CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210607Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Division Direcor
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210607
Priority or Standard	Priority
Submit Date(s)	December 8, 2017
Received Date(s)	December 8, 2017
PDUFA Goal Date	August 8, 2018
Division/Office	Division of Anti-Infective Products/Office of Antimicrobial Products
Review Completion Date	August 6, 2018
Established Name	Tafenoquine
(Proposed) Trade Name	ARAKODA
Pharmacologic Class	Antimalarial
Applicant	60 Degrees Pharmaceuticals, LLC
Formulation(s)	100 mg oral tablet
Dosing Regimen	200 mg once daily for 3 days before travel, 200 mg once weekly for the duration of travel, 200 mg once upon return
Indication/Population	*Prophylaxis of malaria in patients aged 18 years and older*
Recommendation on Regulatory Action	Approval

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
OPV= Division of Pharmacovigilance
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP= Division of Medical Policy Programs

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17	Pediatric Review Committee (PeRC)	PREA PMR and Agreed Initial Pediatric Study Plan	Meshaun Payne PeRC Members

Glossary

AC advisory committee
ACR anticipated clinical regimen
ADME absorption, distribution, metabolism, excretion
ADR adverse drug reaction
AE adverse event
AESI adverse events of special interest
BPCA Best Pharmaceuticals for Children Act
CDC Center for Disease Control and Prevention
CDER Center for Drug Evaluation and Research
CDRH Center for Devices and Radiological Health
CDTL Cross-Discipline Team Leader
CFR Code of Federal Regulations
CI confidence interval
CMC chemistry, manufacturing, and controls
CQ chloroquine
CRF case report form
CRO contract research organization
CRT clinical review template
CSR clinical study report
DAIDS Division of AIDS
DAIP Division of Anti-Infective Products
DMC Data Monitoring Committee
DPV Division of Pharmacovigilance
ECG electrocardiogram
eCTD electronic common technical document
FDA Food and Drug Administration
FDAAA Food and Drug Administration Amendments Act of 2007
FDASIA Food and Drug Administration Safety and Innovation Act
GCP good clinical practice
GLP good laboratory practice
GRMP good review management practice
ICH International Conference on Harmonization
IND Investigational New Drug
ISE integrated summary of effectiveness
ISS integrated summary of safety
ITT intent-to-treat
ITT-E intent-to-treat exposed
MedDRA Medical Dictionary for Regulatory Activities
mITT modified intent to treat

MQ mefloquine
NDA new drug application
NME new molecular entity
OPQ Office of Pharmaceutical Quality
OSE Office of Surveillance and Epidemiology
OSI Office of Scientific Investigation
PD pharmacodynamics
PE protective efficacy
PK pharmacokinetics
PMC postmarketing commitment
PMR postmarketing requirement
PP per protocol
PPI patient package insert
PQ primaquine
PREA Pediatric Research Equity Act
PRO patient reported outcome
PSUR Periodic Safety Update report
REMS risk evaluation and mitigation strategy
SAE serious adverse event
SAP statistical analysis plan
SD standard deviation
TEAE treatment emergent adverse event
TEADR treatment emergent adverse reaction
TQ Tafenoquine
USPI US prescribing information
WHO World Health Organization

1 Executive Summary Office Level Concurrence

Tafenoquine (TQ), ARAKODA, is an 8-aminoquinoline antimalarial drug. In NDA 210607, TQ is being developed for the prophylaxis of malaria. The proposed indication is prevention of malaria in adults for up to 6 months of continuous dosing. TQ will be approved for the indication of prophylaxis of malaria in patients aged 18 years and older. The proposed dose is 200 mg daily for 3 days, followed by 200 mg weekly while in the malarious area and one dose following return from the malarious area. In this NDA, the Applicant has provided substantial evidence for the effectiveness of TQ for the prophylaxis of malaria in adults. Safety findings from the clinical trials are adequately communicated in labeling and additional evaluation of safety will conducted postmarketing through required postmarketing studies and routine pharmacovigilance.

1.1. Product Introduction

Product
Tafenoquine (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).

Proposed Indication
Prevention of malaria in adults for up to 6 months of continuous dosing. The product will be approved for the indication of prophylaxis of malaria in patients aged 18 years and older.

Proposed Dosing Regimen
The proposed regimen is a loading dose of 2 x 100 mg tablets once daily for 3 days before travel to a malarious area, followed by weekly 2 x 100 mg maintenance doses while in the malarious area, followed by one dose of 2 x 100mg in the week following exit from the malarious area.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of TQ for the prophylaxis of malaria in patients aged 18 years and older. In two adequate and well-controlled trials in semi-immune population, TQ was superior to placebo for the protective efficacy endpoint in all randomized subjects. In study 043, 91.9% of placebo subjects developed parasitemia at week 15 compared to 24.6% of TQ subjects, protective efficacy of TQ was 73.3%, 95% CI (54.0%, 84.5%), p <0.001. In study 045, 93.6% of placebo subjects developed parasitemia at 12 weeks compared to 26.9% of TQ subjects, TQ protective efficacy was 71.3%, 95% CI (55.8%, 81.4%), p <0.001.

Study 033, where TQ was compared to mefloquine (MQ) in non-immune deployed military personnel, provided supportive evidence for TQ efficacy at 26 weeks: prophylactic success was

demonstrated in 96.1% of TQ subjects compared to 96.9% of MQ subjects, difference -0.78%, 95% CI (-3.71%, 3.57%).

Additional supportive data for TQ protective effect were generated in a *P. falciparum* blood stage challenge study, where TQ prevented parasitemia and clinical malaria in 12/12 (100%) exposed subjects compared to 0/4 (0%) subjects who received placebo, p, 0.0005 and from Study 30 an active comparative trial in semi-immune individuals.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 210607, the Applicant is seeking approval of tafenoquine (TQ) 100 mg tablets for the prevention of malaria in adults for up to 6 months of continuous dosing. TQ is an 8-aminoquinoline antimalarial drug. Current malaria prophylactic regimens require daily or weekly dosing while in malarious area and for 4 weeks [(doxycycline, mefloquine (MQ), and chloroquine(CQ)] or 1 week (atovaquone–proguanil and primaquine (PQ)) upon return from travel. Primaquine is the only available drug that targets the *P. vivax* and *P. ovale* hypnozoites in the liver and is approved only for the radical cure of *P. vivax* malaria. TQ has a long half-life in humans (approximately 17 days) allowing for weekly dosing while in malarious area and a single dose for terminal prophylaxis upon return from travel.

The Applicant has provided substantial evidence for the effectiveness of TQ for the prophylaxis of malaria in patients aged 18 years and older at the anticipated clinical regimen (ACR) of 200 mg daily for 3 days, followed by 200 mg weekly. Efficacy of TQ is supported by data from randomized, double-blind, controlled (placebo/active), studies in non-immune or semi-immune healthy subjects, as well as a malaria challenge study. In two adequate and well-controlled trials (Studies 43 and 45) in a semi-immune population, TQ was superior to placebo for the protective efficacy endpoint. In Study 043, 91.9% of placebo subjects developed parasitemia at week 15 compared to 24.6% of TQ subjects, protective efficacy of TQ was 73.3%, 95% CI (54.0, 84.5), p <0.001. In Study 045, 93.6% of placebo subjects developed parasitemia at week 12 compared to 26.9% of TQ subjects, TQ protective efficacy was 71.3%, 95% CI (55.8, 81.4), p <0.001. A third trial (Study 33), where TQ was compared to MQ in non-immune deployed military personnel, provided supportive evidence for TQ efficacy at 26 weeks: prophylactic success was demonstrated in 96.1% of TQ subjects compared to 96.9% of MQ subjects, difference -0.78%, 95% CI (-3.71, 3.57). Supportive evidence is provided by a *P. falciparum* blood stage challenge study, where TQ prevented parasitemia and clinical malaria in 12/12 (100%) exposed subjects compared to 0/4 (0%) subjects who received placebo, p <0.0005. Additional supportive evidence is provided by a study that evaluated the efficacy of 24-week TQ prophylaxis compared with MQ in semi-immune subjects. While both TQ and MQ failed to demonstrate protective efficacy in the original parasite slide reading results, a blinded re-reading of the slides showed that the two treatment groups provided significant protection against malaria at Week 25.

The safety of TQ at various doses and regimens was evaluated in clinical trials that enrolled 3,184 subjects. The recommended TQ ACR was evaluated in 825 subjects in 5 controlled clinical trials with 529 subjects exposed to TQ ACR for greater than or equal to 23 weeks. Adverse reactions with TQ ACR exposure include: ophthalmic (reversible vortex keratopathy), hematologic (decrease in hemoglobin levels, hemolytic anemia, and methemoglobinemia), neurologic (headache, dizziness, and motion sickness), psychiatric (sleep disturbances, anxiety, depression/depressed mood), hypersensitivity, and gastrointestinal (diarrhea, nausea, and vomiting). There were no significant cardiac, renal,

or hepatic toxicities observed with TQ ACR. No large mean increase (i.e., >20 ms) in the QTc interval is anticipated for TQ 400 mg, a dose higher than the TQ ACR. No subjects met Hy's Law criteria. Risks associated with TQ exposure are communicated in labeling that includes contraindications regarding use in G6PD deficiency or if G6PD status is unknown, breastfeeding when the infant is found to be G6PD deficient or if G6PD status is unknown, patients with a history of psychotic disorders or current psychotic symptoms and warnings regarding hemolytic anemia, use in subjects with G6PD deficiency, hypersensitivity reactions and psychiatric adverse reactions. Additionally, labeling includes a Medication Guide that is required to be dispensed with each prescription and will provide information about the adverse effects reported with TQ and advice regarding when to seek medical attention. Postmarketing studies will further evaluate ophthalmic, hematologic, neurologic, and psychiatric adverse reactions that may occur with TQ exposure.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Malaria is associated with significant morbidity and mortality. • In 2014, the CDC reported 1,724 confirmed cases of malaria in the U.S., with an overall trend of increase in the numbers of confirmed malaria cases each year. Most cases were due to non-use or non-compliance with chemoprophylaxis. • Chemoprophylaxis can reduce the risk of developing malaria in travelers to malaria endemic countries, including travelers from the US.	• Malaria is a serious life-threatening infectious disease. • The risk of developing malaria can be reduced when travelers are compliant with effective chemoprophylaxis.
Current Prophylaxis Options	• Efficacy rates for existing malaria chemoprophylactic drugs are over 90% and superior to placebo, when used in areas without resistance to the drug. • Doxycycline, MQ, and CQ act on parasites that infect erythrocytes, after they have been released from the initial maturation phase in the liver. These drugs must be continued for 4 weeks after the last exposure to infective mosquitoes (post-exposure prophylaxis) to eradicate any parasites that may still be released from the liver. • Atovaquone–proguanil and PQ act on blood-stage parasites and interfere with the development of actively replicating parasites in the liver. These drugs must be continued for 1 week after exposure to infective mosquitoes ends.	• TQ has activity against the sporozoites, liver and erythrocytic stages of the *Plasmodium* species and a long half-life in humans (approximately 2 weeks) allowing for weekly dosing while in malarious area and a single dose for terminal prophylaxis upon return from travel. • TQ may address a gap with current prophylaxis options in that a single dose upon return from a malaria endemic area could reduce the chance of relapse.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• PQ is the only available drug that acts on the *P. vivax* and *P. ovale* hypnozoites in the liver and is only approved for the treatment/radical cure of *P. vivax* malaria.	
Benefit	Efficacy was demonstrated in randomized, double-blind, controlled, placebo controlled studies in semi-immune healthy subjects, as well as a malaria challenge study. Supportive information was provided in a randomized, double-blind, controlled, active controlled trial in non-immune subjects and a trial comparing TQ to MQ in semi-immune subjects. • Studies 043 and 045: Conducted in semi-immune subjects with the treatment duration of 15 and 12 weeks, respectively. In study 043, 91.9% of placebo subjects developed parasitemia at week 15 compared to 24.6% of TQ subjects, protective efficacy of TQ was 73.3%, 95% CI (54.0, 84.5), p <0.001. In study 045, 93.6% of placebo subjects developed parasitemia at 12 weeks compared to 26.9% of TQ subjects, TQ protective efficacy was 71.3%, 95% CI (55.8, 81.4), p <0.001. • TQ-2016-02: The blood-stage *P. falciparum* challenge study demonstrated a significant effect of TQ compared to placebo in preventing parasitemia in healthy non-immune subjects (prophylactic success proportion: 100% (12/12) versus 0% (0/4) on placebo, Fisher's exact test two-sided p-value 0.0005 • Study 033: There were no observed cases of malaria during the 26-week prophylactic phase in non-immune subjects. Prophylactic success proportions at Week 26 were 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) with a difference of -0.78% and a 95% CI [-2.39%, 3.94%]. There were five cases of *P. vivax*	• The data supports the efficacy of TQ for the prevention of malaria for up to 6 months of continuous dosing in semi-immune and non-immune subjects.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	malaria during the relapse follow-up phase of the trial, with similar rates in the two treatment arms.	
Risk	• Quinoline anti-malarial drugs, such as PQ, MQ, and CQ/hydroxy-CQ, have several known safety issues as noted in their respective labeling. This includes ophthalmic, cardiac, hematologic, renal, neurologic, psychiatric, gastrointestinal, and hepatobiliary effects. • 825 subjects were exposed to the TQ ACR in five clinical trials. However, only 529 subjects were exposed to the TQ ACR for greater than or equal to 23 weeks. This relatively small database for a prophylaxis indication may not sufficient to detect potential low frequency adverse events. • The mean half-life of TQ is 16.5 days (range 10.8 – 27.3 days). Hence, adverse reactions may occur well after initial exposure, or be prolonged. • Limitations in assessing safety: Systematic monitoring for neurologic and psychiatric adverse events was not conducted in TQ ACR trials. Also, difficult to assess the potential for psychiatric AEs as many of the studies excluded patients with known psychiatric illness. Key safety findings associated with TQ ACR exposure include: • *Hematologic*: Decrease in hemoglobin levels, hemolytic anemia, and methemoglobinemia. TQ was not evaluated in individuals with G6PD deficiency, where the risk of hemolytic anemia would be higher. • *Psychiatric*: Sleep disturbances occurred in 2.5% of subjects exposed to TQ ACR. Depression/depressed mood and anxiety were reported in 0.3% and 0.2% of TQ ACR subjects, respectively. A single subject discontinued TQ ACR due to a suicide attempt. Three subjects with an underlying psychotic	• The safety issues identified with TQ ACR include hematologic, psychiatric, ophthalmic and gastrointestinal. • Labeling includes contraindications in individuals with G6PD deficiency or unknown G6PD status, in lactating women when the infant is found to be G6PD deficient or status unknown and in patients with psychotic symptoms or a history of psychotic disorder. • Labeling includes warnings regarding risk of hemolytic anemia in G6PD deficient individuals, risk of decline in hemoglobin in G6PD normal individuals, use in pregnant or lactating women, risk of methemoglobinemia, hypersensitivity, and psychiatric reactions. • TQ should be taken with food. • Labeling also includes a Medication Guide for patients describing adverse reactions reported with TQ and provides advice regarding when to seek medical attention.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	illness, who received 350 to 500 mg of TQ for up to 3 days, experienced psychosis approximately 1 to 3.5 weeks after exposure. • *Ophthalmic*: Reversible vortex keratopathy (corneal deposits). Effects on vision and the retina cannot be fully ascertained with the data provided. • *Gastrointestinal*: Diarrhea, nausea, vomiting, and abdominal pain were common TEAEs. The safety profile of TQ when administered without food has not been assessed in the development program. • There were no clinically significant cardiac, renal, or hepatic toxicities. • TQ has not been studied in pregnant or lactating women.	
Risk Management	• The TQ ACR appears to be effective and reasonably safe for malaria prophylaxis in adults for up to 6 months in the population studied.	• Testing should be performed for G6PD enzyme activity before TQ use to avoid risk of hemolytic anemia. • Risk mitigation strategies include communicating the risks in labeling and a Medication Guide. • A postmarketing observational safety study will include monitoring for (b) (4), hematologic, neurologic, and psychiatric adverse events. • An ongoing placebo-controlled safety trial to further evaluate the long term ophthalmic safety of TQ (neurologic and psychiatric events are secondary endpoints) is a required postmarketing study.

1.4. Patient Experience Data

No patient experience data was submitted as part of this application. Specifically, there were no clinical outcome assessments, patient reported outcomes, observer reported outcomes, performance outcomes, qualitative studies, patient focused drug development/ stakeholder meeting, or observational survey studies.

2 Therapeutic Context

2.1. Analysis of Condition

Malaria is a potentially fatal illness caused by a mosquito-borne parasitic infection of red blood cells. These parasites are protozoans belonging to the genus Plasmodium, and five species are known to infect humans: *P. falciparum (Pf), P. vivax (Pv), P. ovale (Po), P. malariae (Pm),* and *P. knowlesi (Pk)*. *Pv* and *Po* can remain dormant in the liver as hypnozoites, and relapses can occur months, or rarely, several years, after exposure.

The majority of malaria infections worldwide are due to *Pf* or *Pv*. The World Health Organization estimates that there were 216 million cases of malaria in 91 countries in 2016, an increase of 5 million cases over 2015.[1] There were an estimated 445,000 malaria deaths in 2016 globally.

According to the U.S. Centers for Disease Control and Prevention (CDC), the overall trend of confirmed malaria cases has been increasing in the U.S.[2] In 2014, the CDC reported 1,724 confirmed cases of malaria in the U.S.[2] *Pf, Pv, Po,* and *Pm* were identified in 66.1%, 13.3%, 5.2%, and 2.7% of cases, respectively.[2] In addition, among all reported cases, 17% were classified as severe illness, and five persons with malaria died.[2] Of the 1,724 confirmed malaria cases in 2014, malaria importation was highest in those visiting friends and relatives (VFR) (52.8% U.S. civilians, 22.1% foreign residents).[2]

Travelers often take an incorrect regimen or are non-adherent to an appropriate regimen. Among the 310 patients with malaria who reported taking chemoprophylaxis, 222 patients reported specific drug information.[2] The majority, 194 (87.4%), took a regimen recommended by CDC for the region of travel.[2] Of the 194 patients who took CDC-recommended chemoprophylaxis, 74 (38.1%) took doxycycline, 58 (29.9%) took MQ, 49 (25.3%) took atovaquone-proguanil, and 13 (6.7%) took two or more CDC-recommended medications; none took CQ or PQ alone. There were 824 U.S. resident cases with complete information on chemoprophylaxis: 64 patients were adherent to an appropriate regimen, 656 did not take chemoprophylaxis or took an incorrect regimen, and 104 were nonadherent to an appropriate regimen.[2]

Imported malaria has also been described in U.S. military personnel. Of the U.S. resident cases in 2014, 31 (2.7%) occurred in U.S. military personnel, which was an increase from 14 cases in 2013.

2.2. Analysis of Current Treatment Options

The dosing schedule, estimated efficacy rates, and adverse effects for drugs currently recommended for malaria chemoprophylaxis by the CDC are summarized in Table 1. In general, efficacy rates for existing malaria chemoprophylactic drugs are established to be over 90% and superior to placebo, when used in areas without resistance to the particular drug. Key points to consider when prescribing a malaria chemoprophylaxis regimen include the person's age, pregnancy status, travel to drug-resistant regions, daily versus weekly treatment, length of therapy after return from malaria endemic area, and adverse effects.

Antimalarial chemoprophylactic agents such as doxycycline, MQ, and CQ act on parasites that infect erythrocytes, after they have been released from the initial maturation phase in the liver. Hence, these drugs must be continued for 4 weeks after the last exposure to infective mosquitoes to eradicate any parasites released from the liver in the next month. In contrast, atovaquone–proguanil and PQ act on blood-stage parasites and interfere with the development of actively replicating parasites in the liver. Therefore, these drugs need to be continued only for 1 week after exposure ends.

PQ is the only available drug that acts on the *Pv* and *Po* hypnozoites in the liver. It is typically indicated for people who have had either prolonged or intense short exposure to infective mosquitoes in areas where there is a substantial risk of *Pv* or *Po* transmission, even if *Pf* is the predominant local pathogen. Using PQ daily for 14 days after the trip is referred to as presumptive antirelapse therapy. Presumptive antirelapse therapy is used infrequently in practice and only in patients with the most obvious and prolonged exposure to infective mosquitoes, because the risk of relapsing malaria is extremely difficult to quantify for a given location, and because the use of a second, nonconcurrent drug makes prophylaxis more complicated.[3]

Table 1: Drugs Currently Recommended for Malaria Chemoprophylaxis by the U.S. Centers for Disease Control and Prevention: Dosing Schedule and Adverse Effects

Drug	Dosing Schedule	Adverse Effects
Atovaquone -Proguanil (Malarone)	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas.[1,2]	Contraindicated in people with severe renal impairment (creatinine clearance <30 mL/min).[2,3] Not recommended for prophylaxis for children weighing <5 kg, pregnant women, and women breastfeeding infants weighing <5 kg.[2,3]
Doxycycline	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas.[1,2]	Contraindicated in children <8 years of age and pregnant women.[2,4]

Drug	Dosing Schedule	Adverse Effects
MQ	Begin ≥2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas.[2,5,6]	Contraindicated in people allergic to MQ or related compounds (quinine, quinidine) and in people with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in people with psychiatric disturbances or a previous history of depression. Not recommended for people with cardiac conduction abnormalities.[2,5] Black box warning for neuropsychiatric adverse reactions, and required patient medication guide when dispensing.[5]
PQ	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas.[2,8,9]	Contraindicated in people with G6PD deficiency. Also contraindicated during pregnancy and lactation, unless the infant being breastfed has a documented normal G6PD level. Indicated for people who have had prolonged exposure to *P. vivax, P. ovale*, or both. Contraindicated in people with G6PD deficiency. Also contraindicated during pregnancy and lactation, unless the infant being breastfed has a documented normal G6PD level.[2,8]
CQ phosphate OR Hydroxy-CQ sulfate	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas.[2,7]	CQ may exacerbate psoriasis.[2]

[1]Prophylaxis in all malarious areas.
[2]CDC 2018 Yellow Book - Chapter 3 Infectious Diseases Related to Travel https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria#3-10-a-p
[3]Malarone (Atovaquone-Proguanil) Label, updated August 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e27bedfd-c181-44f9-a920-19c2f8cab644
[4]Doxycycline hyclate tablet, delayed release Label, updated January 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2e9d34a2-8173-4202-8187-3994bd8a9e1d
[5]MQ Label, updated September 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=43fde257-36ee-49ea-a03c-01a1a4e1da3d
[6]Prophylaxis in areas with MQ-sensitive malaria.
[7]Prophylaxis only in areas with CQ-sensitive malaria.
[8]PQ Label, updated July 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1bfbf4ae-81b8-4160-a00d-6322aadd4b59
[9]Prophylaxis for short-duration travel to areas with principally *P.vivax*. Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease the risk for relapses of *P. vivax* and *P. ovale.*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

At the time of submission, NDA 210607 was identified for review under the Program for Enhanced Review Transparency and Communication for NME NDAs and original BLAs (known as the Program and described in the PDUFA VI goals letter). On 20 July 2018, KRINTAFEL (tafenoquine) tablets, which contains the same active moiety as that contained in ARAKODA, was approved under NDA 210795 for the radical cure (prevention of relapse) of *P. vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection. Consistent with FDA policy, the review of NDA 210607 has continued to be managed under the Program for process reasons. According to CDER's review process, the signatory authority for applications managed under the Program is generally at the office level. Because this application was managed under the Program, it will be signed at the office level to be consistent with OND practice.

3.2. Summary of Presubmission/Submission Regulatory Activity

This Application is a re-submission after a Refuse-to-File action due to the insufficient data submitted to support the long-term stability of the drug substance and drug product. This application was granted a Priority Review Designation. A Fast Track Designation request was submitted during the NDA review cycle and was granted to the Applicant's IND 129656 on December 28, 2017. A Breakthrough Therapy Designation request submitted during the NDA review cycle was denied.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Four malaria prophylaxis studies (Studies 33, 43, 45, 49) were audited at good clinical practice (GCP) inspections of one foreign clinical investigator (CI) site and the sponsor site. Inspections of studies 33 and 49 including study records were conducted at the CI site (Peter Nasveld; Brisbane, Australia) and at the sponsor site. For Studies 43 and 45 conducted in Kenya and Ghana (respectively), source records were not available for inspection. Study records limited to U.S. Army Medical Materiel Development Activity (USAMDDA) monitoring records, approved protocol, and informed consent documents were audited at the sponsor site.

For Studies 33 and 49, an FDA Form 483 was issued to Dr. Peter Nasveld for minor GCP deficiencies unlikely to be significant. An FDA Form 483 was not issued at the sponsor inspection; given the study sponsorship transfers, the applicant was deemed not responsible for the observed recordkeeping deficiencies. For Studies 33 and 49, study conduct appeared adequately GCP-compliant, including sponsor oversight of study conduct. All audited data were acceptably verifiable against source records and CRFs, and the data for Studies 33 and 49 appear reliable as reported in the NDA. For Studies 43 and 45, the lack of the original study records does not allow for the verification of the reliability of the data submitted. The adequacy of monitoring for Studies 43 and 45 cannot be determined in lieu of the missing original study records.

Please refer to the detailed Clinical Inspection Summary by John Lee, M.D. in DARRTS posted 16 July 2018, Reference ID: 4291707.

Office of Good Clinical Practice

Office of Good Clinical Practice (OGCP) within the Office of Medical Products and Tobacco (OMPT) was consulted to evaluate whether researchers respected and protected the rights and welfare of human research participants in Studies 033, 043 and 045. Summary findings are included here. Please refer to the detailed review by Kevin Prohaska, D.O., M.P.H., Captain (USPHS) in DARRTS posted 29 May 2018, Reference ID: 4269403.

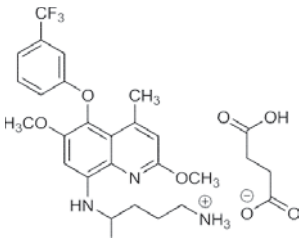
- **Study 033**: Based on the information contained in the Inspector General's report, the final study report for Study 033, and information on the web (e.g., Australian National Guideline), Dr. Prohaska believes the AMI researchers involved with Study 033 took appropriate steps to assure the rights and welfare of human research participants in Studies 033 were protected.
- **Studies 043 and 45**: Based on the review of the information submitted by the Applicant, Dr. Prohaska believes that subjects participating in Study 043 and 45 were ethically treated and their rights and welfare were adequately protected.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No
Sufficient controls to insure safety and efficacy of the commercial product: Yes

Provided below is a brief summary of the product quality assessment from the Office of Pharmaceutical Quality (OPQ). Details of the review findings are referred to the Integrated Quality Assessment (IQA).

TQ is an 8-aminoquinoline, a synthetic analog of PQ with the following structural formula:



Molecular Formula: C24H28F3N3O3·C4H6O4

[redacted] throughout development, tafenoquine succinate was consistently isolated as Form A, the thermodynamically stable form. Available stability data in the NDA support a retest period of [redacted] months for TQ drug substance stored at [redacted] The overall information provided in the NDA for the drug substance, including the proposed specification, was found acceptable.

The drug product is an immediate release tablet for oral administration containing 125.5 mg of tafenoquine succinate, which is equivalent to 100 mg tafenoquine free base.

TQ tablet is described as a dark pink and capsule shaped tablet, embossed with 'TQ100' on one side and plain on the other side.

Table 2. Components and Composition of TQ tablet, 100mg

Component	Quantity (mg/tablet)	Quantity (% wt)	Function	Reference to Standard
Tafenoquine succinate[1]	125.5	(b) (4)	Active ingredient	*Section 3.2.S.4.1*
Microcrystalline Cellulose (b) (4)		(b) (4)		USP/NF/Ph.Eur.
Mannitol				USP/NF/Ph.Eur.
Magnesium Stearate				USP/NF/Ph.Eur.
(b) (4)				
				Type IV DMF (b) (4)
				USP/NF/Ph.Eur.
Total Tablet		(b) (4)		

[1] The amount of tafenoquine succinate required to provide the label claim of tafenoquine is calculated based on the (b) (4)

Each tablet (b) (4) contain compendial excipients. Adequate information was provided in the NDA regarding the drug product formulation development, control of excipients, drug product specification, batch data, analytical methods, and container closure information.

The drug product specification (see table below) includes quality attributes relevant for the proposed dosage form such as appearance, identification, assay, impurities, content uniformity, (b) (4) dissolution, and microbial controls. During the review, several revisions were incorporated in the proposed drug product specification at the Agency's request, (b) (4)

Table 3. Drug Product Specification

Test	Acceptance Criteria	Method
Appearance	Dark pink, capsule-shaped, film-coated tablet, debossed with TQ100 on one side and plain on other side.	Visual inspection
Identification (HPLC)	The retention time of the principal peak in the sample chromatogram corresponds to that of the principal peak in the standard chromatogram.	*Section 3.2.P.5.2.1*
Identification (UV)	The UV spectrum of the principal peak in the sample chromatogram corresponds to that of the principal peak in the standard chromatogram.	*Section 3.2.P.5.2.1*
Assay by HPLC (% label claim)	(b) (4)	*Section 3.2.P.5.2.1*
Drug related impurities by HPLC (% w/w) Any individual impurity Total impurities[1]	(b) (4)	*Section 3.2.P.5.2.1*
Content uniformity (USP <905>)	Acceptance Value (AV) (b) (4)	*Section 3.2.P.5.2.2*
(b) (4)		
Dissolution (% label claim dissolved) (USP <711>)	Not less than (b) (4) in 10 minutes Not less than (b) (4) (Q) in 90 minutes	*Section 3.2.P.5.2.3*
Microbial limits Total aerobic microbial count Total combined yeasts / molds *Escherichia coli* *Salmonella* species	 Not more than (b) (4) cfu/g Not more than (b) (4) cfu/g Absent Absent	USP <61> / <62>

[1] Total impurities include both synthetic impurities and degradation products.

For elemental impurities, the Applicant provided data for the four drug product batches and the levels of all elements (Class 1, 2A, 2B, and 3) were (b) (4) of the respective permitted daily exposures (PDEs).

TQ tablets are packaged in aluminum blisters backed with a peelable layer. One blister card contains eight tablets, and each box (secondary packaging) contains two blister cards for a total of 16 tablets per box. The proposed container closure system was found safe and suitable to protect the drug product.

Based on the assessment of 12 months of long-term and 6 months of accelerated stability data for four representative batches of drug product, the proposed 24-month shelf life has been found acceptable for drug product stored at conditions consistent with the room temperature storage (25°C/60% RH) or below 30°C/75% RH.

The drug product manufacturing process is involves (b) (4) The proposed manufacturing process is considered low risk, and was deemed adequately developed, described, and controlled.

The Biopharmaceutics review focused on the assessment of the proposed dissolution method and acceptance criteria, as bridging was deemed unnecessary due to lack of differences in the quality attributes of the tablets used in the key clinical trials and the tablets intended for commercialization. Tafenoquine succinate exhibits pH-dependent solubility, and is considered a low solubility drug substance (per BCS criteria). The data submitted in the NDA for the currently proposed dissolution method demonstrate its limited discriminating ability. The Applicant's response to FDA request for additional data related to the discriminating and stability-indicating properties of the proposed dissolution method was found not optimal (incomplete dissolution). It was determined that identification of an optimal dissolution method can appropriately be addressed postmarketing.
The Applicant's claim of categorical exclusion under 21 CFR 25.31(b) and statement of no extraordinary circumstance have been found acceptable.

The commercial tafenoquine succinate drug substance manufacturer is (b) (4) and the drug product manufacturer is (b) (4) (b) (4) Several other facilities have been listed in the NDA as the drug substance testing sites. The drug product site and testing facilities have been found acceptable based on the inspectional history and review of the NDA. In addition, the drug substance site (b) (4) was found acceptable following a recent pre-approval inspection (PAI) on (b) (4) Based on the overall information available, the OPF has found the proposed manufacturing facilities adequate to support the NDA.

There are no outstanding product quality issues. OPQ recommends **approval** of the NDA from product quality perspective.

4.3. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

TQ is an 8-aminoquinoline of the established pharmacologic class 'antimalarial'. The nonclinical safety profile consists of Pharmacology, Pharmacokinetics and Toxicology studies, *in vitro* and *in vivo*, in guinea pig, monkey, rabbit, dog, mouse and rat. Pivotal studies discussed in this review include *in vitro* studies in human embryonic kidney-293 cells transfected with hERG cDNA, dog Purkinje fibers assays, single and repeat dose studies (up to 104 weeks); phototoxicity studies in mouse fibroblasts; fertility and pre- and post-natal developmental studies in rat; embryo-fetal developmental studies in rat and rabbit; genetic toxicology studies and carcinogenicity studies in rat and mouse. TQ is poorly absorbed and has a very long elimination half-life but shows highest levels in the lungs, intestines, spleen and liver. Adverse events of special interest were blood cell toxicity and its sequelae (methemoglobinemia, increased reticulocytes, hemosiderin deposits) and phospholipidosis (consistent with the cationic amphiphilic chemical structure of TQ and evidenced by the accumulation of foamy macrophages in the lungs). Adverse effects were largely reversible after a 13-week reversibility period, except for hemosiderin deposits and evidence of phospholipidosis.

Pharmacokinetics:

The rate of absorption after oral TQ was slow in all species with T_{max} generally ranging from 6 to 168 hours after dosing. Absorption was low, ranging from 15% (rat) to 40% (dog), based on total radioactivity in urine and bile after single doses of ^{14}C tafenoquine. C_{max} and AUC were generally proportional to dose. TQ is very highly protein bound (99.5%) and tissue distribution was widespread with highest concentrations observed in the lung, intestines, spleen, liver, kidneys and heart in descending order. Although only seen in low levels, drug related radioactivity in the brain indicated minimal penetration of the blood brain barrier. There was significant plasma accumulation (up to 10-fold) with repeat dosing. Although the sponsor concluded that drug levels had achieved steady state after 8 weeks of repeat dosing, there was a 3-fold increase in AUC between Week 8 and Week 52 in the rat carcinogenicity study. In one study, the elimination $T_{½}$ (h) was calculated to be 193 hours in monkey and 315 hours in dog. After oral administration, most of the absorbed TQ was excreted via the feces, principally as unchanged TQ. There are however a few metabolites formed via O-demethylation, O-dearylation, oxidation, oxidative deamination and/or glucuronidation. TQ levels were not evaluated in pregnant or nursing animals.

Safety Pharmacology:

TQ was a moderate inhibitor of the tail current in human embryonic kidney 293 cells (transfected with hERG cDNA) with an IC_{50} of 0.5 µg/mL (1.1 µM). TQ had no effect on action potential parameters in the dog isolated Purkinje fiber preparation at concentrations up to 10 µmol. There were no adverse effects on cardiovascular function in conscious beagle dogs receiving single oral doses of TQ up to 16 mg/kg, about 3 times the human dose based on C_{max} comparisons. Neurobehavioral assessments in rats conducted up to 48 hours after a single oral gavage dose of TQ (125, 250 or 500 mg/kg) showed lower numbers of mean horizontal movement count at doses 7 times the C_{max} at the recommended dose, but these effects were sporadic and variable. There were no other biologically significant effects. Behaviors observed included posture, eyelid closure, vocalization, motor movements, ease of removal, reactivity to handling, chromodacryorrhea, lacrimation, salivation, condition of coat, gait, posture, ease of locomotion, arousal, piloerection, exophthalmia, number of pools of urine, number of fecal pellets, unformed feces, fasciculation, tremors, convulsions, response to visual approach, auditory assessments, pinna reflex, proprioception, pain perception, pupil response, air righting, grip strength landing foot splay, body temperature and motor activity. A second study, which evaluated rats after multiple doses (juvenile into adulthood) found no effects on motor activity at doses with C max values at 4 times the recommended dose.

Repeat-Dose Toxicology Studies:

Erythrocytes, lungs, spleen, liver and kidneys were identified as the targets of TQ toxicity in repeat dose toxicity studies in rats, mice and dogs treated for up to 2 years. The findings are consistent with the cationic amphiphilic structure of TQ, with the associated phospholipidosis. In dogs, doses up to 4 mg/kg/day for 52 weeks resulted in blue tongue, increased methemoglobin, increased reticulocyte counts, reduced hematocrit, Heinz bodies, accumulation of foamy macro phages, interstitial inflammation in the lung and pigmentation (liver, kidney, spleen, gallbladder, tonsils and lymph nodes). Pigmentation, hemosiderin deposition, increased spleen weights and bone marrow hyperplasia were considered to be related to the toxic effects in the red blood cells, methemoglobinemia, Heinz bodies and reduced hematocrit. This toxicity to the red blood cells and phospholipidosis, (evidenced by foamy macrophages in the lung), may have contributed to the increased lung, liver and spleen weights observed. No NOAEL was determined because of Heinz bodies observed in low dose dogs. TQ toxicities were dose-related and the high dose in the 13-week dog study (6mg/kg) was higher than the high dose in the 52-week study (4 mg/kg) and both doses resulted in excessive toxicities (reductions in body weight). No new toxicities were observed in the 52-week dog study compared to the 13-week study except for pigmentation in additional tissues (kidney, gall bladder, lymph nodes) in the longer study. Similarly, in the rats, findings were also dose related and no new toxicities were observed in the 6-month study, compared to the 13-week study except that bone marrow hyperplasia was not seen in the 13-week study. A NOAEL could not be determined in the 6-month rat study based on the congestion, pigmentation and erythropoiesis in the spleen, and bone marrow hyperplasia in the low dose, (0.5 mg/kg/day) but the NOAEL was 0.5 mg/kg/day in the 13-week rat study, a dose estimated to be equivalent to the clinical exposure based on AUC data from the rat carcinogenicity study.

The main difference between the rats and the dogs was the presence of blue gum, tongue, sclera in the dogs. In 13-week reversibility studies in rats and dogs, the findings observed at the end of 13 weeks were largely reversible after a 13-week recovery period, except for the hemosiderin deposits and changes in the macrophages.

Genetic Toxicology and Carcinogenicity:

TQ induced an equivocal increase in mutation frequency in L5178Y mouse lymphoma cells but was negative in the Ames assay, the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and the *in vivo* rat micronucleus assay. TQ administration was associated with an increase in renal cell adenoma/carcinoma (combined) in male rats in a 2-year carcinogenicity study, but the 2-year carcinogenicity study in mice was negative. It is unclear whether the finding of renal tumors in male rats in the absence of similar findings in female rats and mice indicates a risk to humans taking TQ for prophylaxis.

Reproductive Toxicology:

TQ dosing had no effect on mating or pregnancy at any dose despite maternal toxicity at the highest dose tested. TQ was administered by oral gavage to male rats 29 days prior to cohabitation, during the entire 17-day cohabitation phase and for 21-23 days after cohabitation (67-69 dosing days in total) and to females for 15 days prior to cohabitation, during their cohabitation phase and from gestation day (GD) 0-6 The NOAEL for fertility and early embryonic development in rats is 15 mg/kg/day, about half the clinical dose based on body surface area comparisons.

Developmental toxicity studies were conducted in rats and rabbits. In rabbits, administration of TQ at 16 mg/kg/day to pregnant females during organogenesis resulted in maternal toxicity (decreased food consumption and body weight) and fetal toxicity (abortion). Abortion was also observed at 7 mg/kg, in the absence of maternal toxicity. Based on these findings, the NOAEL for maternal toxicity was 7 mg/kg (about half the clinical dose based on body surface area comparisons) and the NOAEL for embryofetal development was 2 mg/kg/day (about $1/10^{th}$ the clinical exposure based on body surface area comparisons).

TQ was associated with maternal toxicity (reduced bodyweight gain and food intake) and developmental toxicity (reduced bodyweight gain and reduced locomotor activity) in offspring when pregnant rats were dosed from gestational day 0 through postnatal day 20 at 18 mg/kg/day. The NOAEL in the pre- and postnatal development study was 6 mg/kg, equivalent to about $1/5^{th}$ the clinical dose, based on body surface area comparisons.

Other Toxicology:
TQ was a mild to moderate irritant to rabbit skin, and a severe eye irritant.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

TQ is an 8-aminoquinoline antimalarial. The 8-aminoquinolines (including PQ) are a separate class of drugs from the 4-aminoquinolines (e.g. CQ and amodiaquine) and the 4-methanoquinolines (MQ and lumefantrine). The exact mechanism of the antimalarial activity of TQ is unknown.

Details of the pharmacology studies conducted with TQ can be found in the Nonclinical Microbiology Section 8.1 of this review by Dr. Shukal Bala.

Secondary Pharmacology
No secondary pharmacology studies of TQ were conducted.

Safety Pharmacology
Effect of SB 252263–AX on hERG tail current recorded from stably transfected HEK-293 cells (FD2004/00544)

This study examined the effect of TQ at concentrations of 0.06, 0.19, 0.60 and 1.9 µg/mL on the human ether-a-go-go related gene (hERG) tail current in human embryonic kidney-293 (HEK-293) cells transfected with hERG cDNA. Compounds that inhibit the hERG current may prolong the cardiac action potential and the QT interval in patients. TQ inhibited the hERG current by 18 % at 0.06 µg/mL, 36 % at 0.19 µg/mL, 60 % at 0.60 µg/mL and 97% at 1.9 µg/mL compared to 18 % in vehicle controls (treated with 0.3 % DMSO). After correction for the effect of the vehicle, the IC_{50} for the inhibitory effect of TQ on the hERG potassium current was estimated to be 0.5 µg/mL. This IC_{50} value is approximately 250 times the free C_{max} of 0.002 µg/mL at the clinical exposure based on a mean C_{max} of 0.4 µg/mL and plasma protein binding of 99.5%. following repeated 200 mg doses in humans. Under identical conditions, the positive control (100 nM E-4031) inhibited hERG potassium current by 93.1% (n = 3), confirming the sensitivity of the test system.

Effect on action potential parameters in dog isolated cardiac Purkinje fibers (SB-252263 /RSD-1011LJ)

This study evaluated the effects of TQ on intracellularly recorded action potential parameters (action potential duration at 60% and 90% repolarization [APD_{60} and APD_{90}], maximum rate of rise of the upstroke (MRD), upstroke amplitude (UA) and resting membrane potential (RMP) in the dog isolated Purkinje fiber preparation electrically stimulated at 1 and 0.2 Hz. Fibers were exposed to TQ at 1, 10 and 100 µM. At 1 and 10 µM, TQ had no effect on UARMP, or APD_{60} and APD_{90} at stimulation frequencies of 1 and 0.2 Hz. At 100 µM, TQ exposure resulted in variable decreases in RMP, UA and MRD. The effects observed with 100 µM TQ were not associated

with significant changes in APD_{60} and APD_{90}, but these measurements may be unreliable because of the morphological changes in the action potential resulting from the reductions in RMP, UA and MRD. Purkinje fibers exposed to the positive control substance (dl-sotalol hydrochloride, 30 µM) showed statistically significant increases in action potential durations (APD_{60}, and APD_{90} +39% at 1Hz and APD_{60}, +88% and APD_{90} +73% at 0.2Hz. TQ had no effect at concentrations up to 10 µM (about 4.5 µg/mL or about 2250-fold above the free C_{max} of 0.002 µg/mL (based on C_{max} of 0.4 µg/mL and measured plasma protein binding of 99.5%) following weekly 200 mg doses in humans (Study 051).

Single oral dose cardiovascular study in dogs. (SB-252263/RSD-1013G6)

This study evaluated the effects of single oral doses of TQ on cardiovascular function in conscious beagle dogs (n=4 per sex). Dogs received either placebo (gelatin capsule containing 1% (w/v) aqueous methylcellulose + 0.2% (v/v) Tween 80) or 0.5 mg/kg TQ (females) or 16 mg/kg (males). Observations (recorded for six hours immediately after capsule administration and for another six hours, seven days after the treatment) included clinical signs, systolic, diastolic and mean blood pressures, heart rate, lead II electrocardiogram and plasma concentrations of TQ. TQ had no significant effect on clinical signs, blood pressures, heart rate, ECG amplitudes, or ECG intervals. C_{max} and systemic exposure (**$AUC_{(0\text{-}168h)}$**) at the high dose (16 mg/kg, males) were 1.4 µg/mL and 116 µg.h/mL respectively. This C_{max}, was equivalent to about 3 times the C_{max} observed at the recommended human dose (0.4 µg/mL).

Tafenoquine succinate: Neurobehavioral assessment when administered orally in rats (TM59LS)

This neurofunctional assessment study evaluated the effect of a single oral gavage dose of TQ (125, 250 or 500 mg/kg) in Sprague Dawley rats (6/sex/dose group) and consisted of a functional observation of battery (FOB) performed pretest and at 0.5, 3, 6, 24 and 48 hours postdose and a 60-minute locomotor activity assessment performed following the FOB pretest and at 6, 24 and 48 hours postdose. Clinical observations, viability and, body weights were also recorded. On Days 4 and 8, 3 animals/sex were sacrificed and their brains fixed and subjected to histopathology examination. The 500 mg/kg dose was associated with excessive toxicity: mortality in one high dose male and one high dose female and a 16 to 18 % decrease in body weight compared to controls by day 8. Lower numbers of mean horizontal movement count (-76% to -95%) were observed at ≥ 250 mg/kg at 24 hours postdose but was observed in all doses 48 hours after dosing. There were no drug-related effects in the FOB assessment. Hematoxylin and eosin stained sections of the brain showed no evidence of neurodegeneration or other morphological abnormalities and axon morphology (visualized by Bielschowsky's silver stain) was comparable between control and TQ-treated animals. The C_{max} observed in rats at the 125 mg/kg dose was 2.6 µg/mL, or 7 times the human C_{max} following weekly 200 mg doses of TQ (0.4 µg/mL). Based on these results, the NOAEL for neurological function in female rats is 125 mg/kg and in male rats it is ≤ 125 mg/kg, about 7 times the recommended human dose based on C_{max} comparisons.

Cardiovascular and pulmonary effects of WR-238,605 succinate (12)

TQ, was administered intravenously to dogs (6 females/group, at 0 (vehicle) 19, 42 or 65 mg/kg infused over 20 minutes) after which dogs were observed for an additional 100 minutes. Tidal volume, respiratory rate, minute volume, airway compliance, airway resistance, systolic pressure, diastolic pressure, heart rate, cardiac output, stroke volume, dP/dT, mean pulmonary artery pressure, pulmonary vascular resistance, pulmonary wedge pressure, electrocardiographic effects, blood chemistries and hematocrits were reported. Although minimal effects were reported at the low dose, the high dose was associated slightly reduced systolic and diastolic pressures, decreases in heart rate and left ventricular dP/dT as well as increases in cardiac output, stroke volume, pulmonary arterial and wedge pressures, airway resistance, minute volume and respiratory rate. The intravenous route is not the clinical route administration and there was evidence of poor maintenance of anesthesia during this study, therefore the relevance of these findings is unclear.

