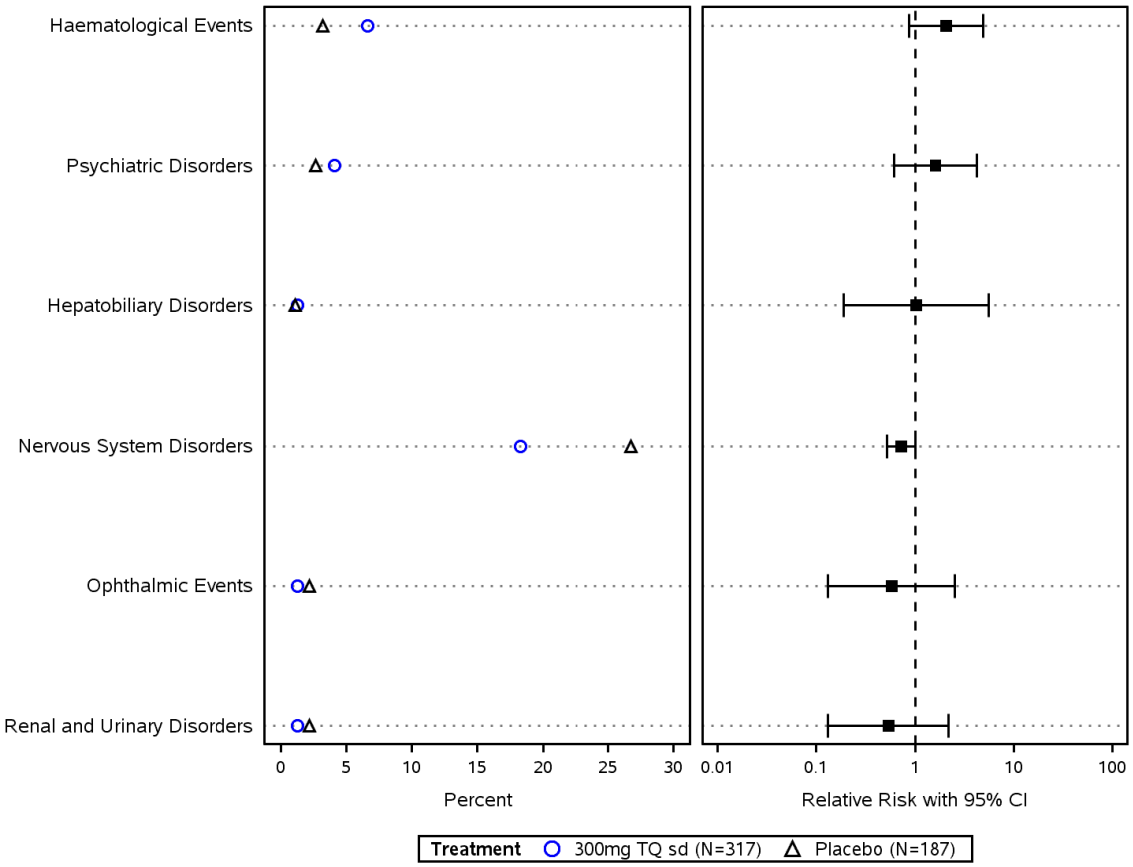
Preferred Term	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)
Any event	**6 (3)**	**12 (4)**	**1 (<1)**
Haemoglobin decreased	2 (1)	11 (3)	0
P. falciparum infection	0	1 (<1)	0
ECG QT prolonged	4 (2)	0	1 (<1)

6.2.4. AEs of Special Interest

The AEs of special interest (AESI) identified are considered risks or potential risks with TQ or treatments within the same class, including Hb-associated events, CNS events (i.e., nervous system disorders and psychiatric disorders), ophthalmic events, hepatobiliary disorders, and renal and urinary disorders.

The analyses on the PC grouping showed no clinically significant differences between the TQ+CQ group compared with the CQ alone group in the relative risk of experiencing hematological, psychiatric, hepatobiliary, ophthalmic, or renal and urinary AEs (Figure 7). The risk of experiencing nervous system disorder AEs was estimated to be lower in the TQ+CQ group compared with CQ alone, which was likely driven by AEs of headache. The risk of a hematological events and psychiatric disorder AEs was estimated to be numerically higher in the TQ+CQ group compared with CQ alone. Of note, these event rates were based on 6-months follow-up.

Figure 7 AEs of Special Interest with Relative Risk and 95% CIs for the Comparison of TQ+CQ vs. CQ alone (PC Safety Population)



TQ+CQ = 300 mg TQ SD (N=317); CQ alone = Placebo (N=187)
Note: Estimated relative risk is adjusted for study and region using the Cochran-Mantel-Haenszel method.

6.3. Laboratory Evaluations

6.3.1. Hepatobiliary Laboratory Abnormalities

Mild asymptomatic elevations in transaminases have been reported for a number of quinolines such as CQ, quinine, and mefloquine, with rare reports of hepatitis [Mathur, 1990; Gotsman, 2000; Wielgo-Polanin, 2005]. Hepatobiliary events were identified as AESIs, based on observations of asymptomatic alanine aminotransferase (ALT) increases with TQ.

Transient, sporadic increases in liver transaminases have been observed in all clinical studies but no clinically significant hepatobiliary effects were observed in the primary studies or in the All Studies groupings. All hepatobiliary AEs were mild or moderate in intensity and no subjects discontinued study treatment or withdrew from any of the 3 primary studies due to hepatobiliary AEs.

Small increases in ALT were observed at Baseline and at early timepoints (Days 3 through 8) in all 3 treatment groups in the PC grouping. Increases in ALT that were considered potentially clinically significant occurred at a higher incidence in the CQ alone group compared with the TQ+CQ and PQ+CQ groups; these were likely disease-related. High bilirubin levels were observed at Baseline across treatment groups in the PC grouping and subsequently resolved with treatment in all 3 treatment groups, as would be expected for recovery from *P. vivax* malaria. Liver function parameters in the TQ+CQ group based on the AP grouping (N 483) showed a similar pattern to the TQ+CQ group based on the PC grouping.

Pooled data from the Clinical Pharmacology grouping show that healthy volunteers treated with TQ did not report hepatobiliary AEs. Transient, asymptomatic, dose-related elevations in liver transaminases (ALT and AST) have been observed in healthy volunteers who received single 300 mg, 600 mg and 1200 mg TQ doses in placebo-controlled Phase 1 studies. At the 300 mg dose, elevations were mild-to-moderate. None of the elevations were severe or considered to be clinically significant.

6.3.2. Renal Function and Parameters

No renal toxicity signal was observed in the AP or PC groupings or across the TQ development program. The proposed 300 mg single dose TQ treatment was associated with small reversible increases in creatinine, which were consistent with the known renal transporter inhibition effect.

There were no renal or urinary SAEs, and no events led to study withdrawal or discontinuation of study treatment.

6.4. Hemoglobin-associated Events and Assessments

In the primary studies in *P. vivax* malaria, the incidence of Hb declines observed in subjects treated with 300 mg single dose TQ was similar to that with PQ 15 mg for 14 days. At the recommended 300 mg single dose of TQ, none of the small Hb decreases were regarded as clinically significant or led to clinical sequelae.

PQ and TQ are both 8-aminoquiolines with a potential to cause drug-induced hemolysis in G6PD-deficient individuals. However, in a WHO review of 8-aminoquinoline safety, even in G6PD-normal individuals, PQ can cause small, non-clinically significant reductions in Hb (10-20 g/L) at standard therapeutic doses [Recht , 2014]. Recovery from malaria is itself associated with a small degree of hemolysis, as infected red blood cells are cleared from the circulation [Woodruff, 1979; Commons, 2017]. This was shown in the primary studies by reticulocytosis that accompanied malaria recovery, as described in the sections that follow. Therefore, it is challenging to detect small levels of drug-induced hemolysis within the context of ongoing disease. This is further confounded by the fact that many patients present with dehydration, as evidenced by high serum urea and hematocrit levels at Screening. Subsequent rehydration and hemodilution may therefore result in artefactual decreases in Hb concentration that are not clinically relevant. The 3 primary studies of TQ in *P. vivax* malaria focused on identifying clinically relevant Hb decreases instead of hemolysis *per se*.

Subjects with AEs that were potentially associated with Hb decreases were identified by clinical review prior to unblinding in all primary studies. In addition, decreased Hb laboratory values were required to be reported as SAEs if they met protocol-defined criteria. In the Phase 3 studies, the criterion was ≥30% or >30 g/L from Baseline or a decrease in absolute Hb below 60 g/L in the first 15 days of the studies. In the Phase 2b study, TAF112582 Part 1, smaller decreases met SAE criteria (≥25% or >25 g/L within the first 15 days).

Hb decreases were also evaluated across populations based on G6PD activity, as noted above and described in the sections that follow. In healthy volunteers (male or female) with normal G6PD enzyme activity (≥70% of site median by spectrophotometry), a 1200 mg TQ dose was associated with small Hb decreases and accompanying rises in total bilirubin that are consistent with drug-induced hemolysis.

Male subjects with G6PD deficiency and female subjects who are homozygous for G6PD deficiency are likely to experience larger decreases in Hb.

For female heterozygotes with G6PD activity ≥70%, the balance of risk versus benefit supports the use of 300 mg single dose TQ. For female heterozygotes with intermediate levels of G6PD deficiency <70%, for the same dose of TQ, subjects with lower G6PD enzyme activity are likely to have greater decreases in Hb than subjects with a higher G6PD activity.

6.4.1. Hemoglobin-related AEs

Hb-associated Events in the Primary Studies (PC and AP Groupings)

In the PC grouping, the incidence of Hb-associated AEs was higher in the TQ+CQ group compared with the CQ alone group, and in both the PC and AP groupings, the incidence was higher in the TQ+CQ groups compared with the PQ+CQ groups (Table 32). No Hb-associated AEs led to withdrawal from the primary studies. However, 3% of subjects in the TQ+CQ group in both groupings had events that lead to interruption or discontinuation of study treatment, compared with ≤1% in the other treatment groups. The majority of the events were mild or moderate in severity; 1 subject in the TQ+CQ group had a Grade 3 event (increased bilirubin).

The most common Hb-associated AE across all treatment groups were decreased Hb and the incidences aligned with the overall incidence of Hb-associated AEs (Table 32). All other Hb-associated AEs occurred in ≤1% of subjects across all treatment groups. There were a small number of subjects across treatment groups with protocol-defined SAEs of decreased Hb during the studies (≤5% in the TQ+CQ groups, ≤2% in the PQ+CQ and CQ alone groups). No subjects required transfusions during the studies.

Table 32 Hb-associated AEs of Special Interest (PC and AP Safety Population)

	PC Grouping			AP Grouping	
	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)	TQ+CQ (N=483) n (%)	PQ+CQ (N=264) n (%)
Overview of Hb-associated AEs					
Any AEs	6 (3)	21 (7)	5 (3)	29 (6)	8 (3)
SAEs	3 (2)	15 (5)	3 (2)	19 (4)	4 (2)
Severe AEs (Grade ≥3)	0	0	0	1 (<1)[a]	0
Drug-related AEs	3 (2)	1 (<1)	1 (<1)	2 (<1)	1 (<1)
AEs leading to withdrawal from study	0	0	0	0	0
AEs leading to interruption or discontinuation of study treatment	2 (1)	11 (3)	0	15 (3)	1 (<1)
Hb-associated AEs, by PT					
Haemoglobin decreased	3 (2)	15 (5)	3 (2)	19 (4)	4 (2)
Fatigue	2 (1)	2 (<1)	0	3 (<1)	0
Dyspnoea	0	2 (<1)	0	2 (<1)	0
Anaemia	0	1 (<1)	2 (1)	1 (<1)	3 (1)
Pallor	0	1 (<1)	0	1 (<1)	0
Hyperbilirubinaemia	1 (<1)	0	0	1 (<1)	1 (<1)
Blood bilirubin increased	0	0	0	1 (<1)	0
Tachypnoea	0	0	0	1 (<1)	0

a. Grade 3 increased bilirubin following *P. vivax* recurrence on Day 99

The adjusted relative risk of experiencing Hb-associated AEs was estimated to be 2.07 (95%CI:0.87,4.94) in the TQ+CQ group compared with CQ alone (Figure 7). The PQ+CQ group AE incidence was similar when compared to CQ alone. These analyses were completed based on event data over the full study periods.

Hb-associated AEs Across the TQ Development Program (All Studies Grouping)

Across the entire TQ development program, the most frequently reported Hb-associated AEs in the All TQ treatment group were consistent with those observed in the TQ+CQ groups in the PC and AP groupings. The only Hb-associated AE reported in ≥1% of subjects in the All TQ and All Placebo groups was fatigue.

6.4.2. Hemoglobin laboratory values and assessments

Hb changes over time were similar across the treatment groups in the PC grouping (Figure 2). In the first 15 days after treatment, there were few subjects (≤2%) with decreases in Hb that met the definition of potential clinical concern (Table 33), but none of the changes were considered clinically significant. Few subjects in the TQ+CQ group had Hb declines after the first 29 days of treatment. No subjects had Hb values less than 60 g/L at any point during the studies.

The profile for Hb changes from baseline for the TQ+CQ group based on the AP grouping (N 483) was consistent with that observed in the TQ+CQ group for the PC grouping.

Table 33 Subjects with Changes from Baseline in Hb of Potential Clinical Concern in the First 15 Days after Treatment (PC Safety Population)

Analysis visit	Category	CQ alone N=187 n (%)	TQ+CQ N=317 n (%)	PQ+CQ N=179 n (%)
Day 3	N	187	315	179
	Low	1 (<1)	4 (1)	0
Day 5	N	186	313	177
	Low	0	3 (<1)	0
Day 8	N	185	312	175
	Low	1 (<1)	4 (1)	0
Day 11	N	184	310	173
	Low	0	5 (2)	1 (<1)
Day 15	N	158	275	143
	Low	0	6 (2)	1 (<1)

In Study 564, the incidence of clinically relevant hemolysis was evaluated as a primary endpoint. The protocol defined clinically relevant hemolysis as a decrease in Hb of ≥30% or >30 g/L from Baseline or an overall decrease in Hb to below 60 g/L, the incidence was low in both treatment groups in G6PD-normal subjects. The majority of

Hb decreases in both treatment groups n Study 564 were low (<20 g/L) and of no clinical concern, and no subjects required a blood transfusion. Only 1 subject in the TQ+CQ treatment group experienced a Hb nadir <80 g/L, which was a Hb decrease of 20 g/L from Baseline to Day 3 that normalized without specific medical intervention. Although the primary endpoint was termed clinically relevant hemolysis, the events meeting these criteria were all based on Hb decreases. There was no evidence of hemolysis based on hemolytic markers of reticulocyte counts and urinalysis. Although it would be expected that the 1 G6PD-deficient female enrolled in the study, who was randomized to PQ+CQ, would have had some degree of hemolysis because of her G6PD heterozygous status, the subject's hematology profile was consistent with laboratory values typically observed in subjects recovering from malaria, including a transient decrease in Hb and transient rise in methemoglobin and reticulocyte counts.

In Study 582 Part 2, the incidence of subjects with Hb decreases >30 g/L or ≥30% from Baseline or >20 g/L to ≤30 g/L during the first 29 days of the study was low across the treatment groups (Table 34). The proportions of subjects with hemoglobin decreases were higher in the TQ+CQ group compared with those in the CQ alone group. These differences were not considered to be clinically significant because few subjects had Hb decreases that fell to below the lower limit of normal, and all subjects fully recovered without blood transfusion or other medical intervention.