SB-252263-AX: Oral juvenile toxicity study in CRL:CD(SD) rat (2015 N 233460)
To assess latent effects of dosing in juvenile rats, TQ was administered orally, every five days to juvenile Crl:CD (SD) rats (10/sex/group at 0 (vehicle),5, 15 or 25 mg/kg/occasion) on postnatal day (PND) 7, 12, 17 and 22 after which the dose levels were then increased to 0 (vehicle) 10, 20 or 50 mg/kg/occasion on PND 27, 32, 37, 42, 47, 52,57 and 62. After at least two weeks without treatment, animals were subjected to a neurobehavioral functional assessment. TQ was not associated with any biologically significant effects on locomotor activity, pre-pulse inhibition of auditory startle response, learning and memory ability (Morris water maze) or brain histopathology. The NOAEL was 25/50 mg/kg, associated with a C_{max} of 1.4 µg/mL, about 4 times the C_{max} following weekly, 200 mg doses in humans (0.4 µg/mL).

SB-252263-AX (TQ): Evaluation of *in vitro* phototoxicity on Balb/c 3T3 fibroblasts using the Neutral Red Uptake assay

Balb/c 3T3 fibroblast cells were treated with a range of concentrations of TQ and positive control chemical (chlorpromazine, CPZ), then tested in the presence and absence of Ultraviolet A light (UV-A). The phototoxic potential of TQ was evaluated using the Neutral Red Uptake assay.

Test material	IC_{50} absence of UVA	IC_{50} presence of UVA	PIF value	MPE value
TQ	7	2	4	0.12
Chlorpromazine	22	1	22	N/A

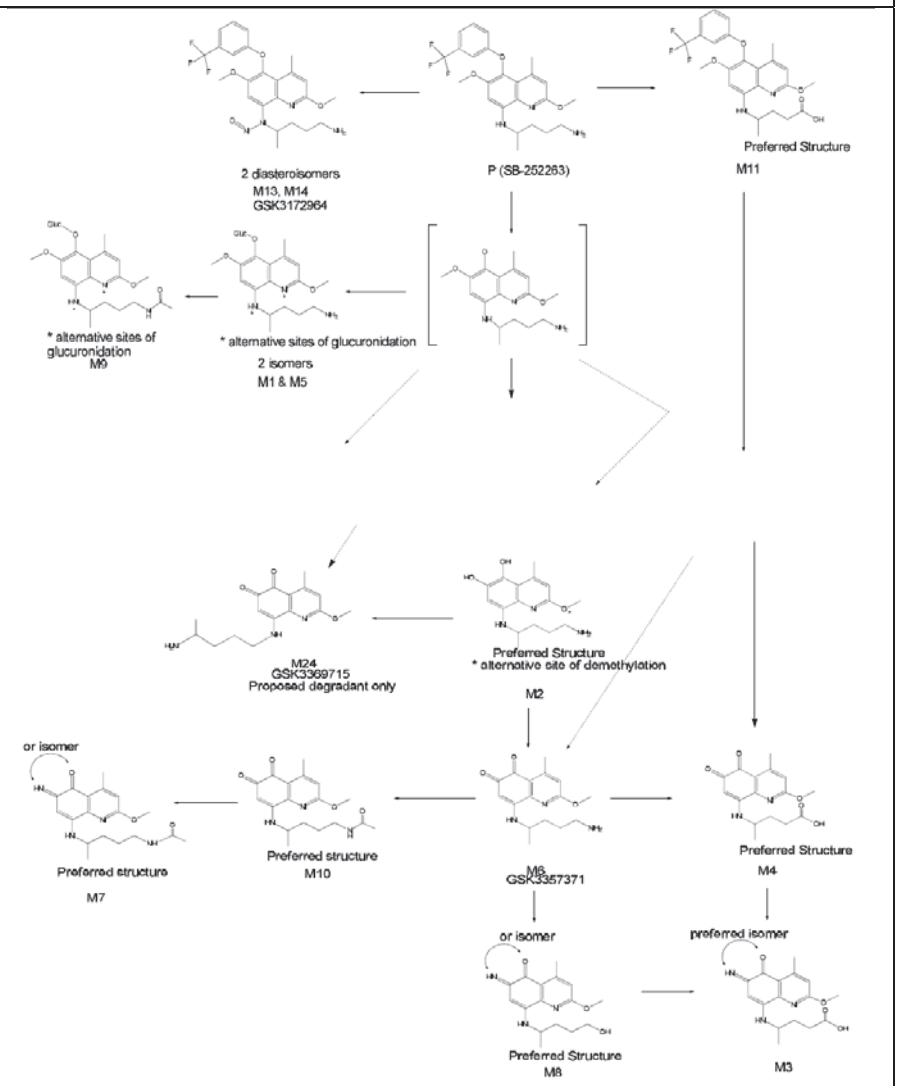
Per the current ICH S10 guideline, these *in vitro* phototoxicity findings are of questionable toxicological relevance since the PIF and MPE values were 4 and 0.12, respectively. Compounds in this category generally do not warrant further photosafety evaluations.

5.4. ADME/PK

Comparisons to human exposures are made by reference to Study 051: 'A Multiple Dose Safety, Tolerance and Pharmacokinetic Study of TQ When Given to Healthy Male and Female Subjects', where repeated 200 mg doses of TQ, resulted in a mean C_{max} of 0.4 µg/mL, an $AUC_{(0\text{-}1\ week)}$: of 56 µg*h/mL in week 10.

Table 4 Major Findings from ADME and PK in Nonclinical Studies

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>An 8-week Oral capsule study in beagle dogs to investigate the pharmacokinetics of SB 252263 and the effect on hepatic levels of cytochrome P4 50 and related parameters. RSD 1011XH</td><td>Absorption of TQ after repeat doses in male dogs
<table>
<tr><td>Dose (mg/kg)</td><td>0.1</td><td>1</td><td>4</td></tr>
<tr><td>T_{max} [h] (Day 1/Day 56)</td><td>8/5</td><td>5/1</td><td>5/7</td></tr>
<tr><td>C_{max} [ng/mL] (Day 1/Day 56)</td><td>9.8/43</td><td>132/698</td><td>494/2178</td></tr>
<tr><td>$AUC_{(0\text{-}24)}$ [µg.h/mL] (Day 1/Day 56)</td><td>0.2/0.8</td><td>2/13</td><td>9/49</td></tr>
</table>
Absorption of TQ after repeat doses in female dogs
<table>
<tr><td>Dose (mg/kg)</td><td>0.1</td><td>1</td><td>4</td></tr>
<tr><td>T_{max} [h] (Day 1/Day 56)</td><td>5/5</td><td>8/5</td><td>5/8</td></tr>
<tr><td>C_{max} [ng/mL] (Day 1/Day 56)</td><td>10/56</td><td>106/812</td><td>467/1504</td></tr>
<tr><td>$AUC_{(0\text{-}24)}$ [µg.h/mL] (Day 1/Day 56)</td><td>0.2/1</td><td>2/17</td><td>8/31</td></tr>
</table></td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Disposition pharmacokinetics and tissue distribution study of WR 238, 605 succinate after oral administration of the drug to rats RSD 1016TF</td><td>Mean tissue concentration of radioactivity in rats 12 hours after dosing µg-(equiv./g)
<table>
<tr><td>Tissue type</td><td>Radioactivity (µg-(equiv./g)</td></tr>
<tr><td>Brain</td><td>2</td></tr>
<tr><td>Eyes</td><td>4</td></tr>
<tr><td>Heart</td><td>22</td></tr>
<tr><td>Kidneys</td><td>41</td></tr>
<tr><td>Liver</td><td>61</td></tr>
<tr><td>Lungs</td><td>154</td></tr>
<tr><td>Muscle</td><td>11</td></tr>
<tr><td>Spleen</td><td>63</td></tr>
<tr><td>Testes</td><td>3</td></tr>
<tr><td>Stomach</td><td>3</td></tr>
<tr><td>Intestine</td><td>81</td></tr>
<tr><td>Whole blood</td><td>2</td></tr>
<tr><td>Plasma</td><td>0.7</td></tr>
<tr><td>Blood cells</td><td>3</td></tr>
</table></td></tr>
<tr><td>A preliminary investigation of the in vitro plasma protein binding of SB 252263 (TQ) in the mouse (RSD-101K 9T)
A preliminary investigation of the in vitro plasma protein binding of</td><td>In vitro plasma protein binding of [^{14} C]SB-252263 (TQ) in the mouse, rat, dog and man
<table>
<tr><td>Species</td><td>% bound</td></tr>
<tr><td>Mouse</td><td>99.8-100</td></tr>
<tr><td>Rat</td><td>99.7-100</td></tr>
<tr><td>Human</td><td>99.5-100</td></tr>
<tr><td>Dog</td><td>99.7-100</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>[14 C]SB-252263 (TQ) in the rat, dog and man (RSD 1016rs)</td><td></td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>Preliminary quantification of the major metabolites of SB-252263 following oral administration of [14 C]SB-252263-AX to the male rat (2 mg free base/kg) and dog (1 mg free base/kg) RSD-101HHT/1</td><td> 
</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Elimination of Drug-Related Material Following a Single Oral Administration of [14C]SB-252263-AX to Male Rats at a Nominal Dose Level of 2 mg free base/kg</td><td>Excretion in intact male rats Following a Single Dose of TQ
<table>
<tr><th>Excretion route</th><th>Recovery of Radioactivity (% Administered Dose)</th></tr>
<tr><td>Urine</td><td>7</td></tr>
<tr><td>Feces</td><td>67</td></tr>
<tr><td>GI tract</td><td>3</td></tr>
<tr><td>Carcass</td><td>13</td></tr>
<tr><td></td><td></td></tr>
</table>
Excretion in bile duct cannulated male rats Following a Single Dose</td></tr>
</table>

Type of Study	Major Findings

Excretion route	Recovery of Radioactivity (% Administered Dose)
Urine	2
Feces	75
Bile	5
GI tract	1
Carcass	8

The Metabolism and Pharmacokinetics of ^{14}C-WR 238605 in Beagle Dogs and in the Rhesus Monkey RSD 1016TH

Pharmacokinetics in whole blood after Single Dose in beagle dog

Dose (mg/kg)	1.7	3.9	8.7	19.5
C_{max} [µg equivalent/mL]	0.5	0.9	5.6	5.5
AUC $_{(0-840)}$ (µg.h/mL)	168	386	2139	2416
T ½ (h)	275	315	175	230

Pharmacokinetics after a Single 1 mg/kg Dose in Monkey

Sample	Plasma	Blood
C_{max} [µg equivalent/mL]	0.15	0.15
AUC $_{(0-840)}$ (µg.h/mL)	32	36
T ½ (h)	165	193

TK data from general toxicology studies

Rat: An 8-week oral gavage study in rats to investigate the pharmacokinetics of SB-252263 and the effect on hepatic levels of cytochrome P450 and related parameters.

- *0, 0.5, 2,9, mg/kg, daily*
- *Samples collected predose, 0.5, 1, 3, 5, 8, and 24 hrs. postdose RSD-1011XG/1*

Accumulation: Up to 10-fold over 56 days

Dose proportionality: C_{max} and AUC $_{(0-24)}$ were approximately dose proportional

Toxicokinetic Parameters for *8-week oral gavage study in rats*

Day	Dose	Sex	C_{max} [ng/mL]	T_{max} (h)	AUC $_{(0-24)}$ (µg.h/mL)
1	0.5	M F	ND ND	ND ND	ND ND
	2	M F	30 29	8 24	0.5 0.5
	9	M F	149 134	8 24	2.9 2.5
56	0.5	M F	41 49	24 1	1 1
	2	M F	188 198	5 24	3.9 4.0
	9	M F	1176 1199	5 5	25 26

Rat: TQ succinate: Neurobehavioral assessment when administered orally in rats

- *125, 250 or 500 mg/kg, single dose*

Mean C_{max} (males and females combined) at the lowest dose was 2.6 µg/mL, about 7 times higher than the clinical dose, based on C_{max} of 0.4 µg/mL following repeated 200 mg doses in humans.

C_{max} and AUC $_{(0-168h)}$ values for TQ in rat plasma after a single oral dose.

	C_{max} (µg /mL)		**AUC $_{(0-168h}$ (µg.h/mL)**	
Dose level (mg/kg)	Males	Females	Males	Females

Type of Study | **Major Findings**

- *Samples collected 1, 3, 5, 8, 24, 48, 72 and 168 hours after dosing.*
- *2017N328989*

125	3.0	2.2	311	292
250	3.8	3.9	489	465
500	5.6	3.80	758	501

Rat: Oral juvenile toxicity study in CRL:CD(SD) rat

- *5, 15 or 25 mg/kg, (PND7 to 26) or 10, 20 or 50 mg/kg PND 27 to 62*
- *Plasma Samples collected 3, 8, 24, 72 or 120 hours after dosing.*
- *2015N233460*

AUC (0-168h), T max and Cmax data in juvenile rats

Dose (mg/kg)		5/10	15/20	25/50
AUC (0-168h) (µg.h/mL)	PND 7 PND 27 PND 62	19 11 19	58 27 37	89 66 100
Cmax (µg /mL)	PND 7 PND 27 PND 62	0.2 0.2 0.4	0.6 0.5 0.6	1.2 1.3 1.4
T max (h)	PND 7 PND 27 PND 62	48 8 3	48 8 3	8 6 8

Mouse: Two-month oral dose toxicokinetic study in mice

- *0.1, 0.3 or 1.0 mg/kg,*

Samples collected Predose, 1, 2, 4, 6, 8, 12 and 24 hours after dosing on Week 8*. RSD-101DSB/1*

Toxicokinetic Parameters for TQ in mice

Dose (mg/kg)		0.1	0.3	1.0
AUC (0-8weeks) (µg.h/mL)	M F	14.5 8.5	42 25	137 91
AUC (0-24h) (µg.h/mL)	M F	0.26 0.15	0.75 0.45	2.4 1.6
Cmax (ng/mL)	M F	0.01 0.01	0.04 0.02	0.12 0.07
Tmax	M F	8 12	12 12	12 6

NAUC (normalized AUC). The systemic exposure from the mouse, study is reported as AUC (0-24 h) at day 56 following repeat dosing (considered to be at the point of steady state). Exposure at the highest dose tested (mean of 114 **µg.h/mL** was about 14 times the clinical exposure (AUC (0-24 h) of 8 **µg.h/mL** after repeated 200 mg doses) based on AUC (0-24 h) comparisons.

TK data from Carcinogenicity studies

Rat: 2 Year Oral oncogenicity Study with WR238605 succinate in Charles River CD rats

- *0, 0.1, 0.5, 1.0 and 2.0 mg/kg, daily*

Accumulation: Up to 3-fold between Week 8 and Week 52 weeks.
Dose proportionality: C max and AUC (0-24) were proportional or supraproportional to dose. The NOAEL was 0.5 mg/kg, which had an AUC (0-24h) of 1.8 µg*h/mL, which was approximately 0.2 times the clinical AUC (0-24h) of 8 µg*h/mL.

Pharmacokinetics parameters at 8 and 52 weeks in rat.

Week	Dose (mg/kg)	Sex	AUC (0-24h) (µg*h/mL)
8	0.1	M F	0.05 0.05

Type of Study	Major Findings					
• Samples collected 1, 2, 4, 8, 12 and 24 hours after dosing on Week 8 and at Week 52 • *RD2007/01198*			0.5	M F	1.0 1.5	
			1.0	M F	2.8 3.6	
			2.0	M F	6.3 7.3	
		52	0.1	M F	0.2 0.2	
			0.5	M F	1.8 1.8	
			1.0	M F	4.2 5.5	
			2.0	M F	8.7 12.7	

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: WR238605 Succinate: One Year Oral Toxicity Study of TQ Succinate in Dogs (Study no. 219)

Key Study Findings

- The mid- and high doses were associated with excessive toxicity as indicated by bodyweights which were more than 10 % lower than controls. Adverse effects at these doses included vomiting, diarrhea, reduced body weight, blue tongue, increased methemoglobin (3.5-13 % HGB), increased reticulocyte count, marginally reduced hematocrit (-13%) increased Heinz bodies (1.3 - 1.9% of RBCs), accumulation of foamy macro phages, interstitial inflammation in the lung, and pigmentation (liver, kidney, spleen, gallbladder, tonsil, and lymph nodes). The accumulation of foamy macro phages in the lungs reflect phospholipidosis, which is a well-known feature of cationic amphiphilic drugs such as TQ. Since Heinz bodies were present at the low dose, no NOAEL could be determined.
- Compared to the 13-week study, the only new findings were pigmentation of the kidneys and macrophages in the gall bladder and lymph nodes.
- Based on pharmacokinetics data from the 8-week dog study, ($AUC_{(0\text{-}24h)}$ of 0.9 µg*h/mL at 0.1 mg/kg), this LOAEL dose was about 0.1 times the clinical exposure ($AUC_{(0\text{-}24h)}$ of 8 µg*h/mL after repeated 200 mg doses in humans).

Conducting laboratory: [redacted] (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.1, 1.0 and 4.0 mg/kg/day
Route of administration:	Oral
Formulation/Vehicle:	Gelatin capsule containing a suspension of TQ in aqueous 1% w/v methylcellulose containing 0.4% v/v Tween 80.
Species/Strain:	Dog / Beagle
Number/Sex/Group:	4
Age:	7-8 months

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	None
Clinical Signs	HD: blue tongue, diarrhea, vomiting.
Body Weights	MD/HD Reduced 10-12 % compared to control
Ophthalmoscopy	Unremarkable
ECG	There were no biologically significant drug-related effects on heart rate, P-wave duration, or PR., QRS, or QT intervals.
Hematology	HD: +1412 % methemoglobin, +180 % reticulocytes, Heinz bodies, -13% hematocrit MD: +775% methemoglobin, Heinz bodies LD: Heinz bodies
Clinical Chemistry	HD: -22 % Albumin/Globulin ratio, +113 % triglycerides.
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	HD: Liver + 43%, lung, + 142 %, Spleen +232 % MD: Lung +27.
Histopathology **Adequate battery:** Yes	MD, HD: intravascular hemolysis, evidenced by tissue pigmentation (possibly hemosiderin) in Kupffer cells, renal cortex epithelium and in macrophages in spleen, gall bladder, tonsil and lymph nodes (mesenteric, mandibular, bronchial and mediastinal). Foamy macrophage accumulation and chronic interstitial inflammation of the lung. Bone marrow hyperplasia. Increased lung, liver and spleen weights

C: control; LD: low dose; MD: mid dose; HD: high dose.

WR238605 Succinate: Six Month Oral Toxicity of TQ in Rats (Study no. 152)

Key Study Findings

- The high dose was associated with excessive toxicity (-26% reduction in body weight)
- Target organ included red blood cells, spleen, bone marrow, kidneys, lungs and liver. Findings were similar to those observed in the 13-week rat study except that bone marrow hyperplasia was not seen in the 13-week study.
- Since congestion, pigmentation and erythropoiesis in the spleen, and bone marrow hyperplasia were observed in the low dose, (0.5 mg/kg/day), a NOAEL could not be determined. The LOAEL dose was similar to the clinical dose (AUC $_{(0\text{-}24h)}$ of 1.7 µg*h/mL) based on data from the two-year carcinogenicity study, (AUC $_{(0\text{-}24h)}$ of 1.8 µg*h/mL at 0.5 mg/kg).

Conducting laboratory: [redacted] (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.5, 2 and 9 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	(aqueous l% methylcellulose/0.2% Tween 80).
Species/Strain:	Rats/CD ® ® Sprague Dawley [redacted] (b) (4)
Number/Sex/Group:	20
Age:	6 weeks
Satellite groups/ unique design:	5 Toxicokinetics animals / dose
Deviation from study protocol:	None with impact on study integrity

Observations and Results: changes from control

Parameters	Major findings
Mortality	HD: One male on Day 137, labored breathing on previous day.
Clinical Signs	HD: rough coat, hunched posture, labored breathing, and piloerection
Body Weights	HD: -26% beginning on day 22
Ophthalmoscopy	Unremarkable
Hematology	HD: +1282 % methemoglobin, -11% RBC count, +85 % reticulocytes, -10 % hemoglobin, + 77% leukocyte count (due primarily to increases in mature neutrophil and lymphocytes), Heinz bodies. MD: +340 % methemoglobin

Parameters	Major findings
Clinical Chemistry	HD: -15 % serum globulin, +62 % total bile acids, -23 % BUN
Gross Pathology	Unremarkable
Organ Weights	HD: +13 % kidney, + 97% Lung. +198 % spleen. + 34 % adrenal MD: +76 % Lung, +22 % spleen, +15 % adrenal
Histopathology **Adequate battery:** Yes	HD: Lung: foamy macrophage accumulation, chronic interstitial inflammation, and hemorrhage, Liver: apoptosis, pigmentation and fatty change, Spleen: congestion, hyperplasia, erythropoiesis, Kidney: pigmentation, Bone marrow: hyperplasia, granulopoiesis, adrenal gland pigmentation and congestion MD: Lung: foamy macrophage accumulation, chronic interstitial inflammation, Spleen: congestion, pigmentation, erythropoiesis, Kidney: pigmentation, Bone marrow: hyperplasia, Adrenal gland pigmentation and congestion. LD: Spleen: congestion, pigmentation, erythropoiesis, Bone marrow: hyperplasia .

C: control; LD: low dose; MD: mid dose; HD: high dose.

General toxicology; additional studies
Repeat-Dose Studies

Thirteen Week Oral Toxicity Study of TQ with a Thirteen Week Recovery Period in rats (Study no. 98)

In rats, oral gavage administration of TQ at 0.5, 6, and 18 mg/kg/day for 13 weeks resulted in reduced the body weight and food consumption and other adverse findings at the mid and high doses. Target organs included the blood (methemoglobinemia, leukocytosis [increased lymphocytes, neutrophils, and/or monocytes]), lungs (alveolar proteinosis (phospholipidosis), inflammation, white lesions, pigmentation, hyperplasia), kidneys (nephrosis, hemosiderin deposits) bone marrow (hemosiderin deposit), spleen (increased spleen weight and hyperplasia). Most of these findings were not detected in rats after a 13-week recovery period, except for hemosiderin pigment (lungs and kidneys) and minimal/mild inflammation of the alveolar macrophages of a few mid- and high-dose animals. The NOAEL was 0.5 mg/kg/day, a dose estimated to be equivalent to the clinical exposure based on AUC data from the rat carcinogenicity study

13 Week Oral Toxicity Study of WR238605 with a 13 Week Recovery Period in Dogs (Study no. 97)

- Oral gavage administration of TQ at 0.1, 2, and 6 mg/kg/day for 13 weeks resulted in dose related adverse events, mostly in the mid and high dose including decreased body weight , methemoglobinemia (with blue gums, blue tongue, blue sclera,), hemolytic anemia (evidenced by reticulocytosis, bone marrow hypercellularity, decrease in bone marrow myeloid/erythroid (M/E) ratio, splenomegaly, extramedullary hematopoiesis, and hemosiderosis in the liver and spleen), leukocytosis, alveolar proteinosis (phospholipidosis), inflammation of the lung, increased kidney weight, hepatotoxicity (liver hypertrophy, subacute inflammation, hemosiderin deposit). These findings were not detected in dogs after a 13-week recovery period, except for minimal/mild inflammation in the lungs and hemosiderin deposit in the liver of a few mid- and high-dose animals. No NOAEL was determined since Hemosiderin deposit and minimal liver inflammation were seen in single low dose animals. Based on pharmacokinetics data from the 8-week dog study, ($AUC_{(0\text{-}24h)}$ of 0.9 µg*h/mL at 0.1 mg/kg), this LOAEL dose was about 0.1 times the clinical dose ($AUC_{(0\text{-}24h)}$ of 8 µg*h/mL).

5.5.2. Genetic Toxicology

In Vitro

[redacted] (b) (4) (TQ): Microbial Mutagenicity study (Study # V23828)

Key Study Findings: Negative
GLP compliance: Yes.
Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2*uvrA*(pKM101) up to 250g/plate; +/- S9
Study is valid: Yes

Study title: Mutation test at the thymidine kinase(TK) locus in mouse lymphoma L5178Y cells.
Study number: G94BE97.702

Key Study Findings: TQ induced and equivocal increase in mutation frequency in the presence of S9 mixture. Not genotoxic in the absence of S9.

GLP compliance: Yes
Test system: L5178Y Mouse Lymphoma Cells*; up to 5 µg/mL; +/-S9]*
Study is valid: Yes

The result was equivocal since the mean mutant frequency was ≥ two-fold of the mean vehicle control mutant frequency (37 $x10^{-6)}$ at only one concentration (2.5 µg/mL) with 10% or greater

total growth (16%). The increase in mean mutant frequency of ≥ two-fold of the mean vehicle control mutant frequency occurring at 5 µg/mL was not considered biologically relevant since these conditions resulted in excessive toxicity as indicated by less than 10% total growth.

Table 5. Mean total growth and mean mutant frequency in mouse lymphoma cells treated with TQ

Test article	TQ Concentration (µg/mL)	Mean total growth 4 hr treatment +S9 (%)	Mean Mutant Frequency ($x10^{-6}$)
DMSO	0	100	37
TQ	0.5	109	36
TQ	0.75	88	65
TQ	1	92	61
TQ	2.5	16	108*
TQ	5	6	132**
Dimethylbenz(a)anthracene	2.5	53	245
Dimethylbenz(a)anthracene	5	7	763

*Mean mutant frequency ≥ two-fold of the mean vehicle control mutant frequency at one concentration with 10% or greater total growth considered an equivocal result

**Mean mutant frequency ≥ two-fold of the mean vehicle control mutant frequency occurring at concentrations with less than 10% total growth considered not biologically relevant.

Study title: CHO/HGPRT Mutation Assay
Study number G94BE97.782
Key Study Findings: Negative
GLP compliance: Yes.
Test system: Chinese Hamster Ovary (CHO-K1-BH4) Cells; up to 10 µg/mL; +/-S9
Study is valid: Yes

In Vivo

Induction of Micronuclei in the Bone Marrow of Treated Rats Study # 802/287
Key Study Findings: Negative

GLP compliance: Yes
Test system: Rat / Charles River SD, bone marrow micronuclei.
Two daily oral gavage doses of the vehicle or TQ (100, 200 or 400 mg/kg/day).
Single dose of cyclophosphamide positive control
Study is valid: Yes

5.5.3. Carcinogenicity

Two-year mouse carcinogenicity study
2 Year Oral Gavage Carcinogenicity Study with TQ in Mice
(Study #G00576)

Key Study Findings: No significant change to survival rate and no dose-dependent carcinogenic effects.
GLP compliance: Yes.
Definitive Doses: Males and females: 0.1, 0.3, 1.0 mg/kg/day.
FDA Dose Concurrence: Yes. Based on data from 13-week mouse study (study #G00576) NOAEL AUC $_{0\text{-}8weeks}$:114 µg.h/mL (mean, both sexes).
Safety Margin: NA

Two-year rat carcinogenicity study
2 Year Oral oncogenicity Study with WR238605 succinate in Charles River CD rats (Study 9200.0 2.04)
Key Study Findings: Two-year oral gavage dosing in rats resulted in reduced survival of both control and TQ-treated animals. A dose-related increase in renal cell adenomas and carcinomas was observed in TQ-treated male rats.

Table 6: Renal adenoma and carcinoma in two-year rat carcinogenicity study

Tumor	TQ dose (mg/kg)					
	0 (Control#1)	0 (Control#2)	0.1 mg/kg	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Renal cell adenoma	0	0	0	0	1	8
Renal cell carcinoma	0	0	0	0	0	1

GLP compliance: Yes.
Definitive Doses: Males and females: 0.1, 0.5, 1.0, 2.0 mg/kg/day.
FDA Dose Concurrence: Yes, Based on data from study #152 (6-month rat study)
NOAEL was 0.5 mg/kg (AUC $_{0\text{-}24h}$ of 1.8 µg.h/mL which was 0.2 times the clinical exposure (AUC $_{0\text{-}24h}$ of 8 µg.h/mL at the recommended clinical dose)

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Oral Fertility and Early Embryonic Development Study of WR238605 Succinate in Rats Study 199
Key Study Findings

- TQ treatment had no effect on mating or pregnancy at any dose despite maternal toxicity at the high dose (mortality, reduced weight gain, minimally reduced numbers of corpora lutea, minimally reduced numbers of implantation sites and minimally reduced number of viable fetuses at the 15 mg/kg dose).

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 1.5, 5.0 and 15 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	1% (w/w) methylcellulose and 0.2% (w/w) Tween®80
Species/Strain:	CD rat from (b) (4)
Number/Sex/Group:	25
Study design:	Daily oral gavage to male rats 29 days prior to cohabitation, during the entire 17-day cohabitation phase and for 21-23 days after cohabitation (67-69 dosing days in total). In females dosing occurred 15 days prior to cohabitation, during their cohabitation phase and from gestation day (GD) 0-6. GD 0 was defined as the day sperm was observed in the vaginal washing. Cesarean sections were performed on GD 20.
Deviation from study protocol affecting interpretation of results:	None

Embryo-Fetal Development

Developmental toxicity (segment II) study of WR 238605 succinate in rats. Study no. 154

Key Study Findings

- Based on a lack of teratogenicity at any dose, the NOAEL for embryofetal development was 30 mg/kg/day. Maternal toxicity (enlarged spleen, reduced body weight and reduced food intake) was observed at 30 mg per kilogram per day (equivalent to the recommended dose based on body surface area comparisons).

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 3, 10, and 30 mg/kg; daily. Positive controls: 1000 mg/kg/day Vitamin A
Route of administration:	Oral gavage
Formulation/Vehicle:	Aqueous 1% methylcellulose/0.2% (w/w) Tween® 80
Species/Strain:	CD rat from (b) (4)
Number/Sex/Group:	25

Study design:	Daily doses were administered by oral gavage from GD 6 to 15. Animals examined on GD 20 after cesarean section
Deviation from study protocol affecting interpretation of results:	No

Table 7. Effect of TQ on reproductive parameters in pregnant rats

Dose (mg/kg)	0 (control)	3	10	30	Vitamin A
Number of females	25	25	25	25	25
Number pregnant	25	25	24	25	25
# animals with rough coat	0	0	0	2	0
# Animals with an enlarged spleen	-	0	1	16	0
Body weight (% control)	294g	100	-4*	-16*	-6
Food consumption (% control)	23g	100	-14*	-44*	-19*
# Viable fetuses	12.1	13.0	12.6	11.5	10.7
Post implantation loss (%)	4	4	5	6	17
External malformations (% litters)	16	0	0	8	100
Skeletal malformations (% litters)	0	5	0	0	85
13th rudimentary ribs	5	0	9	14	0

For controls, group means are shown. For treated groups, percent differences from controls are shown. *Statistical significance ($p \leq 0.05$) was determined using raw data and not percentages.

Incidences of 13th rudimentary ribs were increased at 10 and 30 mg/kg, but this finding was only seen in the presence of maternal toxicity (reduced food consumption and reduced body weight). Published studies have shown that this finding is often (as in this case) associated with maternal stress and maternal toxicity and may be transient.

Developmental toxicity (segment II) study of WR 238605 succinate in rabbits (Study #156)

Key Study Findings

- In high-dose dams, adverse effects included mortality abortion, decreased body weight and decreased food consumption.
- One mid-dose and 3 high-dose dams aborted and were sacrificed early. While the high dose animals experienced severe maternal toxicity (including mortality and reduced the body weight gain), TQ could not be ruled out as the cause of the mid-dose abortion.
- The NOAEL for maternal toxicity was 7 mg/kg (about 0.4 times the recommended human dose based on body surface area comparisons) and for embryofetal toxicity was 2 mg/kg (0.1 times the human dose).
- Since these findings were observed in animals that received at least 12 doses, it is not clear if these findings are likely to be observed in patients receiving the recommended single dose.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 2, 7, and 25 /16mg/kg; daily
Route of administration:	Oral gavage
Formulation/Vehicle:	Aqueous 1% methylcellulose/0.2% (w/w) Tween® 80
Species/Strain:	Rabbit/New Zealand White (b) (4)
Number/Sex/Group:	20
Study design:	Rabbits were dosed daily from GD 6 to 18; Fetuses were delivered by cesarean section on GD 29
Deviation from study protocol affecting interpretation of results:	In the initial study, all dosage formulations were within 10% of their target concentrations prior to and after use except the 25 mg/kg formulation. That post-dose analysis was only within 48% of the target concentration. The high-dose was therefore retested in 20 presumed pregnant rats. The vehicle control was administered to a concurrent of 20 presumed-pregnant rabbits.

Observations and Results

Parameters	Major findings
Mortality	HD (retest): due to mortality and reduced food consumption, the high dose was reduced from 25 to 16 mg/kg/day on GD16.
Clinical Signs	HD(retest): lethargy, labored breathing, abortion, blood in cage pan, reduced food consumption

Table 8. Clinical signs in pregnant TQ treated rabbits

	0	2	7	25/16*	Vitamin A
Females pregnant/on study	18/20	15/20	16/20	19/20	18/20
Scheduled sacrifice	18	15	15	12	18
Animal found dead	0	0	0	2	0
Sacrifice moribund	0	0	0	2	0
Sacrificed/abortion	0	0	1	3	0

Premature delivery	0	0	0	1	0
Total body weight gain (kg)	0.36	0.34	0.33	0.18	0.30
Food consumption (Day 18)	130	130	130	68	

*Retest animals.

In the Initial 25 mg/kg/day group, two animals aborted on GD23 and 1 animal delivered prematurely on GD 29. Food consumption was intermittently reduced (by as much as-17%) compared controls and total body weight gain was reduced by 36% in these animals. In the retest one animal displayed lethargy and was sacrifice moribund on GD10. Another animal had labored breathing and was found dead on GD13. Due to these mortalities and because of reductions in food consumption the dose was lowered to 16 mg/kg/day on GD 15. One animal sacrifice moribund GD 17. Another animal was found dead on GD 22 following clinical observations of blood in cage pan. On GD 23 and 25, 2 animals aborted. Total body weight gain was reduced by 40% compared controls in the retest animals.

Table 9. Pregnancy outcomes in TQ treated rabbits

Dose	Animal ID	Outcome
7	558	Aborted GD 25
(25)*	575	Aborted GD 3
(25)*	580	Aborted GD 25
(25)*	565	Delivered prematurely GD 29
(25)*	570	Broken back, sacrificed moribund GD 12
(25)*	576	Found dead GD 19. Gavage error
Retest 25/16	625	Lethargy, sacrifice moribund GD 10
Retest 25/16	624	Labored breathing, found dead GD 13
Retest 25/16	639	Sacrifice moribund GD 17
Retest 25/16	637	Blood in cage pan, Found dead GD 22
Retest 25/16	622	Aborted GD 23
25/16	630	Aborted GD 25
25/16	631	Suspected abortion GD 24
25/16	627	Blood in cage pan

*Postdose-dose analysis was only within 48% of the target concentration

Table 10. Summary of cesarean section data from rabbits treated with TQ during organogenesis

Dose (mg/kg)	0	2	7	25*	25/16	Vit. A
Females pregnant/on study (n)	18/20	15/20	16/20	16/20	19/20	18/20
Died or euthanized moribund	0	0	0	2	4	0
Abortions/ litters evaluated	0/18	0/15	1/16	3/16	3/19	0/18
Viable fetuses (n)	7.8	8.1	7.4	7.8	9.5	5.7
Post implantation loss (%)	6	2	6	8	4	23
External malformations (% litters)	0	0	0	0		77
Skeletal malformations (% litters)	11	27	33	Not performed	17	88

Dose (mg/kg)	0	2	7	25*	25/16	Vit. A
Visceral malformations (% litters)	0	7	0	0	0	53

Prenatal and Postnatal Development

Oral prenatal and postnatal development study of WR 238605 succinate in rats (Study no.200)

Key Study Findings

- Maternal toxicity (reduced bodyweight gain and food intake) was observed at the high dose. The offspring of these dams showed reduced bodyweight gain and minimal reductions in locomotor activity.
- The NOAEL for F_0 maternal toxicity, F_1 neonatal/developmental toxicity, F1 parental systemic toxicity, and F2 neonatal/early postnatal toxicity was 6 mg/kg/day, about 0.2 times the clinical dose based on body surface area comparisons

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2, 6, and 18 mg/kg; daily

Route of administration: Oral gavage

Formulation/Vehicle: 1% Methylcellulose/0.2% Tween® 80

Species/Strain: Rat, CD © (b) (4)

Number/Sex/Group: 25

Study design: Pregnant females (F_0) were dosed daily from GD 0 through PND 20

F_o data included mortalities, clinical observations, body weight, food consumption, reproductive parameter and gross necropsy observations. Dams euthanized on PND21.
F1 data included mortalities, clinical observations, body weight, preweaning survival, developmental parameters, functional observation battery, motor activity, learning, memory, reproductive parameters and gross necropsy observations.
F_1 offspring (F_2) were sacrificed after examination on the day of parturition

Deviation from study protocol affecting interpretation of results:	None

Observations and Results

Generation	Major Findings
F0 Dams	HD: Maternal toxicity: -31% food consumption, -28 % body weights gain

Dose level (mg/kg)	0	2	6	18
Total weight gain: GD0-PND21(g)	78	69	74	56
Food intake GD15 (g)	23.8	22.9	22.3	16.5

F1 Generation	In pups born to high-dose dams, total body weight gains between PND 4 and PND 21 were reduced (-17 %) in both sexes and total time spent in the rearing posture was slightly reduced (-14%) in females at the mid and high dose 6 and 18 mg/kg.

Table 11. Body weights and rearing posture in pups born to TQ treated rats

Dose level (mg/kg)	**0**	**2**	**6**	**18**
Total weight gain: Males (g)	49	48	47	41
Total weight gain: females (g)	47	45	45	39
Total time rearing (secs)	389	385	340	332

F2 Generation	Unremarkable

5.5.5. Other Toxicology Studies

Impurity Qualification

There are no mutagenic impurities in the proposed TQ Drug Substance Specification. The 4 specified non-mutagenic impurities (b) (4) in the proposed TQ drug substance specification will be maintained at levels (b) (4) the ICH Q3A(R2) quantification limit (<0.15% (b) (4). All other unspecified impurities will be maintained (b) (4) levels <0.10% (b) (4) in accordance with ICH Q3A.

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology (Division of Clinical Pharmacology IV and Division of Pharmacometrics) reviewed the information contained in NDA 210607. The clinical pharmacology information submitted in the NDA supports the approval of ARAKODA (TQ) 100 mg tablets for prevention of malaria in adults for a period of up to 6 months of treatment.

Table 12. Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The evidence of efficacy/safety of TQ for prevention of malaria was supported by clinical studies that were reviewed by the statistical and clinical reviewers. See Sections 7 and 9, respectively.
General dosing instructions	The recommended dosing regimen is a loading regimen of 200-mg (two 100-mg tablets) once daily (QD) for 3 days prior to entering the malarious area, followed by a maintenance regimen of 200 mg once weekly while in the malarious area, and a one-time dose of 200 mg in the week following exit from the malarious area. The total duration of treatment with TQ is up to 6 months. TQ tablets should be taken with food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The pharmacokinetics (PK) of TQ have not been studied in patients with renal or hepatic impairment. If TQ is administered to such patients, monitoring for adverse reactions associated with TQ is needed.
Labeling	The review team has specific content and formatting change recommendations that were communicated to the applicant during labeling discussions.
Bridge between the to-be-marketed and clinical trial formulations	Study TQ-2016-01 serves as a PK bridging study comparing the exposure under fed conditions between the TQ capsule formulation that was used in majority of the clinical trials and the to-be-marketed (TBM) 100 mg tablet formulation of TQ. When administered with food, the PK parameters between the to-be-marketed 2 x 100 mg TQ tablets and TQ 200 mg capsules were comparable. Thus, an adequate PK bridge was established between the TBM tablets and the capsules.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 13. Summary of the Clinical Pharmacokinetics of TQ

Absorption	Following a single 200 mg dose of TQ (two 100-mg TQ tablets) in healthy subjects (N=65) under fed condition in Study TQ-2016-01; mean C_{max} was 147 ng/mL (CV:20.7%), mean AUC_{∞} was 70.1 hr*µg/mL (CV:24.6%), and median T_{max} was 14 hours (range: 6.05 – 72 hours) post-dose.
Distribution	Plasma protein binding >99.5% Apparent volume of distribution is 2470 [Inter-Individual Variability (IIV): 24.1 %] L
Elimination	Mean terminal half-life is approximately 16.5 days in healthy subjects Oral clearance is approximately 4.17 (IIV: 23.6 %) L/h
	Metabolism Negligible metabolism by hepatic CYP450 enzymes No major systemic metabolites observed in blood or plasma following oral administration.
	Excretion The excretion pathway(s) of TQ in humans is unknown. A human ADME study was not performed for TQ. Based on the information submitted in the NDA, it appears that TQ is metabolized to a minimal extent via the liver and majority of an orally administered dose of TQ appears to be eliminated via non-renal pathways.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dose regimen is a loading dose of 200-mg (2 x 100-mg tablets) QD for 3 days prior to entering the malarious area, followed by a maintenance regimen of 200 mg once weekly while in the malarious area, and a one time dose of 200 mg in the week following exit from the malarious area. The total duration of treatment with TQ is up to 6 months. TQ tablets should be taken with food.

The Applicant's proposed dosing regimen is supported by clinical efficacy/safety studies of TQ for prevention of malaria that were reviewed by the statistical and clinical reviewers. See Sections 7 and 9, respectively.

Therapeutic Individualization

A human ADME study was not performed for TQ. The Applicant's rationale for not performing a human ADME study is that TQ is metabolized to a minimal extent via the liver and majority of an orally administered dose of TQ appears to be eliminated via non-renal pathways. (b) (4) Applicant (D) (4)

- *Comment: The Clinical Pharmacology team* (b) (4) *since no PK studies were conducted in patients with hepatic and/or renal impairment, no dose adjustment recommendations can be made. This is reflected in the TQ labeling in Section 8.*

Outstanding Issues

None.

Comprehensive Clinical Pharmacology Review

6.2.3. General Pharmacology and Pharmacokinetic Characteristics

Table 14. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	TQ is an 8-aminoquinoline antimalarial drug [see Section 8.1.1, Microbiology Review for details on mechanism of action of TQ].
Active Moieties	Tafenoquine
QT Prolongation	Based on the review by the QT-IRT team of ECG data collected primarily from PK Study 014 in healthy volunteers, the largest upper bound of the 2-sided 90% CI for the change in QTc interval from baseline was < 20 ms for a TQ dose of 400 mg (i.e., 2 times higher than the recommended dose), and the mean change in QTc was <10 ms. Additionally, no significant relationship between TQ plasma concentrations and changes in the QTc interval was observed. Thus, no large mean increases in the QTc interval (i.e., >20 ms) are anticipated for TQ at the recommended dose of 200 mg and up to a dose of 400 mg.
General Information	
Drug exposure following the therapeutic dosing regimen	PK parameters are not reported from one study following the entire therapeutic dosing regimen. The following information is provided from two studies. Following the 200 mg "loading dose" QD for 3 consecutive days (Days 1-3), followed by another 200-mg dose once of TQ, 7 days later (Day 10) in healthy non-immune adults, the individual subject plasma concentration of TQ for up to Day 20 appear to be approximately 200 ng/mL or greater, following which they begin to

Pharmacology	
	slowly decline over time. During Days 29 through 34, approximately 2 weeks following the last dose of TQ tablet, the TQ concentrations were still approximately 100 ng/mL or greater in majority of the study participants. In this study, the participants received the 200-mg dose of TQ, as 2 x 100 mg of the TBM tablet formulation. TQ 200 mg or placebo was administered orally to participants after their normal breakfast. Food, water and other beverages were not permitted for 60 minutes prior to dosing. A fasting state was maintained by participants for an additional 60 minutes. Following single and multiple dose administration of 200 mg of TQ capsules under fasted conditions in healthy male and female adults, steady state trough concentrations of TQ were reached with the 200 mg once weekly dose regimen (proposed clinical regimen) by approximately Week 5 (35 days). Following 10 weeks of dosing with 200 mg once weekly, the mean plasma accumulation ratio of TQ was approximately 4.4. This extent of plasma accumulation is to be expected, given the mean $T_{1/2}$ of approximately 16 days with the 200 mg once weekly dose regimen.
Healthy vs. Patients	This product is intended for use in adults.
Dose Proportionality	Following oral administration, TQ AUC increased proportionally to dose over the dose range of 100 mg to 400 mg.
Food Effect	A food effect study was not performed with the TBM tablet formulation. Since, in majority of the clinical trials including the pivotal and supporting efficacy and safety trials, TQ capsules were administered with food, the Applicant performed a PK bridging study that demonstrated comparable PK exposure (AUC and C_{max}) between to be to-be-marketed TQ tablet and TQ capsule formulations under fed conditions.
Volume of Distribution	Apparent volume of distribution is 2470 L (IIV: 24.1 %)
Plasma Protein Binding	>99.5%
Substrate transporter systems [*in vitro*]	TQ is unlikely to be a substrate of OATP1B1 and OATP1B3. It is inconclusive as to whether TQ is a substrate of P-gp and BCRP mediated transport.
Elimination	
Half-life	16.5 days (range: 10.83 days – 27.25 days)
Metabolism	
Fraction metabolized (% dose)	Unchanged TQ was the only significant component detected in human plasma.

Pharmacology	
Primary metabolic pathway(s) [*in vitro*]	Overall, TQ metabolism by hepatic CYP450 enzymes is negligible in vitro.
Excretion	
Primary excretion pathways (% dose)	The primary excretion pathways of TQ in humans are unknown.
In vitro interaction liability (Drug as a perpetrator)	
Inhibition/Induction of metabolism	TQ demonstrated *in vitro* inhibition of the following cytochrome P450 isoenzymes: 1A2, 2D6, 2C8, 2C9 and 3A4. In vivo studies in healthy subjects indicated that oral administration of 400 mg TQ did not have significant effects on the PK of the substrates of CYP1A2 (caffeine), CYP2D6 (desipramine), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam).
Inhibition/Induction of transporter systems	In vitro, TQ inhibited metformin transport via human organic cation transporter-2 (OCT2), multidrug and toxin extrusion-1 (MATE1) and MATE2-K transporters. Risk assessments based on unbound C_{max} of TQ following 400 mg QD for 3 days (2 to 6 times the recommended maintenance and loading dose regimens) compared with the corrected (i.e., after accounting for nonspecific binding of TQ to the assay plate) in vitro IC_{50} values indicated that an in vivo DDI potential with OCT2 and MATE substrates may exist. TQ is not likely to be an inhibitor of human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 mediated transport.