Table 34 Hemoglobin Declines over First 29 Days (582 Part 2 Safety Population)

Maximum decline from Baseline	CQ alone (N=133) n (%)	TQ+CQ (N=260) n (%)	PQ+CQ (N=129) n (%)	Total (N=522) n (%)
All subjects				
n	133	259	129	521
≤20 g/L	120 (90)	214 (83)	114 (88)	448 (86)
>20 g/L to ≤30 g/L	11 (8)	31 (12)	12 (9)	54 (10)
>30 g/L or ≥30% of Baseline	2 (2)	14 (5)	3 (2)	19 (4)

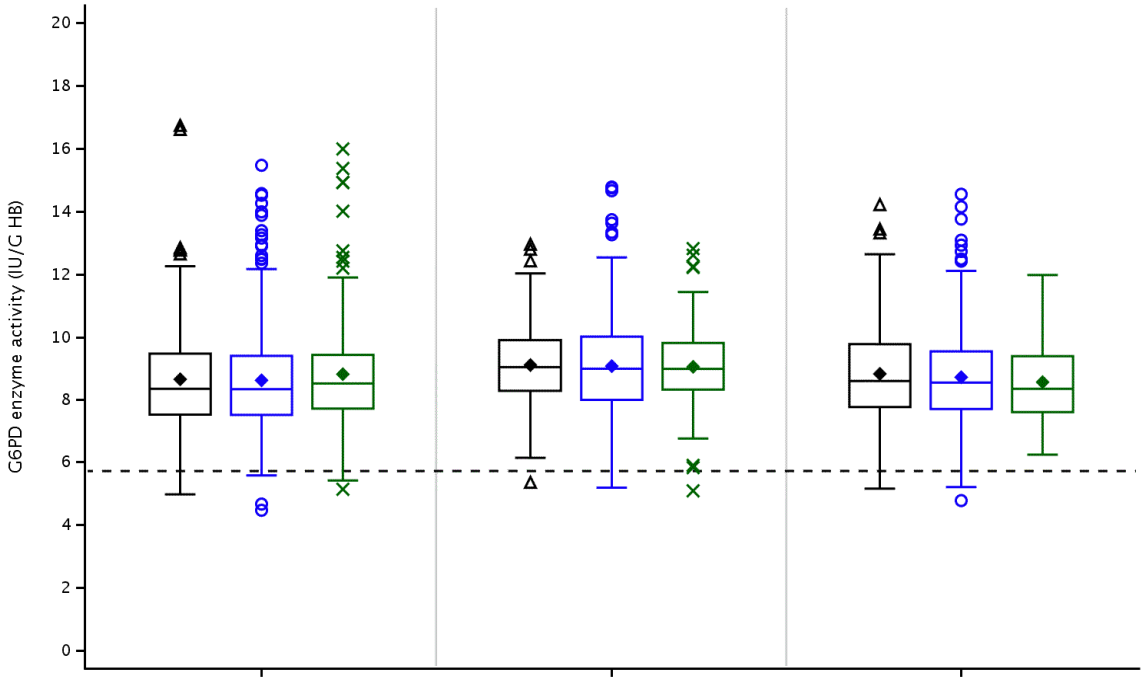
6.4.3. Subjects with G6PD deficiency

G6PD deficiency is known to be a risk factor for hemolysis in subjects treated with 8-aminoquinolines. An assay validation study in healthy G6PD-normal males at each site was used to determine G6PD eligibility requirements for the pivotal trials and found global median G6PD activity was 8.2 International units (IU)/g Hb, with 70% of median at 5.7 IU/g Hb (at 30ºC using Trinity assay). Regional G6PD values at 70% of median were similar across the studied regions: 5.8 for South America, 5.6 for SE Asia, 5.7 for Africa. In this trial, the minimum G6PD enzyme level of any subject was 5.4 IU/g Hb (TAF115226).

A spectrophotometric assay for G6PD enzyme activity was used during screening to exclude subjects with enzyme activity <70% of the site median from the Studies 582 Parts 1 and 2. In addition, all females randomized into the studies, as well as all males who had a protocol-defined SAE of decreased Hb, were genotyped for G6PD deficient alleles.

No clinically meaningful changes in G6PD activity over time were observed in the PC grouping. Values at each time point were consistent across treatment groups (Figure 8).

Figure 8 G6PD Enzyme Activity by Visit and Treatment Group (PC Safety Population)



Subjects			
Placebo	187	128	127
TQ	317	251	250
PQ	179	124	123

Placebo = CQ alone; TQ = TQ+CQ; PQ = PQ+CQ; Day 1 = Screening
Notes: Reference line denotes 5.71 IU/g Hb (70% of global median of 8.16 IU/gHB, obtained from Study TAF115226).
TAF112582 Part 1 data was only collected at Day 1 (i.e., Screening).

Male subjects with G6PD deficiency and female subjects who are homozygous for G6PD deficiency are likely to experience larger decreases in Hb; therefore, TQ must not be given to these individuals.

For female heterozygotes with G6PD activity ≥70%, 300 mg single dose TQ is associated with an acceptable safety profile. Any Hb declines seen were not clinically significant and resolved without specific medical intervention.

For female heterozygotes with intermediate levels of G6PD deficiency (<70%), for the same dose of TQ, subjects with lower G6PD enzyme activity are likely to have greater decreases in Hb than subjects with a higher G6PD activity.

Therefore, patients with G6PD activity <70% of normal must be excluded from treatment with 300 mg single dose TQ.

6.5. CNS Effects

Across the TQ development program, more than 800 subjects have received a cumulative 300 mg dose of TQ over ≤3 days. A comprehensive review of CNS AEs observed showed that all events were mild to moderate in severity and self-limiting.

A limited number of serious psychiatric events have been reported in older TQ studies at doses ≥350 mg, but mainly with multiple doses and in subjects with a prior history of significant psychiatric disorders. Consequently, CNS side effects have been analyzed in detail in the primary studies and across the entire TQ development program.

6.5.1. Results from the radical cure program (PC, AP groupings)

In the PC and AP groupings, no serious CNS AEs were reported, and no subjects withdrew from the studies or discontinued treatment due to CNS AEs. All CNS AEs were self-limiting and mild or moderate in intensity.

The incidence of CNS AEs over the full study period were similar in the TQ+CQ and PQ+CQ treatment groups and lower than in the CQ alone group (Table 35). This difference was driven primarily by AEs of headache, likely associated with malaria recurrence and CQ/PQ re-treatment.

Table 35 CNS AEs by System Organ Class and Preferred Term in the PC and AP Groupings (Safety Populations)

	PC Grouping			AP Grouping	
	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)	TQ+CQ (N=483) N (%)	PQ+CQ (N=264) N (%)
Nervous System Disorders, any event	**50 (27)**	**58 (18)**	**35 (20)**	**105 (22)**	**60 (23)**
Headache	39 (21)	37 (12)	24 (13)	64 (13)	40 (15)
Dizziness	16 (9)	30 (9)	14 (8)	59 (12)	30 (11)
Migraine	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
Syncope	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Tremor	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Somnolence	0	1 (<1)	0	1 (<1)	0
Burning sensation	0	0	1 (<1)	0	1 (<1)
Dysaesthesia	0	0	1 (<1)	0	1 (<1)
Balance disorder	0	0	0	1 (<1)	0
Hypoaesthesia	0	0	0	0	1 (<1)
Psychiatric Disorders, any event	**5 (3)**	**13 (4)**	**8 (4)**	**15 (3)**	**12 (5)**
Insomnia	5 (3)	13 (4)	8 (4)	15 (3)	8 (3)
Anxiety	0	2 (<1)	0	2 (<1)	3 (1)
Depression	0	0	0	0	1 (<1)

Given this confounding factor, CNS events with onset during the first 29 days of the study are considered a better reflection of the AE profile for the active arms (TQ+CQ and PQ+CQ) compared to placebo (CQ only group) (Table 6).

The overall incidence of dizziness was higher (≥3%) in both treatment groups in the AP grouping compared with the TQ+CQ and PQ+CQ groups in the PC grouping due to higher incidence in Study 564. However, the overall incidences of other CNS events were similar across the treatment groups in both pooled groupings (See Table 6, Section 1.4.4.4).

In the TQ+CQ group, the events of anxiety and somnolence were Grade 1 or Grade 2 in severity and transient. None of the events were considered to be related to study treatment by the investigator, however, due to the close temporal relationship to study treatment dosing, and given that these AEs are recognized effects of some quinoline antimalarial drugs and have been observed in prior studies of TQ, a causal role for TQ cannot be dismissed.

Pooled data from the Clinical Pharmacology grouping show that healthy volunteers treated with TQ experienced similar types of CNS events as those observed in *P. vivax*-infected subjects treated with TQ+CQ in the primary studies. The AEs followed the same general pattern as that observed in *P. vivax*-infected subjects, with increasing types of events and incidences at higher doses and longer durations of treatment.

6.5.2. All Studies grouping

Across all clinical studies with TQ across all indications/treatment regimes, there was a broader distribution of CNS AEs observed in the All TQ group compared with the All Placebo group, and the occurrence of various events and increased severity tended to increase with higher TQ doses and longer duration of treatment (Appendix Table 65). This pattern was more pronounced for the psychiatric AEs (Appendix Table 66).

Severe and serious psychiatric disorders reported across the program at any dose or duration

Over all the studies, a limited number of severe or serious psychiatric events (n 7) have been reported in older TQ studies at doses ≥350 mg, and most occurred after multiple doses (Table 36). In addition, there were 2 other medically important cases of mild depression/depressed mood that were included in this evaluation because they were considered medically important for the purposes of a comprehensive review, for a total of 9 subjects. The majority of subjects with these events had a history of significant psychiatric disorders or other confounding factors.

Table 36 Summary of Subjects with Severe or Serious Psychiatric Disorders, or Other Medically Important Events

Study ID	Dose	Event PT (Severity or Verbatim Terms)	Onset	Duration	Resolution	Relationship to Study Drug by the Investigator	Intervention/ Action Taken	Medical History
SB252262/033	1200 mg cumulative	Depression (moderate)	Day 24	87 days	Resolved	Related	Required corrective therapy (paroxetin)/ Withdrawn from study	Closed head injury 3 years prior to study
SB252262/043	750 mg cumulative	Suicidal behavior (associated with alcohol intoxication)[a]	Day 8	1 day after TQ discontinued	Resolved	Related (CQ co-suspect) [b]	Hospitalized and required corrective therapy (intervention unknown)/ Withdrawn due to unstable mental state	Family reported history of marital difficulties and previous suicide threat; no other relevant history or concomitant medications reported at Screening
TAF112582 Part 1	600 mg single dose	Depressed mood[c]	Day 6	Unknown	Resolved	Unrelated (CQ co-suspect)[b]	Hospitalized (on Day 88 for 2 days) with nausea, epigastric pain, diarrhea, and depression; treated with fluoxetine; consulted with psychiatric specialist (findings unknown)	History of depression but no suicidal tendencies; irregular psychiatric consults; frequent but irregular use of diazepam (10 mg)
SB252262/050[d] (Subject (b) (6))	350 mg single dose	Acute psychotic episode (severe)	Day 24	25 days	Recovered	Possibly related	Hospitalized following progressive emotional distress	Two previous episodes of psychosis (not disclosed at Screening)
SB252262/050[d](Subject (b) (6))	500 mg single dose	Psychotic episode (severe)	Day 8	9 days	Recovered	Remotely related	Hospitalized for a pre-scheduled psychiatric admission	Recent diagnosis of schizophrenia (not disclosed at Screening)
SB252262/057 (Subject (b) (6))	5200 mg[e] cumulative	Bipolar depression (mild); Depression (mild)	Day 223 (62 days since last dose)	Lost to follow-up	Unknown	Unlikely related	Bupropion and lithium started on Study Day 223 (ongoing)/Excluded due to a positive hepatitis/HIV screen	No relevant past history or concomitant medications.

Study ID	Dose	Event PT (Severity or Verbatim Terms)	Onset	Duration	Resolution	Relationship to Study Drug by the Investigator	Intervention/ Action Taken	Medical History
SB252262/014	1200 mg cumulative	Paranoid hallucinotic psychosis (serious)	Day 27	3 days	Not resolved	Unrelated	Hospitalized and treated with olanzapine and lorazepam/None	History of "hallucinotic psychosis" 6 months earlier (not disclosed at Screening); no obvious signs of psychosis at Screening; negative drug screen
TAF114582	600 mg single dose	Depressed mood (mild)	Day 4	3 days	Resolved	Related	None	No relevant past medical history or concomitant medications were reported; at the time of the event, subject also reported abdominal pain, diarrhea, and palpitations
SB252262/057 (Subject (b) (6))	1600 mg cumulative	Depressed mood (mild)	Day 37	15 days	Resolved	Unlikely related	None/ No action taken	No relevant past history; treated for a UTI with sulfamethoxazole starting on Day 13 (co-suspect)

Note: UTI=urinary tract infection

a. Family reported that subject had taken "poison." The event was not assigned a body system and therefore does not appear in the pooled output for AEs in the psychiatric disorders SOC.
b. The sponsor considered CQ co-suspect.
c. The SAE was reported after dataset was frozen and, therefore, does not appear in the pooled groupings.
d. Cases from Study SB252262/050 (n=2) are not reported in pooled groupings.
e. Loading dose 200 mg/day for 3 days plus 200 mg weekly for 23 weeks.

Spontaneous Reports of Psychiatric Disorders from Subjects in Australian Defense Force Studies

Spontaneous reports of psychiatric disorders were recently received from 18 subjects who received TQ in prophylaxis studies conducted with the Australian Defense Force (ADF) (Study SB252262/033, Study SB252262/046, and Study SB252262/049).

Within these spontaneous reports from former ADF study participants, which were not medically confirmed, the self-reported medical histories describe more CNS events than were reported at the time and also report persisting long-term effects, many of which appear to overlap with symptoms of PTSD. These include anger outbursts, confusional state, and hallucinations.

Despite the potential underreporting at the time of the ADF clinical trials between 1999-2001, the rate for CNS effects was higher in the ADF study SB252262/033 compared with Study SB252262/57, in which TQ was administered at the same dosing regimen (weekly dosing for 6 months) but in healthy volunteers not serving in deployed armed services. This observation suggests that ADF study subjects may be at increased risk of experiencing CNS effects (see review of epidemiology below). The majority of soldiers were exposed to triggers for PTSD, the symptoms of which are similar to those included in the reports. Although a possible interaction with PTSD has been postulated [Nevin, 2014], due to these confounding factors, it is not possible to draw conclusions on the role of TQ in these cases although a role cannot be dismissed.

A literature review of epidemiology data was conducted to evaluate the background rate estimates of suicidality, depression, and anxiety in military populations. Rates ranged from ~0.1% for completed suicide (range 0.01% to 0.23%), ~6% for suicidal ideation or behavior (range 0.1% to 24%) to ~10% for severe depression and generalized anxiety disorders (ranges 5.1% to 14.5% and 7.3% to 14.5%, respectively) [Belik, 2010;Ilgen, 2010; Skegg, 2010; Waller, 2012; Kapur, 2009; Fanning, 2013; Ramsawh, 2014; Schoenbaum, 2014; O'Toole, 2015; Reger, 2015; Spiess, 2016; Brignone, 2017] High variations were observed depending on the reported study design, endpoints and populations, and higher rates were observed in veterans versus non-discharged military, and in deployed versus non-deployed military populations.

6.5.3. CNS Effects of Antimalarials

CNS side effects have been reported for some antimalarials, including non-quinoline and synthetic quinolines (most noticeably, the 4-quinolinemethanol, mefloquine [MQ], and including 4- and 8-aminoquinolines) [Schmidt, 1948; Schmidt, 1951; Phillips-Howard, 1995; Croft, 2002; Toovey, 2009; FDA, 2013; Ritchie, 2013; Nevin, 2014; McCarthy, 2015; Quinn, 2015; Nevin, 2016; Nevin, 2017; Eick-Cost, 2017]. Continued dosing following the emergence of mild CNS symptoms has been identified as a risk factor for development of more severe events [Mefloquine USPI, 2013], and a past history of mental disorders has been considered a risk factor for MQ-related CNS events. Less historical data appears to be available for 8-aminoquinolines compared with some other quinoline antimalarials [Schmidt, 1948; Loken, 1949; Lee, 1981; Saunders, 2014].

6.5.4. CNS Conclusions

In conclusion, a comprehensive review of CNS AEs showed that in the radical cure program, all CNS events were mild to moderate in severity and self-limiting. This includes the 483 patient in the primary studies and the 330 healthy US volunteers in Study 201807 who received a single TQ dose of 300 mg. While there were no reports of serious psychiatric disorders following 300 mg single dose TQ, cases of depression and psychosis have occurred in subjects following higher single doses of TQ (350 mg to 600 mg) or in multi-dose regimens (e.g. prophylaxis). Most of these events occurred in subjects with a previous history of psychiatric disorders. Serious psychiatric disorders, such as psychosis and depression, have also been associated with some quinoline antimalarials. Caution should be advised with TQ treatment in patients with a current or past history of serious psychiatric disorders. Our current proposed label for 300mg single dose TQ under review by the FDA includes related precautionary language.

The use of 300 mg single dose TQ with concomitant CQ for radical cure of *P. vivax* malaria, as used in the Phase 3 studies of TQ, showed that the risk of CNS effects is low in subjects without an active or past history of serious psychiatric disorders.

6.6. Ophthalmic Events and Assessment

6.6.1. Brief summary of historical data and concerns from the program and other indications

In common with other cationic amphiphilic drugs, TQ has the potential to cause phospholipidosis, a phospholipid storage disorder, leading to phospholipid accumulation in the cornea and reversible keratopathy [Halliwell, 1997; Hollander, 2004]. Photophobia and retinal toxicity have also been reported from quinine and quinidine treatment [Rheeder 1991].

Prior to the 3 primary studies evaluating 300 mg single dose TQ in the radical cure of *P. vivax* malaria, ophthalmic assessments had been conducted in more than 200 TQ-treated subjects across 4 studies (033, 057, 058, TAF106491). The majority of these subjects received supratherapeutic loading doses over 2 to 3 days (≥600 mg) and subsequent long-term maintenance therapy. The most significant ophthalmic finding in subjects from these studies was benign reversible vortex keratopathy, as confirmed by independent experts. There was no signal for retinal toxicity when 900 mg TQ was used in combination with CQ, which is 3 times the TQ dose used in the 3 primary studies.

6.6.2. Results from the radical cure program (PC, AP groupings)

Across the primary studies there was no evidence of retinal toxicity or corneal changes associated with vision changes for the proposed 300 mg single dose TQ. AEs associated with ocular changes were infrequent and similar across the treatment groups in the PC and AP groupings. All events were mild or moderate in severity. There were no ophthalmic SAEs. All of the events had onset within the first 29 days and all resolved. No clinically significant changes to ophthalmic safety parameters were observed, based

on visual acuity measurements, anterior segment examination with evaluation for vortex keratopathy, posterior segment examination including fundus photographs, color perception assessment, and Humphrey visual field perimetry.

6.6.3. Ophthalmic Safety Study 201807

Evaluation of the final data for the placebo-controlled Study 201807, conducted as per regulatory guidance, did not identify any signal for retinal toxicity with use of 300 mg single dose TQ. One subject in each treatment group met the primary endpoint, which was based on a composite of five parameters. Both subjects had an ellipsoid zone disruption (EZD) abnormality detected in 1 eye at Day 90. However, evaluation of the screening images from the subject in the TQ group showed a pre-existing EZD abnormality, and the subject should have been excluded from the study.

Study 201807 was a multi-center, randomized, single-blind, placebo-controlled, parallel-group study of a single, 300 mg oral dose of TQ in healthy adult subjects.

The primary objective of this study was to assess the PD effects of TQ on the retina via spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF). The secondary objective was to assess the overall ophthalmic safety of TQ compared with placebo (i.e., CQ alone).

Following initial screening assessments, eligible subjects underwent baseline ophthalmic examinations. Eligibility was confirmed by masked, independent central review of the baseline ophthalmological assessment data. Eligible subjects were randomized in a 2:1 ratio to 300 mg TQ or matched placebo within 7 days of the screening ophthalmic examinations. Subjects were followed for safety assessments and returned to the clinic for follow-up ophthalmic evaluations at approximately 90 days post-dose.

Ophthalmic assessments included key SD-OCT measurements of central retinal thickness and appearance of the retina on FAF at Screening and Day 90. Visual acuity was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) chart reading. Additional retinal morphology was assessed by SD-OCT and fundus photography captured at Screening and Day 90.

The primary endpoint was the proportion of subjects treated with TQ who developed significant protocol-defined retinal changes from Baseline to Day 90. A subject was considered to have a clinically significant retinal change if any of the following 5 parameters indicated a change from Baseline in either eye: SD-OCT central subfield thickness, SD-OCT total macular volume, SD-OCT central retinal lesion thickness, SD-OCT ellipsoid zone disruption (EZD), or abnormal autofluorescence patterns.

A sample size of 300 subjects was planned to be treated with TQ based on 95% probability of detecting an event when the underlying risk of clinically significant retinal findings at 90-day follow-up was 1%.

6.6.3.1. Primary endpoint – retinal assessments

In the final analysis, the primary endpoint was met by 1 subject in each treatment group, both of whom had EZD (Table 37).

No subject had a change from baseline for FAF.

The upper limit for the 95% one-sided CI for the proportion of subjects with retinal findings in either eye in the TQ group was 1.5%. The difference versus placebo was -0.3% (95% CI -3.1%, 1.3%) (Table 37).

No subjects in either treatment group had retinal findings in both eyes. The upper limit for the 95% one-sided CI for the proportion of subjects with retinal findings in both eyes in the TQ group was 0.9%. The difference versus placebo was 0.0% (95% CI -2.3%, 1.2%) (Table 38).

Table 37 Proportion of Subjects with Retinal Findings in Either Eye in 201807 (Ophthalmic Safety Population)

Endpoint	Retinal changes from baseline	Placebo N=161	TQ 300 mg N=306
Primary	Yes No Upper limit of 95% one-sided CI for proportion of subjects with retinal changes	1 (0.6) 160 (99.4)	1 (0.3) 305 (99.7) 1.5%
Secondary	Difference in proportion with retinal changes TQ vs. Placebo (95% CI)		-0.3% (-3.1%,1.3%)

Table 38 Proportion of Subjects with Retinal Findings in Both Eyes in 201807 (Ophthalmic Safety Population)

Endpoint	Retinal changes from baseline	Placebo N=161	TQ 300mg N=306
Primary	Yes No Upper limit of 95% one-sided CI for proportion of subjects with retinal changes	0 161 (100.0)	0 306 (100.0) 0.9%
Secondary	Difference in proportion with retinal changes TQ vs. Placebo (95% CI)		0.0% (-2.3%,1.2%)

Subject (b) (6) (EZD endpoint) (TQ group)

Subject (b) (6), had ellipsoid zone (EZD) disruption of >15% in width representing change from baseline in one (right) eye at the Day 90 follow up assessment. The contralateral (left) eye did not have a change from baseline. This subject was enrolled in error as there was an ellipsoid zone disruption at baseline and should have been excluded from the trial.

Additionally, there was a difference in the anatomical location of the Day 0 and Day 90 scans. The scan on Day 90 was taken from a superior location compared to the scan at Day 0 explaining the difference in EZD disruption. None of the other 4 parameters of the primary endpoint had changes from baseline. Of note this subject reported no visual AEs and best corrected visual acuity did not change from baseline. Fundus examination and photography were also unchanged from baseline.

Subject (b) (6) (EZD endpoint) (PBO group)

Subject (b) (6) had no EZD at baseline and an EZD of 128 μm at Day 90 follow-up, representing a change from baseline in one (right) eye. The contralateral (left) eye did not have a change from baseline. None of the other 4 parameters of the primary endpoint had changes from baseline.

6.6.3.2. Ophthalmological AEs

The ophthalmological AEs were generally balanced between the treatment groups (Table 39), with most occurring in only 1 subject in 1 or both treatment groups.

Table 39 Ophthalmological AEs Reported in Any Treatment Group (201807 Safety Population)

Preferred term	Placebo N=168	TQ 300mg N=330
Infections and infestations[a]		
Conjunctivitis	0	1 (<1)
Eye disorders		
Any event	7 (4)	9 (3)
Eye irritation	0	2 (<1)
Conjunctivitis allergic	1 (<1)	1 (<1)
Photophobia	1 (<1)	1 (<1)
Vision blurred	1 (<1)	1 (<1)
Corneal deposits	0	1 (<1)
Dry eye	0	1 (<1)
Eye disorder	0	1 (<1)[b]
Foreign body sensation in eyes	0	1 (<1)
Mydriasis	0	1 (<1)
Retinal exudates	0	1 (<1)
Astigmatism	1 (<1)	0
Blepharospasm	1 (<1)	0
Presbyopia	1 (<1)	0
Retinal haemorrhage	1 (<1)	0
Hepatobiliary disorders[a]		
Ocular icterus	0	1 (<1)[c]

a. Only ophthalmological-associated events from this SOC are included.
b. The verbatim text for Subject (b) (6) was 'peripheral pigment change of left eye'.
c. Subject (b) (6) also had ocular events of dry eye and foreign body sensation in eyes.

6.6.3.3. Vortex keratopathy

Vortex keratopathy was reported in 1 subject (TQ group) at the Day 90 assessment. This was not reported as an AE. Post-database freeze, Subject (b) (6) was described as having a Lasik scar with calcium deposits. Review of the source data confirmed this finding was present at baseline and unchanged at Day 90. The ophthalmologist indicated vortex keratopathy as 'absent' at Baseline and at Day 90. Therefore, the report of vortex keratopathy was due to a data entry error. There was no change in visual acuity for this subject from baseline and no ocular AEs were reported. No vortex keratopathy was actually present in this subject.

6.6.3.4. Best corrected visual acuity

The absolute and change from baseline BCVA (logMAR) results (Table 40) and the categorical changes from baseline (Table 41) did not indicate clinically meaningful changes from baseline in either group.

The small number of subjects with a definite change in vision was not considered a clinically significant difference between the treatment groups. The difference in occurrence of possible change in vision was not considered a meaningful difference between the treatment groups.

Table 40 BCVA (logMAR) Results from Assessment (201807 Safety Population)

Data	Treatment	Eye	N	Visit	n	Mean	StdD	Median	Min	Max
Absolute	Placebo	Right	168	Screening	168	-0.055	0.0866	-0.097	-0.20	0.20
			168	Day 90	162	-0.056	0.0959	-0.097	-0.30	0.40
		Left	168	Screening	168	-0.045	0.0924	0.000	-0.30	0.20
			168	Day 90	162	-0.044	0.0996	0.000	-0.30	0.40
	TQ 300mg	Right	330	Screening	330	-0.048	0.0936	0.000	-0.20	0.30
			330	Day 90	308	-0.043	0.0946	0.000	-0.30	0.30
		Left	330	Screening	330	-0.041	0.0948	0.000	-0.30	0.30
			330	Day 90	308	-0.029	0.0980	0.000	-0.30	0.40
Change	Placebo	Right	168	Day 90	162	-0.004	0.0888	0.000	-0.20	0.30
		Left	168	Day 90	162	0.001	0.0817	0.000	-0.20	0.20
	TQ 300mg	Right	330	Day 90	308	0.005	0.0877	0.000	-0.20	0.30
		Left	330	Day 90	308	0.011	0.0904	0.000	-0.30	0.40

StdD=standard deviation

Table 41 BCVA (logMAR) Change from Baseline by Category (201807 Safety Population)

	Placebo N=168				TQ 300 mg N=330			
Eye:	**Right**	**Left**	**Either**	**Both**	**Right**	**Left**	**Either**	**Both**
n	162	162	162	162	308	308	308	308
No	156 (96)	157 (97)	152 (94)	152 (94)	294 (95)	290 (94)	279 (91)	279 (91)
Possible[a]	5 (3)	5 (3)	9 (6)	1 (<1)	13 (4)	16 (5)	26 (8)[c]	2 (<1)
Definite[b]	1 (<1)	0	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)	0

a. A change from baseline ≥0.12 to <0.3 LogMAR
b. A change from baseline ≥0.3 logMAR
c. One TQ subject had a definite change in the right eye and possible change in the left eye and is summarised under Definite.

6.6.4. All Studies Grouping results

Across the TQ development program, ophthalmic AEs occurred in similar proportions of subjects in the All Placebo and All TQ groups, based on the All Studies grouping. Higher proportions of subjects in the All TQ group had corneal verticillata and keratopathy compared with the All Placebo treatment group. These events occurred only at supra-therapeutic and/or long-term doses of TQ. The incidences of retinopathy, retinal disorder, and retinal pigmentation changes were low (<1%) in the All TQ group, based on the All Studies grouping. All of these events were reported with supra-therapeutic and/or long-term doses of TQ and their clinical significance is uncertain.

Photophobia was reported in 6 subjects (<1%) in the All TQ group compared with no subjects in the All Placebo group. Based on sponsor evaluation, 2 events of photophobia showed a clear causal relationship with TQ. In both cases, the events started the day after dosing, were mild and resolved after ≤2 days.

6.7. Other Safety topics

6.7.1. Methemoglobin

Small increases in methemoglobin were observed in both the TQ+CQ and PQ+CQ treatment groups of the PC grouping. Increases in methemoglobin percentages were generally observed more frequently in the PQ+CQ group compared with the other treatment groups in the PC grouping.

6.7.2. Hypersensitivity

Two SAEs of hypersensitivity-related reactions were reported; both were in the healthy volunteer study, TAF114582. The first female received a 300 mg dose of TQ. On Day 17 after dosing, she had lip swelling, itching, and diffuse hives (SAE or urticaria). She also reported difficulty breathing that may have been related to an undisclosed part

history of asthma. The second female received 600 mg of TQ: on Day 18, she had difficulty swallowing, swelling of the throat, some swelling of the hands and feet, and hives (SAE of hypersensitivity). Both events resolved fully with diphenhydramine and corticosteroid treatment. The first case reported difficulty breathing that may have been related to an undisclosed past history of asthma. Both events were judged by the investigator to be possibly related to TQ.

6.7.3. ECGs and QTc Analysis in *P. vivax* Subjects Treated with CQ

There were no differences across the 3 treatment groups in the PC grouping in ECG assessments through 72-hours post-Baseline. There were no subjects with clinically significant abnormal ECG findings in the TQ+CQ group.

Observed changes in QTcF were consistent with the known effects of CQ on QT prolongation and there was no evidence of a clinically significant additional effect on QTcF values in the TQ+CQ group. Differences in QTcF between treatment groups were not considered to be clinically significant. Changes from baseline in QTcF resolved by Day 29 for most subjects across the 3 treatment groups.

Table 42 Summary of Maximum Post-Baseline QTcF Values (msec) Through 72 Hours by Category (PC Safety Population)

QTcF (msec)	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)
N	186	311	178
Increase <30	76 (41)	119 (38)	75 (42)
Increase ≥30 and <60	93 (50)	154 (50)	85 (48)
Increase ≥60 and QTcF ≤480	10 (5)	31 (10)	16 (9)
Increase ≥60 and QTcF >480	7 (4)	7 (2)	2 (1)

The QTcF prolongation observed in the TQ+CQ group based on the AP grouping was consistent with those observed in the PC grouping.

Cardiac Safety in Study TAF114582

Study TAF114582 was a thorough QT study conducted in accordance with the ICH E14 guidance to assess the effect of TQ on cardiac safety related to QT/QTc interval prolongation and the proarrhythmic potential [Green, 2014]. TQ doses of 300 mg single dose, 600 mg single dose and 1200 mg (400 mg once daily x 3 days), along with placebo and the positive control moxifloxacin, were studied in healthy volunteers.

The primary endpoint was change from Baseline in QTcF for a supratherapeutic dose of TQ compared with placebo.

In Study TAF114582, there was no indication of a QT effect at clinical doses of TQ (300 mg and 600 mg) compared with placebo. For the differences in mean changes from

time-matched baseline for QTcF, Bazett-corrected QT duration, and individually-corrected QT duration between TQ 300 mg and TQ 600 mg compared with placebo, the 90% confidence limits were less than 10 msec for all timepoints. The supra-therapeutic dose of TQ 1200 mg showed a maximum effect on QTcF prolongation, which was just within the safety margin of 10 msec to demonstrate lack of effect.

6.7.4. Pregnancy and lactation

There is very limited data on the safety of TQ in pregnancy from the TQ clinical program. Studies in animals have shown no adverse effects of TQ on embryofetal development at concentrations comparable to those achieved at the recommended human dose. However, TQ must not be used in pregnancy because of a risk of hemolysis in G6PD deficiency; and, even if a pregnant woman is not G6PD deficient, the fetus may be G6PD deficient.

It is not known whether TQ is excreted in human milk. TQ should not be used during breastfeeding when the infant has G6PD deficiency or the status is unknown as drug-induced hemolytic anemia may occur.

7. BENEFIT-RISK ASSESSMENT AND CONCLUSIONS

TQ offers high rates of relapse prevention with a simplified (single dose) regimen to aid compliance. It has the potential to play an important role in the elimination of *P. vivax* malaria, which is currently proving refractory. In keeping with the 8-aminoquinoline class, subjects with G6PD deficiency are at risk of hemolysis due to oxidative stress caused by TQ. Use in G6PD deficiency will therefore be contra-indicated and there will be pre-testing for G6PD deficiency. In conjunction with pre-testing for G6PD deficiency, the benefit: risk evaluation for TQ is considered favorable.

7.1. *P. vivax* Malaria is Responsible for Significant Morbidity and Mortality

P. vivax malaria is a global disease with a large geographic distribution, which includes South America, Asia and parts of Africa. Although it has been eradicated from many parts of the world (e.g., southern United States, southern Europe and northern Australia), many of these regions remain receptive to outbreaks of malaria imported by travelers.

In endemic areas, *P. vivax* malaria causes significant morbidity. It's ability to cause severe disease and mortality has previously been overlooked, but is now known to impose a significant clinical burden in many resource-poor settings [Price, 2007; Rahimi, 2014].