6.2.4. Clinical Pharmacology Questions

1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The evidence of effectiveness was supported by clinical studies that were reviewed by the statistical and clinical reviewers in sections 7 and 9, respectively. One of the smaller studies (Study TQ-2016-02) included PK/pharmacodynamic (PD) assessments and is described below.

Study TQ-2016-02: Randomized, double-blinded, placebo-controlled study undertaken in healthy men and women with no previous exposure to malaria infection.

The induced blood stage malaria (IBSM) challenge model was used to assess the schizonticidal activity of TQ against challenge with blood stage *P. falciparum*. A total of 16 healthy volunteers were randomized to receive TQ or placebo in a 6:2 ratio for enough time to reach steady state compared to that achieved with the clinical dosing regimen, after which blood stage parasites

were administered and the volunteers were monitored for parasitemia by quantitative polymerase chain reaction (qPCR). Participants received either TQ 200 mg, as 2 x 100 mg of the to-be-marketed tablet formulation, or placebo, as 2 matching tablets. This occurred QD for three consecutive days (Days 1-3, the "loading dose") and was followed 7 days later by another 200-mg dose of TQ or placebo, given under the same conditions (on Day 10). Food, water and other beverages were not permitted for 60 minutes prior to and following the dosing. Participants returned to the site for daily clinical evaluation and blood sampling for TQ PK and qPCR assessment of parasitemia, which was the PD outcome of this study. Assessment of parasitemia occurred from Day 17 until the time that the qPCR demonstrated positivity for malaria, or, if qPCR remained negative, until approximately Day 32. The study included PK and PD assessments.

The individual plasma concentrations of TQ across time are presented in Figure 1.

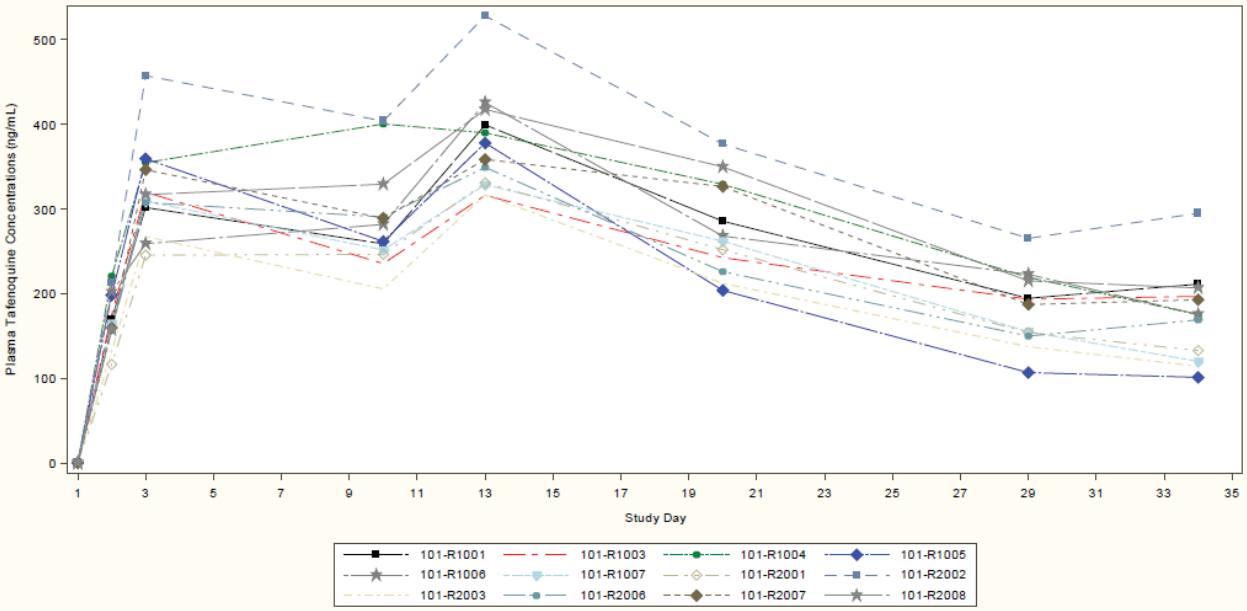


Figure 1. Linear Plot of Individual TQ Plasma Concentrations over Time following Oral Administration of 200 mg of TQ Tablets QD on Days 1 through 3 and at Day 10

Note: Below limit of quantification (BLOQ) is replaced by 0

Source: Applicant's clinical study report, Page 2388, Listing 16.2.5.5

The individual plasma concentration of TQ for up to Day 20 appear to be approximately 200 ng/mL or greater, following which they begin to slowly decline over time. During Days 29 through 34, approximately 2 weeks following the last dose of TQ tablet, the TQ concentrations were still approximately 100 ng/mL or greater in majority of the study participants.
The semi-log plot of mean parasite count over time for both TQ and placebo can be seen in Figure 2.

In contrast to the placebo administration, the oral administration of 200 mg TQ tablet; QD on Days 1 through 3 and at Day 10, appeared to prevent symptomatic blood-stage infection following *P. falciparum* exposure in these malaria- naïve healthy volunteers. Post blood stage *P.*

falciparum challenge (BSPC) inoculum, *P. falciparum* parasites were detected by qPCR in placebo participants only, as evident in Figure 2.

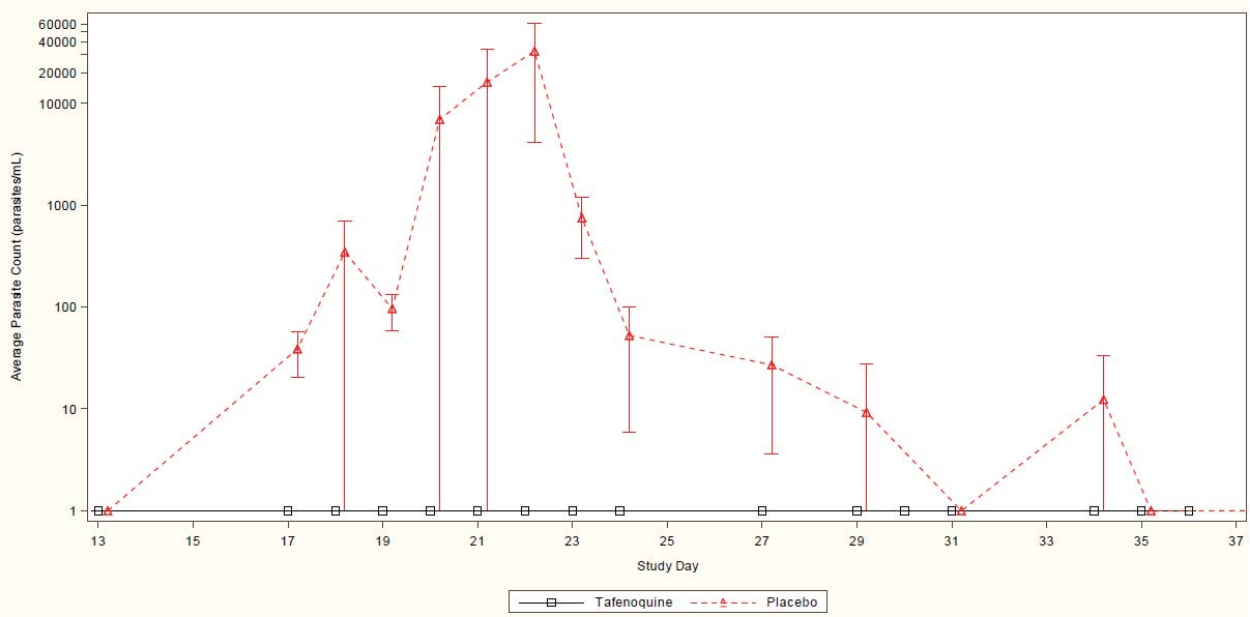


Figure 2. Semi-log Plot of Mean (SD) Parasite Count (Estimated Parasites/mL) over Time following Oral Administration of 200 mg TQ Tablets or Placebo QD on Days 1 through 3 and at Day 10

Note: BLOQ is replaced by 0

Source: Applicant's clinical study report, Page 319, Listing 16.2.6.1

No TQ participant met the criteria for early initiation of Riamet® rescue therapy; all participants received antimalarial treatment at the end of study (EOS), as mandated in the clinical protocol.

Reviewer Conclusion: *Based on the results of this study, the reviewer concurs with the Applicant regarding the adequacy of the dosing regimen employed in this study against P. falciparum blood stage parasites in healthy, non-immune adults (i.e., 200 mg "loading dose" QD for 3 consecutive days (Days 1-3), and followed by another 200-mg dose of TQ 7 days later (Day 10)). However, it is unknown if the Applicant's proposed minimum target trough TQ plasma concentration of 80 ng/mL from this study is appropriate to generalize to the population at-large due to the limited number of participants in this study. As only one dose was studied and the response rate was high, the distribution or range of steady-state trough drug concentrations and their relationship to efficacy are not evaluable from this study. The reviewer defers to the Statistical Reviewer assessment (Section 7) regarding the adequacy of Applicant's Efficacy assessment from Study TQ-2016-02.*

2. **Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

This product is intended for use in adults. Yes, the proposed dosing regimen appears adequate from a Clinical Pharmacology perspective. The proposed dosing regimen is supported by Studies TQ-2016-02 and 006 in addition to the efficacy and safety studies discussed in Section 7 and 9 of the review. See response to Question 1 for details on Study TQ-2016-02. Study 006 will be the focus of discussion here.

Study 006: Dose-ranging evaluation to investigate the three-day loading dose regimen of TQ in terms of efficacy, safety and tolerability in a population of 12-20-year-old residents of a malaria endemic region of Gabon.

This was a placebo-controlled double-blind, parallel group, and single-center study. Subjects who met the study entry criteria were treated with halofantrine 250 mg QD for 3 days with food to clear any existing parasitemia. Four days after the clearance period, a total of 415 subjects free from malaria parasitemia were randomized to receive either TQ capsules 25 mg, 50 mg, 100 mg or 200 mg or placebo QD for 3 days. The study treatment was administered following ingestion of a meal by the subjects. Subjects remaining free from plasmodia species (spp) after study treatment attended 10 weekly follow-up assessments. Blood samples for determination of plasma TQ concentrations were collected 7 and 14 days after the first dose of double blind medication.

A total of 327 (78.8 %) out of 415 subjects that were randomized to receive the study medication completed the study. A summary of reasons for withdrawal from the study are shown in Table 15.

Table 15. Reason for Study Conclusion: Intention-To-Treat Population (Number (%) of Subjects)

Study Conclusion Reason	Treatment Group				
	Tafen 25 mg N=80	Tafen 50 mg N=86	Tafen 100 mg N=82	Tafen 200 mg N=84	Placebo N=83
Completed Study*	61 (76.3%)	73 (84.9%)	61 (74.4%)	74 (88.1%)	58 (69.9%)
Reason for Withdrawal					
Adverse experience**	2 (2.5%)	1 (1.2%)	2 (2.4%)	2 (2.4%)	3 (3.6%)
Loss of prophylactic efficacy†	11 (13.8%)	0	1 (1.2%)	0	12 (14.5%)
Protocol deviation††	5 (6.3%)	9 (10.5%)	16 (19.5%)	8 (9.5%)	10 (12.0%)
Lost to follow-up	1 (1.3%)	3 (3.5%)	2 (2.4%)	0	0
Total Withdrawn	19 (23.8%)	13 (15.1%)	21 (25.6%)	10 (11.9%)	25 (30.1%)

Data source: Table 13.3.2 in Section 11; Listing 13.3 in Appendix B

* Subjects were considered to have completed the study if they satisfied all study entry criteria, completed the three day prophylactic course and attended all the follow-up visits.

** Includes subjects (b) (6) who were withdrawn due to an adverse experience on the Conclusion page but not the Adverse Events page of the CRF. All withdrawn due to unintended pregnancy/abortion.

† Signs and symptoms of malaria appeared after first follow-up (Day 7)

†† Including non-compliance.

Source: Applicant's Clinical Study Report, Page 55, Table 7, Tafen: Tafenoquine

It is worth noting in Table 15 that around 14 % of subjects that received 25 mg of TQ or placebo had to be withdrawn from the study due to the loss of prophylactic efficacy. There was no

withdrawal associated with loss of prophylactic efficacy in the 200 mg and 50 mg dose cohort and only one subject (~ 1 %) had to be withdrawn due to the loss of prophylactic efficacy in the 100-mg dose cohort.

Plasma concentration data were obtained in nearly all (322/332) TQ treated subjects. Mean plasma concentrations increased in an approximately dose proportional manner (Figure 3) with increasing dose from 25 to 200 mg on Days 14 and 28 (i.e., 7 and 14-days post first dose randomized medication).

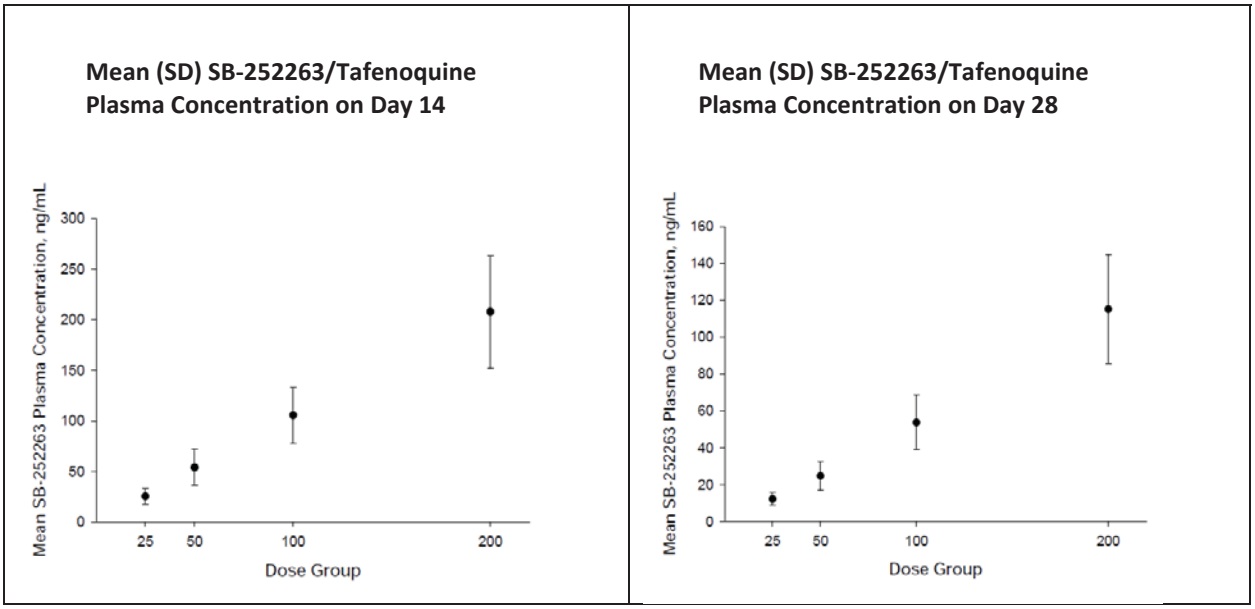


Figure 3. Mean TQ Plasma Concentrations on Day 14 and 28 following Administration of 25 mg, 50 mg, 100 mg and 200 mg TQ Capsules
Source: Applicant's Clinical Study Report, Page 109 and 111

Based on the results of this study, the Applicant concludes that TQ provided prolonged protection against malaria infection using a three-day loading dose regimen in this 12-20-year-old study population. The Applicant further adds that at 10 weeks, a 200-mg three-day dosing regimen provided 100% protective efficacy, with lower levels of protective efficacy at lower doses of TQ.

Reviewer Conclusion: *Based on the review of the PK aspects in this study, the reviewer concludes that the observed $T_{1/2}$ of around 2-3 weeks for the TQ 200 mg capsule in this 12-20-year-old study population were consistent with that reported for TQ 200 mg capsule in other adult volunteer study subjects. The reviewer also agrees with the Applicant's conclusion regarding dose proportionality at TQ doses of 25 to 200 mg.*

The reviewer defers to the Clinical Reviewer assessment regarding the adequacy of Applicant's safety, and tolerability assessment from Study 006. Please refer to the relevant Clinical section of this review for more details regarding this study.

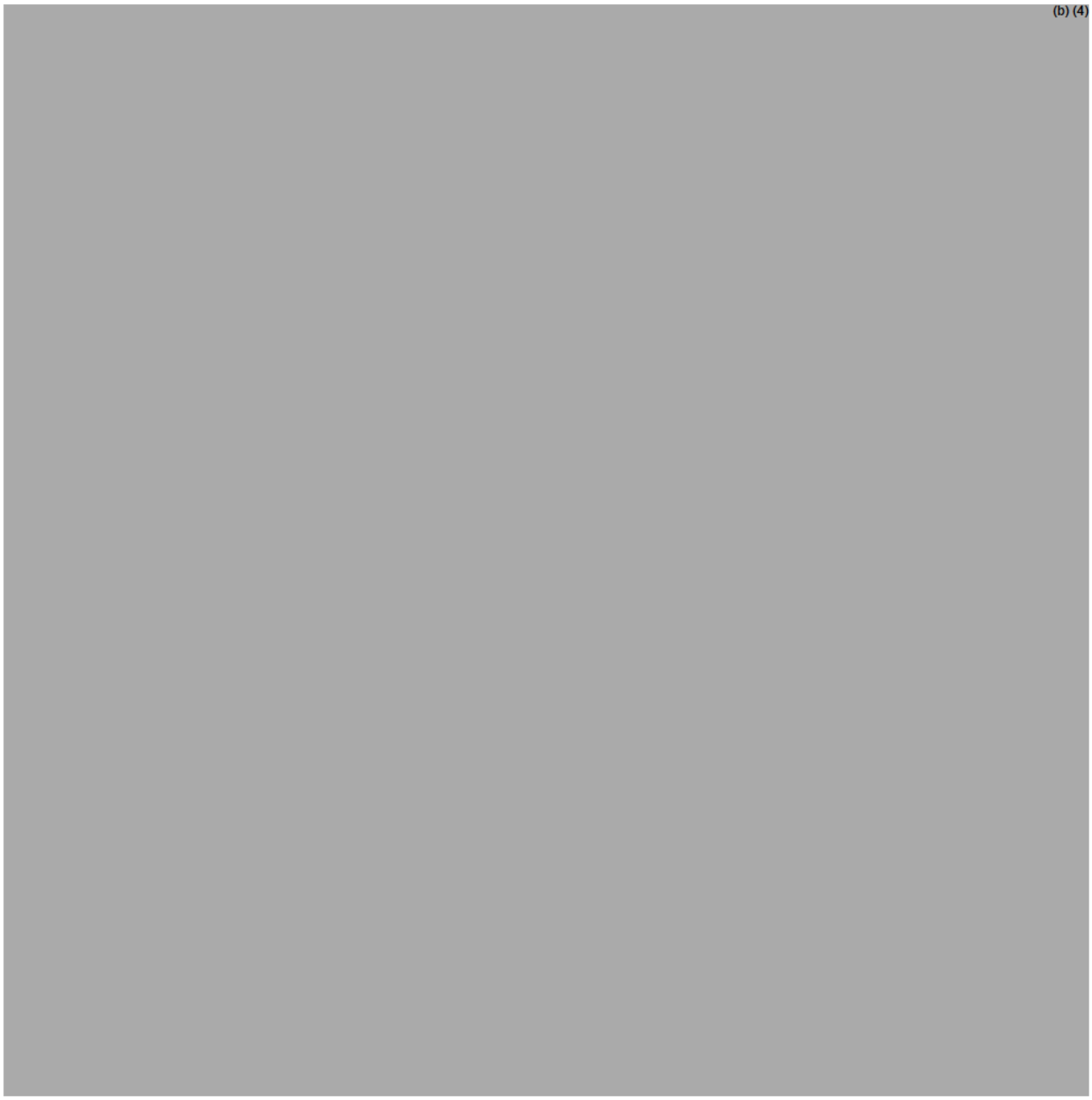
3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Reviewer Conclusion: *The PK of TQ was not studied in patients with renal and/or hepatic impairment. Upon the review of in vitro studies submitted to the NDA, the Clinical Pharmacology review team concluded that TQ undergoes minimal hepatic metabolism based on data from in vitro hepatocyte and microsomal studies. Drug-related material identified in human urine is consistent with the metabolites identified in rat and dog studies. Furthermore, TQ has been administered at even higher doses and at comparable durations to the clinical dosing regimen during the clinical development program. The safety data from these and other such ongoing studies may shed light regarding any safety concerns due to the TQ accumulation in the event of a prolonged drug elimination that may occur in patients with hepatic and/or renal impairment. The Clinical Pharmacology review team does not agree* (b) (4) *As no PK studies were conducted in either hepatically and/or renally impaired patients, no dose adjustment recommendations can be made. This is reflected in Section 8 of labeling*

Hepatic and Renal Impairment:

The Applicant's assessment (b) (4) The reviewer would like to point out the following statement from the Applicant from Section 2.7.2 of the NDA: "Note that no quantitation of TQ distribution throughout the body or of renal vs fecal excretion was performed".

(b) (4)



Other Intrinsic factors:
Based on the population PK analysis, there is no need for dose adjustment based on the intrinsic patient factors such as body weight, gender, age, and race.

4. **Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

TQ tablets should be taken with food. Although a dedicated food effect study was not conducted with the TBM TQ tablet, it is important to note that in majority of the pivotal and supporting efficacy trials, TQ was administered as a capsule formulation under fed conditions.

In addition, Study TQ-2016-01 serves as a PK bridging study comparing the exposure under fed conditions between the TQ capsule formulation and the to-be-marketed tablet formulation. When administered with food, the PK parameters between the to-be-marketed 2 x 100 mg TQ tablets and TQ 200 mg capsules were comparable. Thus, an adequate PK bridge between the TBM tablet and capsule formulations under fed conditions was established. The labeling will be revised to indicate that TQ tablets are to be administered with food. See the ISR for Study TQ-2016-01 for details regarding this PK bridging study.

Summary of Drug-Drug Interactions (DDIs) Studies

The DDI potential of TQ was characterized in in clinical studies with substrates of major cytochrome P450 enzymes (CYP2D6, CYP3A4, CYP2C9, and CYP1A2). Based on the results from these studies, the Clinical Pharmacology review team concludes that clinically significant DDIs of TQ with substrates of these CYP enzymes would be unlikely. An in vitro study was conducted to assess the inhibitory effect of TQ on human transporters OCT2, MATE1 and MATE2-K. At the clinical dosing regimen of TQ, TQ may inhibit OCT2, MATE1, and MATE2-K. In addition, in vitro studies were done to study the potential of TQ as an Inhibitor of human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 mediated transport and as a substrate of BCRP, P-gp, OATP1B1 and OATP1B3. The results indicated that TQ is not likely to be an inhibitor of human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 mediated transport. TQ is not likely to be a substrate of OATP1B1 and OATP1B3. It is unknown if TQ is a substrate of BCRP, P-gp, OAT1, OAT3, OCT2, and MATE mediated transport.

Effect of TQ on the PK of Other Agents

Substrates of CYP enzymes: In vitro, TQ inhibited CYP1A2, CYP2D6, CYP2C8, CYP2C9 and CYP3A4 with Ki values ranging from 2 to 10 µM, with no evidence of metabolism dependent inhibition. Subsequent clinical DDI studies demonstrated no clinically significant effects of TQ on the PK of desipramine (CYP2D6 substrate) (Study SB252263/015), caffeine (CYP1A2 substrate), midazolam (CYP3A4 substrate), and flurbiprofen (CYP2C9 substrate) (Study SB252263/040).

TQ as an Inhibitor of human transporters OCT2, MATE1 and MATE2-K: An in vitro study was conducted to assess the inhibitory effect of TQ on the transport of [^{14}C]-metformin via human OCT2, MATE1 and MATE2-K transporters (Study 2014N212406/XS-0517). The calculated IC_{50} values and estimated $C_{max,u}/IC_{50}$ ratios are summarized in Table 16 .

Table 16. Summary of IC_{50} values and estimated $C_{max,u}/IC_{50}$ ratios for human OCT2, MATE1 and MATE2-K transporters

Transporter isoforms	OCT2	MATE1	MATE2-K
Mean IC_{50} (µM)	0.282	1.99	0.632
Mean IC_{50} -C (µM)[a]	0.0419	0.435	0.170
$C_{max,u}/IC_{50}$ratios	0.037	0.0053	0.016
$C_{max,u}/IC_{50}$-C ratios[b]	0.25	0.024	0.062

[a]: Mean IC_{50}-C: Mean IC_{50} values corrected by the non-specific binding of TQ in the tested system; values were reported by the Applicant from Study 2014N212406/XS-0517

[b]: The Applicant reported a 99.5% protein binding of TQ; the unbound fraction of TQ in plasma ($f_{u,p}$) was set to 1% ($f_{u,p}$ = 0.01) if protein binding was experimentally determined to be < 1% per the in vitro DDI draft guidance; to calculate C_{max} in µM, mean C_{max} ≈ 496 ng/mL (Study 15, where 400 mg TQ is administered once daily for 3 days to attain a pseudo steady state), MW=463.5 g/mol as free base, resulting in an unbound C_{max} value of 0.0107 µM

As shown in Table 16, when the uncorrected values of IC_{50} are used, the $C_{max,u}/IC_{50}$ ratios are lower than the guidance recommended cutoff values (0.1 for OCT2 and 0.02 for MATEs), suggesting that TQ is unlikely to inhibit these transporters at the clinical dosing regimen. However, after correcting for the nonspecific binding of TQ to the assay plate, the corrected $C_{max,u}/IC_{50}$-C ratios using the adjusted lower IC_{50} values are higher than the guidance recommended cutoff values. Thus, at the clinical dosing regimen, TQ may be an inhibitor of OCT2, MATE1, and MATE2-K.

TQ as an Inhibitor of human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 mediated transport: In Study OPT-2017-089, there was <50% inhibition observed at any concentration of TQ (0 – 25 µM) for OAT1, OAT3, OATP1B1, and OATP1B3 and therefore, TQ IC_{50} values are > 25 µM for OAT1, OAT3, OATP1B1, and OATP1B3 -mediated transport. Thus, TQ is unlikely to inhibit any of these transporters at the anticipated concentrations in systemic circulation following the clinical dosing regimen.

TQ IC_{50} for BCRP and P-gp are reported to be 15.0 µM and 5.61 µM respectively. For BCRP and P-gp, if the $I_{gut}/IC_{50} \geq 10$, then TQ has the potential to inhibit these transporters as per the FDA guidance: In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies, October 2017. In case of BCRP, for a dose of 200 mg of TQ (i.e., based on the clinical dosing regimen), the I_{gut}/IC_{50} = 0.11, which is less than 10, thus TQ is unlikely to inhibit BCRP. With regards to TQ inhibitory potential for P-gp, for a dose of 200 mg of TQ, the I_{gut}/IC_{50} = 0.3, which is less than 10, so TQ is unlikely to inhibit P-gp.

Effect of Other Agents on TQ PK

TQ as a Substrate of human OATP1B1, OATP1B3, P-gp, and BCRP transporter: At 0.1 µM, 0.5 µM, and 5 µM of TQ, less than 2-fold difference of uptake was observed in transporter-transfected cells compared to control cells for OATP1B1 and OATP1B3. Therefore, TQ does not appear to be a clinically relevant substrate as defined by regulatory guidance documents for human OATP1B1 or OATP1B3 under these study conditions. Based on the information provided by the Applicant, it was not possible to determine if TQ is a substrate of P-gp and/or BCRP.

It is unknown if TQ is a substrate of OAT1, OAT3, OCT2, and MATE. Since the Applicant determined from their non-clinical studies that TQ is eliminated mostly via non-renal pathways, this is acceptable to the Clinical Pharmacology review team.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Trials

This NDA contains 5 randomized, double-blinded, controlled, efficacy studies with the proposed dose (200 mg) and regimen (3 days followed by weekly), as shown in the following table. 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), and one placebo-controlled *P. falciparum* challenge study in non-immune subjects (Study TQ-2016-02).

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 central site conducted a blinded re-read of the slides. This study will be briefly reviewed. It was found to be not a concern for the efficacy of TQ and is included for completeness.

The NDA also contains Study 058, a treatment trial, which 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 does not inform the efficacy of TQ for prophylaxis and will not be reviewed as part of the efficacy section of this review.

The proposed indication is for the prevention of malaria in adults for a period of up to 6 months of treatment. The proposed prophylaxis dosage contains:

- A loading regimen of 200 mg once daily for 3 days before traveling to a malarious area, followed by
- A maintenance regimen of 200 mg once weekly while in the malarious area, and
- A terminal prophylaxis regimen of 200 mg one time in the week following exit from the malarious area.

No studies tested the final 200 mg one time dose in the week following exit from the malarious area. Additionally, the loading dose was given while in the malarious area for the placebo-controlled studies.

Reviewer comment: *Although no studies tested the single dose after leaving the malarious area, the proposed dosing is a reasonable strategy to ensure that all hypnozoites and/or maturing malaria parasites emerging from the liver are eradicated.*

Table 17. Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients randomized	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
033	MC, R, DB, DD, PG, AC in non-immune subjects (Phase III)	TQ (200 mg for 3 days, then weekly for 25 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 for 3 days) TQ (200 mg once daily for 3 days, then weekly for 10 to 15 weeks) TQ (400 mg once daily for 3 days, then weekly for 10-15 weeks) Placebo /Oral	Parasitemia during 15-week prophylaxis	15 weeks/ 4 weeks	64 61 62 62	G6PD normal adults between 18 and 55 years of age, in good health	1 center/ 1 country (Kenya)
045	Single-center, R, DB, PG, PC, AC in semi-immune subjects	TQ (25, 50, 100, 200 mg once daily for 3 days, then weekly for 12 weeks) MQ Placebo /Oral	Parasitemia during 12-week prophylaxis	12 weeks/ 4 weeks	95 94 94 94 48 96	Male subjects aged 18-60 and female subjects aged 50-60, in good health	1 center/ 1 country (Ghana)
058	R, DB, DD, PG, AC, treatment of *P. vivax* in semi-immune subjects (Phase II)	TQ 400 mg once daily for 3 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 and 200,000 per µL, aged 20 to 60 years old	1 center/ 1 country (Thailand)

Trial Identity	Trial Design	Regimen/schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients randomized	Study Population	No. of Centers and Countries
TQ-2016-02	R, DB, PC, PG, challenge study (blood stage *P. falciparum* challenge inoculum on Day 13, Phase Ib)	TQ (200 mg for 3 days (Days 1-3) and on 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 between 18 and 55 years, in good health	1 center/ 1 country (Australia)
030	R, DB, PC, AC, PG in semi-immune subjects. Only study report is submitted (no datasets). Potential error in outcome assessment.	TQ (200 mg, once daily for 3 days, then weekly for 24 weeks) MQ Placebo /Oral	Parasitemia within 7 days after 24 weeks	24 weeks/4 weeks	104 101 101	Healthy volunteers aged between 18 and 55 years.	1 center/ 1 country (Kenya)

DB: double-blind, DD: double-dummy, MC: multi-centered, AC: Active-controlled, PC: placebo-controlled, PG: parallel-group, R: randomized, TQ: tafenoquine, PQ: primaquine, CQ: chloroquine, MQ: mefloquine

7.1.2. Review Strategy

Data Sources

This NDA was submitted in eCTD format. Data sources include protocols, reporting and analysis plans, study reports, the integrated summaries of efficacy and safety, and data sets (in both Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) formats). There are no data sets submitted for Study 030. Studies 043 and 045 only have limited data sets available. All submitted data sets are available at \\Cdsesub1\evsprod\NDA210607.

Data and Analysis Quality

Overall, the quality of data and analyses was adequate. It is possible to reproduce the primary analyses, from the original data source, for 3 out of 4 studies we reviewed. For Study 043, we requested a clarification for the primary analysis. The Applicant submitted a new data set with clarification on 5/4/2018 (discussed in 7.2.2). The SDTM and ADaM data sets were prepared after the study reports were written, and that may be the cause of some of the results in the study reports differing from those obtained from the submitted data sets. We requested explanations for some of the discrepancies that may have impacted the interpretation of the study results. For minor discrepancies, which would not influence the efficacy conclusions, we did not request further explanations. These discrepancies are noted in the review.

Blinding/un-blinding procedures were generally well documented. Quality control/assurance procedures were documented. Statistical analysis plans were finalized before un-blinding.

Study 030 failed to show efficacy of TQ compared with placebo. The low protective efficacy of the MQ group (active control) suggested that false-positive slide reading was likely to have occurred. While the study was still ongoing, slides were provided to a new unit for a secondary blinded re-reading. Based on the new reading results, TQ was effective, but since this was an unplanned analysis, follow-up was limited due to the early false positive reading, and patient level data were not submitted, the study was reviewed to ensure that the lack of effect seen was not a cause for concern regarding the efficacy of the product.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study 033

Trial Design and Endpoints

This study was a Phase III, randomized, double-blinded, double-dummy, active controlled trial of 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 primary objective was to compare the safety and tolerability of TQ and MQ over a 6-month treatment period. Secondary objectives for efficacy included:

- To assess the effectiveness of TQ and MQ for chemoprophylaxis of *P. falciparum* and *P. vivax*
- To assess the effectiveness of TQ and MQ in preventing post-exposure malaria

There were two phases. The first phase, or prophylactic phase, consisted of a 26-week period during deployment. At the end of the deployment to the malarious area and once the subjects had returned to barracks, the subjects entered a 24-week relapse follow-up phase. Study visits included Days 0, 1, and 2; Weeks 4, 8, 16, 26, 32, 38, 44 (phone), and 50 (phone).

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

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 relapse follow-up phase drug dosing (PQ/placebo).

Prophylactic Success: No clinical malaria, where clinical malaria was defined as a single positive smear (any species) with concurrent clinical signs and symptoms consistent with malaria.

Prophylactic Failure: Clinical malaria.

Secondary Efficacy Endpoints

Secondary efficacy endpoint included:

- Number of subjects experiencing clinical malaria at any time during the study (prophylactic phase plus 6-month relapse follow-up phase);
- Number of subjects with a single positive smear (any species, with or without clinical signs/symptoms) during prophylactic study drug administration;
- Time to clinical malaria (all species) at any time during the study (prophylactic phase plus 6-month relapse follow-up phase);
- Time to single positive smear (all species) with or without clinical signs/symptoms during prophylactic study drug administration.

Inclusion Criteria and Exclusion Criteria

Inclusion Criteria

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

Exclusion Criteria

Exclusion criteria included, but were not limited to:

- Demonstrated glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- History of allergy or intolerance to MQ, PQ or any other 8-aminoquinolines.
- History of psychiatric illness.
- Clinically significant abnormalities (not limited to, abnormal hepatic or renal function) as determined by history, physical examination, or laboratory testing of blood chemistry and hematology.

Statistical Analysis Plan

Analysis Populations

The 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.

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

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

Comment: We used the ITT population as the primary efficacy analysis population, as the PP population is defined using post-randomization information. Exclusions based on information that occurred after randomization and treatment can lead to differences in treatment arms and difficulty in interpreting the trial results.

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 non-inferiority of TQ would be drawn if the upper limit of this CI was no more than 10%. No justification for this non-inferiority margin was initially provided in the study report; however, an updated justification of the non-inferiority margin was provided in the Clinical Overview section of the application. 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 margin in the setting of malaria prophylaxis. The Applicant did summarize evidence on the prevalence of malaria in the region at the time of the trial. This 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.

It was planned to set up an independent data monitoring committee (IDMC) to monitor failure rates over the course of the study if required. However, no adjustment would be made for multiple comparisons. Because there were no failures observed in the study, there were no interim analyses reported.

Missing values for efficacy evaluation were not discussed in the protocol. We will consider the subjects with missing efficacy endpoints as treatment failures in our analysis.

Compliance with Good Clinical Practices

The Study Report states that the study was conducted in accordance with Good Clinical Practices.

Financial Disclosure

No disclosable financial interests were reported for this study. See Appendix 15.2.

Patient Disposition

The study was conducted between October 2000 to May 2001 during a military deployment of the Australian Defense Force in Townsville, Australia and in East Timor (at 7 sites). The first dose was taken on average 5.5 days (from 4 to 12 days) before arriving at East Timor. The following table shows the numbers of subjects screened, randomized, and included in the analysis populations, and reasons for excluding from the PP population. 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 the subjects in the ITT population completed the study. The reasons for not completing the study are included in the table.

Table 18. Study 033: Patient disposition and study populations

	TQ	MQ
Randomized	492	162
Safety	492	162
ITT	492	162
PP	462	153
Excluded from PP population	30 (6.1%)	9 (5.6%)
Reasons for not including in the PP population†		
Taking another antimalarial product	11 (2.2%)	4 (2.5%)
Non-compliant with study medication	1 (0.2%)	2 (1.2%)
Non-compliant with parasitemia monitoring	11 (2.2%)	5 (3.1%)
Not completing the prophylactic phase	19 (3.9%)	5 (3.1%)
Completed prophylactic phase	473 (96.1%)	157 (96.9%)
Completed Study	472 (95.9%)	157 (96.9%)

	TQ	MQ
Reason for withdrawal from study		
AE	12 (2.4%)	4 (2.5%)
Protocol deviation	1 (0.2%)	0
Loss to follow-up	1 (0.2%)	0
Moving out of the endemic area with no reported malaria infection	6 (1.2%)	1 (0.6%)

†Subjects may be classified in multiple categories.

Protocol Violations/Deviations

As shown in the above table, about 6% of the subjects had protocol violations and were excluded from the PP population. The two groups were comparable in terms of proportions of and reason for exclusions.

Demographic Characteristics

Demographic characteristics are listed in the following table. The two groups had similar distributions in these characteristics. All subjects were younger than 65 years old. The majority of the subjects were male and White.

Table 19. Study 033: Demographic characteristics in the ITT population

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

Other Baseline Characteristics

Malaria history is summarized in the following table. Only a small proportion (<3%) of the

subjects had a history of malaria and the two groups were not statistically significantly different.

Table 20. Study 033: Malaria history in the ITT population

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

Source: Adapted from Table 16, Study Report. There were 13 cases in the TQ group in the data set, 8 of which were in the last 6 months.

The proportions of subjects with various medical conditions were comparable between the two groups, as the following table shows.

Table 21. Study 033: Most commonly presenting (>1% of subjects in either group) active medical conditions at screening in the ITT population

	TQ (N=492)	MQ (N=162)
At least one condition, n(%)	95 (19.3)	41 (25.3)
Adverse effect of antibiotic	16 (3.3)	7 (4.3)
Hearing loss	15 (3.0)	6 (3.7)
Adverse effect of analgesic	7 (1.4)	3 (1.9)
Back pain	7 (1.4)*	4 (2.5)
Ear/Mastoid disorder	7 (1.4)*	1 (0.6)
Allergic rhinitis	7 (1.4)	0
Limb pain	6 (1.2)	3 (1.9)†
Skin/subcutaneous disorder (other)	6 (1.2)	2 (1.2)
Toxic effects of venom	1 (0.2)	2 (1.2)
Arthropod-borne disorder (other) ‡	12 (2.4)	4 (2.5)
Inflammation skin/subcutaneous‡	2 (0.4)	3 (1.9)
Nasopharyngitis, acute‡	1 (0.2)	2 (1.2)
Operation, bone/joint‡	4 (1.0)	1 (0.6)
Trauma/injuries, unspecified‡	4 (0.8)	2 (1.2)
Upper respiratory infection, acute‡	4 (0.8)	2 (1.2)
Virus/Chlamyd disease (other)‡	5 (1.0)	0

Source: Table 17, Study Report. *From the ADCM data set, one more subject had this condition; †From the ADCM data set, 2 subjects had this condition; ‡From the ADCM data set, not reported in Table 17.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance is shown in the following table. The compliance was high and comparable between the two groups.

Table 22. Study 033: Treatment compliance

	TQ (N=492)	MQ (N=162)
Medication compliance percentage, n (%)		
<100%	1 (0.2)	1 (0.6)

	TQ (N=492)	MQ (N=162)
100%	465 (98.3)	156 (99.4)
>100%	7 (1.5)	0

Efficacy Results – Primary Endpoint

There were no cases of clinical malaria during the prophylactic phase. We analyzed the primary efficacy endpoint in the ITT population assuming all subjects who withdrew during the prophylactic phase and the three subjects not completing the prophylactic phase due to AE were not prophylactic successes. This analysis indicated that the prophylactic success was greater than 96% for both groups.

These results were similar to the Applicant's PP analysis. The Applicant concluded that the upper limit of the 95% CI of TQ – MQ failure rates was 1%, which was below 25% of an M1 of 7.88% allowing for the conclusion of non-inferiority of TQ to MQ. In the Applicant's ITT population (which excluded three additional subjects, not shown), about 3% of the successes were assumed because these subjects withdrew from the study with no clinical malaria at the time of withdrawal.

Table 23. 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's 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's 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%]	

[a] In the Clinical Overview section of the NDA, the Applicant reported the difference in failure rates of TQ – MQ with 95% CI to be 0% (-2%, 1%). Note that difference in success rates are reported in the table.

Efficacy Results – Secondary and Other Relevant Endpoints

Prophylactic outcome for each treatment group during prophylactic treatment plus relapse follow-up phase is summarized in the following table for the ITT population and PP population. All failures were cases of P. *vivax* malaria occurring in the follow-up phase, accounting for less than 1% prophylactic 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. As noted, 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 those 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 relapse follow-up phase. Therefore, these subjects were not considered as prophylactic success in FDA's ITT analysis.

Table 24. Study 033: Prophylactic outcome based on clinical malaria (all species) at any time during the study (50 weeks) in the ITT and PP population

Prophylactic Outcome, n (%)	**TQ (N=492)**	**MQ (N=162)**
ITT Population (FDA's 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's 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

The Applicant acknowledged that studies carried out without placebo control groups require some demonstration of malaria prevalence in the area at the time of the study. The Applicant considered this could be obtained by monitoring the local population for parasite prevalence and by entomological surveys of the anopheles species present in the area.

The Applicant provided results of two studies performed at the time that study 033 was carried out. The first was a cross-sectional survey of malaria prevalence in the local population at seven locations in the Bobonaro district. The second was an entomological study, collecting night biting mosquitoes in the area. However, the Applicant states that this data from the entomological study is very difficult to interpret due to the low number of mosquitoes collected. Therefore, we will not include it in this review. The Applicant also provided a WHO malaria report in the East Timor area during 1999 and 2001 and a summary of published data.

Cross-sectional Survey

The survey was a community-based study conducted at sites that were within one kilometer of the barracks at which subjects from Study 033 were stationed. One kilometer represents the maximum flying range of the *Anopheles* mosquito, the vector for *Plasmodium* infections. The cross-sectional survey had two phases. 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 around 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 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. This was not surprising, as malaria transmission in this village would not be expected. Parasite prevalence varied between the sites studied, as shown in the following table:

Table 25. Study 033: Supportive data from survey

	Survey Phase 1			**Survey Phase 2**		
Village	*Prevalence P. falciparum %*	Prevalence *P. vivax %*	All species prevalence %	Prevalence *P. falciparum %*	Prevalence *P. vivax* %	All species prevalence %
A	1.0	2.9	3.9	2.5	3.0	6.0
B	1.5	3.5	5.0	3.0	0.5	4.0
C	1.5	2.4	3.9	9.7	2.8	12.5
D	0	1.0	1.0	0	1.5	1.5
E	5.9	12.3	19.7	14.4	16.0	35.3
F	0	6.4	6.4	2.5	6.5	9.0
G	0	0	0	0	0	0
A, B, F - inland flood plain C, D - hill villages E - coastal strip G - mountain village						

Source: Appendix H, Study Report

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. No cases of *P. malariae* were seen in Phase 1 and 4 cases were reported in Phase 2. The Applicant concludes that malaria prevalence can be split into 3 groups of locations: the coastal region, inland region, and mountainous region had the highest, lower, and no transmissions, respectively.

Comment: The exact sample size is actually unknown. Therefore, it was not possible to add confidence intervals for the prevalence rates. In addition, the survey was conducted in a local population. The living conditions of the local population might be different from the living conditions of subjects in Study 033 (military), for example use of mosquito net and mosquito repellents, etc. This might affect the incidence of malaria in the study population. According to a paper by Ashely and White (2014), asymptomatic P. falciparum infections may persist for up to a decade or longer. Therefore, it was difficult to know how many parasitemia cases in this survey were due to infections originating in the timeframe of the trial. Lastly, in a recent response (SN0045) to our information request, most of the soldiers in Study 033 were deployed to more than one region in East Timor. It is not possible to match each subject's location to the villages in this survey. It would be problematic, however, if most subjects spent most of their time in the mountainous region.

The information from this survey is interesting and it suggests that the subjects in Study 033 were likely to be 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 non-inferiority margin.

UN/WHO Malaria Report and Published Data

The Study Report also includes a summary of UN/WHO malaria epidemiology data of reported malaria cases in East Timor. There are figures of the number of weekly cases of malaria occurring between Week 44 of 1999 and Week 43 of 2000, 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 document states that *P. falciparum* is thought to cause between 60 and 80% of all cases.

The study report references literature that documents the incidence of malaria in East Timor. Macdonald (2000) reported significant malaria during February/March 2000, soon before Study 033 was conducted. A paper by Kitchener (2000) also reported on the incidence of malaria around that time period in the Australian Defense Force (ADF). Despite the use of chemoprophylaxis, insect repellents, and permethrin-treated bed nets, 5% of the returned Australian troops developed malaria. The cases with clinical signs while in East Timor (24%) were primarily due to *P. falciparum* while those with symptoms after returning to Australia were primarily due to *P. vivax*. The Study Report states that though this is not conclusive evidence of exposure to malaria in Study 033, it does show the high likelihood that subjects in Study 033 were exposed to both *P. falciparum* and *P. vivax*. We think the Applicant's conclusion is reasonable.

Applicant's Justification of the Noninferiority Margin

The NDA contained a justification of an updated noninferiority margin. In the justification of the noninferiority margin, the Applicant claims that the attack rate in the region was 7.88%. This estimate is based on a complicated calculation using both information obtained from a retrospective 1-year follow-up of Study 033 and information from other sources. It was estimated using assumed anti-relapse efficacy rates of both PQ and TQ (efficacy=0.8213, derived from historical studies for TQ and PQ) along with the observed number of relapses seen during the 1-year follow-up of Study 033 (8: 7 on TQ and 1 on MQ-PQ). Therefore, the total observed *P. vivax* relapse rate was 8/651=1.229% (note: 651(=490+161) was used in this calculation, not 654, the total ITT Population size). The *P. vivax* attack rate in untreated subjects was estimated to be 1.229%/(1-0.8213)=6.88%. 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. 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%).