7.2. Relapse Prevention is Critical to Patient Management and Malaria Eradication

Unlike *P. falciparum, P. vivax* has a hypnozoite stage in its life cycle, which means the parasite may relapse days, weeks or months later following apparently effective treatment. While this is an important source of morbidity suffered by the patient, from a public health point of view, patients with relapsed disease may also serve as a focus for outbreaks, thus frustrating the malaria eradication efforts of national control programs. Compounds of the 8-aminoquinoline class, such as PQ and TQ, are currently the only ones able to target hypnozoites and thus prevent relapse.

PQ is the only 8-aminoquinoline currently available in most countries, but has some disadvantages. Compliance with PQ is poor in the real world, with many patients failing to complete the recommended 14-day course of treatment. Although there is no PQ compliance data from any ICH region, data on antibiotic compliance would predict that PQ compliance would be similarly poor.

Omission of just three doses of PQ results in a 3- to 4-fold reduction in efficacy [Abreha, 2017], which means that the full potential effectiveness of PQ is not seen, and both the patient and public health suffer as a consequence. The influence of PQ compliance on efficacy is suggested by the difference in relative efficacy between PQ and TQ seen in the two parts of TAF112582: In Part 1, PQ compliance was only 68% (efficacy 77.3%), while that for TQ 300 mg was 96% (efficacy 89.2%). In Part 2, the compliance rates were both TQ and PQ were high (TQ: 100%; PQ: 96%) with PQ efficacy (69.6%) and TQ efficacy (62.4%).

Directly observed therapy for 14 days has been shown to increase compliance [Takeuchi, 2010], but it requires increased use of resource not always available in already-stretched national public health programs in malaria-endemic countries.

7.3. TQ is an Efficacious and Simpler Treatment for *P. vivax* Malaria

The pivotal Phase 3 trial (Study 582 part 2) showed that 300 mg single dose TQ had high recurrence-free efficacy. In this trial, at the 6-month primary endpoint, TQ reduced the risk of recurrence by 70% compared to placebo. In addition, TQ was highly efficacious in the two supporting trials, Study 582 Part 1 and Study 564.

TQ efficacy was consistent in all regions studied in Phase 2 and 3.

TQ offers important advantages over PQ. Of most significance, as a single dose treatment, TQ offers a greatly simplified regimen and highly efficacious treatment. In contract to PQ, the single dose regimen facilitates high compliance and would be predicted to ensure ease of use as well as consistent use even in real-world settings. TQ 300 mg single dose can be administered by a health care professional in conjunction with a point-of-care test for G6PD at time of diagnosis.

7.4. Safety Risks and Considerations

The safety profile of 300 mg single dose TQ is acceptable and broadly similar to that of PQ 15 mg for 14 days. TQ is a synthetic analog of PQ and so a similar safety profile may be expected. Neither TQ nor PQ produce clinically relevant Hb declines in G6PD-normal subjects, although both have the risk of drug-induced hemolysis for G6PD-deficient subjects. Both have the risk of methemoglobinemia and both are known to produce GI events such as nausea and vomiting. Both TQ and PQ can cause self-limited CNS events such as dizziness.

7.4.1. Patients at Risk of Clinically Significant Drug-induced Hemolysis can be Identified and Excluded

The primary safety concern for both TQ and PQ is drug-induced hemolysis in patients with G6PD deficiency. The data from Study 582 Part 2 and Study 564 show that excluding patients with a G6PD activity <70% of the site median in normal males is effective at protecting patients from clinically significant Hb declines. The number of subjects with Hb declines across all three studies (Studies 582 Parts 1 and 2, Study 564) was small and no subject required blood transfusion or any other medical intervention. The majority of Hb declines were within the normal range and none were of clinical concern.

Since it is not possible to determine the G6PD status of the unborn fetus, TQ must not be administered to women who are pregnant. TQ must not be used in lactating mothers where the G6PD status of the infant is unknown, because it is not known whether TQ is excreted in breast milk.

7.4.2. Other Safety Considerations

There were no deaths in the three primary studies, Studies 582 Parts 1 and Part 2, and Study 564, or across the radical cure program.

The majority of subjects had AEs that were mild or moderate in severity. Few AEs Grade ≥3 were reported. There were no clinically significant differences between the TQ+CQ group compared to the CQ alone group in the relative risk of hematological, psychiatric, hepatobiliary, ophthalmic, renal or urinary AEs.

TQ 300 mg single dose causes fully reversible asymptomatic elevations in methemoglobin. There is a theoretical increase in risk of symptomatic methemoglobinemia in patients with NADH-dependent methemoglobin reductase deficiency.

The 300 mg single dose TQ was associated with a number of transient and reversible CNS events (insomnia, anxiety, abnormal dreams, headache, dizziness, somnolence). These events are also reported for other antimalarials. None of the events resulted in withdrawal from the study or treatment discontinuation. The risk of CNS effects is judged to be low in subjects without a history of serious psychiatric disorders. Caution is

advised when administering TQ to patients with a history of, or current, serious psychiatric disorders.

In common with other cationic amphiphilic drugs, TQ has the potential to cause phospholipid accumulation in the cornea, which manifests as vortex keratopathy (also called, corneal verticillata). Vortex keratopathy was reported in the older TQ studies which used higher doses for much longer durations. There is no evidence of corneal changes associated with vision change for the proposed 300 mg single dose TQ. There is no evidence of retinal toxicity in the primary studies, in the interim analysis of the ophthalmic safety study 201807, or in the supportive safety study SB252263/057. AEs associated with ocular changes were infrequent and similar across the treatment groups; all events were mild or moderate in severity and there were no ophthalmic SAEs.

Transient, asymptomatic dose-related elevation in liver transaminases were observed in healthy volunteers who received TQ single doses of 300 mg, 600 mg and 1200 mg in placebo-controlled Phase 1 studies. None of the elevations were severe or considered to be clinically significant. In the primary studies of *P. vivax* infected patients, small ALT increases were observed at baseline and at early timepoints in all three treatment groups and were considered disease-related.

No renal toxicity signal was observed for TQ. There were no renal or urinary SAEs and no events leading to study withdrawal or discontinuation of study medication. The proposed 300 mg single dose TQ was associated with small reversible increases in creatinine consistent with its known renal transporter inhibition (OCT2 and MATEs). Renal transporter inhibition by TQ means that patients with creatinine above the normal range should not be co-dosed with metformin, because of the increased risk of lactic acidosis. Drugs with a small therapeutic index that are substrates of the renal transporters OCT2 and MATE must be excluded regardless of renal function (for example, phenformin, buformin, dofetilide, procainamide, and pilsicainide).

TQ 300 mg single dose does not increase QTcF. CQ is known to increase QT, but TQ does not have a clinically significant additional effect on QT when co-dosed with CQ.

7.5. Tafenoquine Risk:Benefit Profile

Tafenoquine 300 mg single dose has a favorable risk:benefit profile in adults and adolescents ≥16 years with G6PD levels ≥70% of normal for the radical cure (prevention of relapse) of *P. vivax* malaria. This is based on safety and efficacy data in 483 *P. vivax* infected subjects exposed to the recommended 300 mg single dose TQ in Phase 2b/3 studies and the broader TQ safety database of > 4000 subjects exposed to various doses and dose regimens.

GSK and MMV believe that TQ can be an important tool in the armamentarium available to clinicians for the treatment of US patients, as well as contribute to global efforts to eradicate *P. vivax* malaria.

8. REFERENCES

References available upon request

Abreha A *et al.* Comparison of artemether-lumefantrine and chloroquine with and without primaquine for the treatment of *Plasmodium vivax* infection in Ethiopia: A randomized controlled trial. *PLoS Med* 2017;14:e1002299.

Angelo KM, Libman M, Caumes E, Hamer DH, Kain KC et al. Malaria after international travel: a GeoSentinel analysis, 2003 2016. Malar J 2017;16:293.

Baird JK *et al*. Noninferiority of glucose-6-phosphate dehydrogenase deficiency diagnosis by a point-of-care rapid test vs the laboratory fluorescent spot test demonstrated by copper inhibition in normal human red blood cells. *Transl Res* 2015;165:677 688.

Barcus MJ *et al.* Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in Northeastern Indonesian Papua. *Am J Trop Med Hyg* 2007;77:984 91.

Battle KE, Karhunen MS, Bhatt S, Gething PW, Howes RE et al. Geographical variation in Plasmodium vivax relapse. Malar J. 2014;13:144.

Belik SL, Stein MB, Asmundson GJG, Sareen J. Are Canadian Soldiers More Likely to Have Suicidal Ideation and Suicide Attempts Than Canadian Civilians? *Am J Epidemiol* 2010;172:1250 1258.

Bitta MA, Kariuki SM, Mwita C, Gwer S, Mwai L, Newton CRJC1, et al. Antimalarial drugs and the prevalence of mental and neurological manifestations: A systematic review and meta-analysis. *Wellcome Open Res.* 2017;2:13.

Brignone E, Fargo JD, Blais RK, Carter ME, Samore MH, Gundlapalli AV. Non-routine Discharge From Military Service: Mental Illness, Substance Use Disorders, and Suicidality. *Am J Prev Med.* 2017;52(5):557-565.

Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371(9606):64-74. doi: 10.1016/S0140-6736(08)60073-2.

Charoenlarp P, Areekul S, Harinasuta T, Sirivorasarn P. The haemolytic effect of a single dose of 45 mg primaquine in G6PD deficient Thais. J Med Assoc Thai. 1972;55:631-638.

Chloroquine US Prescribing Information, Sanofi-Aventis US, 2013

Chu CS *et al.* Haemolysis in G6PD heterozygous females treated with primaquine for *Plasmodium vivax* malaria: A nested cohort in a trial of radical curative regimens. *PLOS Med* 2017;14:e1002224.

Cockburn J, Gibberd RW, Reid AL and Sanson-Fisher RW. Determinants of non-compliance with short term antibiotic regimens. Brit Med J 1987;295:814.

Commons RJ, Thriemer K, Humphreys G, Suay I Sibley CH, et al. The Vivax Surveyor: Online mapping database for Plasmodium vivax clinical trials. Int J Parasitol Drugs Drug Resist. 2017;7:181-190. Doi:10.1016/j.ijpddr.2017.03.003

Crockett M, Kain KC. Tafenoquine: A Promising New Antimalarial Agent. Expert Opinion on Invest Drugs. 2007, 15:5; 705-715.

Croft AM, Herxheimer A. Adverse effects of the antimalaria drug, MQ: due to primary liver damage with secondary thyroid involvement? *BMC Public Health.* 2002;2:6.

Douglas NM *et al*. Unsupervised primaquine for the treatment of *Plasmodium vivax* malaria relapses in southern Papua: a hospital-based cohort study. *PLOS Med* 2017;14: e1002379.

Dow G, Bauman R, Caridha D, Cabezas M, Du F, et al. Mefloquine Induces Dose-Related Neurological Effects in a Rat Model. Antimicrobial Agents and Chem. 2006; 50:1045 1053.

Eick-Cost AA; Hu Z, Clark LL. Neuropsychiatric outcomes after mefloquine exposure among U.S. military service members. *Am J Trop Med Hyg.* 2017;96(1):159-166.

European Centre for Disease Prevention and Control. Rapid Risk Assessment: Multiple reports of locally-acquired malaria infections in the EU. Stockholm. 2017. [https://ecdc.europa.eu/sites/portal/files/documents/RRA-Malaria-EU-revised-September-2017_0.pdf]

Fanning JR, Pietrzak RH. Suicidality among older male veterans in the United States: Results from the National Health and Resilience in Veterans Study. *J Psychiatr Res.* 2013;47:1766e1775

FDA Drug Safety Communications. FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. 29 Jul 2013. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm362227.htm Accessed 26-Sep-2017.

Filler SJ *et al.* Locally acquired mosquito-transmitted malaria: A guide for investigations in the United States. *MMWR* 2006;55(RR13):1 9. [https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5513a1.htm]

George JN *et al*. Primaquine sensitivity in Caucasians: hemolytic reactions induced by primaquine in G-6-PD deficient subjects. J Lab Clin Med 1967;70:80 93.

Gething PW *et al*. A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010. *PLoS Negl Trop Dis* 2012;6:e1814.

GlaxoSmithKline (GSK). Investigational New Drug Application Safety Report (INDSR), 08-Jun-2017.

Gonçalves BP *et al.* Age, weight, and CYP2D6 genotype are major determinants of primaquine pharmacokinetics in African children. *Antimicrob Ag Chemother* 2017;61.

Gotsman I *et al*. Mefloquine-induced acute hepatitis. *Pharmacotherapy* 2000;20:1517 9.

Green JA, Patel AK, Patel BR, Hussaini A, Harrell EJ, McDonald MJ, et al. Tafenoquine at therapeutic concentrations does not prolong Fridericia-corrected QT interval in healthy subjects. *J Clin Pharmacol.* 2014;54(9):995-1005.

Green JA, Mohamed K, Goyal N, Bouhired S, Hussaini A, et al. Antimicrob Agents Chemother. 2016;Oct 3. pii: AAC.01588-16.

Halliwell WH. Cationic amphiphilic drug-induced phospholipidosis. Toxicol Pathol. 1997;25:53-60.

Hodgkinson R *et al*. Effect of intermittent administration of a combination of amodiaquin and primaquine (Camoprim) on the hematocrit of primaquine-sensitive and non-sensitive children. *Am J Trop Med Hyg* 1961;10:128 34.

Hollander DA and Aldave AJ. Drug-induced corneal complications. Curr Opin Ophthalmol. 2004;15:541-8.

Howes RE *et al.* G6PD deficiency: global distribution, genetic variants and primaquine therapy. *Adv Parasitol* 2013;81:133 201.

Howes RE *et al.* Global epidemiology of *Plasmodium vivax*. *Am J Trop Med Hyg* 2016;95:15 34.

Hwang J *et al.* Severe morbidity and mortality risk from malaria in the United States, 1985 2011. *Open Forum Infectious Diseases* 2014;1:ofu034.

Ilgen MA, Bohnert ASB, Ignacio RV, McCarthy JF, Valenstein MM, Kim HM, et al. Psychiatric Diagnoses and Risk of Suicide in Veterans. *Arch Gen Psychiatry.* 2010;67(11):1152-1158.

Ingram RJ *et al*. The clinical and public health problem of relapse despite primaquine therapy: case review of repeated relapses of *Plasmodium vivax* acquired in Papua New Guinea. *Malar J* 2014;13:488.
[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4295472/]

Kaewpruk N, Tan-ariya P, Ward SA, Sitthichot N, Suwandittakul N, Mungthin M. PFMDR1 Polymorphisms Influence on In Vitro Sensitivity of Thai Plasmodium Falciparum Isolates to Primaquine, Sitamaquine and Tafenoquine. Southeast Asian J Trop Med Public Health. 2016 May;47(3):366-76.

Kapur N, While D, Blatchley N, Bray I, Harrison K. Suicide after Leaving the UK Armed Forces A Cohort Study. *PLoS Med.* 2009;6(3):e1000026.

Khantikul N *et al*. Adherence to antimalarial drug therapy among vivax malaria patients in northern Thailand. *J Health Popul Nutr* 2009;27:4 13.

Korte DW, Heiffer MH, Hacker MP, Kintner LD, Hong CB, Lee CC. Subchronic Toxicity of the Antimalarial Drug, Mefloquine HCL. Federation of American Societies for Experimental Biology. 63rd Annual Meeting April 1979.

Korte DW, Heiffer MH, Ellis HV, Hacker MP, Hong CB, Yuan LD, Kintner LD, Lee CC. Chronic Toxicity/Carcinogenicity of Mefloquine HCL. Federation of American Societies for Experimental Biology. 66th Annual Meeting April 1982.

Lee CC, Kinter LD. Subacute toxicity of primaquine in dogs, monkeys, and rats. *Bull World Health Organ.* 1981:59 (3): 439-48.

Lima Jr JC, Pratt-Riccio LR. Major Histocompatibility Complex and Malaria: Focus on Plasmodium vivax Infection. Frontiers in Immunology. 2016;7(13):1-14.

Loken AC, Haymaker W. Pamaquine poisoning in man, with a clinicopathologic study of one case. *Am J Trop Med Hyg.* 1949;29(3):341-352.

Llanos-Cuentas EA *et al*. Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *Lancet* 2014;383:1049 58.

Luzzatto L, Nannelli C, Notaro R. Glucose-6-Phosphate Deficiency. Hematol Oncol Clin N Am 2016;30:373 393.

http://dx.doi.org/10.1016/j.hoc.2015.11.006

Mace KE & Arguin PM. Malaria surveillance United States, 2014. *Surveillance Summaries* 2017;66:1 4.
[https://www.cdc.gov/mmwr/volumes/66/ss/ss6612a1.htm]

Mace KE. Malaria surveillance United States, 2015. *Surveillance Summaries* 2018;67:1 28.
[Published online 2018 May 4. doi: 10.15585/mmwr.ss6707a1]

Manzano JI, Carvalho L, Perez-Victoria JM, Castanys S, Gamarro F. Increased Glycolytic ATP Synthesis in Associated with Tafenoquine Resistance in Leishmania major. Antimicro Agents and Chemo. 2011, 1045-1052.

Mathur S, Dooley J, Scheuer PJ. Quinine induced granulomatous hepatitis and vasculitis. *BMJ* 1990;300:613.

Maxwell NM, Nevin RL, Stahl S, Block J, Shugarts S, Wu AH, et al. Prolonged neuropsychiatric effects following management of chloroquine intoxication with psychotropic polypharmacy. *Clin Case Rep.* 2015;3(6):379-387.

McCarthy S. Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness, and risk-benefit analysis in the Australian Defence Force. *J Parasitol Res.* 2015:287651.

McFarlane AC, Hodson SE, Van Hooff M, Davies C (2011). Mental health in the Australian Defence Force: 2010 ADF Mental Health and Wellbeing Study: Full report, Department of Defence: Canberra.

Mefloquine US Prescribing Information; Sellersville PA USA: TEVA Pharmaceuticals, 2013.

Mikkaichi T, Nakai D, Yoshigae Y, Imaoka T, Okudaira N, Izumi T. Liver selective distribution in rats support the importnce of active uptake into the liver via organic anion transporting polypeptides (OATPs) in humans. Frug Metab Pharma. 2015, Oct;30(5):334-40.

Miller AK, Harrell E, Ye L, Baptiste-Brown S, Kleim JP, et al. Br J Clin Pharmacol. 2013;76(6):858-67. doi: 10.1111/bcp.12160.

Nevin RL. MQ and Posttraumatic Stress Disorder: Chapter 19. Forensic and ethical issues in military behavioural health. Ritchie E.C. Office of the Surgeon General, US Army, Virginia 2014.

Nevin RL, Croft AM. Psychiatric effects of malaria and anti−malarial drugs: historical and modern perspectives. *Malar J.* 2016;15:332.

Nevin RL, Leoutsakos J. Identification of a syndrome class of neuropsychiatric adverse reactions to mefloquine from latent class modeling of FDA adverse event reporting system data. *Drugs R D.* 2017;17:199 210.

Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis.'. Blood Cells Mol Dis 2009; 42: 267 278.

Nqoro. Quinoline-Based Hybrid Compounds with Antimalarial Activity. Molecules. 2017;22:2268; doi:10.3390/molecules22122268.

O'Toole BI, Orreal-Scarborough, Johnston D, Catts SV, Outram S. Suicidality in Australian Vietnam veterans and their partners. *J Psychiatr Res.* 2015;65:30e36.

Overbosch D1, Schilthuis H, Bienzle U, Behrens RH, Kain KC, Clarke PD, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. *Clin Infect Dis.* 2001;33(7):1015-1021.

Peters W, Stewart LB, Robinson BL. The Chemotherapy of Rodent Malaria. LXI. Drug Combinations to Impeach the Selection of Drug Resistance, Part 4: The Potential Role of 8-aminoquinoline. Ann Trop Med Parasitol. 2003 Apr;97(3):221-36.

Phillips-Howard PA, Kuile FO. CNS adverse events associated with antimalarial agents: fact or fiction? Drug Safety. 1995;12(6):370-383.

Price R *et al.* Vivax malaria: neglected and not benign. *Am J Trop Med Hyg* 2007;77:79 87.

Primaquine US Prescribing Information; Sanofi-Aventis Quebec Canada, 2017.

Qualaquin US Prescribing Information (quinine sulfate); Mutual Pharmaceutical Company, USA, 2008.

Queensland Health. *Malaria: Queensland Health Guidelines for Public Health Units,* version 1.1, 2015. Section: Public Health Significance and Occurrence. Brisbane, Australia.
[https://www.health.qld.gov.au/cdcg/index/malaria]

Quinn JC, Complex membrane channel blockade: a unifying hypothesis for the prodromal and acute neuropsychiatric sequelae resulting from exposure to the antimalarial drug mefloquine. *Journal of Parasitol Res.* 2015;368064.

Rahimi BA, Thakkinstian A, White NJ, Sirivichayakul C et al. Severe vivax malaria: a systematic review and meta-analysis of clinical studies since 1900. Malar J 2014;13:481.

Rajapakse S *et al*. Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria. *Cochrane Datab Systemat Rev* 2015;4:CD010458.
[http://doi.org/10.1002/14651858.CD010458.pub2].

Ramsawh HJ, Fullerton CS, Herberman Mash HB, Ng TH, Kessler RC, Stein MB, et al. Risk for suicidal behaviors associated with PTSD, depression, and their comorbidity in the U.S. Army. *J Affect Disord.* 2014;161:116 122.Recht J, Ashley EA, White NJ. Safety of 8-aminoquinoline antimalarial medicines. Geneva: World Health Organization; 2014. Available from: http://www.who.int/malaria/publications/atoz/9789241506977/en/

Reger MA, Smolenski DJ, Skopp NA, Metzger-Abamukang MJ, Kang HK, Bullman TA, et al. Risk of Suicide Among US Military Service Members Following Operation Enduring Freedom or Operation Iraqi Freedom Deployment and Separation From the US Military. *JAMA Psychiatry.* 2015;72(6):561-569.

Rehman HU. Methemoglobinemia. West J Med. 2001;175:193-196.

Rheeder PI, Sieling WL. Acute, persistent quinine-induced blindness: a case report. S Afr Med J. 1991;79:563-4.

Ringqvist A, Bech P, Blenthoj B. Acute and long-term psychiatric side effects of mefloquine: a follow-up on Danish adverse event reports. *Travel Med Infect Dis.* 2015;13:80-88.

Ritchie EC, Block J, and Nevin RL. Psychiatric side effects of mefloquine: applications to forensic psychiatry. *J Am Acad Psychiatry Law.* 2013;41:224-35.

Rueangweerayut R, Bancone G, Harrell EJ, Beelen AP, Kongpatanakul S, Möhrle JJ, et al. Hemolytic potential of tafenoquine in female volunteers heterozygous for glucose-6-phosphate dehydrogenase (G6PD) deficiency (G6PD Mahidol variant) versus G6PD-normal volunteers. *Am J Trop Med Hyg.* 2017;97(3):702-711.

Saunders D, Vanachayangkul P, Imerbsin R, Khemawoot P, Siripokasupkul R, Tekwani B, et al. Pharmacokinetics and pharmacodynamics of (+)-primaquine and (-)-primaquine enantiomers in rhesus macaques (macaca mulatta). *Antimicrob Agents Chemother.* 2014;58(12):7283-7291.

Schmidt IG, Schmidt LH. Neurotoxicity of the 8-aminoquinolones. I. Lesions in the central nervous system of the rhesus monkey induced by plasmocid. *J Neuropathol Exp Neurol.* 1948;7:368-398.

Schmidt IG. Schmidt LH. Neurotoxicity of the 8-Aminoquinoline. Reactions of Various Experimental Animals to Plasmocids. J Comp Neuro, 1949 Dec;91(3): 337-67

Schmidt LH. The Relations Between Chemical Structure and Toxicity Among the 8-Aminoquinolines. First Symposium on Chemical-Biological Correlation. National Research Council. 1950,181-190

Schmidt IG, Schmidt LH. Neurotoxocity of 8-aminoquinolines. III. The effects of pentaquine, isopentaquine, primaquine, and pamaquine on the central nervous system of the rhesus monkey. *J Neuropathol Exp Neurol.* 1951;10(3):231-256.

Schoenbaum M, Kessler RC, Gilman SE, Colpe LJ, Heeringa SG, Stein MB, *et al*. Predictors of Suicide and Accident Death in the Army Study to Assess Risk and Resilience in Service members (Army STARRS) - Results from the Army Study to Assess Risk and Resilience in Service members (Army STARRS). *JAMA Psychiatry*. 2014;71(5):493-503.

Shah SS, Diakite SAS, Traore K, Diakite M, Kwiatkowski DP. A novel cytofluorometric assay for the detection and quantification of glucose-6-phosphate dehydrogenase deficiency. Scientific Reports 2012;2:299.

Skegg K, Firth H, Gray A, Cox B. Suicide by occupation: does access to means increase the risk? *Aust N Z J Psychiatry.* 2010;44:429 434.

Spiess A, Gallaway MS, Watkins EY, Battelle EC, Wills JV, Weir JC et al. The ABHIDE (Army Behavioral Health Integrated Data Environment): A suicide registry. *Mil Behav Health.* 2016;4(1):8-17.

Staines. Treatment and Prevention of Malaria: Antimalarial Drug Chemistry, Action and Use. In: Milestones in Drug Therapy. Springer.Basal, 2012. DOI:10.1007/978-3-0346-0480-2.

Suffoletto B *et al*. A mobile phone text message program to measure oral antibiotic use and provide feedback on adherence to patients discharged from the emergency department. *Acad Emerg Med* 2012;19:949 958.

Takeuchi R et al. Directly-observed therapy (DOT) for the radical 14-day primaquine treatment of malarial on the Thai-Myanmar border. *Malar J* 2010;9:308.

Toovey S. Mefloquine neurotoxicity: a literature review. *Travel Med Infect Dis.* 2009(7):2-6.

Trinity Biotech. Reagents and test for Glucose-6-Phosphate Dehydrogenase (G-6-PDH): Instructions For Use (product code 345-A). Wicklow, Ireland, 2012.

Vennerstrom JL, Nuzum EO, Miller RE, Dorn A, Gerena L, Dande RA et al. 8 aminoquinolines Active against Blood Stage Plasmodium falciparum in vitro Inhibit Haematin Polymerization. Antimicrobial Agents and Chemotherapy. 1999; 43:598-60.

Waller M, Treloar SA, Sim MR, McFarlane AC, McGuire ACL, Bleier J, et al. Traumatic events, other operational stressors and physical and mental health reported by Australian Defence Force personnel following peacekeeping and war-like deployments. *BMC Psychiatry.* 2012;12:88

Wells TNC *et al*. Targeting the hypnozoite reservoir of *Plasmodium vivax:* the hidden obstacle to malaria elimination. *Trends Parasitol* 2010;26:145 151.

Wielgo-Polanin R1, Lagarce L, Gautron E, Diquet B, Lainé-Cessac P. Hepatotoxicity associated with the use of a fixed combination of chloroquine and proguanil. *Int J Antimicrob Agents.* 2005;26(2):176-178.

WHO: Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. 2003. Available at: http://www.who.int/malaria/publications/atoz/whohtmrbm200350/en/ Accessed 06 October 2017.

World Health Organization (WHO). Malaria Microscopy Quality Assurance Manual, Version 1, 2009. Available at: http://apps.who.int/medicinedocs/en/d/Js19135en/. Accessed 14 September 2017.

WHO Guidelines for the treatment of malaria. Third edition. 2015 World Health Organization: Geneva, Switzerland. [http://www.who.int/malaria/publications/atoz/9789241549127/en/]

WHO Review of central nervous system events related to the antimalarial drug, MQ (1985-1990), 1991. WHO/MAL/91.1063.

WHO World Malaria Report 2016. World Health Organization: Geneva, Switzerland. [http://www.who.int/malaria/publications/world-malaria-report-2016/report/en/]

Woodruff AW *et al.* Cause of anaemia in malaria. *Lancet* 1979;313:1055 1057.

9. APPENDIX

9.1. Inclusion/Exclusion Criteria for Study 582 Part 2

9.1.1. Inclusion Criteria

Subjects eligible for enrollment in the study must have met all of the following criteria:

1. Positive Giemsa smear for *P. vivax*
2. Parasite density >100 and <100,000/μL
3. Age: ≥16 years (≥18 years in Ethiopia)
4. A female was eligible to enter and participate in this study if she was non-pregnant, non-lactating, and if she was of:
    a. non-child bearing potential defined as: post-menopausal (12 months of spontaneous amenorrhea or <6 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] >40 mIU/mL), pre-menopausal and had had a hysterectomy or a bilateral oophorectomy (removal of the ovaries) or a bilateral tubal ligation with medical report verification, negative pregnancy test or,
    b. child-bearing potential, had a negative pregnancy test at screening, and agreed to comply with one of the following during the treatment stage of the study and for a period of 90 days after stopping study medication:
        - Use of oral contraceptive, either combined or progestogen alone used in conjunction with double-barrier method
        - Use of an intrauterine device with a documented failure rate of <1% per year
        - Use of depo provera injection
        - Double-barrier method consisting of spermicide with either condom or diaphragm
        - Male partner who was sterile prior to the female subject's entry into the study and was the sole sexual partner for that female.
        - Complete abstinence from intercourse for 2 weeks prior to administration of study medication, throughout the study and for a period of 90 days after stopping study medication.
5. A signed and dated informed consent was obtained from the subject or the subject's legal representative prior to screening. Informed assent was obtained from subjects <18 years, where applicable and written or oral witnessed consent had been obtained from parent or guardian.
6. The subject was able to understand and comply with protocol requirements, instructions, and protocol-stated restrictions and was likely to complete the study as planned.

7. The subject was willing to be hospitalized for 3 days and return to clinic for all follow-up visits, including Day 180
8. QTc <450 msec at screening (based on an average of triplicate ECGs obtained over a brief recording period by machine or manual over-read, if first was >450 msec).

9.1.2. Exclusion Criteria

Subjects meeting any of the following criteria were not eligible for study enrollment:

1. Mixed malaria infections (e.g., identified by Giemsa-stained smear or rapid diagnostic test)
2. Severe *P. vivax* malaria as defined by World Health Organization (WHO) criteria (see study protocol Appendix 4).
3. Severe vomiting (no food or inability to take food during previous 8 hours)
4. Screening hemoglobin (Hb) concentration <7 g/dL.
5. G6PD deficiency, assessed by a quantitative spectrophotometric phenotype assay; any subject with an enzyme level <70% of the site median value for G6PD normals was excluded.
6. Liver function test ALT >2x the upper limit of normal (ULN).
7. Any clinically significant concurrent illness (e.g., pneumonia, septicemia), pre-existing conditions (e.g., renal disease, malignancy), conditions that may have affected absorption of study medication (e.g., vomiting or severe diarrhea), or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure or severe coronary artery disease). These abnormalities may have been identified on the screening history and physical or laboratory examination.
8. Subject who had taken antimalarials (e.g., ACTs, mefloquine, PQ, CQ) or drugs with antimalarial activity (see study protocol Appendix 5) within the past 30 days by history.
9. History of allergy to CQ, mefloquine, TQ, PQ or to any other 4- or 8-aminoquinolines.
10. Any contraindications to CQ or PQ administration including a history of porphyria, psoriasis, or epilepsy (please refer to CQ and PQ locally approved prescribing information).
11. Subject who had previously received study medication for this protocol (all parts) or had received treatment with any other investigational drug within 30 days or 5 half-lives (whichever was longer) preceding the first dose of study medication.
12. History of illicit drug abuse or heavy alcohol intake within 6 months of the study.
13. Subjects who had taken or were likely to require the use of medications from the prohibited medication list (see study protocol Appendix 5), which included the following medications and medication classes:
    - Histamine-2 blockers and antacids.

- Drugs with hemolytic potential.
- Drugs known to prolong the QTc interval.
- The biguanides phenformin and buformin (but excluding metformin).
- Drugs that were substrates of the renal transporters organic cation transporter-2 (OCT2), MATE1, and MATE2-K and have a narrow therapeutic index (e.g., the antiarrhythmic agents dofetilide, procainamide, and pilsicainide).

Ophthalmic sites only - Subjects who had a history of significant ocular disease (e.g., surgery to the globe, glaucoma, diabetic retinopathy) or had evidence of corneal or retinal abnormalities identified in the clinical screening ophthalmologic examination (see study protocol Section 6.1) were excluded from the ophthalmologic portion of the trial (these subjects were permitted to participate in the main portion of the study). For these subjects, definitive central results of the screening digital retinal photographs were *not* required prior to randomization in the study.