The Applicant calculated the effect of MQ compared to placebo to be 7.88% (M1), 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%.

Comment: We find this complicated calculation of the attack rate in the untreated population problematic due to its strong reliance on assumptions, including the relapse efficacy rate of the test product, and the lack of consideration of the variability in various estimates.

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

Gender, Race, Age, and Weight

The following subgroup analyses include all subjects in the ITT population, with known success as prophylactic success and missing data as failure. Due to small sample sizes, the results in some groups (females, Black or African American, or other race) were inconclusive. For other subgroups, there were no concerning differences. As mentioned previously, all subjects were younger than 65 years old; therefore, no subgroup analysis by age was conducted. All five *P. vivax* infections during the follow-up period (4 on TQ and 1 on MQ) were in White males under 35 years old.

Table 26. Study 033: Prophylactic outcome based on clinical malaria (known success, all species) during the prophylactic phase (Week 26) in the ITT population

Prophylactic success, n/N (%)	TQ (N=492)	MQ (N=162)
Gender		
Male	459/478 (96.0%)	150/154 (97.4%)
Female	14/14 (100.0%)	7/8 (87.5%)
Race		
Black or African American	4/4 (100.0%)	1/1 (100.0%)
Other	3/4 (75.0%)	1/1 (100.0%)
White	466/484 (96.3%)	155/160 (96.9%)
Weight (kg)		
<80	215/226 (95.1%)	78/79 (98.7%)
80 or higher	258/266 (97.0%)	79/83 (95.2%)

Geographic Location (Country)

Analysis by country was not applicable, because all solders were from Australia stationed in East Timor. There was no location information within East Timor available for the soldiers as most of the soldiers were deployed to more than one region.

Conclusions

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, we cannot conclusively conclude noninferiority of TQ to MQ. Information provided by the Applicant does

suggest the high likelihood that the area was malarious around the time that Study 033 was conducted and that subjects were likely exposed. Note that the information in females, older subjects, and in races other than White is limited in this study.

7.2.2. Study 043

The primary objective was to determine the chemosuppressive effectiveness of weekly regimens of TQ in preventing falciparum parasitemia compared with placebo. The secondary objectives included obtaining additional safety and tolerance data for further field trials.

Trial Design and Endpoints

This study was a Phase IIb, placebo-controlled, randomized, double-blind parallel group, single center study in Kenya, in an area of holoendemic *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 dosage 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 confirmed parasitemia by Week 15, defined as having two consecutive weekly blood smears positive for *Plasmodia*, read independently by two microscopists blinded to one another's diagnosis. The protective efficacy (PE) of the TQ treatment regimens relative to placebo was derived from the proportion of subjects who were prophylactic failures (confirmed parasitemia) 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

Exclusion criteria included, but were not limited to:

1. Any cardiovascular, liver, neurologic, or renal functional abnormality which in the opinion of the clinical investigators would place the subject at increased risk of an AE or confuse the result.
2. Use of antimalarial drugs not prescribed by study physicians within 2 weeks of study drug initiation.
3. G6PD deficiency.

Statistical Analysis Plan

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.

Comment: In the Study Report and dataset the Applicant refers to both an ITT Efficacy population and an ITT population. Though not defined explicitly, the ITT population appears to be the same as the Safety population. Based on the definition of the safety population, the Safety/ITT population should only exclude subjects based on information prior to randomized treatment (receipt of halofantrine clearance medication and decision whether or not to take randomized treatment). All the other analysis populations exclude subjects based on post-randomized treatment information. Exclusions post-randomized treatment can be impacted by the effect of treatment and can lead to imbalance in treatment arms. However, as discussed below, it appears that the safety population may have excluded subjects for additional reasons. For this reason, we will consider 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 the protective efficacies were 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 was 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. We will consider subjects with missing outcomes as failures in our analysis.

Protocol Amendments

There were no protocol amendments in this study.

Compliance with Good Clinical Practices

According to the protocol, the study center (USAMRU-Kenya) established a quality assurance which allows its laboratory to comply with Good Clinical Practice (GCP) standards of the USA FDA.

Financial Disclosure

There were no financial interests reported for this study. See Appendix 15.2.

Patient Disposition

The study was conducted between May and September of 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 the following table. 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 were not consistent with the Safety/ITT analysis population exclusions as defined. As stated above, we do not agree with all the exclusions from the Applicant's ITT population. Since the specific reasons were not included in the datasets, we conducted the primary analysis on a population of all randomized subjects (with subjects with missing data as failures).

About 77% (182/235) of the subjects in the ITT population completed the study. Reasons for discontinuation included AEs, deviations from protocol, lack of efficacy, and loss to follow-up. Overall, lack of efficacy was the most common reason for discontinuation of the study. Most of the withdrawals were in the placebo group (27 out of 67 withdrawals).

Table 27. Study 043: Patient disposition

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

Protocol Violations/Deviations

A total of 31 subjects did not take a predefined number (between 10 and 15) of weekly prophylactic treatment doses, some of whom were withdrawn for lack of efficacy.

Demographic Characteristics

Demographic characteristics are presented in the following table. As the low dose group contains the dose proposed by the Applicant, we focused on this group. These characteristics were fairly balanced among the TQ low dose group and the placebo group.

Table 28. Study 043: Demographic characteristics in the all randomized subjects

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

Efficacy Results – Primary Endpoint

The following table contains the results of protective efficacy at the end of prophylaxis treatment in all randomized subjects, FDA's primary efficacy analysis. Subjects excluded from the Applicant's Efficacy population were considered as failures in the FDA's All Randomized analysis. The differences in the incidence of parasitemia between the TQ groups and the placebo group were statistically significant. The p-values from 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 considering the most conservative method for handling missing data where missing 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 statistically significant (not shown). The Applicant's primary efficacy analysis yielded a similar conclusion.

Table 29. Study 043: Incidence of parasitemia and protective efficacy at the end of treatment (15 weeks) in all randomized subjects

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

Comment: The above table presents the results from an updated dataset. As stated in Section 7.1.2 of this review, we were unable to replicate the results in the Study Report using the originally submitted datasets for this study. In response to our request for clarification, the Applicant submitted a new dataset. The updated dataset contained a different definition of the primary endpoint: "full period of exposure from the time of the start of the first TQ loading dose until 7 days after the last weekly TQ dose." The number of subjects in the various study populations and cases of parasitemia matched the numbers in Table 20 in Section 2 Summary of Clinical Efficacy of the NDA. The number of parasitemia cases was more than in the study report. However, as there were more parasitemia cases added in the TQ groups than in the placebo group from this dataset, the analysis results were more conservative than the results presented in Table 9 of the Study Report. Though, changing a definition would not typically be considered acceptable, since it led to more conservative analyses we did not seek additional clarification from the Applicant.

Based on the Study Report, the majority (99% or 78/79) of the subjects with infective episode of malaria were infected with *P. falciparum*. *P. malariae* parasites were only detected in one subject in the load only group.

If only one positive smear was used for parasitemia during the prophylactic phase, there were 2, 1, and 1 more parasitemia cases in the TQ load only, low dose, and high dose groups, respectively.

During the follow-up phase, there were 4 new cases of parasitemia: 1 in the TQ 200 mg group, 1 in the TQ 400 mg weekly group, and 2 in the TQ loading group.

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

Gender, Race, Age, and Weight

Since all subjects were younger than 56 years old, all subjects were of the same race, and no weight data were submitted, there were no analyses for age, race, and weight. Similar results were seen for males and females as with the overall population for the comparison of TQ low dose and placebo.

Table 30. Study 043: Incidence of parasitemia at the end of treatment (15 weeks) by gender in all randomized subjects

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

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

Geographic Location (Country)

It was not applicable as the study was only conducted in one center (clinic).

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 developing 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 malaria is *P. falciparum*.

7.2.3. Study 045

This study was (i) To determine the chemosuppressive efficacy of weekly TQ at a range between 25 and 200 mg in preventing falciparum parasitemia compared to placebo, and secondarily to MQ, in subjects semi-immune to malaria, and (ii) To establish the minimum effective prophylactic dose of weekly TQ and to assess the tolerability of that dose.

Trial Design and Endpoints

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 course 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 course 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 during taking weekly doses). Then subjects were followed weekly for 4 weeks.

The primary efficacy endpoint was the first occurrence of malaria 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 Criteria and Exclusion Criteria

Inclusion Criteria

The following inclusion criteria were applied:

1. Willing subjects in good general health.
2. Males aged 18 to 60; females aged 50 to 60 (to exclude women in reproductive ages).
3. Subjects who planned to stay in the study area until the end of the study.

Comment: Pre-menopausal women were excluded from this study. This will limit our ability to assess the treatment effect in young women.

Exclusion Criteria

Exclusion criteria included, but were not limited to:

1. Subjects with any cardiovascular, liver, neurologic, or renal function abnormality which, in the opinion of the clinical investigators, would have placed them at increased risk of an AE or confused the result.
2. Subjects given antimalarial drugs for treatment within two weeks of study drug initiation.
3. Subjects with G6PD deficiency.
4. Subjects with history of psychiatric illness.

Statistical Analysis Plan

Analysis Populations

The following analysis populations are defined.

Full data set: all subjects who completed the radical cure phase successfully, 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

for the primary analysis.

Comment: Completing the loading dose period, receiving at least one dose of weekly prophylactic medication, and having at least one efficacy assessment should not be a criterion for primary efficacy population because all could be impacted by randomized treatment. For this reason, we analyzed the data using the safety data set, which is defined below.

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 prematurely as a result of developing parasitemia. This set was used for a supplementary analysis.

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

Analysis Methods

PE was defined the same 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. We will use a 98.75% level based on Bonferroni method, as there were 4 comparisons (TQ versus placebo) in the study (1-0.05/4).

Missing data were not discussed in the analysis plan. We will consider discontinued subjects with missing parasitemia results as failures in our analysis.

Compliance with Good Clinical Practices

According to the protocol the study would be done under good clinical practices.

Financial Disclosure

There were no financial interests to disclose. See Appendix 15.2

Patient Disposition

The following table shows patient disposition. A total of 513 of 521 randomized subjects were correctly randomized. Eight subjects were randomized in error (allocated a study numbers, hence a randomized treatment) and did not receive the loading dose. Randomization was planned after an 18-day radical cure phase. As they did not start the loading dose, the exclusion of these 8 subjects from analysis is acceptable. The "full data set" excluded an additional four subjects because they did not start weekly dosing. However, since these 4 subjects did start their randomized therapy they will be included in the FDA's primary efficacy analysis.

Most withdrawals were due to subjects having developed parasitemia. The proportions of withdrawal in the placebo group and 25 mg TQ group were the highest. The withdrawals were mainly due to lack of efficacy in the placebo group and due to discontinuation in the TQ groups,

with the highest rate in the TQ 200 mg group. These discontinuations are discussed in the next section. These discontinued subjects are considered as failures in the primary FDA analysis.

Table 31. Study 045: Patient disposition

	Placebo	TQ				MQ
		25 mg	50 mg	100 mg	200 mg	250 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

Protocol Violations/Deviations

According to the study report, 55 subjects in the full data set were excluded from the PP data set. The reasons for exclusion are included in the following table. A higher proportion of subjects in the 200 mg TQ group had at least one protocol violation and the main reasons for withdrawals were due to AE and non-compliance. In the TQ groups, the most common reason for withdrawal due to AE (29 cases) was alanine aminotransferase increased (20 cases). Six subjects in the 200 mg TQ group had alanine aminotransferase increased and were withdrawn due to AE in the ADAE data set. For more detailed safety review of AEs, please see Safety Section 9. A few subjects with a "completed" status in disposition event were also excluded from the PP set. The PP set is not the focus of our analysis.

Table 32. Study 045: Protocol violations leading to safety subjects excluded from the PP 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)	
At least one violation	11(11.7%)	10(10.8%)	19(18.7%)	14(14.9%)	25(25.3%)	6(13.0%)
Age out of range	0	2(2.2%)	0	0	2(2.2%)	0
Prematurely discontinued	8(8.5%)	7(7.5%)	11(12.1%)	8(8.5%)	14(15.4%)	2(4.3%)
Withdrawn due to AE	3(3.2%)	7(7.5%)	7(7.7%)	6(6.4%)	9(9.9%)	0
Withdrawn due to confirmed parasitemia	2(2.1%)	0	0	0	0	0
Withdrawn due to non-compliance	5(5.3%)	0	4(4.4%)	2(2.1%)	4(4.4%)	2(4.3%)

	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)	
Missed doses	0	2(2.2%)	5(5.5%)	5(5.4%)	5(5.5%)	4(8.7%)
Concomitant anti-malarial	1(1.1%)	0	0	0	2(2.2%)	0

Source: Table 7, Study Report. Subjects could have more than one violation. Due to the limited submitted data sources, this table was mainly based on the results from the study report. However, the numbers of withdrawn subjects were from the data set ADSL.

Demographic Characteristics

Demographic characteristics are presented in the following table. All variables were well-balanced among the groups. Note that the mean age for women was higher than the mean age for men because younger women (<50 years old) were not eligible as women of reproductive age were excluded.

Table 33. 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)
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.
Source: Adapted from Table 8, Study Report.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The compliance was high as the drug was administered under direct observation of the field workers. About 76% of subjects took 10 or more doses out of 12 planned doses.

The most commonly used concomitant medications were paracetamol, multivitamin, aspirin,

and amoxicillin. However, use of these medications was balanced and was not likely to affect the efficacy results.

Comment: Note that based on the data submitted we were not able to completely replicate the data summarized in the Study Report. However, the differences were minor and do not lead to different conclusions.

Efficacy Results – Primary Endpoint

The following table shows the results from the primary efficacy analysis. The proposed dosing of TQ 200 mg, was effective compared with placebo, as the 98.75% CI for the protective efficacy of 71.3% [55.8%, 81.4%] was much higher than 0, when considering discontinued subjects as treatment 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 handling of these discontinued subjects did not overly affect the results of the trial. 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 34. 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	6	31	68	75	68	38
Discontinued/Unknown	2	4	12	8	13	2
AE	*1*	*4*	*6*	*6*	*8*	*0*
Non-compliance with study drug	*1*	*0*	*6*	*2*	*5*	*2*
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 the following table (FDA's analysis, considering discontinued subjects as treatment failures or as not having parasitemia,

separately). As expected, the incidence was lower, compared to 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 stricter definition of confirmed parasitemia, there were no observed parasitemia cases in the MQ arm or the two highest TQ arms.

Table 35. 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

Source: Adapted Table 13, Study Report.

The following table 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, except for 4 subjects in the placebo group infected with *P. malariae*, were due to *P. falciparum* species.

Table 36. 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

Source: Table 12, Study Report

There were 13 new cases of parasitemia in the follow-up phase: 1, 3, 8, and 1 in the placebo, TQ 25 mg, 50 mg, and the MQ groups, respectively.

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

Gender, Race, Age, Weight

In the following subgroup analyses, we 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 old or over to assess efficacy. For all other subgroups, results were comparable to the overall population.

Table 37. 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

The following table 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 38. 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)
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.

7.2.4. 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 Applicant submitted the study report without any electronic patient-level data. The review of this study will be brief.

Trial Design and Endpoints

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 free from malaria parasitemia were randomized to receive one of three study treatments; TQ 200 mg, MQ 250 mg, or placebo. Treatment consisted of daily dosing of study medication 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 (a healthy volunteer was defined as one who was free of ailments that might cause difficulty in evaluating drug efficacy or adverse experiences).
- Subjects aged 18-55 years.
- Subjects 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:

- Subjects with positive parasitemia following halofantrine treatment for radical cure.
- Subjects with any medical condition which, in the opinion of the investigator, made the subject unsuitable to enter the study.
- Subjects taking any other anti-malarial product, or who had taken an antimalarial drug other than halofantrine within the previous two weeks.
- Subjects who had received an investigational drug (a new chemical entity not registered for use) within 30 days or 5 half-lives whichever was the longer.
- Subjects with G6PD deficiency.

- Subjects with history of psychiatric illness

Statistical Analysis Plan

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.

Comment: Attending at least one follow-up visit at which assessment of a blood smear took place should not be included as an exclusion from the ITT population, because this was post-randomization information and could influence the efficacy evaluation. We will conduct 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.

Protocol Amendments

There were 4 amendments. In Amendment 3 (7/12/2000), an interim analysis of the data was introduced, due to findings from Week 8 data that an unexpectedly high number of withdrawals from the study due to positive parasitemia. Due to the possibility that one or both of the active treatment groups were not providing protection expected, there was concern over the appropriateness of continuing the study. An independent data monitoring committee met in August 2000. The last dose of study medication occurred on 10/25/2000 and the planned sample size was enrolled.

Compliance with Good Clinical Practices

The study was conducted in accordance with Good Clinical Practice.

Financial Disclosure

There were no financial interests to disclose. See Appendix 15.2.

Patient Disposition

This study was conducted at a single center (clinic) in Kenya between May and November of 2000.

A total of 306 subjects were randomized and 300 were included in the ITT population. The reasons for exclusion from the ITT population were listed in the following table.

Table 39. Study 030: Patient disposition

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

Source: Tables 5 and 6, Study Report

Demographic Characteristics

The following table shows the demographic characteristics in the ITT population. These characteristics were well-balanced across different treatment groups.

Table 40. 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

Efficacy Results – Primary Endpoint

Initial efficacy analyses were based on the slide-reading results from the US Army Medical Research Unit-Kenya. The results were not significant. The low PE of the MQ (positive control) suggested that false-positive slide reading was likely to have occurred.

Table 41. 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

Source: Adapted from Table 22, Study Report

While the study was still ongoing, 364 slide pairs were provided to the Naval Medical Research Unit-2 in Jakarta (NAMRU-2) for blinded re-reading. By the end of the study, a total of 766 slide pairs were provided to the NAMRU-2 for blinded re-reading. The following table shows the comparison of the reading results. Of those that were originally read as positive only 31 were re-read as positive.

Table 42. Study 030: Cross-tabulation of the results from initial slide reading and NAMRU-2 re-reading

Initial reading	Naval Medical Research Unit-2 Re-Reading			
	Positive	Negative	Missing	Total
Positive	31	220	0	251
Negative	5	507	0	512
Missing	0	3	0	3
Total	36	730	0	766

The efficacy results based on the NAMRU-2 blinded sliding reading are as follows: 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. However, due to the errors in slide reading, subjects were not followed for the full follow-up period. Some PE assessments were based on slide reading occurring on or soon after the first dose of the study medication. This might explain why the prophylactic failure rates were lower in this study than in Studies 043 and 045. The results do not measure efficacy at Week 24 (the end of the prophylactic phase).

Table 43. Study 030: Protective efficacy during the prophylaxis treatment period based on first positive smear according to NAMRU-2 blinded slide readers

Applicant's mITT 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
Reviewer's Analysis of All Randomized Subjects	**(N=101)**	**(N=104)**	**(N=101)**
Prophylactic failure	40 (39.6%)	7 (6.7%)	7 (6.9%)
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

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.

Conclusion

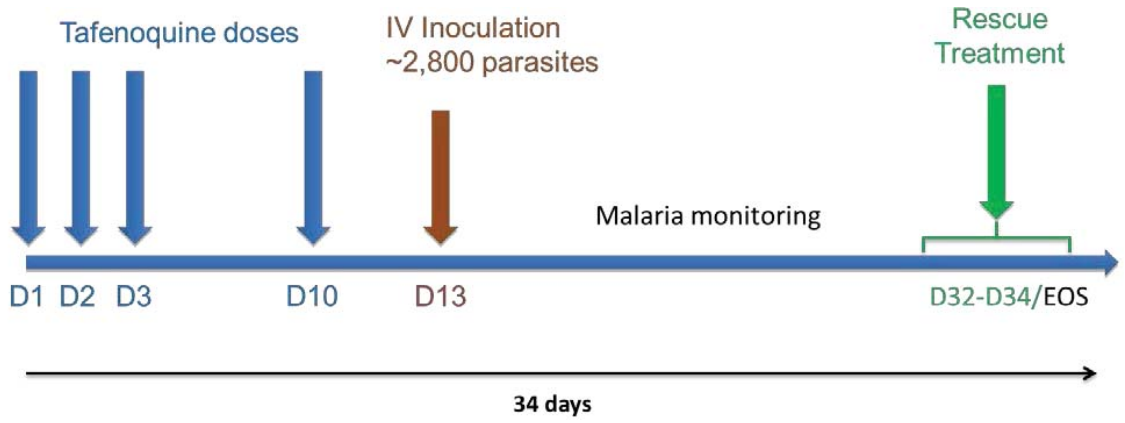
The original results of Study 030 did not show any treatment effect of either TQ or the positive control, MQ. After unplanned but blinded re-reading of the slides many false-positive results were identified, and the timing of the blood sample collection was not at the end of the prophylactic phase (Week 24) for every subject. Therefore, the efficacy results do not reflect the efficacy results at the end of the prophylactic phase. No data sets were submitted to conduct a complete review of this study. Because the re-reading of smear slides was not pre-planned and timing of blood sample collection was not fixed at the end of the prophylactic phase, we could not rely on this study for efficacy. Based on this information as well as the lack of a significant effect of the active control, MQ, the lack of an effect seen in Study 30 does not appear to be a cause for concern.

7.2.5. TQ-2016-02

This was a Phase Ib, randomized, double-blinded, placebo-controlled study in healthy, non-immune adults to determine the schizonticidal activity of TQ after BSPC inoculum.

Trial Design and Endpoints

Two cohorts (21 days apart) of 8 subjects were randomized 6:2 into TQ 200 mg or placebo group. 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 (Riamet® and Primacin™ sensitive) on Day 13. All subjects were treated with rescue therapy at the end of study visit or earlier in the event of malaria or at the discretion of the principle 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 (Riamet treatment), 33, and 34.



Source: Study Report

While the primary endpoint was safety, the primary efficacy endpoints (exploratory) were malaria assessment by qPCR after challenge accompanied by clinical symptoms.

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 greater than 50 kg and a BMI within the range of 18 to 32 kg/m^2 (inclusive)
- At least normal G6PD enzyme activity

Exclusion Criteria

Exclusion criteria included, but were not limited to:

- Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal (including gallbladder), cardiovascular (including a family history of long QT syndrome or sudden death), hepatic, psychiatric, neurologic, or allergic disease (including drug or food allergies, anaphylaxis or other severe allergic reactions but excluding untreated, asymptomatic, seasonal allergies at the time of dosing)
- History of retinal abnormalities, disease of the retina or macula of the eye, visual field defects, hearing disorders (e.g. reduced hearing, tinnitus)
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past five years, regardless of whether there is evidence of local recurrence or metastases

Statistical Analysis Plan

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 blood stage *P. falciparum* challenge 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.

Comment: Note that no subjects were removed from any analysis population in this study.

Analysis Methods

Efficacy data (malaria assessment by qPCR and malaria clinical score based on symptoms) were presented for all participants. The proportion of participants experiencing malaria failure prior to the scheduled Riamet® 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.

Compliance with Good Clinical Practices

The study was in compliance with Good Clinical Practice.

Financial Disclosure

There were no financial interests to disclose. See Appendix 15.2.

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 44. 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

Protocol Violations/Deviations

There were no major protocol deviations. The majority of protocol deviations were non-substantial deviations from procedures for collection and processing PK samples and non-compliance with the visit schedule.

Demographic Characteristics

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

Table 45. Study TQ 2016-02: Demographic characteristics

	Placebo (N=4)	TQ (N=12)
Sex, n(%)		
Male	2 (50.0)	4 (33.3)

	Placebo (N=4)	TQ (N=12)
Female	2 (50.0)	8 (66.7)
Age	4	12
Mean (SD)	34.3 (8.66)	25.3 (3.05)
Median	36.0	25.5
Range	23 – 42	20 – 30
Body weight (kg)		
Mean (SD)	79.65 (11.112)	69.81 (11.238)
Median	78.00	68.35
Range	68.9 – 93.7	56.0 – 97.7
BMI (kg/m^2)		
Mean (SD)	26.50 (2.963)	23.23 (2.934)
Median	23.50	26.90
Range	18.6 – 30.2	22.8 – 29.4
Race, n (%)		
Other	0 (0.0)	1 (25.0)
White	12 (100.0)	3 (75.0)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All subjects were in good health and there were no notable disease characteristics to report.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects completed dosing of TQ or placebo and mandated regimen of Riamet antimalarial rescue treatment. The majority of concomitant medications were ongoing use of contraceptives or intrauterine devices. New concomitant medications included ibuprofen and paracetamol. All concomitant medications were considered by the Investigator to be unlikely to interfere with the interpretation of the study data.

Efficacy – Exploratory Primary Efficacy Analysis

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

Table 46. 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

After parasite inoculum on Day 13, all subjects in the placebo group had detectable parasites from Day 17. All subjects on TQ had 0 parasite counts at all time visits. The following table contains the parasite counts for the placebo subjects.

Table 47. 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	

All subjects had the Day 29 visit and the End of Study/Early termination (EOS) visit. But only one subject had parasite count data at Day 29 and one subjects at EOS visit.

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 malaria definition in the study) and 100% in placebo group (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

This study included healthy, non-immune subjects (all 10 females were between 20 and 40 years old). This challenge model demonstrated that the TQ treated subjects remained clear of blood stage parasites and showed a highly statistically significant treatment effect on the incidence of malaria, compared with the placebo group (0/12 versus 4/4, Fisher's exact p-value=0.0005).

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Efficacy Results

In Studies 043 and 045, parasitemia rates during 15- or 12-week prophylaxis respectively, were comparable. In Study TQ-2016-02, parasitemia by Day 34 after receiving blood-stage *P. falciparum* challenge inoculum on Day 13 was one of the efficacy endpoints. All three studies demonstrated a statistically significant treatment effect in terms of PE or difference in incidence of parasitemia compared with a placebo group (see summary table below).

Table 48. Parasitemia in placebo controlled trials (Discontinued subjects as parasitemia)

Study	Analysis Population	Treatment	Parasitemia	PE [Adjusted CI]*
043	ITT	Placebo	57/62 (91.9%)	73.3% [54.0%, 84.5%]
		TQ	15/61 (24.6%)	
045	mITT	Placebo	88/94 (93.6%)	71.3% [55.8%, 81.4%]
		TQ	25/93 (26.9%)	
TQ-2016-02	ITT	Placebo	4/4 (100%)	
		TQ	0/12 (0%)†	

TQ dose was 200 mg for 3 days, then maintenance dose of 200 mg weekly for 10-15 weeks (Study 043), 12 weeks (Study 045), and 1 week (Study TQ-2016-02). *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 and 045 were conducted in Africa and only included one race (Black). TQ-2016-02 and 033 mainly included White subjects (93.8% and 98.5%). The four studies included only one TQ 200 mg subject who was greater than 65 years old (Study 045). No subject under the age of 17 was enrolled in a TQ 200 mg arm. Therefore, the effect of TQ in a geriatric or pediatric population is essentially unknown. There were large percentages of women in the two studies in Africa (39% in 043 and 30% in 045), but Study 045 limited enrollment to post-menopausal women. Only 3.4% of subjects were women in study 033 and 62.5% were women (10/16) in TQ-2016-02.

These limitations in demographic factors make generalization of the efficacy findings of any particular study to a larger population difficult. However, no concerning trends were seen across the studies in the different subgroups.

7.4. Summary and Conclusions

7.4.1. Summary and Conclusions – Statistics

Four randomized, double-blind, controlled, prophylactic studies in non-immune or semi-immune healthy subjects provided evidence for efficacy of TQ for prophylaxis for up to 6 months of continuous dosing.

Study 033 evaluated the efficacy of 26-week TQ and MQ prophylaxis in non-immune subjects. FDA's analysis resulted in 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 in the two groups when considering subjects withdrawn or missing as not having a prophylactic success, with a difference of -0.78% and a 95% CI [-2.39%, 3.94%]. Because it was not possible to justify a non-inferiority margin due to unknown malaria attack rates, it was not possible to definitively conclude that TQ was non-inferior to MQ. However, the Applicant did provide information that suggested 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 both treatment arms.

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

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

Although the treatment duration varied, and no studies tested the proposed regimen strictly (the final dose after exiting the malarious area was not evaluated), TQ with the proposed dose did provide statistically significant prophylactic effect in Studies 043, 045, and TQ-2016-02. Study 033 provided supportive evidence for the efficacy of TQ; even in the absence of the terminal prophylaxis dose, *P. vivax* relapse rates were similar between TQ alone and MQ followed by 14 days of PQ.

7.4.2. Summary and Conclusions - Clinical

The clinical reviewer concurs with the statistical review. The evidence provided supports efficacy of TQ for malaria prophylaxis for up to 6 months of continuous dosing in semi-immune and non-immune subjects.

8 Clinical Microbiology Review

8.1. Nonclinical Microbiology

8.1.1. Mechanism of Action

The precise mechanism by which TQ, an 8-aminoquinoline, exhibits activity against *Plasmodium* species is not known. Studies with *P. falciparum* and other protozoans suggest that TQ inhibits hematin polymerization and mitochondrial function of the parasite as well as affect the human erythrocytes. Some of the studies supporting the mechanism of action of TQ and its similarities and differences with other aminoquinolines, such as CQ and PQ, are summarized below:

8.1.1.1. Effect on hematin polymerization

Vennerstrom et al. (1999) reported that TQ inhibits polymerization of ^{14}C-hematin; the TQ 50% inhibitory concentration (IC_{50}) was 16 µM (9.31 µg/mL) that was 5-fold lower than CQ (80 µM). PQ was ineffective in inhibiting hematin polymerization even at a concentration of 2500 µM. The activity of TQ and CQ against the asexual blood stage parasites may be due to the similarity in hematin polymerization inhibitory properties of the two drugs; however, PQ does not inhibit hematin polymerization and growth of the asexual blood stage parasites.

8.1.1.2. Effect on mitochondrial function

Effect of TQ on mitochondrial function of *Plasmodium* parasites has not been reported. However, the effect of PQ on the internal structures of the mitochondria of the *P. falciparum* gametocytes has been reported (Lanners, 1991).

Studies with other protozoans, e.g., *Leishmania donovani* and *Trypanosoma brucei*, suggest that TQ can induce mitochondrial dysfunction (Carvalho et al., 2010; 2015). In *L. donovani*, TQ induced mitochondrial dysfunction was associated with the inhibition of cytochrome c reductase (respiratory complex III) activity, decreased oxygen consumption rate, increased production of reactive oxygen species (ROS) and nuclear DNA fragmentation suggesting an apoptosis-like death process. In *T. brucei*, TQ was shown to accumulate in the acidic compartments (acidocalcisomes) leading to a disruption of calcium ion homeostasis, dysfunction of the lysosomes and mitochondria as well as other organelles, increased production of ROS, induction of necrosis, and death of the parasites. PQ or CQ were not tested.

8.1.1.3. Effect on erythrocytes

Bhuyan et al. (2016) reported shrinkage of the human erythrocytes as well as phospholipid scrambling of the erythrocyte cell membrane after incubation with TQ (500 ng/mL) for 48 hours. This was associated with stimulation of Ca^{2+} entry, oxidative stress and possibly activation of casein kinase. Such a TQ induced eryptosis is similar to apoptosis of the parasites. TQ induced eryptosis may be beneficial in sequestering the intracellular parasites. PQ or CQ were not tested.

8.1.2. Activity in vitro

Methods for measurement of in vitro sensitivity of *Plasmodium* species are not standardized and limited to testing in research laboratories. The most common *Plasmodium* species used for in vitro testing is *P. falciparum*. Some of the studies supporting the activity of TQ against different stages of *P. falciparum* and other *Plasmodium* species, are summarized below.

8.1.2.1. Activity against asexual parasites in vitro

8.1.2.1.1. Plasmodium falciparum

Several studies have reported on the in vitro activity of TQ against several laboratory strains and clinical isolates of *P. falciparum*; however, the method used for testing varied. Some of the variations include, the concentrations of parasitized and uninfected erythrocytes used for culture, duration of incubation and the method used to determine inhibition of parasite growth (for details see Appendix-15.4.1, Tables 1A and 1B). The IC_{50} values against the laboratory strains and clinical isolates were ≤7.0 µg/mL and ≤19.3 µg/mL, respectively.

The activity of TQ and its enantiomers and metabolites was similar against the 4 strains of *P. falciparum* tested.

One study (Vennerstrom et al., 1999) reported a comparison of the activity of TQ with two other aminoquinolines (CQ and PQ); the TQ IC_{50} values were lower than PQ against all the 7 strains tested. The TQ IC_{50} values were similar against the CQ sensitive and resistant strains.

The sensitivity of the parasites to TQ may vary from one region to another. For example, Pradines et al. (2006) reported that TQ was more active against isolates from Djibouti (East Africa) than from Gabon (Central Africa) or Senegal (West Africa). Quashie et al. (2013) reported that the TQ IC_{50}s against the isolates from Hohoe and Cape Coast were 2 to 3-fold higher than those from Navrongo, the three sites in Ghana.

Gorka et al. (2013) reported the activity of TQ in combination with CQ or amodiaquine against HB3 (CQ-sensitive) and Dd2 (CQ-resistant) strains of *P. falciparum*. The results suggest a potential for antagonism between TQ and CQ or AQ. However, this may be due to the cytostatic culture conditions in vitro. As the activity of TQ is slower than CQ against the erythrocytic stage of the parasites, TQ was administered in combination with CQ in clinical trials (see Section 7).

8.1.2.1.2. Plasmodium vivax

Russell et al. (2003) reported the activity of TQ against 34 clinical isolates of *P. vivax* from patients, in Thailand, successfully treated with CQ. Testing was performed by a modified World Health Organization microtest for determining *P. falciparum* drug sensitivity. The number of schizonts per 200 asexual stage parasites were counted on stained smears after 24 to 36 hours of incubation (for details see Appendix 15.4.1,Table 1B). The TQ mean IC_{50} and IC_{99} (99%

inhibitory concentration) values were 9.74 and 14 µg/mL, respectively. The TQ IC_{99} value was about 88-fold higher than CQ. PQ was not tested.

8.1.2.2. Activity against gametocytes in vitro or in mosquitoes

8.1.2.2.1. Plasmodium falciparum - in vitro

Studies (Adjalleya et al., 2011; Duffy and Avery, 2013) in vitro with transgenic gametocytes of the NF54 strain of *P. falciparum* suggest that both TQ and PQ inhibit the development of gametocytes especially during early phase i.e., stage I and II (for details see Appendix 15.4.1, Tables 1C).

8.1.2.2.2. *Plasmodium vivax - in mosquitoes*

Ponsa et al. (2003) reported the activity of TQ against the gametocytes of *P. vivax*. The activity was determined by assessing oocyst and sporozoite development within the mosquitoes. Briefly, mosquitoes (*Anopheles dirus*) were fed for 30 minutes on 1 mL of blood, collected from patients, living in Western Thailand and had gametocytes in the blood. All unengorged mosquitoes were removed. On Days 4, 8, 11, and 16 post-infection, mosquitoes were fed on uninfected mice that were administered different doses of TQ and other drugs, 90 minutes prior to feeding of mosquitoes. All engorged mosquitoes were followed, by phase contrast microscopy, for the presence of oocysts in the midgut and sporozoites in the salivary gland on Days 10 and 21, respectively. The results show that TQ was most effective in decreasing the development of oocysts and sporozoites in the mosquitoes treated on Day 4. PQ was not effective in inhibiting sporozoite development (For details see Appendix 15.4.1 Table 1C).

8.1.2.3. Activity against exo-erythrocytic parasites

No studies were conducted to evaluate the activity of TQ against the liver stages of the *Plasmodium* parasite.

Reviewer's comments:
Overall, the studies suggest that TQ is effective in inhibiting the growth of asexual parasites as well as inhibiting the development of early gametocytes of P. falciparum and P. vivax. Activity against the late (mature) gametocytes was lower (only at high concentrations) than early gametocytes.

The sensitivity of the blood stage parasites to TQ may vary from one region to another. CQ resistant strains appear to be sensitive to TQ.

8.1.3. Activity in vivo (Animal Studies)

The activity of TQ was measured in murine and nonhuman primate malaria models of causal prophylaxis (pre-exposure prophylaxis and post-exposure prophylaxis), radical cure, and/or suppressive therapy.

8.1.3.1. Mice

Several studies have reported the causal prophylaxis, radical cure, and/or suppressive activity of TQ in different strains of mice, including CYP2D knock-out and humanized/CYP 2D6 knock-in mice infected with the rodent *Plasmodium* species, *P. berghei* or *P. yoelii*.

Causal prophylaxis: Mice were infected with the sporozoites of the rodent *Plasmodium* species, *P. berghei* or *P. yoelii*. Treatment with TQ was initiated at different time intervals, prior to challenge with sporozoites, on the day of exposure, or 24 hours post-exposure. The results show that TQ is effective in improving survival and preventing infection in the liver as well as blood, when administered prior to challenge or few hours post-exposure of wild type mice to the sporozoites of the *Plasmodium* species. The activity of TQ was dose-dependent and varied with the experimental conditions (for details see Appendix 15.4.2, Table 2A).

In CYP2D knock-out (KO) and/or humanized/CYP 2D6 knock-in mice, a low dose (3 mg/kg) of TQ was not effective in preventing infection. A higher TQ dose (6 mg/kg) was effective in preventing infection in the liver and blood in the CYP2D KO/CYP 2D6 knock-in mice. The studies in the KO mice suggest that TQ is active in the presence of the CYP2D gene cluster. Activity was partially restored when the dose of TQ was adjusted to account for differences between mouse CYP2D and human CYP2D6 enzyme activity.

Radical cure: Treatment with TQ was initiated after the development of parasitemia in mice infected with the sporozoites of *P. berghei*. The results show that TQ alone or in combination with CQ is effective in suppressing parasitemia and relapse (for details see Appendix-15.4.2, Table 2A).

Suppressive activity: TQ was effective as a suppressive therapy, i.e., decreased parasitemia and improved survival of mice challenged with the erythrocytic parasites of *P. berghei* (for details see Appendix-15.4.2, Table 2A).

8.1.3.2. Nonhuman primates

The activity of TQ was reported in nonhuman primates infected with:

- sporozoites of *Plasmodium cynomolgi*
- parasitized erythrocytes of *P. cynomolgi* or *Plasmodium fragile*
- parasitized erythrocytes of *P. falciparum* or *P. vivax.*

P. cynomolgi and *P. fragile* are recognized as biological counterparts of *P. vivax* and *P. falciparum* infections, respectively, in humans. *P. cynomolgi* shares some of the phenotypic and biological characteristics with *P. vivax*; for example, relapse caused by dormant hypnozoites can occur following sporozoite challenge. *P. fragile* is more virulent and, like *P. falciparum,* it undergoes cytoadherence in deep tissue capillaries leading to blockage of microvessels.

8.1.3.2.1. Sporozoites of the P. cynomolgi – Plasmodium species infecting nonhuman primates

Several studies reported the activity of TQ in rhesus macaques infected with *P. cynomolgi*. Studies were designed to measure the causal prophylactic or radical cure effects of TQ treatment.

Causal prophylaxis: Treatment was initiated at different time intervals, prior to challenge with sporozoites, on the day of exposure, or 24 to 48 hours post-exposure. The results show that TQ is effective in preventing or delaying parasitemia. The activity of TQ varied with the experimental conditions including the TQ dose. Overall, the studies support the prophylactic activity of TQ (for details see Appendix-15.4.2, Table 2 B).

Radical cure: Treatment with TQ was initiated after the development of parasitemia. The results show that TQ alone or in combination with CQ is effective in suppressing parasitemia and relapse. Anti-relapse activity is not dependent on CQ (for details see Appendix 15.4.2, Table 2B).

8.1.3.2.2. Erythrocytic parasites of the P. cynomolgi* and *P. fragile* – Plasmodium species infecting nonhuman primates

Rhesus macaques were infected IV with 10^5 parasitized erythrocytes of *P. cynomolgi* or *P. fragile*, and blood smears prepared daily to determine parasitemia. Oral treatment with TQ was initiated for 7 days when parasitemia reached approximately 5000/mm^3 in *P. cynomolgi* infected macaques or 2000/mm^3 in *P. fragile* infected macaques. Macaques were followed until Day 70 after the end of treatment. Macaques, which did not show recrudescence through Day 70, were recorded as cured. It is noted that there was a rise in parasitemia 24 to 48 hours after the first dose. TQ treatment at doses of 0.32 mg/kg/day and 1 mg/kg/day was effective in clearing parasitemia in both *P. cynomolgi* and *P. fragile* infected macaques. However, recrudescence occurred. The highest TQ dose (3.2 mg/kg/day) tested was effective in clearing parasitemia and no recrudescence was observed up to Day 70. PQ, at the same doses was not effective, in preventing recrudescence (for details see Appendix-15.4.2, Table 2B).

8.1.3.2.3. Erythrocytic parasites of P. falciparum and P. vivax – Plasmodium species infecting humans

The suppressive activity of TQ was measured against erythrocytic parasites of *P. falciparum* or *P. vivax* in nonhuman primates, that include

- Panamanian monkeys infected with *P. falciparum* or *P. vivax,* and
- Rhesus macaques including splenectomized monkeys infected with *P. vivax*.

TQ was shown to be effective in clearing or reducing parasitemia in both *P. falciparum* and *P. vivax* infected monkeys; the activity varied with the experimental design and the dose tested. Recrudescence occurred that appears to be dose-dependent (for details see Appendix 15.4.2, Table 2C).

Obaldia et al. (1997) reported the activity of TQ in combination with sub-curative doses of CQ in rhesus macaques infected with erythrocytic stage parasites of the CQ resistant strain (AMRU 1) of *P. vivax*. The results showed that a combination of TQ + CQ was more effective than either drug alone.

Reviewer's Comments:

Overall, the studies support the activity of TQ against the sporozoites, liver stages and erythrocytic stages of the Plasmodium species. Unlike PQ, TQ has activity against the blood stage parasites. The activity of TQ varied with the experimental conditions including the TQ dose. The activity of TQ was not measured, in vivo, against the drug resistant strains of Plasmodium species.

8.1.4. Drug Resistance

A potential for development of resistance of *Plasmodium* species to TQ was not evaluated.

Studies with another protozoan suggest a potential for development of resistance. Manzano et al. (2011) reported a potential for development of TQ resistance in vitro by *Leishmania major*. The mechanism of resistance appears to be due to increased glycolytic ATP synthesis and not increased efflux.

Vennerstrom et al. (1999) reported that *P. falciparum* strains/isolates that are resistant to PQ may be resistant to TQ suggesting a potential for cross-resistance (R2=0.613). However, there does not appear to be any cross-resistance with CQ.

8.2. Clinical Microbiology

Parasitological assessments were based on blood smears in all the clinical studies except Study TQ-2016-02. For Study TQ-2016-02, parasitemia was assessed by polymerase chain reaction (PCR) assay.

8.2.1. Parasitological Assessments by Blood Smears

The parasitological evaluations in the clinical trials include identification of *Plasmodium* species and measurement of parasitemia by Giemsa stained thick and/or thin blood smears. Smears were prepared from blood (without any anticoagulant) collected by finger prick for subjects enrolled in Studies 033, 043, and 045 and whole blood with EDTA for Studies 030 and 033. In general, about 200 high power fields were examined and slides read by at least 2 microscopists; if discordant results were noted, then the slides were examined by a 3rd reader. For study 030, slide reading errors were identified; several slides were shipped to Professor (b) (4) for evaluation (for details see Appendix-15.4.3).

Overall the studies show that TQ is effective for malaria prophylaxis in different countries (for details see Section 7 above). Studies 030, 033, 043, and 045 were conducted in geographic regions known to be endemic for *P. falciparum* and/or *P. viva*x resistant to different anti-malarials; sporadic *P. malariae* and *P. ovale* were reported in East Timor (Study 033) and Ghana (Study 045) at the time studies were conducted (Table 49).

P. falciparum (Study 043 – during presumptive phase and 045 - prophylactic failures) and *P. vivax* (Study 033) were identified in some of the subjects enrolled in the clinical trials (Table 49). In study 045, *P. falciparum, P. ovale* and *P. malariae* were identified in 56.2%, 2.3%, and 8.5%

subjects, respectively, prior to radical treatment with halofantrine. *P. malariae* was identified in 5 subjects (one subject in Study 043, during presumptive phase and 4 subjects in Study 045 in the placebo group) after initiation of prophylaxis.

Table 49: *Plasmodium* species known to be prevalent in the geographic regions at the time clinical studies were conducted.

Study ID; population studied (study site, country)	***Plasmodium* species[a] [malaria prevalence by *Plasmodium* species [b]]**	***Plasmodium* species (based on clinical trial)**	**Known drug resistance[c]**
030 Semi-immune residents (Kombewa, Nyanza Province, Kenya)	*P. falciparum* [In Kombewa (2002-2010), overall malaria prevalence was 47.1 %. *P. falciparum* was the primary malaria species, accounting for 97.3% to 98.3% of positive blood samples. Near study site, cumulative malaria attack rates were ~95% during the "long" and ~75% during the "short" rains. The adult population had ~90% incidence of malaria parasitemia over 10 weeks during a high transmission period.]	*P. falciparum (6.1%) in the TQ group*	Conducted in 2000. Pyrimethamine resistance was present as of 1988. Sulfadoxine resistance was first detected between1993 and 1995.
033 Healthy volunteers - Australian soldiers (Bobonaro District, East Timor)	*P. falciparum* and *P. vivax* [Malaria point prevalence rates ranged from 0 to 35.3% (*P. falciparum*, 0 to 14.4%; *P. vivax*, 0 to 16%). *P. falciparum* was the primary species (60%-80%); remainder was *P. vivax* with very sporadic *P. ovale.*]	*P. vivax* 4/492 (0.8%) in TQ arm and 1/162 (0.6%) MQ arm.	Conducted in 2000-2001. In 1999, in East Timor, *in vitro* resistance was reported to CQ, amodiaquine, and sulfadoxine/ pyrimethamine.
043 Semi-immune residents (Ndori, Nyanza Province, Kenya)	*P. falciparum* [Prevalence of malaria infection among children aged 1–9 years was 83%. *P. falciparum* (>95% of cases) was the primary species.]	**Before halofantrine treatment:** •*P. falciparum* in 172/306 (56.2%) subjects. •*P. ovale* in 7/306 (2.3%) •*P. malariae* in 26/306 (8.5 %). **Post-TQ prophylaxis:** 79 subjects with breakthrough • *P. falciparum* 78. •*P. malariae* in one subject (placebo group).	Conducted in 1997. CQ resistance was widespread. Pyrimethamine resistance was present as of 1988. Sulfadoxine resistance was first detected between 1993 and 1995.