9.2. Inclusion/Exclusion Criteria for Study 582 Part 1

9.2.1. Inclusion Criteria

Subjects eligible for enrolment in the study must have met all of the following criteria:

1. Positive Giemsa smear for *P. vivax*
2. Parasite density >100/μL and <100,000/μL
3. Age: ≥16 years
4. A female was eligible to enter and participate in this study if she was non-pregnant, non-lactating and if she was of:

a. non-child bearing potential defined as: post-menopausal (12 months of spontaneous amenorrhoea or <6 months of spontaneous amenorrhoea with serum FSH >40 mIU/mL), pre-menopausal and had had a hysterectomy or a bilateral oophorectomy (removal of the ovaries) or a bilateral tubal ligation with medical report verification, negative pregnancy test or,

b. child-bearing potential, had a negative pregnancy test at screening, and agreed to comply with one of the following during the treatment stage of the study and for a period of 90 days after stopping study drug

c. Use of oral contraceptive, either combined or progestogen alone used in conjunction with double barrier method as defined below

d. Use of an intrauterine device with a documented failure rate of <1% per year

e. Double barrier method consisting of spermicide with either condom or diaphragm

f. Male partner who was sterile prior to the female subject's entry into the study and was the sole sexual partner for that female

g. Complete abstinence from intercourse for 2 weeks prior to administration of study drug, throughout the study and for a period of 90 days after stopping study drug

5. A signed and dated informed consent was obtained from the subject or the subject's legal representative prior to screening. NB Assent was obtained from subjects <18 years, where applicable and written or oral witnessed consent had been obtained from parent or guardian
6. The subject was able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and was likely to complete the study as planned
7. Willing to be hospitalised for 3 days and return to clinic for all follow-up visits including Day 180
8. QTc <450 msec at screening*

* based on a single QTcF value at screening or as an average of triplicate ECGs obtained over a brief recording period by machine or manual over-read if first was >450 msec.

9.2.2. Exclusion Criteria

Subjects meeting any of the following criteria must not have been enrolled in the study:

1. Mixed malaria infections (e.g., identified by Giemsa-stained smear or rapid diagnostic test)
2. Severe *vivax* malaria as defined by WHO criteria (see Protocol Appendix 4)
3. Severe vomiting (no food or inability to take food during previous 8 hours)
4. Screening Hb concentration <7 g/dL
5. G6PD deficiency, assessed by a quantitative spectrophotometric phenotype assay:

   Males: Any subject with an enzyme level <70% of the site median value for G6PD normals were excluded.

   Females: (i) Those females with a screening Hb ≥10 g/dL were only excluded if their enzyme level was <70% of the site median value for G6PD normals.

   (ii) Those females with Hb ≥7 but <10 g/dL were excluded if an enzyme level was not >90% of the site median value for G6PD normals.

6. Liver function test ALT >2x ULN
7. Any clinically significant concurrent illness (e.g., pneumonia, septicaemia), pre-existing conditions (e.g., renal disease, malignancy), conditions that may affect absorption of study medication (e.g. vomiting or severe diarrhoea) or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure or severe coronary artery disease). These abnormalities may have been identified on the screening history and physical or laboratory examination

8. Subject had taken antimalarials (e.g., ACTs, mefloquine, PQ, CQ) or drugs with anti-malarial activity (see Protocol Appendix 5) within the past 30 days by history
9. History of allergy to CQ, mefloquine, TQ, PQ or to any other 4- or 8-aminoquinolines
10. Any contraindications to CQ or PQ administration including a history of porphyria, psoriasis or epilepsy (please refer to CQ and PQ locally approved prescribing information)
11. Subject who had previously received study medication for this protocol (all parts) or had received treatment with any other investigational drug within 30 days or five half-lives (whichever is longer) preceding the first dose of study medication
12. History of illicit drug abuse or heavy alcohol intake within 6 months of the study

Subjects who had taken or were likely to require the use of medications from the prohibited medication list (see Protocol Appendix 5) which included the following classes:

- Histamine-2 blockers and antacids
- Drugs with haemolytic potential
- Drugs known to prolong the QTc interval

Ophthalmic sites only - Subjects who had a history of significant ocular disease (e.g., surgery to the globe, glaucoma, diabetic retinopathy) or had evidence of corneal or retinal abnormalities identified in the clinical screening ophthalmologic examination were excluded. Definitive central results of the screening digital retinal photographs were *not* required prior to randomisation in the study.

9.3. Data Tables for Supportive Study 582 Part 1

Table 43 Subject Disposition for Study 582 Part 1 (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Completion Status, n (%)							
Completed	54 (98)	54 (95)	56 (98)	54 (96)	47 (94)	54 (100)	319 (97)
Withdrawn (lost to follow up)	1 (2)	3 (5)	1 (2)	2 (4)	3 (6)	0	10 (3)

Table 44 Discontinuation from Study Treatment in Study 582 Part 1 (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Discontinuation from study treatment, n (%)						
No	54 (98)	57 (100)	57 (100)	56 (100)	49 (98)	53 (98)
Yes	1 (2)	0	0	0	1 (2)	1 (2)
Primary for discontinuation, n (%)						
Adverse event	0	0	0	0	0	0
Subject met QTc withdrawal criteria (protocol-defined stopping criterion)	1 (2)	0	0	0	1 (2)	1 (2)

Table 45 Demographic Characteristics for Study 582 Part 1(ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Age (yrs)							
Mean	36.3	34.6	36.2	35.7	36.0	33.6	35.4
SD	13.28	14.09	13.49	15.06	13.91	14.16	13.94
Median	36.0	34.0	36.0	35.0	34.0	28.0	34.0
Minimum	17	16	16	17	16	16	16
Maximum	68	74	64	68	72	68	74
Sex, n (%)							
Male	37 (67)	44 (77)	43 (75)	45 (80)	35 (70)	39 (72)	243 (74)
Female	18 (33)	13 (23)	14 (25)	11 (20)	15 (30)	15 (28)	86 (26)
Race[a], n (%)							
American Indian or Alaska Native	27 (49)	28 (49)	29 (51)	29 (52)	25 (50)	27 (50)	165 (50)
Asian – Central/South Asian Heritage	11 (20)	11 (19)	9 (16)	10 (18)	6 (12)	10 (19)	57 (17)
Asian – South East Asian Heritage	16 (29)	16 (28)	19 (33)	16 (29)	16 (32)	16 (30)	99 (30)
Mixed Race	1 (2)	2 (4)	0	1 (2)	3 (6)	1 (2)	8 (2)
Weight (kg)							
Mean	59.9	59.4	59.4	62.2	60.0	59.3	60.0
SD	11.17	10.55	9.78	13.58	12.61	13.79	11.93
Median	59.0	57.0	59.0	60.0	59.4	57.4	59.0
Minimum	37	44	43	42	40	34	34
Maximum	91	95	84	106	99	101	106
G6PD enzyme activity (IUg/Hb)							
Mean	9.9	9.4	9.2	9.4	9.5	9.2	9.4
SD	2.98	2.89	2.36	2.65	2.55	2.49	2.65
Median	9.1	8.9	8.6	8.8	9.0	8.7	8.8
Minimum	6	6	4	5	5	5	4
Maximum	18	19	15	18	16	17	19
G6PD enzyme activity (as % of site median)							
Mean	116.0	110.7	107.3	113.0	114.3	108.7	111.6
SD	34.53	23.66	20.28	24.62	27.71	19.25	25.45
Median	108.8	106.4	105.9	106.7	108.3	104.0	106.8
Minimum	71	74	74	79	71	72	71
Maximum	246	194	178	190	208	172	246

a. Subjects were categorized based on standard racial groupings, even though all subjects were ex-US.

Table 46 Malarial Signs and Symptoms in Study 582 Part 1(ITT Population)

Severity	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Chills and rigours, n (%)							
Absent	1 (2)	4 (7)	5 (9)	5 (9)	2 (4)	7 (13)	24 (7)
Mild	23 (42)	22 (39)	24 (42)	22 (39)	24 (48)	18 (33)	133 (40)
Moderate	17 (31)	12 (21)	15 (26)	13 (23)	14 (28)	15 (28)	86 (26)
Severe	14 (25)	19 (33)	13 (23)	16 (29)	10 (20)	14 (26)	86 (26)
Headache, n (%)							
Absent	6 (11)	4 (7)	8 (14)	4 (7)	7 (14)	6 (11)	35 (11)
Mild	22 (40)	26 (46)	22 (39)	24 (43)	16 (32)	23 (43)	133 (40)
Moderate	11 (20)	7 (12)	13 (23)	13 (23)	12 (24)	10 (19)	66 (20)
Severe	16 (29)	20 (35)	14 (25)	15 (27)	15 (30)	15 (28)	95 (29)
Dizziness, n (%)							
Absent	26 (47)	32 (56)	33 (58)	31 (55)	24 (48)	27 (50)	173 (53)
Mild	28 (51)	19 (33)	23 (40)	22 (39)	21 (42)	22 (41)	135 (41)
Moderate	1 (2)	6 (11)	0	1 (2)	5 (10)	3 (6)	16 (5)
Severe	0	0	1 (2)	2 (4)	0	2 (4)	5 (2)
Abdominal Pain, n (%)							
Absent	36 (65)	35 (61)	40 (70)	37 (66)	26 (52)	36 (67)	210 (64)
Mild	16 (29)	16 (28)	13 (23)	18 (32)	19 (38)	16 (30)	98 (30)
Moderate	1 (2)	5 (9)	3 (5)	0	4 (8)	1 (2)	14 (4)
Severe	2 (4)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	7 (2)
Anorexia, n (%)							
Absent	32 (58)	29 (51)	38 (67)	33 (59)	16 (32)	29 (54)	177 (54)
Mild	18 (33)	20 (35)	16 (28)	18 (32)	24 (48)	21 (39)	117 (36)
Moderate	5 (9)	7 (12)	2 (4)	5 (9)	9 (18)	4 (7)	32 (10)
Severe	0	1 (2)	1 (2)	0	1 (2)	0	3 (<1)
Nausea, n (%)							
Absent	29 (53)	23 (40)	33 (58)	29 (52)	28 (56)	31 (57)	173 (53)
Mild	24 (44)	28 (49)	21 (37)	23 (41)	20 (40)	18 (33)	134 (41)
Moderate	2 (4)	6 (11)	2 (4)	3 (5)	1 (2)	5 (9)	19 (6)
Severe	0	0	1 (2)	1 (2)	1 (2)	0	3 (<1)
Vomiting, n (%)							
Absent	47 (85)	44 (77)	47 (82)	46 (82)	39 (78)	47 (87)	270 (82)
Mild	6 (11)	8 (14)	9 (16)	8 (14)	8 (16)	4 (7)	43 (13)
Moderate	2 (4)	5 (9)	1 (2)	2 (4)	3 (6)	3 (6)	16 (5)

Severity	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Severe	0	0	0	0	0	0	0
Diarrhoea, n (%)							
Absent	53 (96)	53 (93)	52 (91)	50 (89)	45 (90)	49 (91)	302 (92)
Mild	1 (2)	3 (5)	5 (9)	5 (9)	4 (8)	3 (6)	21 (6)
Moderate	1 (2)	1 (2)	0	1 (2)	1 (2)	2 (4)	6 (2)
Severe	0	0	0	0	0	0	0

Table 47 Previous Episodes of Malaria in Study 582 Part 1 (ITT Population)

Previous malarial episode?	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Yes, n (%)	35 (64)	36 (63)	28 (49)	31 (55)	31 (62)	33 (61)	194 (59)
No, n (%)	20 (36)	20 (35)	27 (47)	25 (45)	18 (36)	21 (39)	131 (40)
Unknown, n (%)	0	1 (2)	2 (4)	0	1 (2)	0	4 (1)

Table 48 Study Medication Compliance and Exposure in TAF112582 Part 1 (Safety Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Number of compliant doses of CQ, n (%)							
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	1 (2)	0	0	0	1 (2)	0	2 (<1)
3	54 (98)	57 (100)	57 (100)	56 (100)	49 (98)	54 (100)	327 (>99)
Subject compliance with TQ treatment, n (%)							
Yes	55 (100)	57 (100)	55 (96)	56 (100)	50 (100)	54 (100)	327 (>99)
Number of outpatient doses of PQ/placebo dosing taken [a], n (%)							
10 or fewer	19 (35)	21 (37)	20 (35)	22 (39)	16 (32)	23 (43)	121 (37)
11 to 13	15 (27)	12 (21)	14 (25)	13 (23)	13 (26)	10 (19)	77 (23)
14 or more	21 (38)	24 (42)	23 (40)	21 (38)	21 (42)	21 (39)	131 (40)

Note: An in-clinic dose which was vomited but where the subject was re-dosed within 4 hours was considered to be compliant.

a. 12 tablets taken was considered perfect compliance. The count of tablets taken was entirely dependent on tablets returned and not directly observed therapy

Table 49 Recurrence-Free Efficacy at Six Months in TAF112582 Part 1 (Kaplan-Meier Analysis) (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Number of Subjects, n (%)						
Subjects observed to relapse prior to Study Day 180	22 (40)	25 (44)	6 (11)	4 (7)	12 (24)	31 (57)
Censored, prior to 6 month assessment [a]	4 (7)	3 (5)	3 (5)	9 (16)	4 (8)	2 (4)
Censored, relapse-free at 6 months	29 (53)	29 (51)	48 (84)	43 (77)	34 (68)	21 (39)
Relapse-free efficacy rate at 6 months, %						
Estimate	57.7	54.1	89.2	91.9	77.3	37.5
95% CI	(43,70)	(40,66)	(77,95)	(80,97)	(63,87)	(23,52)
Difference from CQ at 6 months, %						
Estimated Difference	20.3	16.6	51.7	54.5	39.9	NA
95% CI	(0,40)	(-3,36)	(35,69)	(38,71)	(21,59)	NA
Log Rank Test [b]						
p-value	ND	0.158	<0.0001	<0.0001	0.0004	NA

a. Subjects are censored if they did not have P. vivax at baseline, or failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 6 month assessment.
b. A two-sided log rank test was performed over 6 months using a 5% significance level.
c. ND Not done due to step-down testing procedure to adjust for multiple comparisons.

Table 50 Recurrence-Free Efficacy at 4 Months in TAF112582 Part 1 (Kaplan-Meier Methodology) (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Number of Subjects, n (%)						
Subjects observed to relapse prior to Study Day 120	19 (35)	22 (39)	5 (9)	2 (4)	10 (20)	28 (52)
Censored, prior to 4 month assessment [a]	3 (5)	3 (5)	1 (2)	8 (14)	6 (12)	2 (4)
Censored, relapse-free at 4 months	33 (60)	32 (56)	51 (89)	46 (82)	34 (68)	24 (44)
Relapse-free efficacy rate at 4 months, %						
Estimate	62.3	60.3	89.4	98.1	78.4	46.5
95% CI	(46,75)	(46,72)	(75,96)	(87,100)	(64,88)	(32,60)
Difference from CQ at 4 months, %						
Estimated Difference	15.8	13.8	42.9	51.6	32.0	
95% CI	(-5,36)	(-6,33)	(26,60)	(37,66)	(13,50)	
Log Rank Test [b]						
p-value		0.091	<0.0001	<0.0001	0.002	

a. Subjects are censored if they did not have *P. vivax* at baseline, or failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 4-month assessment.

b. A two-sided log rank test was performed over 4 months using a 5% significance level.

Table 51 Analysis of Recrudescence (Blood Stage Failure) Rates in TAF112582 Part 1 (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Number of Subjects, n (%)						
Recrudescence before Study Day 33	0	1 (2)	0	0	1 (2)	2 (4)
Censored, prior to Study Day 33[a]	2 (4)	1 (2)	1 (2)	0	1 (2)	2 (4)
Censored, no recrudescence by Study Day 33	53 (96)	55 (96)	56 (98)	56 (100)	48 (96)	50 (93)
Recrudescence rate						
Estimate	0.0	1.8	0.0	0.0	3.0	6.1
95% CI	(0,0)	(0,12)	(0,0)	(0,0)	(0,20)	(2,22)

a. Subjects are censored if they did not have *P. vivax* at baseline, or failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 28 days assessment.

Table 52 *P. falciparum* Asexual Parasite Emergence in TAF112582 Part 1 (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Number of subjects with emergent *P. falciparum* at any stage	0	1 (2)	0	0	1 (2)	2 (4)	4 (1)

Table 53 Summary of Time to Parasite, Fever, and Gametocyte Clearance (Intent-to-Treat Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Parasite Clearance, n (%)						
Parasite clearance	46 (84)	51 (89)	50 (88)	45 (80)	44 (88)	51 (94)
Censored	9 (16)	6 (11)	7 (12)	11 (20)	6 (12)	3 (6)
Time to Parasite Clearance (Hours)						
Median	45.0	43.0	42.0	47.0	44.5	42.5
95% CI	(42,49)	(38,50)	(40,45)	(43,59)	(39,48)	(38,48)
Fever Clearance, n (%)						
Fever clearance	20 (36)	24 (42)	19 (33)	21 (38)	14 (28)	21 (39)
Censored	35 (64)	33 (58)	38 (67)	35 (63)	36 (72)	33 (61)
Time to Fever Clearance (Hours)						
Median	11.0	6.5	15.0	19.0	19.5	8.0
95% CI	(4,22)	(4,19)	(5,21)	(5,26)	(4,37)	(5,16)
Gametocyte Clearance, n (%)						
Gametocyte clearance	41 (75)	44 (77)	47 (82)	44 (79)	36 (72)	41 (76)
Censored	14 (25)	13 (23)	10 (18)	12 (21)	14 (28)	13 (24)
Time to Gametocyte Clearance (Days)						
Median	2.0	1.0	1.0	1.0	2.0	2.0
95% CI	(1,2)	(1,2)	(1,2)	(1,2)	(1,2)	(1,2)

9.4. Inclusion/Exclusion Criteria for Study 564

9.4.1. Inclusion Criteria

Subjects eligible for enrollment in the study must have met all of the following criteria:

Safety

9. A female is eligible to enter and participate in the study if she is non-pregnant, non-lactating and if she is of:

   a. Non-childbearing potential defined as: post-menopausal (12 months of spontaneous amenorrhea or <6 months of spontaneous amenorrhea with serum FSH >40 mIU/mL), or pre-menopausal and has had a hysterectomy or a bilateral oophorectomy (removal of the ovaries) or a bilateral tubal ligation, negative pregnancy test or,

   b. Child-bearing potential, has a negative pregnancy test at screening, and agrees to comply with one of the following during the treatment stage of the study and for a period of 90 days after stopping study medication:

   - Use of oral contraceptive, either combined or progestogen alone used in conjunction with double barrier method as defined below.

- Use of an intrauterine device with a documented failure rate of <1% per year
- Use of depo provera injection
- Double barrier method consisting of spermicide with either condom or diaphragm
- Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female.
- Complete abstinence from intercourse for 2 weeks prior to administration of study medication, throughout the study and for a period of 90 days after stopping study medication.

10. The subject has a glucose 6-phosphate dehydrogenase (G6PD) value (measured by a quantitative spectrophotometric phenotype assay) as follows:
    - **Female subjects** must have an enzyme level ≥40% of the site median value for G6PD normal males.
    - **Male subjects** must have an enzyme level ≥70% of the site median value for G6PD normal males.
11. The subject has a screening Hb value as follows:

    •Any subject with a G6PD value ≥70% of the site median value must have a screening Hb value ≥70 g/L.

    •Female subjects with a G6PD value is ≥40% - <70% of the site median value must have a screening Hb value ≥80 g/L.
12. The subject has a QTcF of <450 msec.

    N.B. Reading based on an average of triplicate ECGs obtained over a brief recording period by machine or manual over-read.

Efficacy

13. The subject has a positive malarial smear for *P. vivax*.
14. The subject has a parasite density of >100 and <100,000/µL.

Other

15. Male or female subject aged 16 years or older (18 years or older in Ethiopia) at the time of signing the informed consent.
16. The subject agrees to G6PD genotyping.
17. The subject is willing and able to comply with the study protocol.
18. The subject or parent/legal guardian, as applicable, has given written informed, dated consent; and the subject has given written assent, if applicable, to participate in the study.

9.4.2. Exclusion Criteria

Subjects meeting any of the following criteria were not to be enrolled in the study:

Safety

13. The subject has a mixed malaria infection (identified by a malarial smear or rapid diagnostic test).
19. The subject has severe *P. vivax* malaria as defined by WHO criteria.
20. The subject has a history of allergy to chloroquine, mefloquine, tafenoquine, primaquine, or to any other 4- or 8-aminoquinoline.

Hepatic Disease

21. The subject has a liver ALT >2x ULN.

Concurrent Disease

22. The subject has severe vomiting (no food or inability to take food during the previous 8 hours).
23. The subject has a clinically significant concurrent illness (e.g., pneumonia, septicemia), pre-existing condition (e.g., renal disease, malignancy), condition that may affect absorption of study medication (e.g., vomiting, severe diarrhea), or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure, severe coronary artery disease).
24. The subject has a history of porphyria, psoriasis, or epilepsy.
25. The subject has a history of significant ocular disease (e.g. surgery to the globe, glaucoma, diabetic retinopathy) or has evidence of corneal or retinal abnormalities identified in the clinical screening ophthalmologic examination.

Concurrent Medication

26. The subject has taken anti-malarials (e.g., ACTs, mefloquine, primaquine, or any other 4- or 8-aminoquinoline) within 30 days prior to study entry.
27. The subject has taken or will likely require during the study the use of medications from the following classes:

    - Histamine-2 blockers and antacids
    - Drugs with hemolytic potential
    - Drugs known to prolong the QTcF interval
    - The biguanides phenformin and buformin (but excluding metformin)
    - Drugs that are substrates of the renal transporters OCT2, MATE1 and MATE-2K and have a narrow therapeutic index (for example, the anti-arrhythmic agents dofetilide, procainamide and pilsicainide)

Other

28. The subject has received treatment with any investigational drug within 30 days of study entry, or within 5 half-lives, whichever is longer.
29. The subject has a recent history of illicit drug abuse or heavy alcohol intake, such that full participation in the study could be compromised.

9.5. Data Tables for Supportive Study 564

Table 54 Subject Disposition in Study 564 (Safety Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Completion status, n (%)			
Completed	160 (96)	83 (98)	243 (97)
Withdrawn	6 (4)	2 (2)	8 (3)
Primary reason, n (%)			
Lost to follow-up	4 (2)	2 (2)	6 (2)
Withdrawal by subject	2 (1)	0	2 (<1)

Table 55 Discontinuation from Study Medication in Study 564 (Safety Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Premature discontinuation from study treatment, n (%)			
No	160 (96)	82 (96)	242 (96)
Yes	6 (4)	3 (4)	9 (4)
Reason for discontinuation from study medication, n (%)			
Adverse event	1 (<1)	1 (1)	2 (<1)
Subject reached protocol-defined Hb stopping criteria	2 (1)[a]	1 (1)	3 (2)[a]
Lost to follow-up	1 (<1)	1 (1)	2 (<1)
Physician decision	1 (<1)	0	1 (<1)
Other	1 (<1)	0	1 (<1)

a. In addition to the 2 subjects in the TQ+CQ group reported in Source Table 1.4, another subject in the TQ+CQ group met the Hb stopping criteria and discontinued study medication, but this was not properly recorded in the eCRF.

Table 56 Demographic Characteristics in Study 564(Safety Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Age (years), n (%)			
n	166	85	251
Mean (SD)	37.5 (14.28)	37.7 (14.69)	37.6 (14.39)
Sex, n (%)			
n	166	85	251
Male	114 (69)	53 (62)	167 (67)
Female	52 (31)	32 (38)	84 (33)
Race[a], n (%)			
n	166	85	251
American Indian or Alaska native	87 (52)	43 (51)	130 (52)
Asian (Southeast Asian heritage)	41 (25)	23 (27)	64 (25)
Black or African American	2 (1)	0	2 (<1)
Multiple	36 (22)	19 (22)	55 (22)
Ethnicity, n (%)			
n	166	85	251
Hispanic or Latino, n (%)	122 (73)	61 (72)	183 (73)
Not Hispanic or Latino, n (%)	44 (27)	24 (28)	68 (27)
Body mass index (kg/m^2)			
n	166	85	251
Median (Min, Max)	24.79 (16.7, 48.9)	25.24 (17.4, 40.4)	24.91 (16.7, 48.9)
G6PD enzyme activity (IU/g Hb)			
n	166	85	251
Median (Min, Max)	8.17 (6.0, 13.5)	8.01 (5.1, 14.2)	8.14 (5.1, 14.2)
G6PD enzyme activity (as % of site median)			
n	166	85	251
Median (Min, Max)	97.73 (70.8, 170.5)	94.49 (62.0, 169.2)	96.88 (62.0, 170.5)

Note: All subjects were confirmed to be at least 16 years of age at study entry, consistent with inclusion/exclusion criteria. No subjects from Ethiopia, where subjects were required to be at least 18 years of age, were enrolled in the study (Source: Table 1.5).

a. Subjects were categorized based on standard racial groupings, even though all subjects were ex-US.

Table 57 Malarial Signs and Symptoms in Study 564 (Safety Population)

Symptom/Severity	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Chills and rigors, n (%)			
Absent	9 (5)	5 (6)	14 (6)
Mild	32 (19)	22 (26)	54 (22)
Moderate	62 (37)	23 (27)	85 (34)
Severe	63 (38)	35 (41)	98 (39)
Headache, n (%)			
Absent	7 (4)	5 (6)	12 (5)
Mild	23 (14)	13 (15)	36 (14)
Moderate	59 (36)	28 (33)	87 (35)
Severe	77 (46)	39 (46)	116 (46)
Dizziness, n (%)			
Absent	72 (43)	36 (42)	108 (43)
Mild	64 (39)	27 (32)	91 (36)
Moderate	28 (17)	21 (25)	49 (20)
Severe	2 (1)	1 (1)	3 (1)
Abdominal pain, n (%)			
Absent	117 (70)	68 (80)	185 (74)
Mild	40 (24)	12 (14)	52 (21)
Moderate	9 (5)	5 (6)	14 (6)
Anorexia, n (%)			
Absent	80 (48)	49 (58)	129 (51)
Mild	46 (28)	15 (18)	61 (24)
Moderate	36 (22)	19 (22)	55 (22)
Severe	4 (2)	2 (2)	6 (2)
Nausea, n (%)			
Absent	76 (46)	44 (52)	120 (48)
Mild	63 (38)	27 (32)	90 (36)
Moderate	26 (16)	13 (15)	39 (16)
Severe	1 (<1)	1 (1)	2 (<1)
Vomiting, n (%)			
Absent	117 (70)	71 (84)	188 (75)
Mild	38 (23)	11 (13)	49 (20)
Moderate	11 (7)	3 (4)	14 (6)
Diarrhea, n (%)			
Absent	140 (84)	73 (86)	213 (85)
Mild	24 (14)	11 (13)	35 (14)
Moderate	2 (1)	0	2 (<1)
Severe	0	1 (1)	1 (<1)
Pruritus/itching, n (%)			
Absent	151 (91)	76 (89)	227 (90)
Mild	7 (4)	6 (7)	13 (5)
Moderate	8 (5)	3 (4)	11 (4)

Symptom/Severity	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Coughing, n (%)			
Absent	141 (85)	65 (76)	206 (82)
Mild	20 (12)	19 (22)	39 (16)
Moderate	5 (3)	1 (1)	6 (2)

Table 58 Previous Malarial Episodes in Study 564 (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Previous malarial episode, n (%)			
Yes	132 (80)	63 (74)	195 (78)
No	32 (19)	22 (26)	54 (22)
Unknown	2 (1)	0	2 (<1)

Table 59 Study Medication Compliance and Exposure in Study 564 (Safety Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Number of compliant doses of CQ, n (%)			
n	166	85	251
2	1 (<1)	1 (1)	2 (<1)
3	165 (>99)	84 (99)	249 (>99)
Subject compliance with TQ treatment, n (%)			
Yes	165 (>99)	84 (99)	249 (>99)
Total number of PQ doses taken, n (%)			
n	166	85	251
<12	6 (4)	1 (1)	7 (3)
at least 12	160 (96)	83 (98)	243 (97)
Missing	0	1 (1)	1 (<1)
Subjects with detectable PK at Day 8 or Day 15 visits, n (%)			
n		84	
Yes		84 (100)	
Subjects with at least 12 doses of PQ and detectable PK at Day 8 or Day 15 visits, n (%)			
n		83	
Yes		82 (99)	

Table 60 Recurrence-Free Efficacy over 6 Months in TAF116564 (Kaplan-Meier Analysis) (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)
Number of Subjects, n (%)		
Subjects observed to recurrence prior to or at 6 months	42 (25)	20 (24)
Censored, prior to 6-month assessment	12 (7)	5 (6)
Censored, recurrence-free at 6 months	112 (67)	60 (71)
Recurrence-free efficacy rate at 6 months, %		
Estimate (95% CI)	72.7 (64.8,79.2)	75.1 (64.2,83.2)
Hazard ratio of risk of recurrence TQ+CQ vs PQ+CQ		
Estimate (95% CI)	0.984 (0.577,1.678)	

Figure 9 Survival Curves for Recurrence-Free Efficacy over 6 Months in TAF116564 (mITT Population)

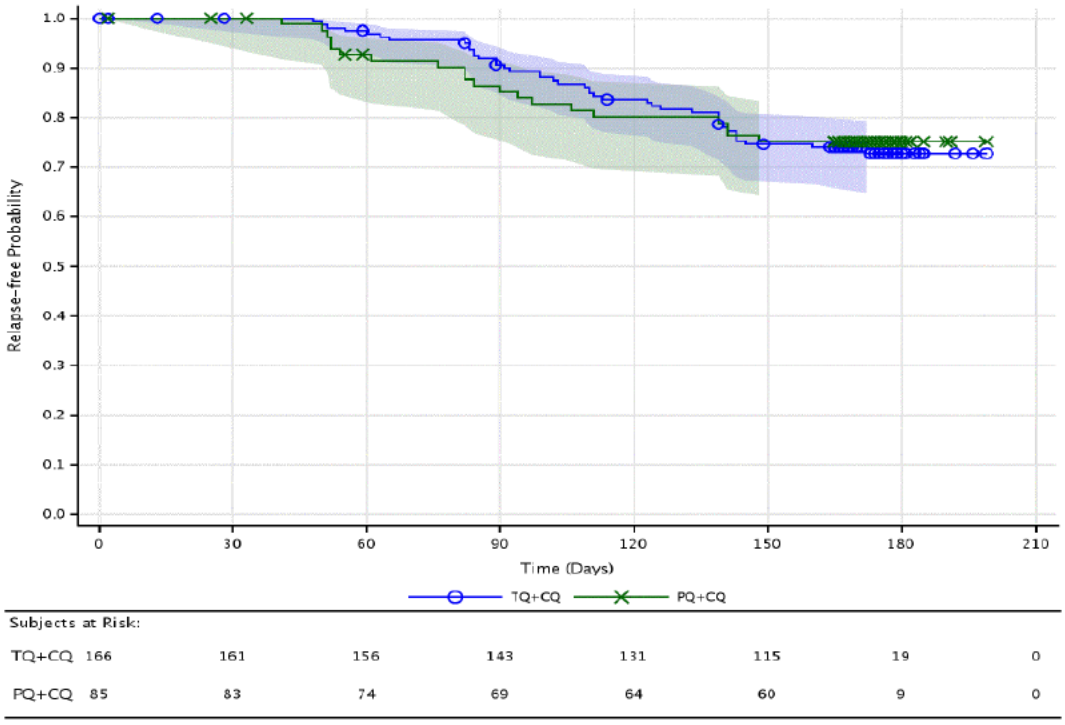


Table 61 Recurrence-Free Efficacy at 6 Months in TAF116564 with Missing=Failure (Logistic Regression) (mITT Population)

					Comparison with PQ+CQ	
Treatment	N	n	Subjects Recurrence-Free (%)	Subjects with a Recurrence (%)	Odds Ratio of Recurrence[a]	95% CI
TQ+CQ	166	166	112 (67)	54 (33)	1.141	(0.643,2.027)
PQ+CQ	85	85	60 (71)	25 (29)		

a. Odds ratios <1 suggest a smaller chance of recurrence as compared with PQ+CQ.

Table 62 Recurrence-Free Efficacy at 4 Months in TAF116564 (Kaplan-Meier Methodology) (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)
Number of Subjects, n (%)		
Subjects observed to recurrence prior to or at 4 months	29 (17)	16 (19)
Censored, prior to 4-month assessment	10 (6)	6 (7)
Censored, recurrence-free at 4 months	127 (77)	63 (74)
Recurrence-free efficacy rate at 4 months, %		
Estimate (95% CI)	82.3 (74.9,87.7)	79.7 (68.9,87.1)
Hazard ratio of risk of recurrence TQ+CQ vs PQ+CQ[a]		
Estimate (95% CI)	0.815 (0.442,1.503)	

a. A hazard ratio less than 1 indicates a lower chance of recurrence with TQ+CQ as compared with PQ+CQ.

Table 63 Recurrence-Free Efficacy at 4 Months in TAF116564 with Missing = Failure (Logistic Regression) (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)
Number of subjects, n	166	85
Subjects recurrence-free, n (%)	127 (77)	63 (74)
Subjects with a recurrence, n (%)	39 (23)	22 (26)
Odds ratio of recurrence (TQ+CQ comparison with PQ+CQ)		
Estimate (95% CI)[a]	0.858 (0.465, 1.583)	

Odds ratios less than 1 suggest a smaller chance of recurrence as compared with PQ+CQ.