Study ID; population studied (study site, country)	*Plasmodium* species[a] [malaria prevalence by *Plasmodium* species [b]]	*Plasmodium* species (based on clinical trial)	Known drug resistance[c]
045 Semi-immune residents (Kassena-Nankana District, Northern Ghana)	*P. falciparum* [Prevalence of smear-positive malaria ranged from 53.3% at the end of the dry season (October-April) to 84.5% at the end of the wet season (April-October). Almost all (>98%) malaria was due to *P. falciparum; P. malariae* and *P. ovale* constituted <2% of all infections The Applicant states that prior to conducting Study 045, preliminary studies had shown that for adults who had completed radical cure treatment for malaria, the 20-week cumulative incidence of re-infection by *P. falciparum* was nearly 100%.]	*P. falciparum* in all subjects except *P. malariae* in 4 subjects in the placebo group.	Conducted in 1998. CQ antimalarial efficacy decreased by 10% between 1994 and 2004. In 2002, malaria treatment failure with CQ was 6%-25%, and parasite clearance rates were sometimes below 50%.

[a] For prophylaxis studies, the *Plasmodium* species based on epidemiological findings.
[b] Prevalence based on epidemiological findings of the region, if known, when the study was conducted.
[c] Known drug resistance by the *Plasmodium* species in the geographic region when the study was conducted.
Source: NDA

8.2.2. Parasitological Assessments by PCR

The parasitological evaluations in Study TQ-2016-02 were based on real time 18S quantitative (q) PCR for the detection of *P. falciparum* asexual parasites. Although gametocytes were to be measured using *pfs25* mRNA reverse transcriptase PCR assay, the validation report and study results were not included in the NDA.

The real time 18S qPCR was performed at (b) (4) Briefly, the assay targeted three specific sites on 18S rRNA gene across the genome of *P. falciparum* (chromosome 1, 11 and 13) and utilized a fluorescent TaqMan hydrolysis probe to detect template accumulation in a PCR reaction. The calibrator used was prepared from a (b) (4) of this calibrator formed the standard that was used to create the standard curve each time testing of clinical specimens was performed. Each qPCR run included the standard curve and two negative controls (water or uninfected human blood nucleic acid extracts) with study samples. The assay validation was performed in the same laboratory where testing of clinical specimens for the Study TQ-2016-02 was performed. The performance of the qPCR assay does support the specificity of the assay for *P. falciparum* and determining the asexual parasite density (for more details see Appendix-15.4.3). The Applicant had proposed an endpoint to measure efficacy as follows:

> 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 parasites/mL and 2-fold increase within 48 hours.

The data supporting the threshold of >5,000 asexual blood stage estimated parasites/mL for evaluating efficacy was not available for review. However, the assay does support qualitative findings.

The results show that TQ administered on Days 1, 2, 3 and 10 followed by challenge on Day 13 with ~2800 erythrocytic parasites of the 3D7 strain of *P. falciparum* was effective in suppressing parasitemia in all 12 subjects; the parasites were below the limit of detection (< 0.1 estimated parasites/µL) of the PCR assay. All subjects in the placebo group were PCR positive with mean density of 39 estimated parasites/µL on Day 17; the parasite density increased over time. Malaria signs and symptoms occurred in 3/12 (25%) subjects in the TQ group with a maximum individual overall score of 2 (mild severity) and all the 4 in placebo group (mild to moderate severity) with a maximum individual overall score of 4 (for details see Section 7). The results suggest that the threshold of >5,000 estimated parasites/mL may not be appropriate as signs and symptoms of malaria were reported in subjects treated with TQ in subjects with no PCR positive findings.

Reviewer's Comments:
Overall, the studies support the prophylactic activity of TQ in areas known to be endemic for P. falciparum and P. vivax. Sporadic instances of P. malariae and P. ovale were reported in east Timor and Ghana at the time clinical trials were conducted. Also, prophylactic failures due to P. vivax in Study 033 and P. malariae in Studies 043 and 045 were reported.

8.2.3. Interpretative Criteria

The Applicant has not requested any interpretive criteria in the labeling. This is appropriate as the tests to measure in vitro sensitivity of parasites of the *Plasmodium* species are not standardized and their use is limited to research laboratories.

9 Review of Safety

9.1.1. Safety Review Approach

More than 20 clinical trials evaluating TQ were submitted by the Applicant. Most of these studies were conducted during 1992 to 2006. Phase 1, 2, and 3 single and multiple dose trials are summarized in Table 50.

Table 50. Summary of phases 1, 2, and 3 studies conducted through 30 April 2016.

Study No. (Publication)	Study Design[a]	Study Objectives	Tafenoquine Doses Administered	Population
Phase 1 Single-Dose Studies in Healthy Volunteers				
050 (Brueckner-1998b)	R, DB, PC	PK and safety in fasted state	4 -600 mg	N=75; 75M/0F
052 (Karle-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 and gender effects	400 mg	N=32;16M/16F
022	R, PG	PK and safety in fed vs fasted state and gender effects	200 mg	N=40; 20M/20F
Phase 1 Multiple-Dose Studies in Healthy Volunteers				
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-2009)	R, PC	Renal and ocular safety	200 mg daily x 3 days, then weekly x 23 weeks	N=120; 73M/47F
Phase 1 Drug-Drug Interaction Studies in Healthy Volunteers				
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
Phase 1 Single-Dose Study: Malaria Challenge in Healthy Volunteers				
053 (Brueckner-1998a)	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

Study No. (Publication)	Study Design[a]	Study Objectives	Tafenoquine Doses Administered	Population
Phase 1 Multiple-Dose Studies: Malaria Challenge in Healthy Volunteers				
054	R, DB, PC	Determine whether TQ was prophylactic against *P falciparum* malaria 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
Phase 2 and 3: Malaria Prophylaxis Studies				
006 (Lell-2000)	R, DB, PC	Malaria prevention in semi-immune subjects of Lamaréné, Gabon (highly endemic *P falciparum)*	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 *P falciparum*)	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 *P falciparum* and *P vivax*)	200 mg daily x 3 days, then 200 mg weekly throughout deployment	N=654; 632M/22F
043 (Shanksl-2001)	R, DB, PC, PG	Determine the chemosuppressive effectiveness of weekly regimens of TQ in preventing *P falciparum* parasitemia compared with placebo in semi-immune Kenyan subjects.	400 mg daily x 3days or 200 mg daily x 3 days, then 200 mg weekly for 10-15 weeks or 400 mg daily x 3days, then 400 mg weekly for 10-25 weeks	TQ groups 174; 109M/65 F
044 (Kocisko-2000, Edstein-2001b, Edstein-2003, Walsh-2004a)	R, DB, PC	Determine the efficacy of monthly doses of TQ vs. placebo in the chemoprophylaxis of multi-drug resistant *P falciparum* and *P vivax* in Thailand	400 mg daily x 3days, then 400 mg monthly	TQ n=104 Placebo n=101

Study No. (Publication)	Study Design[a]	Study Objectives	Tafenoquine Doses Administered	Population
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 3 days, then 25 mg weekly for 12 weeks; or 50 mg daily x 3 days, then 50 mg weekly for 12 weeks; or 100 mg daily x 3 days, then 100 mg weekly for 12 weeks; or 200 mg daily x 3 days, then 200 mg weekly for 12 weeks	All Groups n=509: TQ Groups n=369; 238M/131 F
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 *P vivax* 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
Phase 2: *P Vivax* Treatment Studies				
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; DB=Double-blind; PC=Placebo-controlled trial; PG=Parallel-group; O=Open-label; SS=Single sequence; TP=Two-period; NR=Nonrandomized; C=Crossover; DDI = Drug-drug interaction; AC=Active Comparator ; NC=Negative control; CQ=Chloroquine; AC=Active control; TQ=tafenoquine; M=male; F=female .

[b] Study 057was 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.

Source: NDA 210607 Module 5.3.5.3 Integrated Summary of Safety (SN18 submitted 15 February 2018), Table 1. Note that, according to the Clinical Study Report for Study 051, subjects received 750 mg TQ weekly, rather than 600 mg, as stated in the table.

Comparative trials most relevant to the evaluation of clinical safety of the TQ ACR, TQ 200

mg/day x 3 days, then 200 mg/week, are summarized in Table 51 . Four trials included a placebo arm (030, 043, 045, and 057), while two (030 and 033) had MQ as an active comparator. Specific safety issues known to be associated with quinoline antimalarials were evaluated for individual studies and in pooled analyses of the controlled studies utilizing TQ ACR for an extended time and is referred to as the 'Extended Dosing Safety Set'. Studies 030, 033, 043, 045 plus one Phase 1 study (Study 057) enrolled subjects with the TQ ACR (n=825) and constitute the Extended Dosing Safety Set.

Study 033 enrolled the most number of subjects with TQ ACR 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 healthy volunteers with a planned TQ treatment for >23 weeks (n=81), and is considered a key supportive safety study. Study 057 was designed to evaluate renal and ocular safety and enrolled civilians in the U.S. and United Kingdom, as well as non-deployed military personnel in the U.S.

Table 51. Key Trials used to Evaluate Clinical Safety

Study	Treatment Arms (*n*, safety population)	Total Number of Subjects	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)	306	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)	654	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)	235	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)	513	12 wks
057	**TQ 200 mg/d x3, then 200 mg/week (81)** Placebo (39)	120	23 wks

TQ= tafenoquine, MQ=placebo, d=days, wks=weeks

[1]*Although the planned duration of treatment for Study 030 was 24 weeks, 11 subjects overall received 24 weeks of therapy and 7 of these subjects were in the TQ group. Most subjects were exposed to TQ for < 12 weeks (72/104 [69%]).*

Pooled Analysis Groups

Pooling of data can provide a larger database to detect lower frequency events and permit explorations of possible drug-demographic or drug-disease interactions in subgroups of the population. It is acknowledged that there are inherent weaknesses of pooling safety data from trials with heterogeneous study designs. Hence, analyses of specific studies alone were also conducted to evaluate a particular adverse event. The primary pooled analysis group was the Extended Dosing Safety Set (Table 52). This pooled analysis group differs from the Applicant's pooled analysis, in that Study 044, a study which compared TQ 400 mg monthly versus placebo, was not included Extended Dosing Safety Set by the Agency.

Table 52: NDA 210607: Pooled analysis groups of clinical trials

Pooled Analysis Group	Studies included by Agency	Studies included by Applicant
Extended Dosing Safety Set	043, 045, 030, 033, 057	043, 045, 030, 033, 057, 044

Subgroups within the Extended Dosing subset 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, an assessment of the impact of deployment-related extrinsic factors contributing to adverse events in deployed military subjects (Study 033) versus non-deployed subjects (Studies 030, 043, 045, and 057) receiving the ACR was possible.

JReview Version 12.0.1-1067 or MedDRA Adverse Event Diagnostics (MAED) Version 1.8 were the programs used to conduct the analyses. Multiple occurrences of the same event in the same patient were counted only once. The majority of the key safety result tables presented in the updated ISS (SN 18, submitted 15 February 2018) could be replicated by this reviewer. When analysis results were the same as those described in the Applicant's submission, the Applicant's tables were used in this review, for the sake of efficiency. Because results from the Extended Dosing Safety Set reflect data for the TQ ACR, this pooled dataset was used for most key analyses. In addition, sub-group safety analyses of subjects in the Extended Dosing Safety Set receiving TQ ACR for 23 to 24 weeks duration was conducted by the reviewer. Please see section 9.1.5 regarding the review approach for analysis of specific safety issues.

Several disciplines were consulted during the safety review and their recommendations are incorporated in this review. These disciplines included the Division of Cardiovascular and Renal Products, Division of Neurology Products, Division of Psychiatry Products, and Division of Transplant and Ophthalmology Products in the Center for Drug Evaluation and Research (CDER), as well as the Ear, Nose and Throat Devices Branch in the Center for Devices and Radiological Health (CDRH).

9.1.2. Review of the Safety Database

Overall Exposure

A total of 3184 subjects were exposed to TQ in the clinical development program (Table 53). A total of 825 subjects received TQ ACR of 200 mg daily for 3 days, then 200 mg weekly. Five-hundred-twenty-nine of these subjects received the TQ ACR for ≥23 weeks and the majority of the subjects were non-immune.

Table 53: Summary of TQ exposure

Description	Number of subjects exposed
Clinical trials	3184
Multiple TQ doses	3008
TQ ACR[1] any duration (mean 21.2 weeks)[2]	**825**
TQ ACR ≥23 weeks – All (actual)	**529**
TQ ACR ≥23 weeks - Non-immune	522

[1]TQ ACR: TQ 200 mg daily for 3 days, then 200 mg weekly.
[2]Range:10 to 29 weeks.

During clinical development, TQ doses < 200mg, 200mg, and > 200mg were studied for median durations ranging from 1 day to ~ 25 weeks. Planned TQ exposure by dose and duration is summarized in Table 54.

Table 54: NDA 210607: Study Subject Planned Drug Exposure by Dose and Duration of Exposure

Duration	Number of Subjects who Received Tafenoquine Dosing Regimen (Study No.)									Total
	< 200 mg OD[a]	200 mg OD	<200 mg OD x 3 days, then <200 mg weekly	200 mg OD x 3 days, then 200 mg weekly[b]	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)	--	--	--	93 (003, 047, 050, 052, 053)		--	--	176
3 days	248 (006)	490 (006, 049)	--	--	161 (049)	610 (014, 043, 049, 058)		--	--	1509
3 days with concomitant medication (DDI studies[c])	--	--	--	--	--	28 (040) 34 (015)		--	--	62
6 days	--	--	--			11 (047)		--	--	11
7 days	--	--	--		--	52 (047)		--	--	52
10 weeks							24 (051)			24
10-15 weeks	--	--	--	55 (043)	--	--		--	--	55
10-25 weeks	--	--	--					59 (043)	--	59
12 weeks	--	--	280 (045)	93 (045)	--	--		--	--	373

Duration	Number of Subjects who Received 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	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	
20 weeks[d]									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] OD=once daily.
[b] ACR=Anticipated Clinical Regimen.
[c] DDI=Drug-drug Interaction. These included: Study 040 for DDI with midazolam, flurbiprofen, and caffeine; Study 015 for DDI with desipramine.
[d] Protocol stipulated a dosing duration of 5 months, equivalent to ~ 20 weeks.

Source: NDA 210607, Module 5.3.5.3, Integrated Summary of Safety, Table 4. (SN18 submitted 15 February 2018).

In the Extended Dosing Set, the overall mean duration of exposure in the TQ ACR group was

21.2 weeks, with a range from < 10 to 29 weeks (Table 55, Table 56). In the studies with a planned duration of TQ ACR exposure of 23 to 24 weeks (030, 033, 057), the mean duration of exposure was 23.3 weeks (SD 7.93, median 27.6, min 0.1, max 29.6). Note that, although the planned duration of treatment for Study 030 was 24 weeks, 11 subjects overall received 24 weeks of therapy and 7 of these subjects were in the TQ group. Most subjects were exposed to TQ for <12 weeks (72/104 [69%]). The Applicant seeks an indication where the TQ ACR will be used up to 6 months (24 weeks). There were 529 subjects exposed to the TQ ACR for ≥23 weeks.

Table 55: Duration of actual TQ exposure for subjects receiving TQ ACR– Extended Dosing Safety Set

Actual Study Drug Exposure (weeks)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	Study ID (number of subjects exposed to TQ ACR)
<10	103 (12.5%)	175 (59.3%)	71 (23.0%)	**030** (64), **033** (6), **043** (6), **045** (14), **057** (13)
10 to <16	167 (20.2%)	87 (29.5%)	68 (22.0%)	**030** (19), **033** (10), **043** (48), **045** (79), **057** (11)
16 to <23	26 (3.2%)	3 (1.0%)	6 (1.9%)	**030** (14), **033** (5), **043** (1), **057** (6)
23 to 24	58 (7.0%)	30 (10.2%)	7 (2.3%)	**030** (6), **033** (1), **057** (51)
>24	471 (57.1%)	0	157 (50.8%)	**030** (1), **033** (470)

Table 56: Drug exposure in studies that utilized the TQ ACR, Placebo and MQ Groups.

	TQ 200 mg x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg x 3 days, then 250 mg weekly (n=309)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 045, 057**	**030, 033, 045**
Duration of Exposure (weeks)			
Mean (SD)	21.2 (8.6)	9.4 (5.9)	18.9 (9.6)
Median	26.4	7.9	25.9
Min, Max	0.1, 29.6	0.1, 24.0	0.3, 29.6
Subjects (n, %) with Exposure ≥ 24 weeks	475 (57.6%)	0	158 (51.1%)
Number of Study Doses			
Mean (SD)	23.8 (8.60)	12 (5.8)	21.6 (9.61)
Median	29.0	10	28.0
Min, Max	1, 32	1, 27	2, 32

Source: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 15. Note, in the reviewer's analysis, there was one subject who received placebo for 24 weeks in Study 030. Also, the reviewer's describes subjects exposed to TQ for greater than 24 weeks, while the Applicant uses greater than or equal to 24 weeks.

Relevant characteristics of the safety population:

Demographics

There were 825 subjects across 5 studies (Studies 030, 033, 043, 045, and 057) who received the TQ ACR.

In the Extended Dosing Safety Set, most subjects were 20 to 49 years old (82%) and male (84%) (Table 57). In addition, 64% of subjects were White, while 31% of the subjects were African.

In the studies with a planned duration of TQ ACR exposure of 23 to 24 weeks (030, 033, 057), demographics were similar to the Extended Dosing Safety Set group, with the exception of race. The majority of subjects were 20 to 49 years old (87%) and male (87%). However, 78% of subjects were White, while 15% of the subjects were African.

Table 57. Subject demographics in Extended Dosing Safety Set, (Studies 030, 033, 043, 045, and 057)

Characteristics	**Category**	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Sex [n (%)]	Female	133 (16.1%)	111 (37.6%)	55 (17.8%)
	Male	692 (83.9%)	184 (62.4%)	254 (82.2%)
Age Category [n (%)]	<20	81 (9.8%)	40 (13.6%)	41 (13.3%)
	>=50	67 (8.1%)	57 (19.3%)	22 (7.1%)
	20-49	677 (82.1%)	198 (67.1%)	246 (79.6%)
Age >=18 [n (%)]	Age Category >=18	823 (99.8%)	293 (99.3%)	307 (99.4%)
Age >=12 to <18 [n (%)]	Age Category >=12 to <18	2 (0.2%)	2 (0.7%)	2 (0.7%)
Race Group [n (%)]	African	252 (30.6%)	256 (86.8%)	147 (47.6%)
	Asian	9 (1.1%)	0	0
	Black	26 (3.2%)	10 (3.4%)	0
	Hispanic or Latino	3 (0.4%)	1 (0.3%)	0
	Other: Australian Aboriginal	5 (0.6%)	0	1 (0.3%)
	Other: Australian Islander	1 (0.1%)	0	1 (0.3%)
	Other: Caribbean Islander	1 (0.1%)	0	0
	Other: Multiracial Identity	0	2 (0.7%)	0
	Other: Pacific Islander	1 (0.1%)	0	0
	Papua New Guinean	1 (0.1%)	0	0
	White	526 (63.8%)	26 (8.8%)	160 (51.8%)
Race [n (%)]	Asian	9 (1.1%)	0	0

Characteristics	Category	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)
	Australian Aboriginal	5 (0.6%)	0	1 (0.3%)
	Black or African American	278 (33.7%)	266 (90.2%)	147 (47.6%)
	Other	7 (0.9%)	3 (1.0%)	1 (0.3%)
	White	526 (63.8%)	26 (8.8%)	160 (51.8%)

Special considerations

In Phase 2-3 malaria prophylaxis studies, subjects with different inherent malaria immunity (non-immune Australian military personnel and semi-immune African residents) were studied. There were 252 semi-immune subjects (Studies 030, 043, 045) enrolled in African studies where anti-malarial pretreatment was administered to clear any existing parasites before prophylactic TQ regimen was initiated. There were 573 non-immune subjects who did not receive pre-treatment, primarily ADF military personal on active duty (Study 033,) and healthy volunteers enrolled in a targeted renal-ocular safety study (Study 057). Most subjects exposed to the TQ ACR for ≥23 weeks were non-immune (semi-immune n=7; non-immune n=522).

Adequacy of the safety database:

Although the Applicant has an adequate number of subjects for a safety assessment of 6 months' exposure according to the 2005 FDA Guidance for Pre-market Safety (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126958.pdf), for the indication of prophylaxis where the product is administered to generally healthy individuals, a database of 529 subjects exposed to the drug regimen for the proposed dose and duration is considered relatively small. Regarding products intended for long-term treatment of non-life-threatening conditions, (e.g., continuous treatment for 6 months or more or recurrent intermittent treatment where cumulative treatment equals or exceeds 6 months), the ICH and FDA have generally recommended that 1500 subjects be exposed to multiple doses of the investigational product (with 300 to 600 exposed to relevant doses for 6 months, and 100 exposed to relevant doses for 1 year). In this Application, a total of 471 subjects were exposed to the ACR for 6 months or greater (≥24 weeks), with 3008 total subjects exposed to TQ in multiple doses. Furthermore, 522 non-immune subjects were exposed to the ACR for ≥23 weeks. The Applicant currently proposes an indication using TQ up to 6 months.

Reviewer Comment: *The safety database is adequate to allow review of major adverse events associated with 6 month TQ ACR exposure. Adverse events of low incidence, or associated with greater than 6-month exposure, cannot be ascertained.*

9.1.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The majority of study level data for the safety review were only contained in the ISS datasets, which combined data from 21 studies (Table 58). Traceability of data from case report forms to legacy clinical datasets and conversion to ISS datasets could not be confirmed for several studies. Case report forms with patient level data were not submitted for most studies contained in the ISS.

Different and outdated Medical Dictionary for Regulatory Activities (MedDRA) versions for the studies precluded any comparative analyses outside of the ISS for studies with SDTM datasets. For those studies where the Applicant provided the individual study data, the number of subjects in the ISS ADSL dataset is consistent with the study's tabulation dataset.

Table 58: Summary of 21 studies comprising Integrated Summary of Safety dataset, and individual study data.

Study	Subjects in ISS ADSL	Individual Study Data Submitted
003	32	None
006	426	ADPC only
014	58	None
015	34	None
022	40	ADPC only
030	518	None
033	663	Full SDTM and ADaM
040	28	ADPC and ADPP only
043	249	ADSL and ADEFF only
044	263	None
045	868	Full SDTM and ADaM
047	124	None
049	1,558	None
050	75	None
051	36	None
052	18	None
053	6	None
054	12	None
057	121	None
058	70	ADSL and ADEFF only
933	183	Some SDTM and ADaM

Source: NDA 210607 JumpStart Data Fitness Session, Slide 44.

Input from the Office of Computational Science's JumpStart team was obtained to evaluate the key datasets. The Applicant submitted an updated ISS report on 15 February 2018 (SN18).

In addition, the report for a Thorough QT (TQT) study conducted by GlaxoSmithKline (GSK) was available for review through a right of reference to GSK IND; however, TQT datasets and ECG waveforms were not available. The Applicant submitted legacy datasets with ECG data for review by the QT-IRT team on 26 February 2018.

Finally, source documents for Studies 043 and 045 (conducted in in Kenya and Ghana, respectively) which contribute to substantial evidence for efficacy of TQ for malaria prophylaxis were not available for an onsite audit. Data obtained from Studies 043 and 045 are included in the safety analyses. Data variability in Study 043 and Study 045 was examined in the ISS

datasets for the following: 1. Birthdays; 2. Enrollment preference; 3. Weekend enrollment; 4. Constant findings; and 5. Digit preference. The only notable data variability report was Birthdays. There were a high number of subjects enrolled in study 045 born on June 15th of various years. The study 045 Clinical Study Report (CSR) Methods of Analysis section 2.6.4 notes that 'since birthdays were not known, all subjects' birthdays are recorded as the midpoint of the year of birth (i.e. 15th June)'. Similarly, in study 043, there were a high number of subjects born on January 1st of various years. A possible explanation could not be located in the study 043 CSR. However, it would be reasonable to assume that subjects' birthdays were not known and recorded as the beginning of the year of birth (i.e. 1st Jan).

Reviewer comment: *The reviewer conducted the majority of the safety analyses on the ISS dataset. However, several studies included in the ISS datasets were conducted more than 20 years ago and traceability of data from CRFs to Legacy Clinical Datasets and conversion to ISS datasets could not be verified for most studies. This may be considered an issue for data integrity. Note that an inspection of Study 033, a key study used for safety analyses was conducted and the data were considered reliable.*

Categorization of Adverse Events

Safety was assessed through vital sign measurements, monitoring of clinical signs and symptoms, physical examinations, clinical laboratory testing, and monitoring of adverse events (AEs). Selected studies also targeted safety assessments for TQ's ocular, cardiac, hematologic and renal effects.

In the ISS dataset, AEs were coded per MedDRA, Version 15.0 and summarized by preferred term and body system. In addition, for studies where AEs were initially coded per the World Health Organization (WHO) Adverse Reaction Terminology (ART) dictionary, the Applicant re-coded AEs per MedDRA, Version 15.0. Records in the ISS ADAE dataset match approximately 99% to MedDRA version 15.0. AEs not found in MedDRA version 15.0 would be excluded from analysis tools using MedDRA dictionaries. See Table 59.

Table 59: Adverse events in Integrated Summary of Safety not found in MedDRA version 15.0

AEDECOD	Record Count
Unknown	1
Headache Tension	2
Laceration	77
Tinea Infection	19

Source: NDA 210607 JumpStart Data Fitness Session, Slide 54.

Severity was assessed by the Investigator as Mild, Moderate, or Severe.

ISS safety analyses used the 'Safety Analysis Set', defined as all patients who had been

randomized and received at least one dose of study drug. Unless otherwise noted, 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.

No inferential statistics were conducted for the ISS safety analyses.

Reviewer comment: *The Applicant's categorization of adverse events is acceptable. When the Applicant's tables are shown in the review, the Clinical Reviewer conducted separate analyses which replicated the Applicant's results.*

Routine Clinical Tests

Clinical laboratory evaluations included hematology and serum chemistry. Because the laboratory data of the original studies were collected according to differing schedules, a mock visit schedule was defined for all studies, to allow for mapping and comparisons of multiple studies. The newly defined visits included: Baseline, Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Week 2, 3-4, 6-8, 10, 12, 16-18, 20, and 24-26 and Follow-up Weeks 1-2, 3-4, 6-8 and 12. Baseline was defined as the last non-missing measurement on or prior to the first study drug dosing. Data collected during unscheduled visits, or visits marked as 'additional', were incorporated using the laboratory date relative to the treatment start date. Unscheduled visits which occurred after the last treatment, but not within the same treatment window as another scheduled visit, were incorporated with the follow-up visit. Follow-up visits were summarized separately from prophylactic visits regardless of the timing in which the follow-up visits occurred. Summary descriptive statistics for laboratory values and changes from baseline were tabulated for each visit by treatment group. If there was no pre-dose laboratory data, then change from baseline was not calculated.

In contrast to laboratory measurements, a different approach for vital signs was taken. Per the Applicant, visits where vital signs were collected were mapped using weekly visits in order to best utilize the amount of weekly vital signs data collected for individual studies. Descriptive statistics for change from baseline were produced for vital signs assessed on post-baseline visits.

Disposition

In the Extended Dosing Safety Set, 656 (79.5%)subjects exposed to the TQ ACR completed the prophylactic phase, (Table 60). A total of 169 (20.5%) subjects in the TQ ACR group withdrew from the study. The top reasons for withdrawal in this subset was adverse experience (n=19 [2.3%]) and insufficient therapeutic effect (n=90 [10.9%]); both reasons for withdrawal are numerically higher than that observed in subjects receiving TQ loading doses only.

Table 60: Subject Disposition –Extended Dosing Safety Set

	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo** (n=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Disposition			
Completed study	656 (79.5%)	89 (30.2%)	205 (66.3%)
Withdrew from study	169 (20.5%)	206 (69.83%)	104 (33.66%)
Reason for Withdrawal			
Adverse Experience	19 (2.3%)	1 (0.3%)	5 (1.6%)
Clinically Significant Ophthalmic Findings	1 (0.1%)	1 (0.3%)	0 (0%)
Clinically Significant Renal Findings	1 (0.1%)	0 (0%)	0 (0%)
Did Not Meet Eligibility Criteria	0 (0%)	2 (0.7%)	0 (0%)
Insufficient Therapeutic Effect	90 (10.9%)	177 (60.0%)	89 (28.8%)
Lost to Follow-up	11 (1.3%)	9 (3.1%)	1 (0.3%)
Moved Outside of Endemic Area with no Reported Malaria Infection	6 (0.7%)	0 (0%)	1 (0.3%)
Other	17 (2.1%)	5 (1.7%)	3 (1.0%)
Protocol Deviation	8 (1.0%)	3 (1.0%)	3 (1.0%)
Unknown	16 (1.9%)	8 (2.7%)	2 (0.7%)

Reviewer comment: *The percentage of subjects who withdrew from the study due to insufficient therapeutic effect in the TQ ACR group is 10.9%. Please refer to Section 7, Statistical and Clinical Evaluation for details on the efficacy assessment.*

9.1.4. Safety Results

Summary of Adverse Events

A summary of subjects completing each trial in the Extended Dosing Safety Set, and subjects experiencing serious adverse events (SAEs) and treatment emergent adverse events (TEAEs), is included in Table 61. Because this is a pooled analysis of heterogeneous studies, cross-group comparisons were not made.

Table 61: Summary of Adverse Events – Extended Dosing Safety Set

Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Completed Study	656 (79.5%)	89 (30.2%)	205 (66.3%)
Deaths[1]	0	0	0
At least one SAE	47 (5.7%)	10 (3.4%)	11 (3.6%)
Withdrawn due to SAE	11 (1.3%)	1 (0.3%)	2 (0.6%)
At least one TEAE	692 (83.9%)	189 (64.1%)	249 (80.6%)
Withdrawn due to TEAE	34 (4.1%)	10 (3.4%)	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 (Subject (b) (6), Study 045). Subject (b) (6), was a 53-year-old Ghanaian male randomized to receive TQ 50 mg weekly. The patient had been experiencing abdominal pain before study entry, which was not reported to investigators at enrollment. The patient was hospitalized for abdominal pain and dysentery at 75 days after his first TQ dose. A differential diagnosis of hepatocellular carcinoma, abdominal tuberculosis and cirrhosis was made, and treatment with study medication was stopped. 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. Hepatocellular carcinoma was reported as a serious adverse event.

Reviewer comment: *It is unlikely that the reported death is related to TQ exposure. There were no deaths reported in patients receiving the ACR.*
Note that the death flag in the revised ISS dataset is missing for Subject (b) (6) and the outcome of the adverse event is listed as 'unknown'. However, the dictionary derived term, 'hepatic neoplasm malignant' and the flag for 'withdrawn due to AE' is there for this subject. The Applicant does report this subject as a death in their revised ISS Report.

Serious Adverse Events

A total of 49 SAEs were reported among 47 (5.7%) subjects who received the TQ ACR (Table 62). SAEs found in the TQ arm, which were not identified in the placebo arm, 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%]). The majority of SAEs in the Injury, poisoning, and procedural complications SOC and in the Infections and Infestations SOC in the TQ ACR group were in subjects enrolled in Study 033 and are considered not related to TQ.

Table 62: Serious Adverse Events: TQ ACR versus Placebo and MQ

	TQ 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily x 3 days, then 250 mg weekly (n=309)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 045, 057**	**030, 033, 045**
Total Number of Serious Adverse Events	49	11	12
Number (%) of Subjects with at Least One Serious Adverse Event	47 (5.7%)	10 (3.4%)	11 (3.6%)
Infections and Infestations	20 (2.4%)	7 (2.3%)	4 (1.3%)
Malaria	2 (0.2%)	3 (1.0%)	0
Pneumonia	1 (0.1%)	2 (0.68%)	1 (0.3%)
Amebic colitis	3 (0.4%)	0	0

	TQ 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily x 3 days, then 250 mg weekly (n=309)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 045, 057**	**030, 033, 045**
Cellulitis	2 (0.2%)	0	0
Gastroenteritis	3 (0.4%)	0	0
Orchitis	1 (0.1%)	0	1 (0.3%)
Tonsillitis	1 (0.1%)	1 (0.3%)	0
Appendicitis	1 (0.1%)	0	0
Cholera	1 (0.1%)	0	0
CMV infection	0	0	1 (0.3%)
Dysentery	1 (0.1%)	0	0
Helminth infection	1 (0.1%)	0	0
Hookworm infection	0	0	1 (0.3%)
Periorbital cellulitis	1 (0.1%)	0	0
P falciparum infection	0	1 (0.3%)	0
Urinary tract infection	1 (0.1%)	0	0
Viremia	1 (0.1%)	0	0
Eye Disorders	7 (0.8%)	1 (0.3%)	1 (0.3%)
Keratopathy	5 (0.6%)	0	0
Retinal Disorder	2 (0.2%)	0	1 (0.3%)
Metamorphopsia	0	1 (0.3%)	0
Injury, Poisoning, and Procedural Complications	6 (0.7%)	1 (0.3%)	2 (0.6%)
Thermal Burn	2 (0.2%)	0	0
Arthropod Bite	0	0	1 (0.3%)
Arthropod Sting	0	0	1 (0.3%)
Fall	1 (0.1%)	0	0
Gunshot Wound	1 (0.1%)	0	0
Limb Injury	1 (0.1%)	0	0
Road Traffic Accident	0	1 (0.3%)	0
Upper Limb Fracture	1 (0.1%)	0	0
Wound	1 (0.1%)	0	0
Gastrointestinal Disorders	3 (0.4%)	1 (0.3%)	1 (0.3%)
Abdominal Pain	1 (0.1%)	0	1 (0.3%)
Diarrhea	1 (0.1%)	0	0
Vomiting	0	1 (0.3%)	0
Abdominal Pain Upper	1 (0.1%)	0	0
Irritable Bowel Syndrome	1 (0.1%)	0	0
Investigations	5 (0.6%)	2 (0.7%)	0
GFR decreased	5 (0.6%)	2 (0.7%)	0
Nervous System Disorders	2 (0.2%)	0	0

	TQ 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily x 3 days, then 250 mg weekly (n=309)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 045, 057**	**030, 033, 045**
Headache	1 (0.1%)	0	0
Loss of Consciousness	0	0	0
Visual Field Defect	1 (0.1%)	0	0
Skin and Subcutaneous Tissue Disorders	2 (0.2%)	0	1 (0.3%)
Ingrown nail	2 (0.2%)	0	0
Rash	0	0	1 (0.3%)
Psychiatric Disorders	1 (0.1%)	0	1 (0.3%)
Anxiety	0	0	1 (0.3%)
Suicide Attempt	1 (0.1%)	0	0
Blood and Lymphatic System Disorders	1 (0.1%)	0	0
Hemolytic anemia	1 (0.1%)	0	0
Pregnancy, Puerperium, and Perinatal Conditions	0	0	1 (0.3%)
Ectopic Pregnancy	0	0	1 (0.3%)

Source: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 24.

SAEs leading to study discontinuation are discussed in the section on Dropouts and/or Discontinuations Due to Adverse Effects.

Reviewer comment: *SAEs of concern occurring in subjects exposed to the TQ ACR which should be reflected in labeling include 'keratopathy', 'retinal disorder', 'abdominal pain', and 'glomerular filtration rate decreased'. In addition, the association of TQ ACR exposure to the following SAEs cannot be ruled out: 'suicide attempt' and 'hemolytic anemia'. See section on Serious Adverse Events Leading to Discontinuation for details.*

Dropouts and/or Discontinuations Due to Adverse Effects

Adverse Events Leading to Study Discontinuation

In the TQ Extended Dosing Safety Set ACR group, 47 (5.7%) of 825 subjects experienced an SAE and 34 (4.1%) of 825 subjects developed a TEAE that led to study discontinuation. Because this is a pooled analysis of heterogeneous studies, it is difficult to draw comparisons with the Placebo and MQ groups.

In the TQ ACR group, the most common TEAEs leading to study discontinuation were 'investigations' TEAEs (11 subjects), including increased ALT (6 subjects), decreased hemoglobin (3 subjects), and decreased GFR (2 subjects). The second most common reasons for discontinuations were 'injury, poisoning, and procedural complications' (6 subjects) and 'infections and infestations' (6 subjects). Note that the TQ ACR group includes subjects from

Study 033 which enrolled deployed military personnel. All subjects who discontinued due to increased ALT and decreased hemoglobin were enrolled in Study 045, where minor deviations in laboratory parameters led to study discontinuation. See Table 63.

TEAEs leading to study drug withdrawal were the same as study withdrawal, with the exception of lactose intolerance which was a reason for withdrawal from the study.

Table 63. Adverse events leading to discontinuation: TQ ACR versus placebo and MQ groups – Extended Dosing Safety Set.

	TQ 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily x 3 days, then 250 mg weekly (n=309)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 045, 057**	**030, 033, 045**
Total Number of SAEs	49	11	12
Total Number (%) of Subjects with at Least One SAE	47 (5.7%)	10 (3.4%)	11 (3.6%)
Total Number of Adverse Events Leading to Discontinuation	46	10	7
Number (%) of Subjects with at Least One Adverse Event Leading to Discontinuation	34 (4.1%)	10 (2.5%)	5 (1.6%)
Investigations	11 (1.3%)	3 (1.2%)	0
ALT increased	6 (0.7%)	1 (0.3%)	0
Hemoglobin decreased	3 (0.4%)	1 (0.3%)	0
GFR decreased	2 (0.2%)	0	0
Platelet count decreased	0	1 (0.3%)	0
Infections and Infestations	6 (0.7%)	5 (1.3%)	1 (0.3%)
Malaria	4 (0.5%)	5 (1.3%)	0
CMV hepatitis	0	0	1 (0.3%)
Pneumonia	1 (0.1%)	0	0
Viral infection	1 (0.1%)	0	0
Injury, Poisoning, and Procedural Complications	6 (0.7%)	0	0
Fall	1 (0.1%)	0	0
Gunshot wound	1 (0.1%)	0	0
Joint injury	1 (0.1%)	0	0
Meniscus lesion	1 (0.1%)	0	0
Soft tissue injury	1 (0.1%)	0	0
Thermal burn	1 (0.1%)	0	0
Upper limb fracture	1 (0.1%)	0	0
Gastrointestinal Disorders	2 (0.2%)	0	1 (0.3%)
Abdominal pain	0	0	1 (0.3%)
Abdominal pain upper	1 (0.1%)	0	0
Irritable bowel syndrome	1 (0.1%)	0	0

	TQ 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily x 3 days, then 250 mg weekly (n=309)
Musculoskeletal and Connective Tissue Disorders	2 (0.2%)	0	1 (0.3%)
Musculoskeletal pain	2 (0.2%)	0	0
Arthralgia	0	0	1 (0.3%)
Nervous System Disorders	2 (0.2%)	1 (0.3%)	0
Headache	0	1 (0.3%)	0
Hyperesthesia	1 (0.1%)	0	0
Visual field defect	1 (0.1%)	0	0
Psychiatric Disorders	2 (0.2%)	0	1 (0.3%)
Anxiety	0	0	1 (0.3%)
Depression	1 (0.1%)	0	0
Suicide attempt	1 (0.1%)	0	0
Blood and Lymphatic System Disorders	2 (0.2%)	0	0
Hemolytic anemia	2 (0.2%)	0	0
Eye Disorders	1 (0.1%)	1 (0.3%)	0
Metamorphopsia	0	1 (0.3%)	0
Night blindness	1 (0.1%)	0	0
Visual acuity reduced	1 (0.1%)	0	0
Skin and Subcutaneous Tissue Disorders	1 (0.1%)	0	1 (0.3%)
Rash	1 (0.1%)	0	1 (0.3%)
Hepatobiliary Disorders	1 (0.1%)	0	0
Hyperbilirubinemia	1 (0.1%)	0	0
Jaundice cholestatic	1 (0.1%)	0	0
Metabolism and Nutrition Disorders	1 (0.1%)	0	0
Lactose intolerance	1 (0.1%)	0	0

Source: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 26.

Serious Adverse Events Leading to Discontinuation

There was only one subject with an SAE leading to study discontinuation in the placebo group, metamorphopsia (n=1). In the MQ group, there were two subjects, each with one SAE leading to discontinuation, 'anxiety' (n=1) and 'rash' (n=1).

In the TQ Extended Dosing Safety Set ACR, there were 11 subjects with SAEs leading to study discontinuation including: 'hemolytic anemia' (n=1), glomerular filtration rate decreased (n=2), 'visual field defect' (n=1), and 'suicide attempt' (n=1). Other SAEs leading to discontinuation in the ACR group include 1 subject each for 'abdominal pain upper', 'irritable bowel syndrome', 'pneumonia', 'fall', 'gun shot wound', 'thermal burn', and 'upper limb fracture' (Table 64). There was one subject in the TQ group withdrawn from the study due to pregnancy. In the TQ ACR group, SAEs leading to study withdrawal occurred within 16 weeks of actual exposure.

Table 64: Serious Adverse Events Leading to Study Drug Discontinuation or Study Withdrawal – Integrated Summary of Safety Dataset – Safety Population

USUBJID	Actual Treatment	Age (years)	Sex	Race	Start Day	Duration (days)	System Organ Class	Dictionary Derived Term	Verbatim Term	Severity	Outcome	Causality (by Investigator)
(b) (6)	TQ 200 mg	25	M	Black or African American	18	5	Infections and infestations	Pneumonia	PNEUMONIA	SEVERE	RECOVERED/ RESOLVED	UNLIKELY
	TQ 200 mg	31	F	Black or African American	4	25	Blood and lymphatic system disorders	Hemolytic anemia	HEMOLYTIC ANAEMIA	MILD	RECOVERED/ RESOLVED	POSSIBLE
	TQ 200 mg	25	M	White	44	230	Gastrointestinal disorders	Irritable bowel syndrome	IRRITABLE BOWEL SYNDROME	MODERATE	RECOVERED/ RESOLVED	UNLIKELY
	TQ 200 mg	21	M	White	52	187	Injury, poisoning and procedural complications	Gun shot wound	GUN SHOT WOUNDS	SEVERE	RECOVERED/ RESOLVED	NOT RELATED
	TQ 200 mg	22	M	White	21	17	Gastrointestinal disorders	Abdominal pain upper	UPPER ABDOMINAL PAIN	MODERATE	RECOVERED/ RESOLVED	POSSIBLE
	TQ 200 mg	21	M	White	90	51	Injury, poisoning and procedural complications	Thermal burn	BURNS	SEVERE	RECOVERED/ RESOLVED	NOT RELATED
	TQ 200 mg	24	M	Black or African American	9	3	Psychiatric disorders	Suicide attempt	VOLUNTEER BECAME ACUTELY INTOXICATED WITH ETHANOL. FAMILY REPORTED THAT HE HAD ALSO TAKEN POISON FOR SUICIDE	SEVERE	RECOVERED/ RESOLVED	NOT RELATED
	TQ 200 mg	21	M	White	88	175	Investigations	Glomerular filtration rate decreased	27.2 % DECLINE IN CONRAY CLEARANCE	MILD	RECOVERED/ RESOLVED	UNLIKELY
	TQ 200 mg	45	F	White	85	39	Investigations	Glomerular filtration rate decreased	REDUCTION IN GFR GREATER THAN 20%	MILD	RECOVERED/ RESOLVED	UNLIKELY
	TQ 200 mg	43	F	White	3	68	Injury, poisoning and procedural complications	Fall, Upper limb fracture	FALL CAUSING FRACTURE ELBOW	SEVERE	RECOVERED/ RESOLVED	NOT RELATED
	TQ 200 mg	45	F	White	22	40	Nervous system disorders	Visual field defect	REDUCTION IN VISUAL FIELDS BY MORE THAN 10 DB AT A GIVEN POINT	MILD	RECOVERED/ RESOLVED	POSSIBLE
	MQ 250 mg	18	M	Black or African American	3	4	Psychiatric disorders	Anxiety	SEVERE ANXIETY REACTION	SEVERE	RECOVERED/ RESOLVED	POSSIBLE
	MQ 250 mg	30	M	White	56	65	Skin and subcutaneous tissue disorders	Rash	SKIN RASH	MODERATE	RECOVERED/ RESOLVED	UNLIKELY
	Placebo	39	M	White	85	29	Eye disorders	Metamorphopsia	AMSLER GRID METAMORPHOPSIA IN BOTH EYES	MILD	RECOVERED/ RESOLVED	UNLIKELY

Note: TQ=tafenoquine; MQ=mefloquine; M=male; F=female. Subjects in TQ arm received 200 mg daily for 3 days, then 200 mg weekly.

Case narratives for the 5 SAEs leading to study discontinuation relevant to safety concerns for TQ follow.

'Hemolytic anemia' (n=1)

- Subject (b) (6) (Study 030) was a 31 year old female in the TQ group who developed mild hemolytic anemia on Day 3 of the study. Her G6PD status was recorded as normal on two occasions, using the same technique, prior to entering the study. At baseline her bilirubin was slightly elevated at 38.5 umol/L (reference range 0.0-34.2 umol/L) which had increased to 174.4- umol/L three days later. At baseline her hemoglobin (14.4 g/dL) and hematocrit (44%) values were within reference range, six days later both had become out of range (hemoglobin 9.0 g/dL (ref 10-18 g/dL), hematocrit 28.1% (ref 31-51%). The investigator initially suspected acute hepatitis but after additional examinations concluded the signs and symptoms were most consistent with hemolytic anemia. Cholestatic hepatitis and bilirubinemia were also reported in the same subject. She was treated with multivitamins and ferrous sulfate and the event resolved after 25 days. The investigator considered the event to have a suspected relationship to study treatment and the subject was withdrawn from the study.

Reviewer comment: *TQ exposure may be related to hemolytic anemia in this case.*

'Glomerular filtration rate decreased' (n=2)

- *Subject* (b) (6) *(Study 057):* This 22-year-old male subject was enrolled in a safety study evaluating the renal and ophthalmic effects of TQ 200 mg for 6 months in healthy volunteers. The subject received oral TQ 200 mg once daily for three days, followed by oral TQ 200 mg once weekly for 23 weeks; 87 days after the first dose of the investigational product, and one week after the last dose, results of a Conray clearance showed a 27.2% decline in the subject's glomerular filtration rate. At baseline, the Conray clearance was 170.9 ml/min. At week 12, the Conray clearance was 108 ml/min. A repeat Conray clearance at week 12 was 124.4 ml/min. Creatinine was 1.1 mg/dl at baseline and 1.3 mg/dl at 12 weeks. Microalbuminuria remained normal. There was no active urinary sediment or proteinuria. The investigator thought that most likely the baseline hyperfiltration value was spuriously elevated, and consulted with the nephrology service who attributed the high baseline GFR to chamomile tea ingestion. A renal/bladder ultrasound on (b) (6) was normal with no evidence for hydronephrosis or renal mass. Per the protocol, this event was clinically significant (or requiring intervention). Treatment with investigational product was discontinued due to this event, and the subject was withdrawn from the study. The event was considered resolved after 168 days. The investigator reported the serious event as unlikely related to treatment with investigational product. The investigator also considered the serious event to be possibly associated with the protocol design.

Reviewer comment: *TQ exposure may be related to decreased GFR in this case.*

- *Subject* (b) (6) *(Study 057):* This 45-year-old female subject was enrolled in a safety

study evaluating the renal and ophthalmic effects of TQ 200 mg for 6 months in healthy volunteers. Baseline glomerular filtration rate (GFR): 113 ml/min (30 minutes), 140 ml/min (60 minutes) and 116 ml/min (90 minutes) The subject received oral TQ 200 mg once daily for three days, followed by oral TQ 200 mg once weekly for 23 weeks, commencing. Approximately 12 weeks (83 days) after commencing investigational product, the subject developed 21 % decrease in GFR considered to be serious as defined per protocol. GFR values were 71 ml/min at 30 minutes, 106 ml/min at 60 minutes and 115 ml/min at 90 minutes (average= 97 ml/min), serum creatinine was 74 umol/L and blood urea was 3.3 mmol/L (normal ranges unspecified). Therapy with investigational product was discontinued and the subject withdrawn from the study. GFR values at week 13 were 97 ml/min at 30 minutes, 100 ml/min at 60 minutes and 90 ml/min at 90 minutes (average= 96 ml/min, a 22% reduction in the GFR), serum creatinine was 73 umol/L and blood urea was 4.9 mmol/L. Apart from the decrease in GFR, the subject was clinically well. At week 17, the average GFR was 68 ml/min, a 44% reduction in the GFR, serum creatinine was 72 umol/L, blood urea was 3.9 mmol/L and creatinine clearance was estimated to be 86 ml/min. The investigator considered that the decreased GFR was unlikely related to the investigational product, and cited variability of GFR measurements as a possible cause. Re-testing of the samples showed an average GFR at baseline to be 118 ml/min, at week 12 of 104.9 ml/min (11.1 % decrease in GFR), and at week 13 of 102 ml/min (decrease of 13.6%). The results were reviewed by the study Renal IDMC and were not considered to be significant. At week 17, GFR was reported to be 88.8 (decrease of 24.7%). This final result showed a greater than 20% drop in renal function.

Reviewer comment: *TQ exposure may be related to decreased GFR in this case.*

'Visual field defect' (n=1)

- *Subject* (b) (6) *(Study 057): Subject* (b) (6) *(Study 057):* This 45-year-old female subject received TQ 200 mg once daily for three days, followed by TQ 200mg weekly, commencing on (b) (6). Approximately three weeks after starting treatment with TQ, the subject developed a mild reduction in visual field. A Humphreys visual field analyzer 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 due to this event and the subject was withdrawn from the study. The subject received no treatment for this event. The event resolved approximately six weeks after onset. The investigator reported the reduction in visual field as possibly related to treatment with investigational product.

Reviewer comment: *TQ exposure may be related to visual field defect in this case.*

'Suicide attempt' (n=1)

- *Subject* (b) (6) *(Study 043):* Eight days after TQ exposure (200 mg weekly), the subject

was acutely intoxicated with ethanol. The family reported that the subject had marital problems and had threatened suicide. The subject had ethanol in 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.

Reviewer comment: *TQ exposure may have exacerbated an underlying psychiatric condition in this case.*

Reviewer comment: *Adverse events overall, and serious adverse events specifically, leading to study discontinuation were higher in the TQ ACR group compared to MQ and placebo groups. SAEs leading to study drug discontinuation in the TQ ACR include subjects experiencing submission-specific safety concerns: 'hemolytic anemia' (n=1), glomerular filtration rate decreased (n=2), 'visual field defect' (n=1), and 'suicide attempt' (n=1). A review of these five cases raises concern that TQ may have contributed to the observed SAEs.*

Significant Adverse Events

A summary of adverse events by severity is shown in Table 65. The incidence of moderate and severe TEAEs in the TQ ACR was 12.1% and 1.0%, respectively.

Table 65: Summary of Adverse Events by Severity in the Extended Dosing Safety Set

	TQ 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo** (n=295)	**MQ 250 mg daily x 3 days, then 250 mg weekly** (n=309)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 057**	**030, 033, 045**
Total Number of Adverse Events	3496	1045	1445
Mild	3026 (86.6%)	922 (88.2%)	1311 (90.7%)
Moderate	423 (12.1%)	108 (10.3%)	125 (8.7%)
Severe	35 (1.0%)	8 (0.8%)	7 (0.5%)
Missing	12 (0.3%)	7 (0.7%)	2 (0.1%)
Number of Subjects with at Least One AE			
Mild	401 (48.6%)	138 (34.8%)	163 (52.8%)
Moderate	247 (29.9%)	44 (11.1%)	81 (26.2%)
Severe	33 (4.0%)	13 (3.3%)	5 (1.6%)
Missing	11 (1.3%)	63 (15.9%)	0

Source: Adapted from NDA 210607 Module 5.3.5.3 Integrated Summary of Safety (SN18 submitted 15 February 2018), Table 21.

In the TQ ACR group, the incidence of TEAEs designated possibly or probably related to the study drug per the Investigators was 5.7% and 2.9%, respectively (Table 66).

Table 66: Incidence of Treatment Related Adverse Events Reported by the Investigator

	TQ 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo** (n=295)	**MQ 250 mg daily x 3 days, then 250 mg weekly** (n=309)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 045, 057**	**030, 033, 045**
Total Number of Adverse Events	3496	1045	1445
Total Not Related	2584 (73.9%)	581 (55.6%)	1114 (77.1%)
Total Related	912 (26.1%)	464 (44.4%)	330 (22.8%)
Unlikely	610 (17.4%)	399 (30.7%)	271 (18.8%)
Possible	201 (5.7%)	54 (38.2%)	53 (3.7%)
Probable	101 (2.9%)	11 (1.1%)	6 (0.4%)
Definite	0	0	0
Total Missing	0	0	1 (0.1%)

Source: Adapted from NDA 210607 Module 5.3.5.3 Integrated Summary of Safety (SN18 submitted 15 February 2018), Table 22.

When information on the severity of the TEAE was recorded, the distribution of severe TEAEs was similar across treatment arms, except for gastroenteritis). In the TQ arm, there were 6 (0.7%) TEAEs of 'gastroenteritis' versus none in the placebo and MQ arms. There is one severe TEAE of 'suicide attempt' which is discussed in the section on SAEs Leading to Discontinuation.

Please see Table 65 regarding the number of TEAEs and subjects where information on severity is missing.

Table 67: Treatment Emergent Adverse Events Reported as Severe – Extended Dosing Safety Set

Body System or Organ Class Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Subjects with at least one TEAE of Severe Intensity	33 (4.0%)	7 (2.4%)	5 (1.6%)
Gastrointestinal disorders			
Abdominal pain	1 (0.1%)	-	-
Diarrhea	1 (0.1%)	-	-
Esophagitis	-	1 (0.3%)	-
Vomiting	-	1 (0.3%)	-
Infections and infestations			
Appendicitis	1 (0.1%)	-	-
Bronchitis	1 (0.1%)	-	-

Body System or Organ Class **Dictionary Derived Term** Number of subjects (%)	**TQ 200 mg daily for 3 days then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Cellulitis	1 (0.1%)	-	1 (0.3%)
Cytomegalovirus hepatitis	-	-	1 (0.3%)
Cytomegalovirus infection	-	-	1 (0.3%)
Dysentery	1 (0.1%)	-	-
Gastroenteritis	6 (0.7%)	-	-
Helminthic infection	1 (0.1%)	-	-
Malaria	2 (0.2%)	2 (0.7%)	-
Esophageal candidiasis	-	1 (0.3%)	-
Oral herpes	1 (0.1%)	-	-
Otitis externa	2 (0.2%)	-	-
Periorbital cellulitis	1 (0.1%)	-	-
Pneumonia	1 (0.1%)	1 (0.3%)	-
Urinary tract infection	1 (0.1%)	-	-
Vestibular neuronitis	1 (0.1%)	-	-
Viremia	1 (0.1%)	-	-
Injury, poisoning and procedural complications			
Arthropod bite	1 (0.1%)	-	-
Arthropod sting	-	-	1 (0.3%)
Fall	1 (0.1%)	-	-
Gun shot wound	1 (0.1%)	-	-
Soft tissue injury	1 (0.1%)	-	1 (0.3%)
Thermal burn	1 (0.1%)	-	-
Upper limb fracture	1 (0.1%)	-	-
Investigations			
Liver function test abnormal	-	-	-
Musculoskeletal and connective tissue disorders			
Back pain	1 (0.1%)	-	-
Musculoskeletal pain	1 (0.1%)	-	-
Nervous system disorders			
Headache	2 (0.2%)	1 (0.3%)	-
Migraine	1 (0.1%)	1 (0.3%)	-
Psychiatric disorders			
Anxiety	-	-	1 (0.3%)
Suicide attempt	1 (0.1%)	-	-

Treatment Emergent Adverse Events and Adverse Reactions

There were 692 (83.9%) subjects in the TQ ACR group who experienced a treatment emergent adverse event (TEAE). TEAEs occurring in ≥1% subjects in the TQ ACR group are summarized in Table 68. Notable TEAEs occurring in the TQ ACR group included, but are not limited to, keratopathy (8.2%), diarrhea (12.7%), gastroenteritis (25.3%), nasopharyngitis (13.1%), back pain (14.1%), arthralgia (7.4%), and lethargy (2.9%). The majority of subjects experiencing 'gastroenteritis', 'diarrhea', or 'nasopharyngitis' were enrolled in Study 033, where TQ or MQ

was administered to deployed ADF soldiers. Keratopathy was only documented as a TEAE in Study 033. Study 033 did not have a placebo group.

Table 68: Select Treatment Emergent Adverse Events Occurring in ≥1% of Subjects: TQ ACR vs Placebo and MQ – Extended Dosing Safety Set

Body System or Organ Class	Dictionary Derived Term	TQ 200 mg daily for 3 days then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)
Blood and lymphatic system disorders	Anemia	10 (1.2%)	7 (2.4%)	1 (0.3%)
	Ear pain	11 (1.3%)	4 (1.4%)	1 (0.3%)
	Motion sickness	21 (2.5%)	0	9 (2.9%)
Eye disorders	Conjunctivitis	24 (2.9%)	18 (6.1%)	13 (4.2%)
	Keratopathy	68 (8.2%)	0	0
Gastrointestinal disorders	Abdominal pain	49 (5.9%)	34 (11.5%)	36 (11.7%)
	Abdominal pain upper	16 (1.9%)	9 (3.1%)	7 (2.3%)
	Constipation	20 (2.4%)	8 (2.7%)	19 (6.1%)
	Dental caries	9 (1.1%)	10 (3.4%)	6 (1.9%)
	Diarrhea	105 (12.7%)	9 (3.1%)	33 (10.7%)
	Dyspepsia	13 (1.6%)	13 (4.4%)	13 (4.2%)
	Gastritis	13 (1.6%)	8 (2.7%)	2 (0.6%)
	Gastroesophageal reflux	14 (1.7%)	1 (0.3%)	6 (1.9%)
	Nausea	50 (6.1%)	6 (2.0%)	18 (5.8%)
	Vomiting	31 (3.8%)	5 (1.7%)	11 (3.6%)
General disorders	Asthenia	3 (0.4%)	2 (0.7%)	1 (0.3%)
	Chest pain	18 (2.2%)	5 (1.7%)	11 (3.6%)
	Fatigue	15 (1.8%)	14 (4.7%)	5 (1.6%)
	Seasonal allergy	20 (2.4%)	0	4 (1.3%)
Infections and infestations	Amoebiasis	9 (1.1%)	6 (2.0%)	4 (1.3%)
	Body tinea	17 (2.1%)	4 (1.4%)	7 (2.3%)
	Bronchitis	12 (1.5%)	9 (3.1%)	6 (1.9%)
	Cellulitis	11 (1.3%)	6 (2.0%)	7 (2.3%)
	Furuncle	10 (1.2%)	5 (1.7%)	3 (1.0%)
	Gastroenteritis	212 (25.7%)	18 (6.1%)	70 (22.7%)
	Impetigo	8 (1.0%)	0	1 (0.3%)
	Nasopharyngitis	108 (13.1%)	7 (2.4%)	27 (8.7%)
	Otitis externa	11 (1.3%)	4 (.4%)	1 (0.3%)
	Pharyngitis	8 (1.0%)	10 (3.4%)	11 (3.6%)
	Rhinitis	17 (2.1%)	18 (6.1%)	18 (5.8%)
	Sinusitis	17 (2.1%)	2 (0.7%)	7 (2.3%)
	Tinea infection	9 (1.1%)	0	3 (1.0%)
	Tinea pedis	24 (2.9%)	0	7 (2.3%)
	Tonsillitis	27 (3.3%)	2 (0.7%)	3 (1.0%)

Body System or Organ Class	Dictionary Derived Term	TQ 200 mg daily for 3 days then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)
	Upper resp. tract infection	112 (13.6%)	56 (19.0%)	60 (19.4%)
	Urinary tract infection	12 (1.5%)	9 (3.1%)	7 (2.3%)
	Viral infection	48 (5.8%)	6 (2.0%)	23 (7.4%)
	Wound sepsis	8 (1.0%)	6 (2.0%)	0
Investigations	Alanine aminotransferase abnormal	1 (0.1%)	1 (0.3%)	1 (0.3%)
	Alanine amino transferase increased	12 (1.5%)	6 (2.0%)	4 (1.3%)
Metabolism and nutrition disorders	Decreased appetite	15 (1.8%)	6 (2.0%)	6 (1.9%)
Musculoskeletal and connective tissue disorders	Arthralgia	61 (7.4%)	14 (4.7%)	30 (9.7%)
	Back pain	116 (14.1%)	25 (8.5%)	41 (13.3%)
	Musculoskeletal pain	38 (4.6%)	24 (8.1%)	28 (9.1%)
	Myalgia	27 (3.3%)	26 (8.8%)	14 (4.5%)
	Neck pain	17 (2.1%)	3 (1.0%)	7 (2.3%)
Nervous system disorders	Dizziness	22 (2.7%)	8 (2.7%)	17 (5.5%)
	Headache	178 (21.6%)	94 (31.9%)	92 (29.8%)
	Headache tension	1 (0.1%)	0	1 (0.3%)
	Lethargy	24 (2.9%)	0	11 (3.6%)
	Migraine	3 (0.4%)	3 (1.0%)	2 (0.6%)
Psychiatric disorders	Abnormal dreams	5 (0.6%)	0	2 (0.6%)
	Insomnia	10 (1.2%)	3 (1.0%)	1 (0.3%)
Renal and urinary disorders	Dysuria	3 (0.4%)	1 (0.3%)	1 (0.3%)
Reproductive system and breast disorders	Breast pain	1 (0.1%)	0	0
	Dysmenorrhea	10 (1.2%)	7 (2.4%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	Asthma	2 (0.2%)	0	0
	Cough	50 (6.1%)	35 (11.9%)	35 (11.3%)
	Nasal congestion	13 (1.6%)	3 (1.0%)	2 (0.6%)
	Oropharyngeal pain	30 (3.6%)	8 (2.7%)	11 (3.6%)
Skin and subcutaneous tissue disorders	Heat rash	53 (6.4%)	0	18 (5.8%)
	Ingrowing nail	12 (1.5%)	0	4 (1.3%)
	Pruritus	19 (2.3%)	22 (7.5%)	21 (6.8%)
	Rash*	28 (3.4%)	9 (3.1%)	10 (3.2%)

**Rash includes rash generalized, rash maculopapular, rash papular, rash pruritic and rash vesicular.*

Source: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 54.

Investigations

The percentage of subjects with any TEAE within the Investigations SOC for the TQ ACR group was 3.4% (Table 69). 'Alanine aminotransferase increased' was the only TEAE occurring at ≥1% in the TQ ACR group.

There were five subjects in the TQ ACR with GFR decreased, all of which were considered a SAE and two discontinued due to the SAE. (See sections on Serious Adverse Events, Serious Adverse Events Leading to Discontinuation, and 9.1.5 Analysis of Submission Specific Safety Issue – Renal.)

Table 69: Treatment Emergent Adverse Events within Investigations SOC – 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Subjects with any TEAE within Investigations System Organ Class	28 (3.4%)	21 (7.1%)	17 (5.5%)
Alanine aminotransferase increased	12 (1.5%)	6 (2.0%)	4 (1.3%)
Glomerular filtration rate decreased	5 (0.6%)	2 (0.7%)	-
Haemoglobin decreased	3 (0.4%)	1 (0.3%)	-
Blood creatinine increased	2 (0.2%)	1 (0.3%)	2 (0.6%)
Blood bilirubin increased	2 (0.2%)	1 (0.3%)	3 (1.0%)
Full blood count abnormal	1 (0.1%)	-	-
Blood creatinine abnormal	1 (0.1%)	-	1 (0.3%)
Blood bilirubin abnormal	1 (0.1%)	4 (1.4%)	3 (1.0%)
Urine analysis abnormal	1 (0.1%)	-	-
Alanine aminotransferase abnormal	1 (0.1%)	1 (0.3%)	1 (0.3%)
Haematocrit abnormal	-	1 (0.3%)	-
Haematocrit decreased	-	1 (0.3%)	-
Haematocrit increased	-	1 (0.3%)	1 (0.3%)
Heart rate irregular	-	1 (0.3%)	-
Blood creatinine decreased	-	-	1 (0.3%)
Liver function test abnormal	-	-	1 (0.3%)
Platelet count decreased	-	2 (0.7%)	2 (0.6%)

Hematology

For information regarding the effect of TQ and hematologic laboratory parameters, refer to Section 9.1.5 Analysis of Submission Specific Safety Issue – Hematologic.

Hepatobiliary

For information regarding the effect of TQ and hepatobiliary laboratory parameters, refer to Section 9.1.5 Analysis of Submission Specific Safety Issue – Hepatobiliary.

Vital Signs

There were no subjects in the TQ ACR group with a TEAE within the Investigations SOC relevant to Vital Signs. Pyrexia (within the General Disorders and Administration Site Conditions SOC) was reported in 0.8% (n=7) subjects in the TQ ACR group, 5.6% (n=22) in the placebo group, and 0.6% (n=2) in the MQ group.

Blood pressure changes from baseline over time in TQ exposed subjects are summarized in Table 70. Blood pressure was within normal limits at baseline in all treatment groups. Clinically meaningful changes in blood pressure from baseline and at week 24 were not observed; however, only 5% to 10% subjects had blood pressure measurements recorded at this time point.

Table 70: Blood pressure changes over time in TQ exposed subjects.

			Mean (SD) Change from Baseline (mmHg)						
	Studies	Mean Baseline (SD)	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Diastolic (mmHg)									
Tafenoquine 200 mg Loading Only (N=491)	006 and 049	69.9 (7.3)	--	--	--	--	--	--	--
Tafenoquine 400 mg Loading Only (N=552)	043, 049, and 058	67.1 (8.6)	-0.7 (10.0)	2.7 (9.5)	--	--	--	--	--
ACR – Tafenoquine 200 mg load and weekly full population (N=825)	030, 033, 043, 045, and 057	71.0 (11.2)	12.2 (9.4)	2.0 (11.6)	2.6 (11.2)	0.1 (8.1)	2.3 (8.7)	3.0 (8.6)	-1.5 (8.8)[a]
ACR – Tafenoquine 200 mg load and weekly in non-African Studies (N=573)	033 and 057	72.9 (9.7)	-1.8 (7.1)	2.2 (8.8)	1.7 (7.3)	1.0 (6.6)	0.4 (6.7)	6.1 (6.5)	-2.5 (7.1)[b]
ACR – Tafenoquine 200 mg load and weekly in African Studies (N=252)	030, 043 and 045	70.4 (11.5)	-2.9 (12.7)	2.0 (12.1)	2.8 (11.8)	-2.8 (11.3)	3.0 (9.4)	0.8 (9.4)	3.8 (14.4)[c]
Systolic (mmHg)									
Tafenoquine 200 mg Loading Only (N=491)	006 and 049	115.1 (10.9)	--	--	--	--	--	--	--
Tafenoquine 400 mg Loading Only (N=552)	043, 049, and 058	112.2 (12.7)	-1.3 (10.2)	-0.5 (11.6)	--	--	--	--	--
ACR – Tafenoquine 200 load and weekly full population (N=825)	030, 033, 043, 045 and 057	116.0 (14.4)	-2.3 (13.8)	2.5 (12.9)	5.3 (13.2)	-1.0 (10.5)	5.2 (17.8)	8.4 (14.0)	-2.7 (10.7)[a]
ACR – Tafenoquine 200 mg load and weekly in non-African Studies (N=573)	033 and 057	120.5 (12.5)	-1.5 (10.0)	3.5 (8.4)	7.1 (12.2)	-0.5 (8.6)	3.2 (12.6)	9.6 (10.0)	-4.2 (9.6)[b]
ACR – Tafenoquine 200 mg load and weekly in African Studies (N=252)	030, 043 and 045	114.6 (14.7)	-3.7 (18.8)	2.3 (13.6)	4.9 (13.4)	-2.7 (15.6)	5.9 (19.4)	7.5 (16.7)	5.7 (12.8)[c]

[a] N=65.
[b] N=55.
[c] N=10.

Source: NDA 210607 Module 5.3.5.3 Integrated Summary of Safety (SN18 submitted 15 February 2018), Table 39.

Reviewer comment: *In the population studied, it does not appear that TQ was associated with changes in vital signs, including blood pressure. It should be noted that the number of subjects with blood pressure measurements at week 24 was relatively small compared to baseline.*

Electrocardiograms (ECGs)

Please refer to Section 9.1.5 Analysis of Submission Specific Safety Issue - Cardiac.

QT

Please refer to Section 9.1.5 Analysis of Submission Specific Safety Issue - Cardiac.

Immunogenicity

There were no SAEs or study discontinuations from the Immune System Disorders SOC in subjects receiving the TQ ACR in the Extended Dosing Safety Set. There were 2 (0.2%) subjects in the TQ ACR group and 8 (2.6%) subjects in the MQ group who experienced the TEAE of hypersensitivity. The two subjects (Subject (b) (6)) with the TEAE of hypersensitivity (verbatim term: allergic reaction) were enrolled in Study 033 and experienced the TEAE on Study Day 165 and 183. The event was mild or moderate severity, lasted one day, and resolved for both subjects. One subject was treated with a single oral dose phenergan while the other was treated with a single oral dose of metcolopramide and loratidine. Hypersensitivity for the two subjects in the TQ ACR group was not considered related to the study drug by the Investigator.

Seasonal allergies occurred at an incidence of 2.4% in TQ ACR subjects versus 1.3% in MQ subjects and 0% in placebo subjects (Table 71). Nineteen of the 20 subjects receiving the TQ ACR were enrolled in Study 033, while the remaining individual was enrolled in Study 057. Study 033 enrolled ADF soldiers who were deployed to a malaria endemic region, presumably a new environment for them. Study 057 enrolled healthy volunteers.

Table 71: TEAEs within Immune System Disorders SOC – 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Subjects with any TEAE within Immune system disorders System Organ Class	25 (3.0%)	1 (0.3%)	13 (4.2%)
Seasonal allergy	20 (2.4%)	-	4 (1.3%)
Hypersensitivity	2 (0.2%)	-	8 (2.6%)
Allergy to arthropod sting	1 (0.1%)	-	-
Allergy to arthropod bite	1 (0.1%)	-	-
Reaction to azo-dyes	1 (0.1%)	-	-
House dust allergy	-	1 (0.3%)	-
Food allergy	-	-	1 (0.3%)

The incidence of TEAEs in the TQ ACR group for the SMQ Anaphylactic Reactions was 12%

(Table 72). The TEAEs of 'asthma' (n=3), 'dyspnea' (n=2), and 'reversible airways obstruction' (n=1) only occurred in the TQ ACR group.

Table 72: TEAEs within the Anaphylactic Reaction SMQ – 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Subjects with any TEAE within Anaphylactic Reaction SMQ	99 (12.0%)	58 (19.7%)	58 (18.8%)
Cough	50 (6.1%)	35 (11.9%)	35 (11.3%)
Rash	25 (3.0%)	2 (0.7%)	7 (2.3%)
Pruritus	19 (2.3%)	22 (7.5%)	21 (6.8%)
Asthma	2 (0.2%)	-	-
Erythema	2 (0.2%)	-	-
Ocular hyperaemia	2 (0.2%)	-	-
Urticaria	1 (0.1%)	3 (1.0%)	1 (0.3%)
Bronchospasm	1 (0.1%)	-	-
Dyspnoea	1 (0.1%)	-	1 (0.3%)
Rash pruritic	1 (0.1%)	-	-
Reversible airways obstruction	1 (0.1%)	-	-
Sneezing	1 (0.1%)	1 (0.3%)	-
Swelling face	1 (0.1%)	1 (0.3%)	-
Angioedema	-	-	1 (0.3%)
Eye pruritus	-	1 (0.3%)	-
Eyelid oedema	-	1 (0.3%)	-
Pruritus generalised	-	1 (0.3%)	-
Rash generalized	-	1 (0.3%)	-

Reviewer comment: *It does not appear that the TQ ACR is associated with increased risk of immunogenicity in the population studied.*

9.1.5. Analysis of Submission-Specific Safety Issues

TQ is an 8-amino-quinoline which may share characteristics with quinoline drugs currently approved for malaria prophylaxis or treatment: PQ (also an 8-amino-quinoline), MQ (a 4-quinolinemethanol derivative), as well as the two similar 4-aminoquinolines, CQ and hydroxy-CQ. A focused safety review evaluated TQ for issues known to occur with exposure to these drugs (Table 73).

Table 73: Selected safety issues in labeling for approved quinoline antimalarials

Focused Safety Review	**PQ** 8-aminoquinoline (Label updated 20 July 2017) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1bfbf4ae-81b8-4160-a00d-6322aadd4b59	**MQ** 4-quinolinemethanol (Label updated 12 Sept 2016) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=43fde257-36ee-49ea-a03c-01a1a4e1da3d	**CQ and hydroxy-CQ** 4-aminoquinoline (Label updated 11 April 2017) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=56f3380c-9411-417a-a3f7-fe4025900c75 (Label updated 03 July 2013) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=35314d43-3dec-46dd-8975-56f257b2f408
1. Ophthalmic	None.	• *Warnings:* Ocular Effects including optic neuropathy and retinal disorders. • *Postmarketing Adverse Reactions:* Visual impairment, vision blurred, cataracts, retinal disorders, optic neuropathy. • *Animal Toxicology:* Ocular lesions in rats fed MQ daily for 2 years. • *Long-use:* Periodic ophthalmic examinations recommended.	• *Contraindications:* patients with retinal or visual field changes regardless of etiology • *Warnings:* irreversible retinal damage with prolonged or high dose therapy • *Adverse Reactions:* Irreversible retinal damage; visual disturbances, visual field defects, reversible corneal opacities have also been reported.
2. Cardiac	• *Precautions:* Potential Prolongation of QT Interval. • *Adverse Reactions:* Cardiac arrhythmia and QT interval prolongation.	• *Warnings:* QTc Interval Prolongation and Drug Interactions. • *Precautions:* Cardiac Effects including myocardiac depressant, prolong PR interval, prolong QTc interval. • *Adverse Reactions Clinical:* cardiopulmonary arrest in one patient shortly after ingesting a single prophylactic dose of MQ while concomitantly using propranolol. • *Adverse Reactions Postmarketing:* circulatory disturbances (hypotension, hypertension, flushing, syncope), chest pain, tachycardia or palpitation, bradycardia, irregular heart rate, extrasystoles, A-V block, and other transient cardiac conduction alterations.	• *Adverse reactions:* Rarely, hypotension, electrocardiographic change (particularly, inversion or depression of the T-wave with widening of the QRS complex), and cardiomyopathy. • *Overdosage:* Arrhythmias.

Focused Safety Review	**PQ** 8-aminoquinoline (Label updated 20 July 2017) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1bfbf4ae-81b8-4160-a00d-6322aadd4b59	**MQ** 4-quinolinemethanol (Label updated 12 Sept 2016) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=43fde257-36ee-49ea-a03c-01a1a4e1da3d	**CQ and hydroxy-CQ** 4-aminoquinoline (Label updated 11 April 2017) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=56f3380c-9411-417a-a3f7-fe4025900c75 (Label updated 03 July 2013) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=35314d43-3dec-46dd-8975-56f257b2f408
3. Hematologic	• *Contraindications*: Acutely ill patients suffering from systemic disease manifested by tendency to granulocytopenia, patients receiving concurrently other potentially hemolytic drugs or depressants of myeloid elements of the bone marrow. • *Warnings:* Hemolytic anemia and G6PD deficiency. • *Precautions and Adverse Reactions:* Advises blood monitoring during therapy. Observe closely if used in patients with leukopenia, hemolytic anemia in G6PD deficient individuals, and methemoglobinemia in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficient individuals.	• *Precautions:* Agranulocytosis and Aplastic Anemia. • *Adverse Reactions:* Transient elevation of transaminases, leukopenia and thrombocytopenia in patients with acute malaria who received treatment doses. During prophylactic administration, transient elevation of transaminases, leukocytosis or thrombocytopenia was observed.	• *Precautions:* Monitor complete blood count with prolonged therapy. Use with caution in patients with G-6-PD deficiency. • *Adverse Reactions:* Rarely, pancytopenia, aplastic anemia, reversible agranulocytosis, thrombocytopenia and neutropenia.
4. Renal	*Geriatric Use:* Dosing selection	Not applicable.	*Geriatric Use:* Dosing selection
5. Nervous	*Adverse Reactions:* dizziness	*Boxed Warning:* Neuropsychiatric Adverse Reactions *Warnings:* 1. Psychiatric and Neurologic Adverse Reactions 2. Neurologic Adverse Reactions	• *Precautions:* Risk of provoking seizures; auditory effects • *Adverse Reactions:* Convulsive seizures, mild and transient headache, polyneuritis. Neuropsychiatric changes including psychosis, delirium, anxiety, agitation, insomnia, confusion, hallucinations, personality changes and depression. • *Overdosage:* Arrhythmias

Focused Safety Review	PQ 8-aminoquinoline (Label updated 20 July 2017) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1bfbf4ae-81b8-4160-a00d-6322aadd4b59	MQ 4-quinolinemethanol (Label updated 12 Sept 2016) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=43fde257-36ee-49ea-a03c-01a1a4e1da3d	CQ and hydroxy-CQ 4-aminoquinoline (Label updated 11 April 2017) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=56f3380c-9411-417a-a3f7-fe4025900c75 (Label updated 03 July 2013) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=35314d43-3dec-46dd-8975-56f257b2f408
6. Psychiatric	None	*Boxed Warning:* Neuropsychiatric Adverse Reactions *Warnings:* 1. Psychiatric and Neurologic Adverse Reactions 2. Psychiatric Adverse Reactions	*Adverse Reactions:* Nervousness, emotional lability, psychosis, suicidal behavior, delirium, anxiety, agitation, insomnia, confusion, hallucinations, personality changes and depression.
7. Hepatobiliary	None	*Precautions:* Long term-use. Periodic evaluation of hepatic function should be performed during prolonged prophylaxis. *Adverse Reactions Postmarketing:* Hepatobiliary Disorders: drug-related hepatic disorders from asymptomatic transient transaminase elevations to hepatic failure.	*Precautions:* Caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs *Adverse Reactions:* Hepatitis increased liver enzymes, anorexia, nausea, vomiting, diarrhea, abdominal cramps
8. Gastrointestinal	*Adverse Reactions:* nausea, vomiting, epigastric distress, and abdominal cramps.	Not applicable.	*Adverse Reactions:* Anorexia, nausea, vomiting, diarrhea, abdominal cramps.

9.15.1 Ophthalmic

Ocular effects associated with TQ exposure were investigated due to known safety concerns with MQ and CQ/h-CQ (Table 73).

Ophthalmologic Disorders Discontinuations and SAEs

There was 1 subject (b) (6) with TEAE of 'night blindness' and 'visual acuity reduced' leading to study discontinuation. This subject also experienced an SAE of 'visual field defect' under the Neurologic Disorders SOC. The case narrative for Subject (b) (6) (Study 057) can be found in Section 9.1.4 Safety Results, SAES leading to discontinuation.

Drugs with cationic amphiphilic structures, such as TQ, CQ and hydroxy-CQ, can cause corneal epithelial deposits or vortex keratopathy. Vortex keratopathy typically has no effect on visual acuity and few ocular symptoms. Corneal deposits usually resolve with cessation of drug.

The TEAE of 'keratopathy' occurred in 5 (0.6%) subjects receiving the TQ ACR, (Table 74). The TEAE of 'retinal disorder' occurred as an SAE in 3 subjects, all in Study 033: 2 (0.2%) subjects in the TQ group, and 1 (0.3%) subject in the MQ group.

Table 74. Ophthalmologic Adverse Events: TQ ACR Group versus 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Ophthalmologic TEAEs leading to discontinuation			
Night blindness	1 (0.1%)	0	-
Visual acuity reduced	1 (0.1%)	0	-
Metamorphopsia	-	1(0.3%)	-
Ophthalmologic SAEs			
Keratopathy	5 (0.6%)[1]	0	-
Retinal disorder	2 (0.2%)	0	1 (0.3%)
Metamorphopsia	-	1(0.3%)	-
Ophthalmologic TEAEs occurring ≥1% study subjects			
Keratopathy	68 (8.2%)[1]	0	-
Conjunctivitis	24 (2.9%)	18 (6.1%)	13 (4.2%)

[1]All subjects in Study 033.

Ophthalmologic TEAEs

Two ophthalmologic TEAEs occurred at incidences ≥1% in the TQ ACR group, conjunctivitis and keratopathy), (Table 74). Keratopathy occurred at a higher incidence in the TQ ACR group (8.2%) versus 0 subjects in both the placebo and MQ groups, with 0.6% of the total subjects experiencing an SAE in the TQ group. All subjects with keratopathy were enrolled in Study 033.

Study 033

Corneal Disorders SMQ

Most of the trials did not perform the ophthalmic examinations necessary to evaluate for keratopathy. A Corneal Disorders SMQ was conducted for Study 033 (Table 75). There were 15.4% (76/492) subjects in the TQ ACR group with a TEAE within the Corneal disorders SMQ versus 1.9% (3/162) subjects in the MQ group. There were 68/492 (13.8%) subjects with TEAE of keratopathy in the TQ ACR group. In comparison, there were zero subjects in the MQ group with a TEAE of keratopathy. Five of the 68 subjects with keratopathy were considered to have a SAE. Per the Applicant, these 5 cases were categorized as SAEs before understanding that the subjects had vortex keratopathy.

Table 75: Corneal Disorders Standard MedDRA Query – Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=492)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=162)
Subjects with any TEAE within Corneal disorders SMQ	76 (15.4%)	3 (1.9%)
Chemical burns of the eye	1 (0.2%)	-
Chemical eye injury	-	2 (1.2%)
Corneal abrasion	1 (0.2%)	1 (0.6%)
Eye disorder	-	-
Eye injury	1 (0.2%)	-
Foreign body in eye	4 (0.8%)	-
Foreign body sensation in eye	1 (0.2%)	-
Keratopathy	68 (13.8%)	-
Photophobia	1 (0.2%)	-

In Study 033, 95 participants (74 TQ group and 21 MQ group) underwent detailed ophthalmic assessments. At the 6-month examination, corneal deposits (vortex keratopathy) were noted in 69 (93%) of the TQ participants but in none of the 21 MQ participants. Corneal deposits were not recorded at screening in any of the participants who underwent slit lamp examination. The keratopathy was asymptomatic and was not associated with changes in vision. Resolution of corneal changes occurred in 61% (42 of 69) subjects at 3 months after the end of the prophylactic period. All participants had complete resolution of their corneal deposits (vortex keratopathy) within 1 year after the end of TQ dosing per the Applicant.

Reviewer comment: *The keratopathy observed in subjects exposed to the TQ ACR appeared to be asymptomatic and reversible. It is consistent with vortex keratopathy noted with cationic amphiphilic compounds.*

Retinal Disorders SMQ

In most of the trials, ophthalmic examinations were not performed the to evaluate for retinal disorders. A Retinal Disorders SMQ was conducted for Study 033 (Table 76). Overall, the incidence of retinal disorders was similar between treatment groups; 1.4% (7/492) subjects in the TQ group versus 1.9% (3/162) subjects in the MQ group. The three TEAEs of retinal disorders in this study were considered serious.

Table 76: Retinal Disorders Standard MedDRA Query – Study 033, Safety Population

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=492)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=162)
Subjects with any TEAE within Retinal disorders SMQ	7 (1.4%)	3 (1.9%)
Visual impairment	3 (0.6%)	1 (0.6%)
Retinal disorder	2 (0.4%)	1 (0.6%)
Visual acuity reduced	1 (0.2%)	-

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=492)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=162)
Photophobia	1 (0.2%)	-
Vision blurred	-	1 (0.6%)

In Study 033, 86 participants underwent fundoscopic examinations by slit lamp examination in an unblinded manner. Retinal abnormalities (i.e. granularity/pigmentation of retinal pigment epithelium, hard drusen) were noted in 41.9% (31 of 74) TQ participants and in 28.6% (6 of 21) MQ participants at the end of dosing at the 6-month visit. Vision was not affected in any of the participants. At the 3-month visit after the end of the prophylactic period, retinal abnormalities were noted in 36.4% (27 of 74) TQ participants and in 19.0% (4 of 21) MQ participants. Fundus fluorescein angiograms (FFA) were performed in 15 of the 31 cases with retinal findings. Results were considered abnormal in 28.6% (4 of 14) TQ participants and in 100% (1 of 1) MQ participants; however, there were no baseline retinal photography data at screening for comparison. An Ophthalmology Advisory Board, convened by the Applicant recommended that, due to the equivocal nature of these data, principally due to lack of baseline comparison data, the only way to definitively exclude a drug effect is to perform prospective studies with baseline fundus photographs.

Reviewer comment: *The following is an excerpt from the Division of Transplant and Ophthalmology (DTOP) consult. "The Applicant asserts that their expert ophthalmology advisory board concluded that the lack of baseline retinal photography data meant that the relevance of the retinal findings (observed on fundoscopy and fundus fluorescein angiograms) could not be ascertained. These subjects were recruited from the Australian Army when on deployment to East Timor. This population would not be expected to have granularity/pigmentation of retinal pigment epithelium [RPE] or hard drusen at baseline, end of treatment or after 3 month follow-up fundoscopic examinations. The presence of these retinal findings indicates a potential problem with the quality of the fundoscopic examinations and/or their interpretation or potential drug effect." See review by William Boyd, M.D., in DARRTS dated 11 May 2018, Reference ID: 4259036.*

Study 057

The Applicant conducted prospective assessments of ophthalmic findings in Study 057 ('renal-ocular safety study'). Study 057 was a randomized, double-blind, placebo-controlled study to evaluate the safety and tolerability, specifically renal and ophthalmic effects, of TQ 200 mg per week for 6 months in healthy volunteers. The primary ophthalmic safety endpoint was the proportion of subjects with impaired night vision due to corneal deposits, as measured by the Forward Light Scatter Test (FLST). Keratopathy was present at screening in 14.3% (10/70) subjects in the TQ ACR group and 21.9% (7/32) subjects in the placebo group. Night vision, as assessed via the FLST, was unimpaired in the TQ-treated and placebo groups.

Treatment-emergent keratopathy was observed more frequently among subjects receiving TQ

(21.4% [15/70]) than among subjects receiving placebo (12.5% [4/32]). Within 6 weeks of onset, keratopathy in all 4 subjects in the placebo group resolved. Within 12 weeks of onset, keratopathy in 14 subjects in the TQ group resolved. Keratopathy in the remaining TQ-treated subject resolved by Week 48.

Reviewer comment: *The following is an excerpt from the DTOP consult. "It is not clear why subjects with keratopathy at screening were included in this trial. The presence of retinal findings not seen at screening indicates a potential problem with the quality of the fundoscopic examinations and/or their interpretation or a potential drug effect." See review by William Boyd, M.D., in DARRTS dated 11 May 2018, Reference ID: 4259036.*

Study 058

In Study 058, adult subjects with confirmed *P. vivax* malaria received either TQ 400 mg/day for 3 days (Days 1 – 3), or combination treatment with CQ + PQ (CQ 100 mg on Days 1 and 2, CQ 500 mg on Day 3, and PQ 15 mg on Days 3 through 16).

Corneal and retinal examinations, as well as digital photographs were performed at baseline and Days 28 and 90. Twelve of 46 (26.1%) subjects receiving TQ had corneal deposits at Day 28, while there were none in the PQ/CQ group. Eleven of the 12 keratopathies were Grade 1 while one was a Grade 2. By the Day 90 assessment, the corneal deposits were considered resolved by the investigator in 6 of the subjects. Two subjects were lost to follow-up prior to the Day 90 assessment. In the remaining 4 subjects, the corneal deposits were still present at the Day 90 assessment and their TEAEs were assessed as ongoing.

In the TQ group, retinal pigmentation was observed at the Day 28 assessment in 19.6% (9/46) patients with *P. vivax* malaria, and this pigmentation was still present in 8 of the 9 TQ-treated malaria subjects at Day 90. In contrast, 4.2% (1/24) of the *P. vivax* subjects in the CQ+PQ group developed retinal findings. In both groups, retinal findings were not associated with any change in vision. An Independent Data Monitoring Committee (IDMC), which included two ophthalmic experts, found no difference in visual function tests between the TQ 400 mg group and the CQ+PQ group at Day 28 assessment. In addition, a blinded review of the retinal digital photographs was conducted at the Fundus Photograph Reading Center, University of Wisconsin, and found no evidence of anatomical changes consistent with retinal toxicity. Finally, an Ophthalmology Advisory Board, convened on 31 October 2001 agreed that there was no evidence of any impact on vision in subjects taking TQ.

Reviewer comment: *The following is an excerpt from the DTOP consult. "The vortex keratopathy seen with TQ in Study 058 was not followed to resolution in all subjects; four subjects had ongoing keratopathy at last examination and two subjects were lost to follow-up. These subjects should have been followed to resolution of the keratopathy. Pseudochromatic color plates (e.g. Ishihara) are not generally recommended for use as a gross estimate of acquired color loss and central visual dysfunction. They do not assess blue/yellow deficiencies which are*

the most common acquired defects. The presence of abnormal retinal findings (reported as "retinopathy") indicates a potential problem with the drug product or the quality of the fundoscopic examinations and/or their interpretation. The expert ophthalmology panels did not conclude that retinal findings were absent; they concluded that the findings were not expected to impact vision. It is not clear how they arrived at this conclusion." See review by William Boyd, M.D., in DARRTS dated 11 May 2018, Reference ID: 4259036.

Ongoing Study - Protocol 60PH04

The Applicant has an ongoing ophthalmologic safety study, Protocol 60PH04. This is a single site, randomized, double-blind, placebo-controlled study to assess the long-term safety of TQ conducted under the Applicant's IND 129656. The study's objective is to assess the ophthalmic safety of TQ during 12 months of exposure versus placebo in 600 healthy volunteers using Spectral Domain Optical Coherence Tomography (SD-OCT) and Quantitative Fundus Auto Fluorescence (qFAF). The Division of Transplant and Ophthalmologic Products (DTOP) reviewed this protocol with comments provided on 01 September 2017. The Applicant agreed to incorporate DTOP recommendations into their protocol.

Ophthalmology Consult

William M. Boyd, M.D., Clinical Team Leader, Division of Transplant and Ophthalmology Products (DTOP), reviewed the ophthalmologic data and provided the following summary and recommendations. The full DTOP consult is posted in DARRTS on 11 May 2018, Reference ID: 4259036.

1. As noted throughout this review, the presence of retinal findings not seen at screening indicates a potential problem with the quality of the fundoscopic examinations and/or their interpretation or potential drug effect.

2. Provided that 60° Pharmaceuticals LLC, commits to adequately completing and reporting Protocol No. 60PH04: A Single Site, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Long-term Safety of TQ to the Agency, there is adequate safety data contained within this application to permit approval of TQ with revisions to the proposed labeling.

<u>Recommendations</u>
TQ is reasonably safe for use for up to 6 months of continuous dosing provided the suggested revisions regarding ophthalmic findings are made to the proposed labeling.

Ophthalmologic monitoring is not recommended provided the applicant commits to completing and reporting results for Protocol No. 60PH04: A Single Site, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Long-term Safety of TQ to the Agency. Upon completion of the trial, the data can be reviewed for reassessment of the need for ophthalmic monitoring.

Reviewer comment: *Ophthalmologic findings with use of TQ, including 'vortex keratopathy' and retinal disorders should be reflected in Section 6 (Adverse Reactions) of labeling.*

9.15.2 Cardiac

Cardiac effects associated with TQ exposure were investigated due to known safety concerns with PQ, MQ, and CQ/h-CQ.

Cardiac Disorders TEAEs

In the Extended Dosing Safety Set, there were no subjects exposed to TQ or MQ with a TEAE in the Cardiac Disorders SOC. There was one subject in the placebo group with a TEAE of 'palpitations'. In the entire ISS safety population, there were 2 subjects in the 400 mg TQ loading only group who had Cardiac Disorders TEAEs. Subject (b) (6) had a TEAE of 'sinus bradycardia' and 'atrioventricular disassociation' while Subject had a TEAE of 'palpitations'.

There were no reported cardiac-related SAEs and no study discontinuations due to cardiac-related TEAEs.

Cardiac arrhythmias SMQ

An SMQ for cardiac arrhythmias in the Extended Dosing Safety Set revealed 2 (0.2%) subjects with a TEAE of 'syncope' in the TQ ACR group, and 1 subject each (3 total, 0.8%) with a TEAE of 'palpitations', 'loss of consciousness' and 'heart rate irregular' in the placebo group (Table 77). No subjects in the MQ group were identified with TEAEs for this SMQ.