Table 64 Analysis of Time to Parasite, Fever, and Gametocyte Clearance in TAF1164564 (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)
Parasite Clearance, n (%)		
Parasite clearance achieved	166 (100)	85 (100)
Censored, parasite clearance not achieved	0 (0)	0 (0)
Time to Parasite Clearance (hours)		
Median (95% CI)	41 (38,45)	44 (41,49)
Fever Clearance, n (%)		
Fever clearance achieved	65 (39)	32 (38)
Censored, at Baseline	101 (61)	53 (62)
Censored, fever clearance not achieved	0	0
Time to Fever Clearance (hours)		
Median (95% CI)	10 (7, 19)	13 (8, 22)
Gametocyte Clearance, n (%)		
Gametocyte clearance achieved	102 (61)	54 (64)
Censored, at Baseline	64 (39)	31 (36)
Censored, gametocyte clearance not achieved	0	0
Time to Gametocyte Clearance (hours)		
Median (95% CI)	38 (37, 43)	41 (37, 48)

9.6. Pooled Data Tables

Table 65 Adverse Events in the Nervous System Disorders SOC Reported Across the TQ Development Program (All Studies Safety Population)

Preferred Term, Grouped by Medically and/or Symptomatically-Related	All Placebo[a] (N=794) n (%)	300 mg TQ Total ≤3 days (N=807) n (%)	>300 mg TQ Total ≤3 days (N=1482) n (%)	>300 mg TQ Total >3 days (N=1445) n (%)	All TQ[b] (N=4129) n (%)
Any event	**170 (21)**	**142 (18)**	**240 (16)**	**269 (19)**	**734 (18)**
Headache	149 (19)	98 (12)	164 (11)	211 (15)	544 (13)
Migraine	4 (<1)	3 (<1)	0	3 (<1)	8 (<1)
Sinus headache	1 (<1)	0	0	4 (<1)	4 (<1)
Tension headache	0	0	0	2 (<1)	2 (<1)
Head discomfort	0	0	1 (<1)	0	1 (<1)
Visual field defect	0	0	0	1 (<1)	1 (<1)
Lethargy	0	0	28 (2)	28 (2)	56 (1)
Somnolence	1 (<1)	3 (<1)	21 (1)	1 (<1)	25 (<1)
Amnesia	0	0	0	1 (<1)	1 (<1)
Depressed level of consciousness	0	1 (<1)	0	0	1 (<1)
Disturbance in attention	0	0	1 (<1)	0	1 (<1)
Dysgeusia	1 (<1)	0	17 (1)	1 (<1)	18 (<1)
Paraesthesia	0	0	3 (<1)	4 (<1)	8 (<1)
Hypoaesthesia	1 (<1)	0	3 (<1)	1 (<1)	4 (<1)
Hyperaesthesia	0	0	0	1 (<1)	2 (<1)
Burning sensation	0	0	0	0	1 (<1)
Coordination abnormal	0	0	0	2 (<1)	2 (<1)
Balance disorder	0	1 (<1)	0	0	1 (<1)
Dizziness	24 (3)	62 (8)	56 (4)	33 (2)	171 (4)
Syncope	0	2 (<1)	1 (<1)	2 (<1)	5 (<1)
Presyncope	0	0	0	1 (<1)	1 (<1)
Dizziness postural	1 (<1)	0	0	0	0
Loss of consciousness	1 (<1)	0	0	0	0
Tremor	0	1 (<1)	1 (<1)	2 (<1)	4 (<1)
Muscle contractions involuntary	0	0	1 (<1)	0	1 (<1)
Sciatica	0	0	0	2 (<1)	3 (<1)
Post herpetic neuralgia	0	0	1 (<1)	1 (<1)	2 (<1)
Trigeminal neuralgia	0	0	0	1 (<1)	1 (<1)

Note: Preferred terms are grouped by those considered medically and/or symptomatically related; only selected columns are displayed.

Note: Data from clinical pharmacology studies SB252263/003, SB252263/050, SB252263/051, SB252263/052, SB252263/053, and SB252263/054 were not included in the All Studies grouping because validated datasets containing subject-level data could not be located (SB252263/003) or were not available to GSK (i.e. remaining 5 US army-sponsored studies). A manual review of safety listings for these studies was conducted and important safety data are described.

a. The placebo group includes healthy volunteers treated with placebo and *P. vivax* subjects treated with CQ alone in Study TAF112582 and Study SB252263/047.

b. Includes 392 subjects who received < 300mg total dose and 3 subjects who received a total 300mg dose > 3 days

Table 66 Adverse Events in the Psychiatric Disorders SOC Reported Across the TQ Development Program (All Studies Safety Population)

Preferred Term, Grouped by Medically and/or Symptomatically-Related	All Placebo[a] (N=794) n (%)	300 mg TQ Total ≤3 days (N=807) n (%)	>300 mg TQ Total ≤3 days (N=1482) n (%)	>300 mg TQ Total >3 days (N=1445) n (%)	All TQ[b] (N=4129) n (%)
Any Event	**8 (1)**	**16 (2)**	**19 (1)**	**37 (3)**	**79 (2)**
Insomnia	8 (1)	15 (2)	12 (<1)	15 (1)	48 (1)
Abnormal dreams	0	1 (<1)	0	6 (<1)	7 (<1)
Sleep disorder	0	0	0	3 (<1)	3 (<1)
Nightmare	0	0	0	2 (<1)	2 (<1)
Agitation	0	0	0	2 (<1)	2 (<1)
Anxiety	0	2 (<1)	0	0	2 (<1)
Anxiety disorder	0	0	0	2 (<1)	2 (<1)
Irritability	0	0	1 (<1)	0	2 (<1)
Neurosis	0	0	0	1 (<1)	1 (<1)
Panic attack	0	0	0	1 (<1)	1 (<1)
Psychotic disorder	0	0	1 (<1)	0	1 (<1)
Stress	0	0	0	1 (<1)	1 (<1)
Euphoric mood	0	0	1 (<1)	2 (<1)	3 (<1)
Depressed mood	0	0	1 (<1)	1 (<1)	2 (<1)
Depression	0	0	0	2 (<1)	2 (<1)
Bipolar disorder	0	0	0	1 (<1)	1 (<1)
Disinhibition	0	0	1 (<1)	0	1 (<1)
Mood altered	0	0	1 (<1)	0	1 (<1)
Alcoholic hangover	0	0	0	1 (<1)	1 (<1)
Tic	0	0	1 (<1)	0	1 (<1)

Note: Preferred terms are grouped by those considered medically and/or symptomatically related; only selected columns are displayed.

Note: Data from clinical pharmacology studies SB252263/003, SB252263/050, SB252263/051, SB252263/052, SB252263/053, and SB252263/054 were not included in the All Studies grouping because validated datasets containing subject-level data could not be located (SB252263/003) or were not available to GSK (i.e. remaining 5 US army-sponsored studies). A manual review of safety listings for these studies was conducted and important safety data are described.

Note: A subject in Study SB252263/043, included in the All Studies grouping, was reported to make a suicide attempt associated with alcohol intoxication. The event was not assigned a body system and therefore does not appear in the psychiatric disorders output. The event is described in Table 36.

a. The placebo group includes healthy volunteers treated with placebo and *P. vivax* subjects treated with CQ alone in Study TAF112582 and Study SB252263/047.

b. Includes 392 subjects who received < 300mg total dose and 3 subjects who received a total 300mg dose > 3 days

9.7. Additional TQ Clinical Studies

Table 67 Tabular Listing of All Clinical Studies Submitted to NDA210975 – Tafenoquine for the Radical cure of *P. vivax* malaria

Study Identifier	Study Description
Studies of tafenoquine for the Radical Cure (prevention of relapse) Indication	
TAF112582 (Part 1)	Subjects >=16 years with confirmed P. Vivax infection and >70% normal G6PD levels, stratified by baseline parasite count (<=7500/uL, >7500/uL)
TAF112582 (Part 2)	Subjects >=16 years with confirmed P. Vivax infection and >70% normal G6PD levels
TAF116564	Normal and G6PD-deficient P. Vivax-infected subjects
SB252263/022	Phase I Food effect study in healthy volunteers
TAF114582	Phase I Thorough QT study in healthy volunteers
201807	Phase I Ophthalmic safety study in healthy volunteers
SB252263/015	Phase I Drug-drug interaction study with desipramine in healthy volunteers
SB252263/040	Phase I Drug-drug interaction study with midazolam, flubiprofen and caffeine in healthy volunteers
TAF106491	Phase I Drug-drug interaction study with chloroquine in healthy volunteers
200951	Phase I Drug-drug interaction study with artemether-lumefantrine, and dihydroartemisinin-piperaquine tetraphosphate in healthy volunteers
TAF110027	Phase I dose escalation study in healthy volunteers and G6PD deficient healthy volunteers
201780	Phase I study in healthy volunteers to determine the effects of tablet aging (dissolution profiles) on the PK of TQ
TAF115226	Non-interventional study in healthy volunteers to establish site level normal ranges for G6PD enzyme activity
Supportive studies of tafenoquine in other indications or with other dose regimens	
SB252263/050[a]	Phase1 PK study in healthy male subjects
SB252263/051[a]	Phase1 PK study in healthy male subjects
SB252263/052[a]	Phase1 PK study in healthy male subjects
SB252263/053[a]	Phase1 Malaria challenge study healthy subjects
SB252263/054[a]	Phase1 Malaria challenge study in healthy subjects
SB252263/001	Phase 1 study in normal and G6PD-deficient healthy female subjects
SB252263/003[a]	Phase 1 PK, Food effect in healthy subjects
SB252263/014	Phase 1 relative bioavailability study in healthy subjects
SB252263/057	Phase 1 Ophthalmic and Renal Safety Study in healthy subjects
SB252263/006	Phase II Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/030	Phase III Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/033	Phase III Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/043	Phase II Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/044	Phase II Malaria Prophylaxis Non-immune male subjects
SB252263/045	Phase II Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/049	Phase II Malaria Prophylaxis Non-immune healthy Subjects
SB252263/036[a]	Pediatric subjects (6 mo to 14 yrs)
SB252263/046	Phase II treatment P. vivax-infected subjects with no documented G6PD deficiency
SB252263/047	Healthy subjects and P. Vivax-infected subjects with normal G6PD
SB252263/058	Treatment of 20-60 year-old subjects with confirmed P. Vivax infection and normal G6PD

a. Complete and validated datasets from studies SB252263/003, 036, 050,051, 052,053, and 054 were unavailable and have been excluded from pooled analyses

Document 1

Case Line Listing

Cases Count: 32

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
163217	29/03/2001	[redacted]		M	25	[redacted]	Chloroquine -Suspected Tafenoquine CT -Suspected Chloroquine -Other drug Doxycycline Hyclate -Other drug Primaquine Phosphate -Other drug Quinine -Other drug	[redacted]	Infection parasitic
163375	05/04/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
163376	05/04/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
164025	30/04/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
164026	30/04/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
164339	07/05/2001	[redacted]		U	??	[redacted]	Tafenoquine CT -Suspected		Visual impairment
377817	22/03/2016			F	??	[redacted]	Lariam (Mefloquine Hydrochloride) -Suspected Tafenoquine CT -Suspected		Completed suicide
392376	27/07/2016	[redacted]		M	28	[redacted]	Tafenoquine CT -Suspected	[redacted]	Depression Pain Post-traumatic stress disc
393834	23/08/2016			M	99	[redacted]	Mefloquine Hydrochloride -Suspected Tafenoquine CT -Suspected		Completed suicide
396130	29/09/2016	[redacted]		M	??	[redacted]	Lariam (Mefloquine Hydrochloride) -Suspected Tafenoquine CT -Suspected		Brain injury Toxicity to various agents
403837	18/02/2017	[redacted]		M	30	[redacted]	Tafenoquine CT -Suspected	[redacted]	Amnesia Depression Anxiety

Case Line Listing

Cases Count: 32

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
403839	18/02/2017	[redacted]		M	29	[redacted]	Tafenoquine CT -Suspected	[redacted]	Malaria Encephalopathy Drug ineffective
403840	18/02/2017	[redacted]		M	23	[redacted]	Tafenoquine CT -Suspected		Amnesia Headache Depression Nausea Insomnia Abdominal pain upper Tinnitus Post-traumatic stress disc
403842	18/02/2017		Unknowr	M	39	[redacted]	Tafenoquine CT -Suspected		Anxiety Sleep terror Irritability Anger Hallucination Post-traumatic stress disc
403846	19/02/2017	[redacted]		M	39	[redacted]	Tafenoquine CT -Suspected	[redacted]	Aggression Nausea Anger Abdominal pain upper Syncope
403848	18/02/2017	[redacted]		M	20	[redacted]	Tafenoquine CT -Suspected	[redacted]	Blood calcium increased Insomnia Liver function test abnorm Mental disorder Anger

Case Line Listing

Cases Count: 32

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
403849	18/02/2017	[redacted]		M	44	[redacted]	Tafenoquine CT -Suspected Doxycycline -Other drug	4	Headache Depression Nausea Adjustment disorder Loss of consciousness
403850	19/02/2017		[redacted]	M	39	[redacted]	Tafenoquine CT -Suspected		Aggression Anxiety Depression Nausea Abnormal dreams
403852	19/02/2017	[redacted]		M	46	[redacted]	Tafenoquine CT -Suspected	5642	Depression Anxiety Vertigo Post-traumatic stress disc
403853	19/02/2017		[redacted]	M	40	[redacted]	Tafenoquine CT -Suspected		Mental disorder
403854	19/02/2017		[redacted]	M	34	[redacted]	Tafenoquine CT -Suspected		Anxiety Depression Anger Alcoholism
403858	19/02/2017	[redacted]		M	25	[redacted]	Tafenoquine CT -Suspected		Anxiety Depression Aggression Anger Emotional poverty Confusional state
403921	20/02/2017	[redacted]		M	25	[redacted]	Tafenoquine CT -Suspected	60	Anxiety Panic attack Anger Nightmare Post-traumatic stress disc

Case Line Listing

Cases Count: 32

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
403922	20/02/2017	1[redacted]		M	28	[redacted]	Tafenoquine CT -Suspected	0	Amnesia Anxiety Aggression Paranoia Dizziness Abdominal pain Abnormal dreams Vertigo Tinnitus Mood swings Hallucination Diarrhoea Confusional state
404011	21/02/2017	[redacted]		M	23	[redacted]	Mefloquine Hydrochloride -Suspected Tafenoquine CT -Suspected	98	Abnormal behaviour Coordination abnormal Anxiety Depression Vision blurred Sleep disorder Gastrooesophageal reflux disease Tinnitus Suicidal ideation Photophobia Confusional state Irritable bowel syndrome

Case Line Listing

Cases Count: 32

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
404026	21/02/2017		[redacted]	M	43	[redacted]	Tafenoquine CT -Suspected		Pain Memory impairment Disturbance in attention Dizziness Fatigue Slow response to stimuli Post-traumatic stress disc Hypoacusis Pericarditis
404214	23/02/2017		[redacted]	M	37	[redacted]	Tafenoquine CT -Suspected Calamine -Other drug Chlorsig (Chloramphenicol) -Other drug Symbicort (Budesonide-Formoterol Fumarate Dihydrate) -Other drug Tineafax Ointment (Tolnaftate) -Other drug		Anxiety Depression Dissociation Disturbance in attention Panic attack Agitation Vertigo Tinnitus Hallucination Mood swings Suicidal ideation Muscle twitching Confusional state
404422	28/02/2017			M	??	[redacted]	Mefloquine Hydrochloride -Suspected Tafenoquine CT -Suspected		Completed suicide
411237	06/06/2017	[redacted]		M	30	[redacted]	Mefloquine Hydrochloride -Suspected Tafenoquine CT -Suspected		Nightmare Condition aggravated
414013	12/07/2017	[redacted]		M	31	[redacted]	Tafenoquine CT -Suspected	[redacted]	Abnormal behaviour Anxiety Depression Rash Suicidal ideation

Case Line Listing

Cases Count: 32

Case No.	Report Date	Onset Date	State	Sex	Age	Outcome	Medicine	Onset Time	Reaction
417864	11/09/2017			M	41	Unknown	Lariam (Mefloquine Hydrochloride) -Suspected Tafenoquine CT -Suspected		Central nervous system le Haematotoxicity
424376	21/12/2017			M	??	Unknown	Tafenoquine CT -Suspected		Depression Anxiety Brain injury Alcohol abuse Suicidal ideation Mood swings Post-traumatic stress disc

Selection Parameters : Date Range: 01/01/1960 To 31/12/2059 Medicine Status: Clinical trials, General marketing, Individual patient use, Intensive monitoring, Overdose, Post marketing surveillance, Special access scheme Medicine Names: Tafenoquine CT