Table 77: Cardiac Arrhythmias Standard MedDRA Query – 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)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Subjects with any TEAE within Cardiac arrhythmias SMQ	2 (0.2%)	3 (0.8%)	-
Syncope	2 (0.2%)	-	-
Heart rate irregular	-	1 (0.3%)	-
Loss of consciousness	-	1 (0.3%)	-
Palpitations	-	1 (0.3%)	-

When the SMQ was applied to the entire safety population of the ISS, additional TEAEs were noted for subjects in other TQ dosing groups. In the TQ 400 mg QD group, there were 2 (0.4%)

subjects with TEAEs, 'syncope' (n=1, 0.2%) and 'palpitations' (n=2, 0.4%). In the TQ 400 mg loading dose only group, there was one subject (0.8%) with TEAEs of 'atrioventricular disassociation' and 'sinus bradycardia'.

Thorough QT Study Results

The Applicant did not submit datasets and the ECG waveforms for the thorough QT (TQT) study to the NDA. This was communicated as a potential review issue to the Sponsor at the time of filing. The Applicant was requested to submit ECG datasets and waveforms obtained through the course of other studies including Studies 033, 014, 015, 022, 050, and 051. The QT-IRT Team was consulted to evaluate these data.

A Clinical Study Report for a TQT study not conducted by the Applicant, was submitted (TAF114582). TAF114582 was a Phase 1 randomized, placebo-controlled study to evaluate the effect of TQ on the ECG with focus on cardiac repolarization (QTc duration) in 260 healthy subjects. There were 5 study arms with 52 subjects per arm: placebo, moxifloxacin 400mg (single dose on Day 3), TQ 300 mg (single dose on Day 3), 600 mg (single dose on Day 3), and 1200 mg (400 mg qd for 3 days).

No deaths during the study. SAEs were reported in 6 subjects (Table 78). There was one subject who withdrew from the study due to a TEAE: Subject (b) (6) (TQ 1200 mg) experienced mild nausea and vomiting on Day 1. The nausea and vomiting resolved after 9 hours and 1 hour, respectively. There were no episodes of syncope in any group and one episode of presyncope in the moxifloxacin group. There were no episodes of ventricular tachycardia, fibrillation, or seizures during the study. There was no effect on Fridericia corrected QT (QTcF) prolongation after a single TQ dose of 300 mg or 600 mg. There was a mean 6.6 msec prolongation of QTcF compared to placebo at 72 hours post-final-dose in a group that received a total TQ dose of 1200 mg over 3 days (TQ 400 mg for 3 days), a dose higher than the TQ ACR.

Table 78: Summary of all serious adverse events occurring in TAF114582

Preferred Term	Placebo (N=52)	Moxi (N=52)	TQ 300mg (N=52)	TQ 600mg (N=52)	TQ 1200mg (N=52)
Subjects with Any SAE, n (%)	1 (2)	0	1 (2)	4 (8)	0
Blood CPK increased	1 (2)	0	0	2 (4)	0
Hemoglobin decreased	0	0	0	1 (2)	0
Hypersensitivity	0	0	0	1 (2)	0
Urticaria	0	0	1 (2)	0	0

Clinical Study Report TAF114582, Table 18. Note, reviewer unable to replicate data for this table because datasets not submitted.

QT-IRT Consult

The Interdisciplinary Review Team for QT Studies (QT-IRT), Division of Cardiovascular and Renal Products, reviewed the ECG data and provided the following summary and recommendations. The QT-IRT consult is posted in DARRTS dated 04 May 2018, Reference ID: 4258285.

The data was primarily from Study 014, a randomized, open-label, parallel group bioequivalence study. In this study, 58 healthy subjects were randomized to receive a single dose of TQ 400 mg Phase 2 capsule (existing formulation), TQ 400 mg Phase 3 capsule (novel formulation), and TQ 400 mg Phase 3 tablet (novel formulation) on 3 consecutive days. No large mean increase (i.e., >20 ms) in the QTc interval is anticipated for TQ 400 mg. This conclusion is based on by-time analysis of Study 014. 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). The QT-IRT team also provided suggestions for labeling.

Reviewer comment: *Based on the data submitted, no large mean increase (i.e., >20 ms) in the QTc interval is anticipated for TQ 400 mg. Please refer to Clinical Pharmacology Section for additional information.*

9.15.3 Hematologic

Hematologic effects associated with TQ exposure were investigated due to known safety concerns related to hemolysis and methemoglobinemia with PQ, CQ/hydroxy-CQ, and MQ (Table 73).

Hematologic Discontinuations and SAEs

Hematologic TEAEs leading to study discontinuation in the TQ ACR group included decreased hemoglobin (n=3 [0.4%]) and hemolytic anemia (n=2 [0.2%]) (Table 79). Of note, all 3 withdrawals due to decreased hemoglobin occurred in Study 045 where withdrawal criteria guided the investigator to discontinue subjects for minor changes in laboratory parameters. Laboratory guidelines values for exclusion were: hemoglobin <12 g/dL for males or <10 g/dL for females, platelets <100,000/mm^3, and WBC <3000/μl^3. In all 3 cases, the decrease in hemoglobin was considered mild and 'non-serious', did not require treatment, and resolved in 28 to 50 days.

Table 79: Summary of Hematologic Adverse Events: TQ ACR Group versus 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Hematologic TEAEs leading to discontinuation			
Hemoglobin decreased	3 (0.4%)	1 (0.3%)	0
Hemolytic anemia	2 (0.2%)	0	0
Platelet decreased	0	1 (0.3%)	0
Hematologic SAEs			

Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Hemolytic anemia	1 (0.1%)	0	0
Hematologic TEAEs occurring ≥1% study subjects			
Anemia	10 (1.2%)	7 (2.4%)	1 (0.3%)
Leukocytosis	8 (1.0%)	5 (1.7%)	8 (2.6%)
Thrombocytopenia	10 (1.2%)	9 (3.1%)	4 (1.3%)

Withdrawals due to hemolytic anemia occurred in Subject (b) (6) in Study 030 and in Subject (b) (6) in Study 057. Neither subject required treatment and anemia resolved in both subjects within 1 month.

- *Subject (b) (6) (Study 030):* The case narrative for Subject (b) (6) can be found in the section on serious adverse events leading to discontinuation.

- *Subject (b) (6) (Study 057):* This is a 40-year-old Black male who presented with decreases of hemoglobin and hematocrit 23 days after the first dose of study treatment and 2 days after the previous/last dose of treatment. At this time point, the subject had a hemoglobin concentration of 10.9 g/dL (Baseline value: 13.1 g/dL), a hematocrit of 32.3% (Baseline value: 40%), and a haptoglobin concentration of 0.270 g/L (Baseline value: 0.350 g/L). It should be noted that although this subject was reported to have hemolytic anemia, his relevant laboratory tests did not meet the criteria for hemolysis as defined in the protocol (i.e., 15% decrease from baseline in hemoglobin/hematocrit and at least a 50% decrease from baseline in haptoglobin). The decreases were assessed by a hematologist who diagnosed the subject with mild hemolytic anemia. The subject was withdrawn from the study on Day 28 and the event was reported as 'resolved' 97 days after the onset of the event without any corrective therapy. DNA analysis of the G6PD gene for this subject revealed no mutations. The hemolytic anemia was considered by the investigator to be probably related to study drug.

Hematologic TEAEs in the Extended Dosing Set

TEAEs from the Blood and Lymphatic System Disorders and Investigations System Organ Class are summarized in Table 80.

Three hematological TEAEs occurred at incidences ≥1% in the TQ ACR group (anemia, leukocytosis, and thrombocytopenia).

Table 80: Blood and Lymphatic System Disorders and Investigations System Organ Class Treatment Emergent Adverse Events in TQ ACR Group – 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Subjects with any TEAE within Blood and Lymphatic Disorders or Investigations SOC	58 (7.0%)	26 (8.8%)	33 (10.7%)
Blood and Lymphatic system disorders			
Anemia	10 (1.2%)	7 (2.4%)	1 (0.3%)
Thrombocytopenia	10 (1.2%)	9 (3.1%)	4 (1.3%)
Leukocytosis	8 (1.0%)	5 (1.7%)	8 (2.6%)
Hemolytic anemia	2 (0.2%)	0	-
Normochromic normocytic anemia	2 (0.2%)	0	-
Iron deficiency anemia	1 (0.1%)	0	2 (0.6%)
Microcytosis	1 (0.1%)	0	-
Platelet disorder	1 (0.1%)	0	1 (0.3%)
Neutrophilia	1 (0.1%)	0	-
Microcytic anemia	1 (0.1%)	2 (0.7%)	-
Lymphadenopathy	1 (0.1%)	1 (0.3%)	1 (0.3%)
Investigations			
Alanine aminotransferase increased	12 (1.5%)	6 (2.0%)	4 (1.3%)
Glomerular filtration rate decreased	5 (0.6%)	2 (0.7%)	-
Hemoglobin decreased	3 (0.4%)	1 (0.3%)	-
Blood creatinine increased	2 (0.2%)	1 (0.3%)	2 (0.6%)
Blood bilirubin increased	2 (0.2%)	1 (0.3%)	3 (1.0%)
Full blood count abnormal	1 (0.1%)	0	-
Blood bilirubin abnormal	1 (0.1%)	4 (1.4%)	3 (1.0%)
Blood creatinine abnormal	1 (0.1%)	0	1 (0.3%)
Alanine aminotransferase abnormal	1 (0.1%)	1 (0.3%)	1 (0.3%)

Hemolytic Disorders SMQ

An SMQ was conducted for Hemolytic Disorders for the safety population of all studies in the ISS. There were 6 subjects total, all exposed to TQ, with a TEAE within the Hemolytic Disorders SMQ (Table 81). There were four subjects in the Extended Dosing Safety Set, 2 of whom received the TQ ACR. Two of these subjects were discussed previously ((b) (6) in Study 030 and (b) (6) in Study 057). The other two subjects (b) (6) were enrolled in Study 043 and in the TQ 400 mg loading dose only treatment arm. Two subjects in Study 058 were enrolled in the *P. vivax* treatment study and experienced hemoglobinuria after receiving TQ 400 mg.

Table 81: SMQ Hemolytic Disorders: Integrated Summary of Safety Set – Safety Population

Unique Subject Identifier	*Study Identifier*	*Age*	*Sex*	*Actual Treatment*	*Body System or Organ Class*	*Dictionary-Derived Term*	*Analysis Start Relative Day*	*Analysis End Relative Day*	*Severity Intensity*	*Serious Event?*	*Action Taken with Study Treatment*	*Withdrawn Due to AE?*	*Outcome of Adverse Event*	*Causality by Investigator*
(b) (6)	30	31	F	TQ 200 mg	Blood and lymphatic	Hemolytic anemia	4	28	MILD	Yes	DRUG	Yes	RECOVERED/ RESOLVED	POSSIBLE

Unique Subject Identifier	Study Identifier	Age	Sex	Actual Treatment	Body System or Organ Class	Dictionary-Derived Term	Analysis Start Relative Day	Analysis End Relative Day	Severity Intensity	Serious Event?	Action Taken with Study Treatment	With-drawn Due to AE?	Outcome of Adverse Event	Causality by Investigator
					system disorders						WITH-DRAWN			
(b) (6)	43	39	F	TQ 400 mg (Loading only)	Blood and lymphatic system disorders	Hemolysis	1	118	MISSING	No	DOSE NOT CHANGED	No	RECOVERED/ RESOLVED	PROBABL
	43	34	F	TQ 400 mg (Loading only)	Blood and lymphatic system disorders	Hemolysis	4	11	SEVERE	Yes	UNKNOWN	Yes	RECOVERED/ RESOLVED	PROBABL
	57	40	M	TQ 200 mg	Blood and lymphatic system disorders	Hemolytic anemia	24	120	MILD	No	DRUG WITH-DRAWN	Yes	RECOVERED/ RESOLVED	PROBABL
	58	20	M	TQ 400 mg + Placebo	Renal and urinary disorders	Hemoglobinuria	-1	8	MILD	No	UNKNOWN	No	RECOVERED/ RESOLVED	NOT RELATED
	58	25	M	TQ 400 mg + Placebo	Renal and urinary disorders	Hemoglobinuria	29	32	MILD	No	DOSE NOT CHANGED	No	RECOVERED/ RESOLVED	NOT RELATED

Note: TQ=tafenoquine; M=male; F=female. Subjects in TQ arm received 200 mg daily for 3 days, then 200 mg weekly.

Changes in Hemoglobin levels

The percentage of subjects with hemoglobin decrease ≥3 g/dL was 2.3% in the TQ ACR group of the Extended Dosing Safety Set (Table 82).

Table 82: Subjects with interval Hb change in the Extended Dosing Safety Set

Hemoglobin Change (Decrease) from Baseline – Interval Categories Number of subjects (%)	**TQ 200 mg daily for 3 days then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=295)	**MQ 250 mg daily for 3days, then 250 mg weekly** (n=309)
≥1 g/dL to < 2g/dL decrease	293 (35.5%)	58 (19.7%)	80 (25.9%)
≥2 g/dL to < 3g/dL decrease	64 (7.8%)	11 (3.7%)	13 (4.2%)
≥3 g/dL decrease	19 (2.3%)	3 (1.0%)	5 (1.6%)

Changes in Methemoglobin Levels

Increased methemoglobin levels were observed with TQ exposure (Table 83). Physiological concentrations of methemoglobin are approximately 1–2%, and methemoglobin levels of 1%-3% are usually asymptomatic in normal individuals. Methemoglobin levels above 15% may result in cyanosis, and at levels of 20 to 50%, patients can show dyspnea, headache, fatigue, dizziness, syncope, and weakness.

Methemoglobin laboratory values were available for Study 033 and Study 043. Among subjects

who received the TQ ACR, 15% of subjects in Study 033 and 74.6% subjects in Study 043 experienced methemoglobin levels ≥1%. One subject (0.2%) from Study 033 and nine (16.4%) from Study 043 had a methemoglobin level ≥5% at any time during the study and none had reported TEAEs.

One subject (b) (6) in the TQ ACR group was reported to have a methemoglobin level ≥10% (value=113%) recorded at week 3-4 follow-up; however, this result appears to be a spurious level or a data entry error as this subject had methemoglobin levels <2% before and after this measurement, and the subject was not reported as a death.

No subjects had a TEAE of 'blood methemoglobin increased' or 'methemoglobinemia' in the Extended Dosing Safety Set, including subjects receiving the TQ ACR.

Table 83: Highest actual methemoglobin value during study – Study 033 and Study 043 Safety Population

Methemoglobin level – Highest Actual Value During Study	TQ 200 mg x 3 days, then 200 mg weekly (ACR)	Placebo	MQ 250 mg x 3 days, then 250 mg weekly
Any level ≥1%			
033	74/492 (15.0%)	Not applicable	0
043	41/55 (74.6%)	3/61 (4.9%)	Not applicable
≥3% to <5%			
033	9/492 (1.8%)	Not applicable	0
043	7/55 (12.7%)	0	Not applicable
≥5%			
033	1/492 (0.2%)	Not applicable	0
043	9/55 (16.4%)	0	Not applicable

Dose and Duration of TQ Exposure and Hematologic Effects

In Study 058 (Clinical Use Studies Pool), in the arm where subjects received 400 mg TQ daily for 3 days (no weekly doses) for treatment of *P. vivax*, there were 22 subjects total with TEAE of 'methemoglobinemia' (n=1) or 'blood methemoglobin present' (n=22). Methemoglobin levels transiently increased in subjects receiving TQ with the mean peak level occurring at Day 7 (9.05%). Most subjects returned to within or near the normal range (1 to 3%) by Day 21 (mean 3.26%). Subjects with elevated methemoglobin levels were asymptomatic and did not require corrective therapy, including the 4 subjects who met the criterion (methemoglobin level ≥20%) for a protocol defined SAE. The mean peak methemoglobin level in subjects receiving PQ plus CQ was 1.9% at Day 7, with the maximum peak level of 5.9%.

In Study 051, where TQ doses of 200 mg, 500 mg, or 750 mg were administered to healthy volunteers weekly for 10 weeks (active drug [n=8] and placebo [n=4] in each dose cohort; total n=36). Regardless of treatment group, there was a dose and duration related accumulation of methemoglobin which appeared to plateau by week 6 of dosing and then peak at 10 weeks. An associated macrocytosis and hyperchromia was observed, possibly due to methemoglobin

accumulation. Abnormal mean values for hemoglobin, hematocrit or RBC count were not reported in this study.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Similar to PQ, G6PD-deficient individuals are at risk of hemolysis when exposed to TQ. Although almost all TQ studies excluded subjects with G6PD deficiency, there were 8 subjects with G6PD deficiency or other hemoglobinopathies who received TQ in 5 clinical trials. These subjects did not receive the TQ ACR. Most subjects showed no signs or symptoms of hemolysis, and all affected subjects ultimately recovered, typically after receiving outpatient oral treatments (Table 84). One subject (Study 043, Subject (b) (6) required hospitalization and transfusions after receiving 400 mg TQ in the three-day load-only group, a dose that is twice that of the loading dose for the TQ CR. Narratives for cases of decreased hemoglobin or hemolysis in known or suspected G6PD-deficient subjects are summarized in Table 84.

Table 84: Case summaries of hemoglobin or hemolysis in known or suspected G6PD-deficient subjects

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)	Subject (b) (6) 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)	Subject (b) (6) 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.

Study 030 Phase 2 Exclusion for G6PD deficiency	Study 030	TQ 200 mg x 3 days (loading dose)	**Subject** (b) (6) 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	**Subject** (b) (6) 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.

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	**Subject** (b) (6) 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	**Subject** (b) (6) 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	**Subject** (b) (6) 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.

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

SD52 Clinical Amendment, Response to Information Request.

Reviewer comment: *In the population studied, there appears to be an association of decreasing hemoglobin levels and methemoglobin levels ≥1% with overall TQ ACR exposure, and is reflected in labeling. The TQ ACR was not studied in individuals with G6PD deficiency, where the risk of hemolytic anemia would be high. Labeling includes a contraindication for use of TQ in subjects with G6PD deficiency. There appear to be dose- and duration- effects of TQ on methemoglobin levels in the populations studied.*

9.15.4 Renal

Renal effects associated with TQ exposure were investigated due to safety concerns identified in preclinical studies (tubular nephropathy, necrosis and dilation) and in Study 033. In addition, the Applicant conducted Study 057, a long-term 'renal-ocular' safety study.

Renal effects associated with PQ, MQ and CQ/h-CQ are minimal per current labeling.

Renal discontinuations and SAEs

In the Investigations SOC, there were 5 (0.6%) subjects in the TQ group, 2 (0.7%) in the placebo group and none in the MQ group who experienced a TEAE of 'GFR decreased'. All 5 of the TEAEs of 'GFR decreased' were classified as SAEs (Table 85). All subjects (TQ and placebo) with a TEAE of 'GFR decreased' were enrolled in Study 057, the healthy volunteer 'renal-ocular safety study'. Study 057 did not have an MQ group.

Two (0.2%) subjects in the TQ ACR group were withdrawn from the study due to 'GFR decreased', and both were in Study 057 (renal-ocular safety study) (Subjects (b) (6) and (b) (6) (Table 85). In both discontinued subjects, serum creatinine remained within the normal range and the decrease in GFR was considered mild, resolving without treatment. See section 9.1.4 Safety Results - Serious Adverse Events Leading to Discontinuation for case narratives on the two subjects withdrawn due to 'GFR decreased'.

Table 85: Summary of Renal Adverse Events: TQ ACR Group versus 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=295)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)
Renal investigations TEAEs leading to discontinuation			
GFR decreased[1]	2 (0.2%)	-	-
Renal and urinary disorders TEAEs leading to discontinuation	-	-	-
Renal investigations SAEs	-	-	-
GFR decreased[1]	5 (0.6%)	2 (0.7%)	
Renal and urinary disorders SAEs	-	-	-
Renal investigations TEAEs occurring ≥1% study subjects	-	-	-
Renal investigations TEAEs occurring in <1% subjects	-	-	-
GFR decreased[1]	5 (0.6%)	2 (0.7%)	
Blood creatinine increased	2 (0.2%)	1 (0.3%)	2 (0.6%)
Blood creatinine abnormal	1 (0.1%)	-	1 (0.3%)

[1]*All subjects with TEAE 'GFR decreased' in TQ and placebo groups were enrolled in Study 057.*

Renal Investigations TEAEs

'Blood creatinine increased' or 'blood creatinine abnormal' occurred in 3 (0.4%) subjects in the TQ group, 1 (0.3%) subject in the placebo group, and 3 (1%) in the MQ group (Table 85).

Renal and Urinary Disorders TEAEs

For the Extended Dosing Safety Set, as well as Study 033, the percentage of subjects with TEAEs within the Renal and Urinary Disorders SOC was less than 1% in the TQ ACR, placebo, and MQ groups (Table 86).

Table 86: TEAEs within the Renal and Urinary Disorders System Organ Class – Extended Dosing Safety Set and Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)		Placebo (n=396)[1]	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	
	Extended Dosing Safety Set (n=825)	Study 033 Subjects Only (n=492)	Extended Dosing Safety Set (n=295)	Extended Dosing Safety Set (n=309)	Study 033 Subjects Only (n=162)
Any subject with TEAE within Renal and urinary disorders SOC	7 (0.8%)	4 (0.8%)	2 (0.7%)	2 (0.6%)	1 (0.6%)
Dysuria	3 (0.4%)	1 (0.2%)	1 (0.3%)	1 (0.3%)	-

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)		Placebo (n=396)[1]	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	
	Extended Dosing Safety Set (n=825)	Study 033 Subjects Only (n=492)	Extended Dosing Safety Set (n=295)	Extended Dosing Safety Set (n=309)	Study 033 Subjects Only (n=162)
Hematuria	2 (0.2%)	1 (0.2%)	1 (0.3%)	-	-
Urinary hesitation	1 (0.1%)	1 (0.2%)	-	-	-
Urethral discharge	1 (0.1%)	1 (0.2%)	-	-	-
Urinary retention	1 (0.1%)	1 (0.2%)	-	-	-
Proteinuria	-	-	1 (0.3%)	-	-
Pollakiuria	-	-	-	-	-
Enuresis	-	-	-	1 (0.3%)	1 (0.6%)

[1]*Study 033 did not have a placebo group.*

Acute Renal Failure SMQ

An SMQ for Acute Renal Failure on the Extended Dosing Safety Set revealed similar results as previously discussed (Table 87).

Table 87: TEAEs within the Acute Renal Failure SMQ – 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=295)	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)
Subjects with any TEAE within Acute renal failure SMQ	8 (1.0%)	4 (1.4%)	3 (1.0%)
Glomerular filtration rate decreased[1]	5 (0.6%)	2 (0.7%)	-
Blood creatinine increased	2 (0.2%)	1 (0.3%)	2 (0.6%)
Blood creatinine abnormal	1 (0.1%)	-	1 (0.3%)
Proteinuria	-	1 (0.3%)	-

[1]All subjects with TEAE 'GFR decreased' in TQ and placebo groups were enrolled in Study 057.

Additional Results – Study 033

In study 033, where ADF soldiers received study medication during deployment (TQ n=492, MQ n=162), mean serum creatinine increased slightly from baseline in both groups with the greatest increase in mean serum creatinine in the TQ group, 16.2 umol/L (0.18 mg/dL; standard deviations not provided), seen between Weeks 2 and 6 (Table 88). More subjects in the TQ group had an increase from baseline in serum creatinine of >25% compared to MQ at some timepoints during the study, including at the final visit (11.3% vs. 7.1%). The differences had resolved by the follow-up visit (6.0% vs. 8.2%). Note that MQ is not known to have renal toxicity.

Table 88: Creatinine changes from baseline – Study 033

Creatinine							
	Base-line (umol/L)	Days 0-10	2-6 weeks	7-12 weeks	13-21 weeks	22-30 weeks	Follow-up
Mean change in creatinine from baseline							
Tafenoquine	88.7	6.1	16.2	13.2	9.6	12.1	7.0
(N)	479	475	474	477	468	454	454
Mefloquine	88.7	5.3	10.7	8.0	5.0	8.8	6.7
(N)	156	152	155	156	155	151	152
Percentage subjects with creatinine increased from baseline value (+25%)							
Tafenoquine	n/a	5.4% 26/480	18.9% 92/487	16.3% 80/490	8.7% 42/481	11.3% 53/467	6.0% 28/467
Mefloquine	n/a	6.5% 10/155	9.4% 15/160	8.1% 13/161	10.0% 16/160	7.1% 11/156	8.2% 13/158

Source: Adapted from NDA 210607, Clinical Study Report 033, Table 42.

Reviewer comment: *The following is an excerpt from the Division of Cardiorenal Products (DCRP) consult by Dr. Smith. 'It is not clear whether the observed increases in serum creatinine >25% above baseline were transient or persistent.' See review by Kimberly Smith, M.D., in DARRTS dated 24 May 2018, Reference ID: 4268053.*

A long-term renal follow-up study was conducted in a cohort of subjects with serum creatinine concentrations ≥ 0.02 mmol/L (0.23 mg/dL) above baseline at the end of the prophylactic phase and/or at follow-up. There were 246 subjects with an increased serum creatinine concentration at end of prophylaxis and/or follow-up with 183 (TQ n=147; MQ n=36) subjects consenting to take part in the follow-up. Ten subjects were referred for renal follow-up for criteria outlined in Table 89. Per the Applicant, all 10 subjects were confirmed by the renal physician as having no clinical evidence of chronic renal injury.

Table 89: Subjects referred for renal assessment follow-up (Study 033)

	Treatment Group	
	Tafenoquine	Mefloquine
	N = 147	N = 36
Referred for renal Follow-up	7 (4.8%)	3 (8.3%)
Creatinine above upper limit of normal	0	1 (2.8%)
Creatinine ≥ 0.03 mmol/L above Baseline	2 (1.4%)	1 (2.8%)
Clinically significant urinalysis result	5 (3.4%)	2 (5.6%)

Source: NDA 210607 SD1, Module 2.7.6 Synopses of Individual Studies, Table 78.

Reviewer comment: *Per the DCRP consult, 'Although there is some variability in creatinine readings, there are no obvious trends suggesting a progressive decline in renal function. We could not locate narratives of these cases or information regarding any additional evaluation performed by the clinical nephrology consultant'. See review by Kimberly Smith, M.D., in*

DARRTS dated 24 May 2018, Reference ID: 4268053.

Additional Results – Study 057

Because of findings from study 033, the Applicant conducted prospective assessments of renal findings in Study 057 ('renal-ocular safety study'). Study 057 was a randomized, double-blind, placebo-controlled study to evaluate the safety and tolerability, specifically renal and ophthalmic effects, of TQ 200 mg for 6 months in healthy volunteers. The primary renal safety endpoint was the mean change in GFR from Baseline to Week 24, measured via the iothalamate-clearance technique. The primary analysis was a non-inferiority analysis with a margin of -15% of the mean iothalamate GFR value at baseline for all subjects, which was calculated to be -0.247 mL/s/1.73m^2 (or 14.8 mL/min/1.73m^2).

Reviewer comment: *Per the DCRP consult, 'It is not clear how the non-inferiority margin was selected. A decline in GFR of ~15 mL/min/1.73 m^2 over 6 months would be a large decline if it reflected an irreversible loss of renal function'.*

Only 53/81 (65.4%) TQ and 29/39 (74.4%) of placebo subjects completed the study. Nearly all subjects were withdrawn for the reason "other" which includes "withdrawn consent, spurious renal data, poor compliance, lost to follow-up, and 'incorrect subject technique'", or "protocol deviation (including noncompliance)".

Reviewer comment: *Per the DCRP consult, 'Reasons for premature discontinuation … may reflect difficulties with performing assessments of measured GFR; however, we could not locate details regarding the nature of these discontinuations'.*

As shown in Table 90, the 95% confidence interval for the treatment difference ranges from -10 mL/min (i.e., a greater decline in renal function in the TQ group) to 2.7 mL/min (i.e., a greater decline in renal function in the placebo group).

Table 90: **Mean change in GFR from baseline to Week 24 – Study 057, Renally Evaluable Population, Modified Observed Case Dataset**

	Tafenoquine n=81	Placebo n=39	Treatment Difference (95% CI)
Subjects included in analysis	50 (62%)	23 (59%)	
Adjusted mean change (mL/min)	1.4	5.0	-3.7 (-10, 2.7)

Source: Adapted from Clinical Study Report for Study 057, Table 18.

Source: Division of Cardiorenal Products Consult, Table 2 (adapted from Study 057 Clinical Study Report, Table 18.

The applicant conducted sensitivity analyses for the primary endpoint ("Worst Case Analysis," "Safety Population") that confirmed the primary endpoint finding. In addition, the applicant provided the results of secondary endpoints based on change in iothalamate GFR (i.e., change in

GFR from baseline to Week 12, percentage change in GFR from baseline to Weeks 12 and 24) that are similar to the primary endpoint results.

Reviewer comment: *Per the DCRP consult, 'There is substantial missing data with only ~60% of randomized study subjects contributing to the analyses, rendering the results largely uninterpretable'.*

The Applicant identified four subjects in the TQ group with a ≥20% decrease in iothalamate GFR: one at Week 12, one at Week 18, and two at Week 24. No subjects had a decline of this magnitude in the placebo group. Three subjects in the TQ group and one in the placebo group had an increase in serum creatinine from baseline of at least 0.3 mg/dL.

The Applicant defined 'clinically significant urinalysis finding' as urine protein, blood, or glucose >trace or urine RBC/hpf >0. Such findings were identified at Week 24 in two (3.6%) TQ and three (11.5%) placebo subjects. According to the applicant, no meaningful changes in renal function were seen in those subjects who had corresponding creatinine/GFR data.

An adverse event of 'Glomerular filtration rate decreased' was reported for five (6.2%) TQ and two (5.1%) placebo subjects. All events were classified as serious for unclear reasons, but were reported as mild in severity. The event resulted in study drug discontinuation for two (2.5%) TQ subjects (*Subjects* (b) (6) described previously) per protocol-defined stopping rules.

Reviewer comment: *Per the DCRP consult, 'According to the Clinical Study Report, the Renal IDMC made several recommendations regarding the conduct of the study in March 2005 including 1) "to implement the analysis of all GFR samples in the US laboratory"; 2) "to implement the analysis of creatinine for all GFR serum and urine samples from that point onwards"; 3) "to review data anomalies and take appropriate action"; 4) "to clarify GFR inclusion criteria to allow correction for body surface area when considering baseline GFR values 75-80 mL/min"; 5) "to clarify protocol procedures to allow for repeat GFR measurements before permanent discontinuation of study subjects due to suspected spurious GFR data"; and 6) "to review all SAE reports and clarify them in accordance with the reviews described, as well as the urinalysis results. All other cases of reported GFR decrease were to be reviewed to determine if any met the criteria for an SAE." It is not clear what the basis was for these recommendations, but they suggest that there may have been concerns with trial conduct and data quality.*

Renal Consult

Kimberly Smith, M.D. form DCRP provided the following summary and recommendations with a focus on Study 033 and Study 057. An excerpt from Dr. Smith's consult follows.

'Our assessment of the data is as follows:

- *In Studies 033 and 057, the applicant identified several subjects with elevations in serum*

creatinine and/or decreases in GFR. We note that the applicant has not provided details regarding these cases, and the data provided are not presented in a clear and comprehensive manner; however, none of the referenced cases appear to represent intrinsic renal injury. Several of the cases were reviewed by nephrologists and/or a renal IDMC who concurred with this assessment. Although the applicant notes that a greater number of TQ subjects had an elevated urinary albumin/creatinine ratio during the study, no additional details are provided, and it is not clear that these changes were clinically relevant.

- *In Study 057, which was intended to assess renal safety, the 95% confidence interval for the treatment difference between TQ and placebo on the mean change in iothalamate GFR from baseline to Week 24 ranges from -10 mL/min (i.e., a greater decline in renal function in the TQ group) to 2.7 mL/min (i.e., a greater decline in renal function in the placebo group). Only ~60% of randomized subjects contributed to this analysis. Also, based on recommendations made by the renal IDMC in March 2005, there appear to have been questions regarding trial conduct. As such, we find these results to be largely uninterpretable.*

- *In Study 033, a small increase in mean serum creatinine was observed in both treatment arms. Generally speaking, aside from causing intrinsic renal injury, drug-induced changes in creatinine can result from a hemodynamic effect, a change in production of creatinine, interference with the creatinine assay, or interference with the renal tubular secretion of creatinine. It is not clear whether the subjects, who were deployed soldiers, could have had other exposures that led to a mean increase in creatinine levels in the study through a hemodynamic effect or through a change in the production of creatinine (e.g., changes in climate, diet, or physical exertion) or whether TQ is likely to interfere with the creatinine assay. We note that in vitro studies show that TQ inhibits the renal transporters MATE1, MATE2-K, and OCT2. These data suggest that TQ could increase serum creatinine through inhibition of renal tubular secretion of creatinine; however, the trial data were not analyzed in a way that allows us to determine whether TQ leads to elevations in serum creatinine that follow the expected time course of such an effect (i.e., an early increase, a plateau, and a decrease with treatment discontinuation). We would also want to know whether the in vitro data suggest that the reported effects on renal transporters would be expected to occur at clinically relevant exposures. We defer to clinical pharmacology on this issue. We note that Study 057 included both serum creatinine and measured GFR, which ideally could help sort out this issue (i.e., drugs that inhibit the tubular secretion of creatinine cause an increase in serum creatinine without a corresponding change in measured GFR); however, as noted above, we question the integrity of these data and, therefore, question whether there is utility in conducting additional analyses of this trial.'*

Reviewer comment: *No major renal toxicity was observed with the TQ ACR in the population studied. However, TQ may be associated with decreased GFR in the population studied, particularly with exposures ≥23 weeks. 'GFR decreased' associated with TQ exposure is*

reflected in the Adverse Reaction section of labeling.

9.15.5 Neurologic

Nervous system effects associated with TQ exposure were investigated due to known safety concerns with PQ, MQ and CQ/hydroxy-CQ (Table 73 and Table 91). MQ label includes a boxed warning regarding the neuropsychiatric adverse reactions which can occur during and after MQ administration.

Table 91: Labeling: Neurologic and Psychiatric Concerns for Quinoline Antimalarials

Label Section	**PQ Label** *(updated 20 July 2017)*	**MQ label** *(updated 12 September 2016)*	**CQ and hydroxy-CQ** 4-aminoquinoline (updated 11 April 2017 and 03 July 2013)
Boxed Warning	Not applicable	Mefloquine may cause neuropsychiatric adverse reactions that can persist after mefloquine has been discontinued. Mefloquine should not be prescribed for prophylaxis in patients with major psychiatric disorders. During prophylactic use, if psychiatric or neurologic symptoms occur, the drug should be discontinued and an alternative medication should be substituted (see WARNINGS).	Not applicable
Contraindications	Not applicable	Mefloquine should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders, or with a history of convulsions.	Contraindicated in the presence of retinal or visual field changes attributable to any 4-aminoquinoline compound or any other etiology.
Warnings	Not applicable	<u>Psychiatric and Neurologic Adverse Reactions</u> Mefloquine may cause neuropsychiatric adverse reactions in adults and children. Neuropsychiatric symptoms can be difficult to identify in children. Therefore, vigilance is required to monitor for the occurrence of these symptoms, especially in non-verbal children. <u>Psychiatric Adverse Reactions</u> Psychiatric symptoms ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior can occur with mefloquine use. Symptoms may occur early in the course of mefloquine use. In some cases, these symptoms have been reported to continue for months or years after mefloquine has been stopped. Cases of suicidal ideation and suicide have been reported. Mefloquine should not be prescribed for prophylaxis in patients with active depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders. Mefloquine should be used with caution in patients	Patients on long-term therapy should be questioned and examined periodically, including testing knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug.

Label Section	**PQ Label** *(updated 20 July 2017)*	**MQ label** *(updated 12 September 2016)*	**CQ and hydroxy-CQ** 4-aminoquinoline (updated 11 April 2017 and 03 July 2013)
		with a previous history of depression. 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. Neurologic Adverse Reactions Neurologic symptoms such as dizziness or vertigo, tinnitus, and loss of balance have been reported. These adverse reactions may occur early in the course of mefloquine use and in some cases have been reported to continue for months or years after mefloquine has been stopped. Dizziness or vertigo, tinnitus, and loss of balance have been reported to be permanent in some cases. During prophylactic use, if neurologic symptoms occur, the drug should be discontinued and an alternative medication should be substituted. Caution should be exercised with regard to activities requiring alertness and fine motor coordination, such as driving, piloting aircraft, operating machinery, and deep-sea diving, while symptoms persist. Mefloquine may increase the risk of convulsions in patients with epilepsy. The drug should therefore be prescribed only for curative treatment in such patients and only if there are compelling medical reasons for its use (see PRECAUTIONS: Drug Interactions). Concomitant administration of mefloquine and quinine or chloroquine may increase the risk of convulsions.	
Precautions	Not applicable	Information for Patients: Medication Guide (*truncated, excerpt from label*) that some patients are unable to take this medication because of side effects, including dizziness or vertigo and loss of balance, and it may be necessary to change medications. In some patients it has been reported that these symptoms may continue for months or years after discontinuation of the drug and can be permanent in some cases; • that insomnia may occur	In patients with preexisting auditory damage, chloroquine should be administered with caution. Patients with a history of epilepsy should be advised about the risk of chloroquine provoking seizures.

Label Section	PQ Label *(updated 20 July 2017)*	MQ label *(updated 12 September 2016)*	CQ and hydroxy-CQ 4-aminoquinoline (updated 11 April 2017 and 03 July 2013)
		• that if the patients experience psychiatric adverse reactions such as acute anxiety, depression, restlessness or confusion, or suicidal ideation, the drug should be discontinued and an alternative medication should be substituted;	
Adverse Reactions	Nervous System: Dizziness	Postmarketing The most frequently reported adverse reactions are nausea, vomiting, loose stools or diarrhea, abdominal pain, dizziness or vertigo, loss of balance, and neuropsychiatric events such as headache, somnolence, and sleep disorders (insomnia, abnormal dreams). These adverse reactions may occur early in the course of mefloquine use. It has been reported that dizziness or vertigo, tinnitus and hearing impairment, and loss of balance may continue for months or years after discontinuation of the drug and may be permanent in some cases. More severe neuropsychiatric disorders have been reported such as: sensory and motor neuropathies (including paresthesia, tremor and ataxia), convulsions, agitation or restlessness, anxiety, depression, mood swings, panic attacks, memory impairment, confusion, hallucinations, aggression, psychotic or paranoid reactions and encephalopathy. Cases of suicidal ideation and suicide have been reported.	*Psychiatric disorders:* Nervousness, emotional lability, psychosis, suicidal behavior, delirium, anxiety, agitation, insomnia, confusion, hallucinations, personality changes and depression. *Nervous system disorders:* Dizziness, headache, convulsive seizures, mild and transient headache, polyneuritis. *Auditory:* Nerve type deafness; tinnitus, reduced hearing in patients with preexisting auditory damage.
Overdosage	Symptoms of overdosage of PQ phosphate include... central nervous system... *(truncated excerpt from label)*	In cases of overdosage with mefloquine, the symptoms mentioned under ADVERSE REACTIONS may be more pronounced.	Headache, drowsiness, convulsions.

Nervous System Disorders Discontinuations and SAEs

In the TQ ACR group, there was one subject each with the SAE of headache [redacted] (b) (6) and visual field defect [redacted] (b) (6) The one subject experiencing a visual field defect was withdrawn from the study. In addition, one subject with a non-serious TEAE of hyperesthesia [redacted] (b) (6) was withdrawn from the study. Case narratives for the withdrawn subjects follow. There were no subjects in the MQ group experiencing an SAE in the Nervous System Disorders SOC.

- *Subject* (b) (6) *(Study 057):* The case narrative can be found in the section on SAEs leading to discontinuation.

- *Subject* (b) (6) *(Study 033):* This is a 26-year-old White male ADF soldier, hepatitis B carrier positive, reported moderate hyperesthesia on Study Day 12 (Study-033). 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 'suspected' related to TQ, was treated using unspecified non-medicinal modalities and resolved after 130 days.

> ***Reviewer comment:*** *It does not appear that TQ was associated with hyperesthesia in the one reported case.*

Table 92: Summary of Nervous System Adverse Events: TQ ACR Group versus Placebo and MQ

	TQ 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily x 3 days, then 250 mg weekly (n=309)
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 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%)	94 (31.9%)	92 (29.8%)
Dizziness	22 (2.7%)	8 (2.7%)	17 (5.5%)
Lethargy	24 (2.9%)	0	11 (3.6%)

Source:Module 2.7.4 Summary of Clinical Safety, Table 35.

Nervous System Disorders TEAEs

The number of subjects with TEAEs within the Nervous System Disorders SOC in the Extended Dosing Safety Set was as follows: TQ ACR (27.5%), placebo (37.1%) and MQ (36.6%) (Table 93). Headache, lethargy, and dizziness all occurred at ≥1% in the TQ ACR group. When analyzing subjects in Study 033 alone, the incidence of headache, lethargy and dizziness was similar in the TQ and MQ groups (Table 93).

Several low incidence TEAEs in the TQ ACR group to note include: 'paresthesia', 'coordination abnormal', 'somnolence', 'syncope', 'tremor', 'hyperesthesia', 'hypoesthesia', 'presyncope', and 'visual field defect'. The four subjects with paresthesia in the TQ ACR group were enrolled in Study 033 (ADF soldiers) with all events described as mild and unrelated by the investigator. Paresthesia occurred in the right forearm with secondary paresthesia (n=1), left temple region (n=1), left arm (n=1) and left lower leg (n=1).

Reviewer comment: *It should be noted that systematic monitoring for neurologic TEAEs was not conducted in these studies, and the true incidence of neurologic TEAEs may be underestimated.*

Table 93: TEAEs within the Nervous System Disorders System Organ Class – Extended Dosing Safety Set and Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)		Placebo (n=295)[1]	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	
	Extended Dosing Safety Set (n=825)	Study 033 Subjects Only (n=492)	Extended Dosing Safety Set (n=295)	Extended Dosing Safety Set (n=309)	Study 033 Subjects Only (n=162)
Any subject with TEAE within Nervous System Disorders SOC	227 (27.5%)	110 (22.4%)	101 (34.2%)	113 (36.6%)	44 (27.2%)
Headache	178 (21.6%)	72 (14.6%)	94 (31.9%)	92 (29.8%)	29 (17.9%)
Lethargy	24 (2.9%)	23 (4.7%)	-	11 (3.6%)	11 (6.8%)
Dizziness	22 (2.7%)	7 (1.4%)	8 (2.7%)	17 (5.5%)	2 (1.2%)
Paresthesia	4 (0.5%)	4 (0.5%)	-	1 (0.3%)	1 (0.6%)
Migraine	3 (0.4%)	2 (0.4%)	3 (1.0%)	2 (0.6%)	2 (1.2%)
Sinus headache	3 (0.4%)	-	1 (0.3%)	-	-
Coordination abnormal	2 (0.2%)	2 (0.4%)	-	1 (0.3%)	1 (0.6%)
Sciatica	2 (0.2%)	1 (0.2%)	-	-	-
Somnolence	2 (0.2%)	1 (0.2%)	1 (0.3%)	1 (0.3%)	-
Syncope	2 (0.2%)	1 (0.2%)	-	-	-
Tremor	2 (0.2%)	2 (0.4%)	-	-	-
Amnesia	1 (0.1%)	1 (0.2%)	-	-	-
Headache tension	1 (0.1%)	1 (0.2%)	-	1 (0.3%)	-
Hyperesthesia	1 (0.1%)	1 (0.2%)	-	-	-
Hypoesthesia	1 (0.1%)	1 (0.2%)	1 (0.3%)	1 (0.3%)	1 (0.6%)
Presyncope	1 (0.1%)	1 (0.2%)	-	-	-
Tension headache	1 (0.1%)	1 (0.2%)	-	-	-
Visual field defect	1 (0.1%)	-	-	-	-
Dizziness postural	-	-	1 (0.3%)	-	-
Dysgeusia	-	-	1 (0.3%)	-	-
Paresis	-	-	-	1 (0.3%)	1 (0.6%)
Sensory loss	-	-	-	1 (0.3%)	1 (0.6%)

[1]Study 033 did not have a placebo group.

Reviewer comment: *The results of neurologic TEAEs in the Extended Dosing Safety Set highlight the issue of pooling heterogenous studies to make safety conclusions.*

The following is an excerpt from the DNP consult: "The fact that MQ has warnings in the label for dizziness or vertigo, tinnitus and loss of balance is not consistent with what is described in this table. One would expect that the MQ rates for these adverse events would be higher than placebo, therefore putting in question the interpretability of the findings in the extended dosing safety set."

Furthermore, regarding Study 033, the following is an excerpt from the DNP Consult: "Although the rates of neurological AEs are higher in the MQ-treated subjects (study 033), it is concerning that the rates of neurological adverse events for TQ are similar to those of MQ, which is a known neurotoxin."

See review by Laura Jawidzik, M.D., in DARRTS, dated 08 June 2018, Reference ID: 4275488.

Neurologic adverse event reporting rates for Study 057 and the pool of studies 030, 043 and 045 are further summarized in Table 94 and Table 95.

Table 94: Table Neurologic Adverse Event Reporting Rates in Study 057 (n [%]) – Safety population

Adverse Event	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) N=81 n (%)	Placebo N=39 n (%)
Headache*	31 (38.3)	23 (59.0)
Myalgia	6 (7.4)	0
Fatigue and lethargy	6 (7.4)	4 (10.3)
Fall, dizziness, lightheadedness	3 (3.7)	3 (7.7)
Visual disturbance	4 (4.9)	3 (7.7)
Tinnitus	1 (1.2)	0

Source: Reviewer created table from ADaM datasets ADAE and ADSL for study 057,
*Includes headache and migraine
Source: NDA 210607, Division of Neurologic Products Consultative Review, Table 3.

Reviewer comment: *Study 057 is a small study, and definitive safety conclusions are difficult to make. All subjects experiencing myalgia in Study 057 were in the TQ ACR group (7.4%). In addition, the one case of tinnitus in the TQ ACR group is notable. The TEAEs of myalgia and tinnitus should be reflected in labeling.*

The following is an excerpt from the DNP Consult, "For study 057, neurological adverse event rates are similar to placebo. However, this safety study was focused on obtaining renal and ocular safety data so it is possible that neurological adverse events were under-reported."

Table 95 Neurologic Adverse Event Reporting Rates in Study 030, 043, 045 (n [%]) – Safety population

Adverse Event	TQ 400mg weekly N=59	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) N=252 n (%)	Placebo N=256 n (%)	* MQ 250 mg daily for 3 days, then 250 mg weekly N=147 n (%)
Headache	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)

*Study 043 did not have a MQ arm

Source: NDA 210607 Division of Neurologic Products Consultative Review, Table 5.

***Reviewer comment:** Results from the pooled analyses of Study 030, 043 and 045 are difficult to interpret. Like the other studies in the Extended Dosing Safety Set, systematic monitoring for neurologic TEAEs were not conducted in these studies. Myalgia and visual disturbance occurred at a similar incidence in the TQ ACR and MQ groups.*

Vestibular Disorders SMQ

An SMQ for Vestibular Disorders on the Extended Dosing Safety Set and Study 033 Safety population revealed 'dizziness' and 'motion sickness' occurring at ≥1% in both the TQ and MQ groups (Table 96).

Table 96: Vestibular Disorders Standard MedDRA Query – Extended Dosing Safety Set and Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)		Placebo (n=295)[1]	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	
	Extended Dosing Safety Set (n=825)	Study 033 Subjects Only (n=492)	Extended Dosing Safety Set (n=295)	Extended Dosing Safety Set (n=309)	Study 033 Subjects Only (n=162)
Subjects with any TEAE within Vestibular disorders SMQ	46 (5.6%)	30 (6.1%)	8 (2.7%)	27 (8.7%)	11 (6.8%)
Dizziness	22 (2.7%)	7 (1.4%)	8 (2.7%)	17 (5.5%)	2 (1.2%)
Motion sickness	21 (2.5%)	21 (4.3%)	-	9 (2.9%)	8 (4.9%)
Meniere's disease	1 (0.1%)	-	-	-	-
Vertigo	1 (0.1%)	1 (0.2%)	-	-	-

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)		Placebo (n=295)[1]	MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	
	Extended Dosing Safety Set (n=825)	Study 033 Subjects Only (n=492)	Extended Dosing Safety Set (n=295)	Extended Dosing Safety Set (n=309)	Study 033 Subjects Only (n=162)
Vestibular neuronitis	1 (0.1%)	1 (0.2%)	-	-	-
Vertigo positional	-	-	-	1 (0.3%)	1 (0.6%)

[1]Study 033 did not have a placebo group

Neurologic TEAEs, Time of Onset and Duration of TEAEs – Study 033

In Study 033, the time of onset for most subjects experiencing a neurologic TEAE was higher during the prophylactic phase for both the TQ ACR and MQ groups (Table 97).

Table 97: Neurologic Treatment Emergent Adverse Events with First Onset During the Prophylactic and Follow-Up Phase – Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=492)			MQ 250 mg daily for 3 days, then 250 mg weekly (n=162)		
	Total	Prophylactic Phase	Follow-up Phase	Total	Prophylactic Phase	Follow-up Phase
Any subject with TEAE within Nervous System Disorders SOC	110 (13.3%)	99 (20.1%)	17 (3.5%)	44 (14.2%)	36 (22.2%)	10 (6.2%)
Headache	72 (8.7%)	66 (13.4%)	8 (1.6%)	29 (9.4%)	21 (13.0%)	9 (5.6%)
Lethargy	23 (2.8%)	16 (3.3%)	7 (1.4%)	11 (3.6%)	9 (5.6%)	2 (1.2%)
Dizziness	7 (0.8%)	6 (1.2%)	1 (0.2%)	2 (0.6%)	2 (1.2%)	-
Paresthesia	4 (0.5%)	4 (0.8%)	4 (0.8%)	1 (0.3%)	1 (0.6%)	1 (0.6%)
Migraine	2 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.6%)	1 (0.6%)	1 (0.6%)
Sinus headache	-	-	-	-	-	-
Coordination abnormal	2 (0.2%)	2 (0.4%)	-	1 (0.3%)	1 (0.6%)	-
Sciatica	1 (0.1%)	1 (0.2%)	-	-	-	-
Somnolence	1 (0.1%)	1 (0.2%)	-	-	-	-
Syncope	1 (0.1%)	1 (0.2%)	-	-	-	-
Tremor	2 (0.2%)	2 (0.4%)	-	-	-	-
Amnesia	1 (0.1%)	1 (0.2%)	-	-	-	-
Headache tension	1 (0.1%)	1 (0.2%)	-	-	-	-
Hyperesthesia	1 (0.1%)	1 (0.2%)	-	-	-	-
Hypoesthesia	1 (0.1%)	1 (0.2%)	-	1 (0.3%)	1 (0.6%)	-
Presyncope	1 (0.1%)	1 (0.2%)	-	-	-	-
Tension headache	1 (0.1%)	1 (0.2%)	-	-	-	-

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=492)			MQ 250 mg daily for 3 days, then 250 mg weekly (n=162)		
	Total	Prophylactic Phase	Follow-up Phase	Total	Prophylactic Phase	Follow-up Phase
Paresis	-	-	-	1 (0.3%)	1 (0.6%)	-
Sensory loss	-	-	-	1 (0.3%)	1 (0.6%)	-

Division of Neurology Products Consult

The Division of Neurology Products (DNP) reviewer, Laura Jawidzik, M.D., provided the following recommendations:

a. From a neurologic perspective, is TQ reasonably safe to use for up to 6 months of continuous dosing?

The neurological AE profile seems reasonably safe based on the data that has been provided with the application. There were some limitations in these data to assess neurologic safety. There was no follow-up safety data on several cases of persistent dizziness or tinnitus to determine whether these cases resolved; therefore, we are unable to definitively say that no permanent neurologic sequelae will occur with up to 6 months of dosing. This point is of relevance as permanent neurological adverse reactions are a known risk of MQ. In addition, the follow-up safety period for these studies was relatively short and, at times, only covered 2 half-lives rather than the preferred 5 half-lives following the last dose; therefore, some neurologic adverse events resulting from the study drug may have been missed. The longest follow-up period was 24 weeks (study 057) and information form this study may be limited in its ability to detect neurological AEs as it was designed as a renal and ocular study Concerningly, study 033 shows similar rates of neurological AEs between TQ and MQ, a known neurotoxin, which at least raises the possibility that these drugs may be found to have similar safety profiles with the accumulation of additional exposure of subjects in the postmarketing setting. The safety database demonstrates relatively high rates of neurologic adverse events in the placebo groups, and it is not clear why this is the case.

b. What neurologic monitoring, if any, should be conducted for individuals on TQ prophylaxis for up to 6 months of continuous dosing?

Patients taking TQ should be asked specifically about neurological symptoms such as myalgia, dizziness, vertigo, tinnitus, and visual problems in terms that they can readily understand (i.e., room spinning, sensation of movement, ringing in the ears, muscle pain, etc.). The drug should be discontinued if subjects are experiencing these symptoms. Any patient that develops these neurologic symptoms should been seen by a neurologist for a neurologic evaluation and should be followed until resolution.

Reviewer comment: *In the population studied, there appears to be Neurologic effects, associated with both TQ ACR and MQ exposure. It is important to note that systematic monitoring for neurologic TEAEs was not conducted in these studies, and the true incidence of neurologic TEAEs may be underestimated.*

In the population studied, the TQ ACR was similar to MQ and was associated with the neurologic TEAEs of 'headache', 'lethargy' and 'dizziness'. This should be reflected in labeling. In addition, low incidence neurologic TEAEs of concern in the TQ ACR, such as visual field defect, tinnitus, and myalgia should be reflected in labeling. There is not adequate data to assess the use of TQ in individuals with underlying neurologic conditions. Occurrence of neurologic TEAEs after TQ discontinuation cannot be assessed.

In both the TQ and MQ groups, the majority of subjects with 'motion sickness' were enrolled in Study 033. Deployed ADF soldiers may have been exposed to unique travel circumstances by air, sea, and land. However, MQ labeling includes 'vertigo' as an adverse reaction and the association of TQ with 'motion sickness' cannot be excluded, as both randomized groups were presumably exposed to the same environmental factors. The following vestibular disorders-related TEAEs should be considered for labeling: 'motion sickness', 'vertigo' and 'vestibular neuronitis'.

9.15.6 Psychiatric

Psychiatric effects associated with TQ exposure were investigated due to known psychiatric adverse reactions with MQ and CQ/hydroxy-CQ (Table 73 and Table 91).

Study Exclusion Criteria

For the studies included in the Extended Dosing Safety Set, exclusion criteria for psychiatric disorders differed (Table 98). In the studies with a MQ control arm, individuals with a history of psychiatric disorder were excluded, consistent with current labeling for MQ.

Table 98: 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

Source: Adapted from Division of Psychiatric Products (DPP) Consultative Review, Table 2.

Reviewer comment: *The following is an excerpt from the DPP consult. 'None of the 5 trials utilized a rating scale during treatment to assess psychiatric symptoms such as depression, anxiety, psychosis, insomnia, or suicidal ideation. This fact should be kept in mind in reviewing*

the adverse event (AE) reporting rates from these trials because lack of systematic monitoring for psychiatric symptoms likely resulted in underestimation of the actual incidence of these events.' See review by Gregory Dubitsky, M.D., in DARRTS dated 18 May 2018, Reference ID: 4265346.

Psychiatric Disorders Discontinuations and SAEs

Psychiatric TEAEs leading to study discontinuation in the TQ ACR group included depression (Subject (b) (6) and suicide attempt (Subject (b) (6)), each of which occurred in 1 (0.1%) subject (Table 99). Case narratives for the withdrawn subjects follow.

- *Subject (b) (6) (Study 043):* The case narrative for Subject (b) (6) can be found in the section on SAEs leading to discontinuation.

- *Subject (b) (6) (Study 033):* This is 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.

***Reviewer comment:** Given the timing of onset of symptoms, it is possible that TQ exposure was associated with depression in this case.*

Psychiatric TEAEs leading to study discontinuation in the MQ group included severe anxiety (Subject (b) (6) 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.

Table 99: Summary of Psychiatric Adverse Events (Discontinuations and SAEs): TQ ACR Group versus 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Psychiatric TEAEs leading to discontinuation			
Depression	1 (0.1%)	-	-
Suicide Attempt	1 (0.1%)	-	-
Anxiety	-	-	1 (0.3%)
Psychiatric SAEs			
Suicide Attempt	1 (0.1%)[1]	-	-
Anxiety	-	-	1 (0.3%)[1]

[1]SAE led to discontinuation.

Psychiatric Disorders TEAEs

In the Extended Dosing Safety Set, the number of subjects with TEAEs within the Psychiatric Disorders SOC was as follows: TQ ACR 3.9% (32/825), MQ 3.2% (10/309) and placebo 0.8% (3/396) (Table 100).

Several low incidence TEAEs in the TQ ACR arm include: 'abnormal dreams', 'sleep disorder', 'anxiety disorder', 'depression', 'euphoric mood', 'agitation', 'stress', 'bipolar disorder', 'depressed mood', 'panic attack', 'neurosis' and 'suicide attempt'. TEAEs occurring in both the TQ ACR and MQ groups include 'insomnia', 'abnormal dreams', 'nightmare', 'sleep disorder', and 'depression'.

Reviewer comment: *As systematic monitoring for psychiatric TEAEs was not conducted in these studies, the true incidence of psychiatric TEAEs may be underestimated.*

Table 100: TEAEs within the Psychiatric Disorders System Organ Class – Extended Dosing Safety Set and Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)		**Placebo** (n=295)[1]	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)	
	Extended Dosing Safety Set (n=825)	**Study 033 Subjects Only** (n=492)	**Extended Dosing Safety Set** (n=295)	**Extended Dosing Safety Set** (n=309)	**Study 033 Subjects Only** (n=162)
Any subject with TEAE within Psychiatric Disorders SOC	32 (3.9%)	25 (5.1%)	3 (1.0%)	10 (3.2%)	7 (4.3%)
Insomnia	10 (1.2%)	8 (1.6%)	3 (0.8%)	1 (0.3%)	1 (0.6%)
Abnormal dreams	5 (0.6%)	5 (1.0%)	-	2 (0.6%)	2 (1.2%)
Nightmare	3 (0.4%)	3 (0.6%)	-	1 (0.3%)	1 (0.6%)
Sleep disorder	3 (0.4%)	2 (0.4%)	-	2 (0.6%)	2 (1.2%)
Anxiety disorder	2 (0.2%)	2 (0.4%)	-	-	-
Depression	2 (0.2%)	1 (0.2%)	-	1 (0.3%)	1 (0.6%)
Euphoric mood	2 (0.2%)	2 (0.4%)	-	-	-
Agitation	2 (0.2%)	2 (0.4%)	-	-	-
Stress	1 (0.1%)	1 (0.2%)	-	-	-
Bipolar disorder	1 (0.1%)	-	-	-	-
Depressed mood	1 (0.1%)	-	-	-	-
Panic attack	1 (0.1%)	1 (0.2%)	-	-	-
Neurosis	1 (0.1%)	-	-	-	-
Suicide attempt	1 (0.1%)	-	-	-	-
Anxiety	-	-	-	2 (0.6%)	-
Loss of libido	-	-	-	1 (0.3%)	-
Somnambulism	-	-	-	1 (0.3%)	1 (0.6%)

[1]*Study 033 did not have a placebo group.*

In both the TQ and MQ group, Study 033 accounted for most the Psychiatric TEAEs observed in the Extended Dosing Safety Set. For example, in the TQ group, almost all the subjects experiencing 'insomnia', 'abnormal dreams', 'nightmare', 'sleep disorder', 'anxiety disorder', 'depression', 'euphoric mood', 'agitation' and 'stress' in the Extended Dosing Safety Set were enrolled in Study 033 (Table 100). Study 033 enrolled ADF soldiers deployed to hostile combat conditions. The incidence of TEAEs within the Psychiatric Disorders SOC was numerically higher in the TQ group than in MQ (5.1% [25/492] vs. 4.3% [7/162], respectively (Table 101). In addition, subjects with any sleep disturbance were similar in both the TQ ACR and MQ groups (3.5% [17/492] vs. 3.7% [6/162]), respectively).

Table 101: 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)	**MQ 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.
Source: Adapted from DPP Consultative Review, Table 3.

Reviewer comment: *The following is an excerpt from the DPP consult. 'Because the types of reactions associated with MQ cover a wide spectrum, a comparison of the incidence of any psychiatric AE is of primary interest. The percentage of patients with any psychiatric AE was slightly higher in the TQ group than in the MQ group. The inclusion of a placebo control would have been useful in ascertaining the contribution of TQ and MQ to these events as opposed to other factors such as the stress of military deployment to a potentially hazardous area.'*

Psychiatric AE reporting rates for Study 057 and the pool of studies 030, 043 and 045 are further summarized in Table 102 and Table 103.

Table 102: Psychiatric Adverse Event Reporting Rates in Study 057 (n [%]) – Safety population

Adverse Event	Taf 200 N=81	Placebo N=39
Depression[12]	2 (2.5%)	0
Insomnia	2 (2.5%)	2 (5.1%)
Any Psychiatric AE	4 (4.9%)	2 (5.1%)

[12] Includes depression and depressed mood. One patient with depression also had an AE of bipolar disorder the same day, which is not enumerated separately here.
Source: DPP Consultative Review, Table 4.

Table 103: Psychiatric Adverse Event Reporting Rates in Study 030, 043, 045 (n [%]) – Safety population

Adverse Event	Taf 200 N=252	Placebo N=256	Mefloquine N=147
Anxiety[13]	1 (0.4%)	0	2 (1.4%)
Insomnia	0	1 (0.4%)	0
Loss of Libido	0	0	1 (0.7%)
Suicide Attempt	1 (0.4%)	0	0
Any Sleep Symptom[14]	1 (0.4%)	1 (0.4%)	0
Any Psychiatric AE	3 (1.2%)	1 (0.4%)	3 (2.0%)

[13] Includes anxiety and neurosis.
[14] Includes insomnia and sleep disorder.
Source: DPP Consultative Review, Table 5.

Reviewer comment: *Similar to study 033, analysis of Study 057 and the pooled studies 030, 043, and 045 suggests that the risk of a psychiatric AEs with TQ and MQ therapy are comparable.*

Psychiatric Disorders SMQs

A SMQ for 'Depression and Suicide/Self-injury' on the entire safety population of the ISS revealed 2 subjects with 'depression', 1 subject with 'depressed mood' and 1 subject with 'suicide attempt' in the TQ ACR group (Table 104 and Table 105). The percentage of subjects with TEAEs within the Depression and Suicide/Self-injury SMQ was similar for the TQ ACR (0.5%), placebo (0.2%) and MQ (0.3%) groups in the Extended Dosing Safety Set.

The subject (b) (6) with 'suicide attempt' in the TQ ACR group is discussed in the section on SAEs Leading to Discontinuation. In the group receiving TQ 600 mg (not shown in table), TEAEs included 'mood altered' (n=2) and 'altered psychomotor activity' (n=1).

In Study 033, there was 1 subject each in the TQ ACR and MQ arms with a TEAE of 'depression' (Table 104). No other TEAEs within the 'Depression and Suicide/Self-injury' SMQ were noted for Study 033. As noted previously, subjects with a history of a psychiatric disorder or drug or alcohol abuse were excluded from enrollment in Study 033.

Table 104: TEAEs within the Depression and Suicide/Self-injury SMQ – 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Subjects with any TEAE within Depression and Suicide/Self-injury SMQ	4 (0.5%)	-	1 (0.3%)
Depression	2 (0.2%)	-	1 (0.3%)
Depressed mood	1 (0.1%)	-	-
Suicide attempt	1 (0.1%)	-	-

Table 105: Case Summaries of TEAEs within the Depression and Suicide/Self-injury SMQ – Extended Dosing Safety Set

USUBJID	Treatment Group	Age (years)	Sex	Race	Dictionary Derived Term	Reported Term	Start Day of Event	Duration of Event (Days)	Severity	Outcome	Causality by Investi-gator
(b) (6)	TQ 200 mg	24	Male	Black or African American	Suicide attempt	VOLUNTEER BECAME ACUTELY INTOXICATED WITH ETHANOL. FAMILY REPORTED THAT HE HAD ALSO TAKEN POISON FOR SUICIDE	9	3	SEVERE	RECOVERED /RESOLVED	NOT RELATED
	TQ 200 mg	25	Fem ale	White	Depressed mood	"FEELING A BIT DEPRESSED"	38	15	MILD	RECOVERED /RESOLVED	UNLIKELY
	TQ 200 mg	28	Male	White	Depression	DEPRESSION	25	87	MODER ATE	RECOVERED /RESOLVED	POSSIBLE
					Depression	DEPRESSION	25	Ongoing	MODER ATE	NOT RECOVERED /NOT RESOLVED	POSSIBLE
	TQ 200 mg	28	Male	White	Bipolar disorder	BIOPOLAR DISORDER (NEW DIAGNOSIS)	224	Ongoing	MILD	NOT RECOVERED /NOT RESOLVED	UNLIKELY
					Depression	DEPRESSION (NEW DIAGNOSIS	224	Ongoing	MILD	NOT RECOVERED /NOT RESOLVED	UNLIKELY
	MQ 250 mg	39	Male	White	Depression	DEPRESSION	69	Ongoing	MODER ATE	NOT RECOVERED /NOT RESOLVED	UNLIKELY

Note: Table lists only the TEAE for the Depression and Suicide/Self-injury SMQ. Subjects may have experienced additional TEAEs not shown in table.

SMQs for 'Psychosis and Psychotic Disorders' on the entire safety population of the ISS revealed

three subjects, who received TQ doses of 350 to 500 mg (single or loading for 3 days), with a TEAE of 'psychotic disorder' (n=2) or 'psychosis' (n=1) (Table 106). These TEAEs occurred 8 to 28 days after study drug administration. All three patients had a history of psychosis /schizophrenia. No subjects in the TQ ACR, placebo, or MQ groups were identified in this SMQ. In addition, no TEAEs within the 'Psychosis and Psychotic Disorders' SMQ were noted for Study 033.

Table 106: Case Summaries of TEAEs within the 'Psychosis and Psychotic Disorders' SMQ – ISS Safety Population

USUBJID	Actual Treatment	Age (years)	Sex	Race	Dictionary Derived Term	Reported Term	Start Day of Event	Duration of Event (Days)	Severity	Outcome	Causality
(b) (6)	TQ 400 mg (Loading only)	23	Male	White	Psychotic disorder	PARANOID HALLUCINOTIC PSYCHOSIS (SUSPECTED)	28	Ongoing	MODERATE	NOT RECOVERED /NOT RESOLVED	UNLIKELY
	TQ 500 mg (Loading only)	30	Male	Black or African American	Psychotic disorder	PSCHOTIC EPISODE	8	10	SEVERE	RECOVERED /RESOLVED	UNLIKELY
	TQ 350 mg (Loading only)	22	Male	White	Dizziness	LIGHTHEADEDNESS	1	1	MILD	RECOVERED /RESOLVED	PROBABLE
					Acute psychosis	ACUTE PSYCHOTIC EPISODE	20	27	SEVERE	RECOVERED /RESOLVED	POSSIBLE

Reviewer comment: *There may be an association of TQ exposure and AEs under Depression and Suicide/Self Injury SMQ. In addition, the occurrence of TEAEs within the Psychosis and Psychotic Disorders SMQ at day 8 to 28 after TQ (350 mg to 500 mg) administration is notable, given the long half-life of TQ.*

Psychiatric TEAEs, Time of Onset and Duration of TEAEs – Study 033

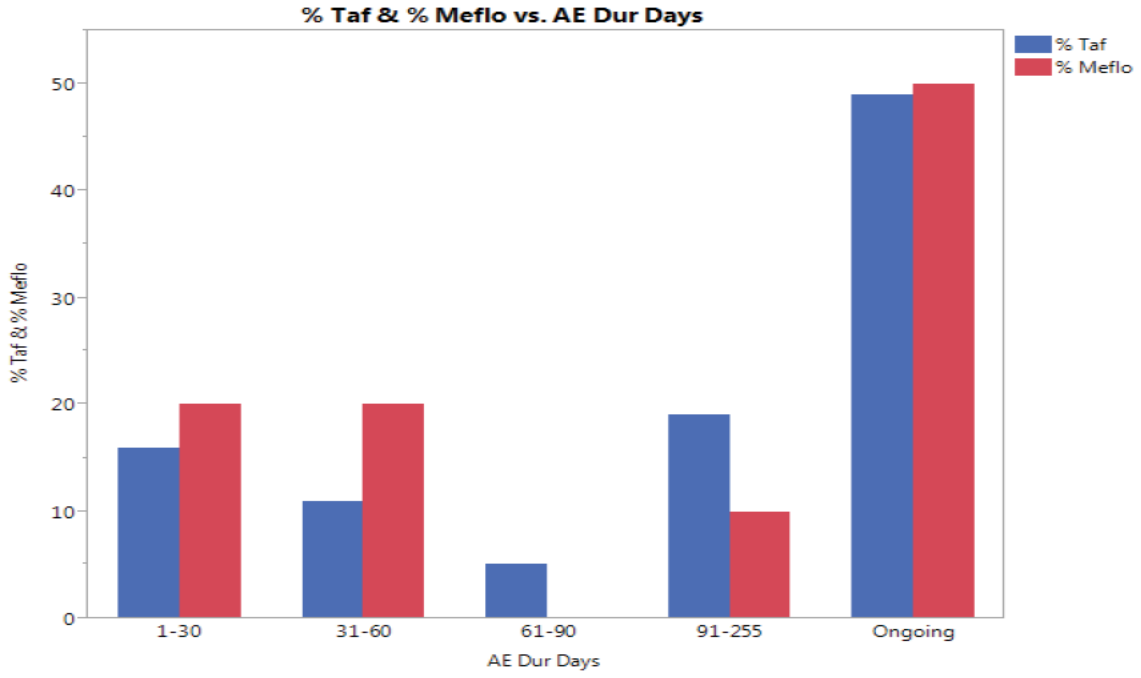
In order to understand the Psychiatric TEAEs during and after TQ ACR exposure, psychiatric TEAEs during the prophylactic and follow-up phase were analyzed. In Study 033, the time of onset for most subjects experiencing a psychiatric TEAE was higher during the prophylactic phase for both the TQ ACR and MQ groups (Table 107). However, the duration of TEAEs first occurring in the prophylactic phase often lasted into or beyond the follow-up phase for both the TQ ACR and MQ groups (Figure 4).

Table 107: Psychiatric Treatment Emergent Adverse Events with First Onset During the Prophylactic and Follow-Up Phase – Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=492)			MQ 250 mg daily for 3 days, then 250 mg weekly (n=162)		
	Total	Prophylactic Phase 26 week ±4 weeks	Follow-up Phase 24 weeks	Total	Prophylactic Phase 26 week ±4 weeks	Follow-up Phase 24 weeks
Any subject with TEAE within Psychiatric Disorders SOC	25 (5.1%)	21 (4.3%)	4 (0.8%)	7 (4.3%)	6 (3.7%)	1 (0.6%)
Insomnia	8 (1.6%)	7 (1.4%)	1 (0.2%)	1 (0.6%)	1 (0.6%)	-

Dictionary Derived Term Number of subjects (%)	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=492)			MQ 250 mg daily for 3 days, then 250 mg weekly (n=162)		
	Total	Prophylactic Phase 26 week ±4 weeks	Follow-up Phase 24 weeks	Total	Prophylactic Phase 26 week ±4 weeks	Follow-up Phase 24 weeks
Abnormal dreams	5 (1.0%)	5 (1.0%)	-	2 (1.2%)	1 (0.6%)	1 (0.6%)
Nightmare	3 (0.6%)	3 (0.6%)	-	1 (0.6%)	1 (0.6%)	-
Sleep disorder	2 (0.4%)	2 (0.4%)	-	2 (1.2%)	2 (1.2%)	-
Anxiety disorder	2 (0.4%)	1 (0.2%)	1 (0.2%)	-	-	-
Depression	1 (0.2%)	1 (0.2%)	-	1 (0.6%)	1 (0.6%)	-
Euphoric mood	2 (0.4%)	2 (0.4%)	-	-	-	-
Agitation	2 (0.4%)	2 (0.4%)	-	-	-	-
Stress	1 (0.2%)	-	1 (0.2%)	-	-	-
Bipolar disorder	-	-	-	-	-	-
Depressed mood	-	-	-	-	-	-
Panic attack	1 (0.2%)	-	1 (0.2%)	-	-	-
Neurosis	-	-	-	-	-	-
Suicide attempt	-	-	-	-	-	-
Anxiety	-	-	-	-	-	-
Loss of libido	-	-	-	-	-	-
Somnambulism	-	-	-	1 (0.6%)	-	1 (0.6%)

Figure 4: Duration of Psychiatric Adverse Events – Study 033 Safety Population



Reviewer comment: *In Study 033, the time of onset of psychiatric TEAEs occurred frequently during the prophylactic phase for both TQ and MQ. These TEAEs were often of a long duration, lasting beyond the follow-up phase.*

TQ Exposure, Combat Conditions and Psychiatric Disorders TEAEs

ADF soldiers were enrolled in Study 033 and deployed under combat conditions on United Nations peacekeeping duties in East Timor from October 2000 to April 2001. All subjects were healthy adults, ages 18 to 55 years, G6PD normal, and with no history of psychiatric disorders or seizures.

In order to understand the potential impact of a hostile combat environment on psychiatric TEAEs in the TQ ACR group, the percentages of subjects with specific types of TEAEs were compared for the TQ ACR group as a whole (n=825) versus the deployed military subjects in Study 033 (n=492) and versus non-deployed non-ADF subjects who received the TQ ACR (n=333) (Table 108). Overall, deployed ADF subjects in Study 033 experienced a higher incidence and a greater variety of psychiatric TEAEs than did non-deployed (civilian) subjects. Sleep-related TEAEs occurred at a higher incidence among deployed military subjects (18/25 [72%]) versus non-deployed subjects (3/7 [43%]).

Table 108: Subjects with Psychiatric Adverse Events in TQ ACR Populations: Deployed Military (Australian Defense Force) Subjects versus Non-Deployed Subjects

	Number (%) of Subjects		
	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)
Studies Included	**030, 033, 043, 045, 057**	**033**	**030, 043, 045, 057**
Number (%) of Subjects with Any AE	692 (83.9%)	467 (94.9%)	225 (67.6%)
Number (%) of Subjects with Injury, Poisoning, and Procedural Complications	231 (28.0%)	196 (39.8%)	35 (10.5%)
Number (%) of Subjects with Psychiatric Disorders	32 (3.9%)	25 (5.1%)	7 (2.1%)
Number (%) of Subjects with 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%)
Number (%) of Subjects with Other Psychiatric Disorders			
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%)

Source: Module 2.7.4 Summary of Clinical Safety, Table 38.

To further explore the potential impact of a hostile combat environment on psychiatric TEAEs in the TQ ACR group, an SMQ for Hostility/Aggression was conducted (Table 109). The percentage of subjects experiencing a TEAE within the Hostility/Aggression SMQ was similar overall in the TQ ACR group (5.7%) and the MQ group (4.5%). There were no TEAEs occurring at ≥1% in this SMQ. Low incidence TEAEs identified in the TQ ACR group, and not occurring in the placebo and MQ groups, include agitation (n=2) and bipolar disorder (n=1). When comparing results for Study 033, where ADF soldiers were enrolled, TEAEs in this SMQ were higher in the TQ ACR group (7.5%) versus the MQ group (3.7%); however, the majority of the TEAEs were lacerations (TQ ACR group 5.9%).

Table 109: TEAEs within the Hostility/ Aggression SMQ – Extended Dosing Safety Set and Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days then 200 mg weekly (ACR)** (n=825)		**Placebo**[1] (n=396)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)	
	Extended Dosing Safety Set (n=825)	**Study 033 Subjects Only** (n=492)	**Extended Dosing Safety Set** (n=396)	**Extended Dosing Safety Set** (n=309)	**Study 033 Subjects Only** (n=162)
Subjects with any TEAE within Hostility/Aggression SMQ	47 (5.7%)	37 (7.5%)	9 (2.3%)	14 (4.5%)	6 (3.7%)
Laceration	37 (4.5%)	29 (5.9%)	6 (1.5%)	12 (3.9%)	5 (3.1%)
Gun shot wound	4 (0.5%)	4 (0.8%)	-	1 (0.3%)	1 (0.6%)
Injury	3 (0.4%)	2 (0.4%)	3 (0.8%)	1 (0.3%)	-
Agitation	2 (0.2%)	2 (0.4%)	-	-	-
Bipolar disorder	1 (0.1%)	-	-	-	-

[1]Study 033 did not have a placebo arm.

Reviewer comment: *In Study 033, it is not clear whether the stress of military deployment to a potentially hazardous area, exposure to TQ or MQ, and/or enhanced monitoring of subjects contributed to the incidence of psychiatric TEAEs observed.*

Adverse event rates among deployed soldiers from Study 033 were compared with the rates in non-deployed subjects from the pool of Studies 030, 043, 045, and 057, all of whom were treated with the proposed TQ treatment regimen.

The following is an excerpt from the DPP consult. 'In their analysis, the rate of any psychiatric AE in Study 033 was about 2.5-fold higher than in the non-deployed subjects (5.1% vs. 2.1%); this difference is statistically significant (p=0.04, 2-tailed Fisher's exact test).' This is not surprising 'given the increased levels of stress likely experienced by deployed ADF soldiers who are separated from their families and living in an isolated, potentially hostile area. But these soldiers were randomized in a 3:1 ratio to TQ or MQ. The stress burden and propensity to develop a psychiatric reaction related to stress or factors other than the study drug should have been similar between the two treatment groups. Had a placebo arm been included in this study and demonstrated a risk of any psychiatric AE comparable to the drug arms, [one] could conclude that the observed rates were not likely attributable to either drug. Also, consider that if MQ had conferred additional risk (as one might expect based on previous MQ experience) to an underlying level of stress present in both groups, the MQ rate would have been appreciably higher than the TQ rate. This was not the case. As it stands, the risk of a psychiatric AE among TQ-treated soldiers appears to be comparable or slightly higher than the risk among MQ treated soldiers.'

TEAEs among subjects with known or suspected psychiatric history

Because of the time frame when the TQ studies were carried out, subjects with a previous psychiatric history were not excluded from participating. However, after the risk of psychiatric AEs with MQ treatment was identified, any TQ trial with an MQ comparator included a psychiatric exclusion. There were 6 subjects (Table 110) with known or suspected psychiatric history at baseline among 21 TQ clinical trials prior to 2013. None of the subjects received the TQ ACR. Four of these subjects experienced neuropsychiatric TEAEs, while 2 subjects did not. The 4 neuropsychiatric TEAEs included psychosis (n=3, also described in Table 106), and nervousness (n=1).

Table 110: Safety outcomes in subjects with evidence of Psychiatric history at baseline – all clinical studies

Study No. Phase[a] Neuro-psychiatric Exclusion?	Details of Neuropsychiatric Adverse Event			
	TQ Dose	Subject Demographics	Subject's Baseline Psychiatric History	Description of Adverse Event
050 Phase 1 No exclusion[b]	TQ 350 mg, single dose	Subject (b) (6) 22 y.o. White male, healthy volunteer	Hospitalizations for psychiatric illness not disclosed at screening.	SAE – Acute psychotic episode described as "possibly" related to study drug but considered more likely to represent a manifestation of concomitant illness. (*Study-050 CSR, Section V*)
	TQ 500 mg, single dose	Subject (b) (6) 30 y.o. Black male, healthy volunteer	History of schizophrenia not disclosed at screening	SAE – Psychotic episodes considered "remotely" related to study drug. (Study-050 CSR, Section V)
001 Phase 1 No exclusion	TQ 8 mg, single dose	Subject (b) (6) 44 y.o. Black female with G6PD deficiency, otherwise healthy	No psychiatric history disclosed.	AE – Moderate "nervousness" considered not related to study drug in a subject who was self-medicating with several concomitant "prohibited medications", including diazepam, promethazine, and tramadol. (*Study-001* CSR, Table 4.7, Table 9.8)
044 Phase 2 Exclusion for significant "neurologic" history only.	TQ 400 mg x 3d, then 400 mg monthly	Subject (b) (6) 21 y.o. Thai male, healthy soldier	Taking lorazepam at baseline for an undocumented indication	No Neuropsychiatric AEs Subject discontinued Ativan during the study and experienced no psychiatric AEs
045 Phase 2 Exclusion for neuropsychiatric history	TQ 25 mg x 3d then 25mg weekly	Subject (b) (6) 44 y.o. male, African adult, healthy	Anxiety treated with diazepam at baseline.	No Neuropsychiatric AEs Eight days before receiving the loading dose of TQ, the subject discontinued diazepam, and he experienced no psychiatric AEs
014 Phase 1 No exclusion	TQ 400 mg od for 3 days, with Desipramine 100 mg on Day 1 and Day 11	Subject (b) (6) 44 y.o. male, healthy volunteer	History of psychosis not disclosed at screening.	SAE - Paranoid hallucinotic psychosis considered unrelated to study drug. (*Study-014 CSR, Section 5.4*)

[a] Safety information was available for Studies 050, 051, 052, 003, 022, 014, 015, 040, 001, 057, 053, 054, 043, 044, 045, 006, 030, 033, 046, 047, and 049.
[b] This study did exclude subjects with "serious past diseases," and investigator indicated that the two subjects with neuropsychiatric SAEs would have been excluded based on this criterion, had the subjects revealed their psychiatric histories to study personnel at screening.

Source: NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 49.

Reviewer comment: *The following is an excerpt from the DPP consult. 'The psychiatric histories of the 3 TQ-exposed subjects* (b) (6) *apparently were unknown at the time of study enrollment. TQ has a half-life of 17 days, per the Applicant's labeling. Thus, the onset of a drug-related event a few weeks after the last dose is plausible. These cases suggest that TQ may increase the risk of exacerbation in patients with a history of psychiatric illness and*

contraindication in such patients is advisable.'

Postmarketing Reports

To fulfill International Conference on Harmonisation of Good Clinical Practice and/or FDA pharmacovigilance requirements, GlaxoSmithKline (GSK) shared 4 IND safety reports on 08 June 2017 for subjects who participated in Study 049 (n=1) and Study 033 (n=3). These reports were made about 15 years after the end of the studies and were not medically verified. Verbatim narratives for these 4 cases follow.

- *Subject* (b) (6) *(Study 049):* A 47-year-old male subject received a 3-day loading dose of TQ 400 mg in Study 049 (b) (6). He reported 'acquired brain injury' (encephalopathy), with chronic symptoms including anxiety, depression, cognitive impairment, vertigo, tinnitus and hearing problems, with onset (not specified which events) within 1 month of the start of dosing. Prior to the study he stated that he was fit and with no history of mental illness, 'verified by regular screening'. He had a relapse of *P. vivax* malaria several months after completing dosing. Testing identified the CYP2D6*4 allele (intermediate metaboliser), which the former study subject thought might be involved in TQ metabolism. He continues with psychotherapy, psychopharmacology, occupational therapy, physiotherapy and speech therapy.

  Applicant Comment: Study Records for Subject (b) (6) *indicate that this male subject was 29 years old at the time of study entry and had no significant past medical history. He received 3 doses of TQ 400 mg* (b) (6) *and his only reported AEs were mild nausea and abdominal pain for 1 day circa the dosing period.*

- *Subject* (b) (6) *(Study 033):* A 36-year-old male, who received treatment with TQ 200 mg weekly for 6 months in Study 033, reports that abnormal liver function tests and insomnia were recorded in his Australian Defence Force (ADF) file during the study. This former study subject indicated Day 20 was the onset date for adverse events. He also reports 'calcium build up in the eyes' and long term mental problems; he states that 'anger issues continue to be debilitating even after 16 years', suggesting that anger issues started at the time of the study and have continued. He can no longer work and has 'severe mental health problems'.

  Applicant comment: Subject (b) (6) *was a White male who was 20 years old when he took part in the study. He had a history of back pain (onset year* (b) (6) *that was ongoing at study entry. He successfully completed 27 weeks of study dosing with TQ 200 mg* (b) (6) *His adverse events included: 1) abnormal dreams of "mild" intensity (Day 0 - Day 211) that did not require treatment and were considered "suspected related" to TQ; and 2) insomnia of mild-to-moderate intensity (Day 0 –continuing) that did not require treatment and was considered "suspected related" to TQ. In addition, he reported the AE of "shoulder pain", and received concomitant medications for both back pain (ibuprofen) and shoulder pain (diclofenac). Other concomitant medications were albendazole and Ivermectin.*

- *Subject* (b) (6) *(Study 033):* A 42-year-old male in the TQ arm of Study 033 reports anxiety, anger, PTSD, panic attacks and nightmares which started during the study on Day 13 and have continued long term. The reporter states that 'there are certain things I cannot do anymore because of the anxiety'. The subject also reports that the he is currently taking antidepressants.

  Applicant comment: Study Records indicate that Subject (b) (6) *was a White male, 25 years old at study entry, with a past medical history of vivax malaria* (b) (6) *He successfully completed 26 weeks of study dosing with TQ 200 mg* (b) (6) *During the study, the subject reported multiple infections and trauma related to deployment, including gastroenteritis on Day 29 (required IV treatment), followed by a laceration on Day 35. He next developed sinusitis on Day 117, and was treated for more than 4 months with multiple medications, including dextromethorphan, pseudoephedrine, and oxymetazoline. The subject reported anxiety of "mild" intensity (Day 108 – continuing) that did not require treatment and was considered "not related" to the study drug.*

  ***Reviewer comment**: This case demonstrates potential for recall bias for long term adverse events occurring post-exposure. The report indicated that anxiety occurred at Day 13 and the subject was unable to do 'certain things' as a consequence. However, study records indicate anxiety occurred at Day 108 and was of mild intensity.*

- *Subject* (b) (6) *(Study 033):* A 37-year-old male in the TQ arm of Study 033 reports that he was suffering from the following conditions, some or all of which he recalls, began by one month after the start of dosing and are ongoing: 'hallucinations, vertigo, confusion, lack of concentration, wild mood swings, tinnitus, anxiety and panic attacks, depression, suicidal thoughts, long dissociative periods, agitation, excessive twitching/convulsing at onset and during sleep'. The reporter states that the events caused significant or long term incapacity and that he has been prescribed antidepressants.

  Applicant comment: Study Records indicate that Subject (b) (6) *was a White male, 26 years old at study entry. Baseline history data show no reported history of concussion or other injury/illness. He successfully completed 27 weeks of study dosing with TQ 200 mg* (b) (6) *His only reported AE was "mild" motion sickness/vertigo that began on Study Day 64 and did not require treatment. Motion sickness resolved after 130 days and was considered "not related" to study drug.*

Division of Psychiatry Products Consult

The Division of Psychiatric Products (DPP) reviewer, Gregory Dubitsky, M.D. provided the following recommendations:

1. From a psychiatric perspective, is TQ reasonably safe to use for up to 6 months of continuous dosing?

In so far as there were no deaths from psychiatric causes or serious psychiatric AEs that can be attributed directly to TQ exposure in the safety database, TQ appears to be reasonably safe for up to 6 months of continuous dosing from a psychiatric standpoint. However, there are two significant limitations in assessing the psychiatric safety of TQ from these data.

First, there was no systematic monitoring for psychiatric symptoms during any of the 5 key safety studies reviewed above. Although it seems likely that serious and severe psychiatric AEs were detected and documented, many non-serious or less severe psychiatric symptoms may have been missed and, thus, the apparent psychiatric AE rates presented above may substantially underestimate the true incidence. For example, abnormal dreams and insomnia have been reported to occur in greater than 10% of prophylactic users of MQ.[10] This is much higher than the rate seen in the MQ-treated patients in Study 033, where 3.7% of patients reported any sleep symptom. This suggests that detection of psychiatric AEs in these studies was not adequate.

Second, only 825 patients received the proposed dose of TQ for any duration and, of these, 596 patients received the proposed dose for 24 weeks in the 5 analyzed clinical trials. While the absence of an adverse event from this experience provides some measure of assurance that the event has a true incidence not greater than 0.5% (1/200) with 6 months of exposure, serious psychiatric AEs at a lower rate may not have been occurred in this sample. Consider that the estimated incidence of serious neuropsychiatric AEs with MQ has been reported to range from 1/607 to 1/20,000.[11] Assuming the highest MQ incidence rate, a sample size of 1800, with no serious psychiatric AEs in this sample, would be required to nominally rule out this level of risk with TQ.

In sum, although there are no clear data indicating a major psychiatric risk that would preclude approval of TQ, the accuracy of the apparent psychiatric AE incidence rates is questionable and the sample size is not sufficient to confidently rule out the risk of serious psychiatric AEs that might occur at a low rate comparable to that of MQ.

2. What psychiatric monitoring, if any, should be conducted for individuals on TQ prophylaxis for up to 6 months of continuous dosing?

The risk of any psychiatric AE with TQ appears to be roughly comparable to that with MQ based on reporting rates from Study 033 and the pool of the 5 key studies examined above. In view of the psychiatric risk associated with MQ, I recommend that clinicians actively query patients at each visit for the occurrence of a wide spectrum of psychiatric symptoms including suicidal thoughts, depressed mood, anxiety or nervousness, trouble sleeping, nightmares or vivid dreams, hallucinations, and delusional thoughts. As part of a Risk Evaluation and Mitigation Strategy (REMS), a checklist of relevant psychiatric symptoms could be devised with advice on referring the patient for psychiatric examination and discontinuing TQ therapy.

Reviewer comment: *In the population studied, psychiatric effects, particularly sleep symptoms, appeared to be associated with both TQ and MQ exposure. It is important to note that systematic monitoring for psychiatric TEAEs was not conducted in these studies, and the true incidence of psychiatric TEAEs may be underestimated.*

In the population studied, TQ ACR was associated with the Psychiatric Disorders TEAE of 'insomnia' and should be reflected in labeling. In addition, low incidence Psychiatric Disorders SOC TEAEs of concern in the TQ ACR, such as 'abnormal dreams', 'nightmare', 'sleep disorder', 'depression', 'suicide attempt', 'agitation', 'anxiety disorder' and 'panic attack' should be reflected in labeling.

The occurrence of psychiatric TEAEs after TQ discontinuation cannot be assessed. TQ exposure at different doses than the ACR in subjects with an underlying psychiatric diagnosis was associated with psychiatric TEAEs. Contraindications for use in patients with an underlying psychiatric diagnosis should be considered in labeling.

The impact of combat-related factors in deployed military populations receiving the TQ ACR on Psychiatric TEAEs cannot be adequately ascertained. Military subjects may become more prone to the psychiatric effects of extrinsic environmental factors due to TQ or MQ exposure. In Study 033, psychiatric TEAEs were similar in the TQ and MQ groups.

9.15.8 Gastrointestinal

Gastrointestinal effects associated with TQ exposure were investigated due to known safety concerns with PQ, MQ and CQ/h-CQ noted in the respective labels. Nonclinical repeat-dose studies of oral TQ in 3 animal species (mice, rats and dogs) showed gastrointestinal effects of reduced food consumption and reduced weight gain after exposure.

Gastrointestinal Disorders Discontinuations and SAEs

Discontinuations due to gastrointestinal TEAEs included 1 subject each with 'abdominal pain upper' and 'irritable bowel syndrome' in the TQ ACR group. Gastrointestinal SAEs in the TQ ACR group included 1 subject each with 'abdominal pain', 'diarrhea', 'abdominal pain upper' and 'irritable bowel syndrome' (Table 111).

Table 111: Summary of Gastrointestinal Adverse Events (Discontinuations and Serious Adverse Events): TQ ACR Group versus 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Gastrointestinal TEAEs leading to discontinuation	2 (0.2%)	-	1 (0.3%)
Abdominal pain	-	-	1 (0.3%)
Abdominal pain upper	1 (0.1%)	-	-
Irritable bowel syndrome	1 (0.1%)	-	-
Gastrointestinal SAEs	3 (0.4%)	-	1 (0.3%)
Abdominal pain	1 (0.1%)	-	1 (0.3%)
Abdominal pain upper	1 (0.1%)	-	-
Irritable bowel syndrome	1 (0.1%)	-	-
Diarrhea	1 (0.1%)	-	-

Gastrointestinal Disorders TEAEs

Gastrointestinal Disorders SOC TEAEs occurring at incidences ≥1% in the TQ ACR group included: abdominal pain, abdominal pain upper, constipation, dental caries, diarrhea, dyspepsia, gastritis, gastroesophageal reflux disease (GERD), nausea, and vomiting (Table 112).

In Study 033, the incidence of Gastrointestinal Disorders TEAEs was numerically lower in the TQ than in the MQ group (36.2% [178/492] vs. 40.7% [66/162], respectively). Specific TEAEs ≥1% were numerically lower in the TQ vs. MQ groups ('diarrhea' 18.1% vs. 19.8%; 'nausea' 6.9% vs. 9.3%; 'vomiting' 4.9% vs. 5.6%; and 'abdominal pain' 4.1% vs. 6.2%; respectively).

Table 112: TEAEs within the Gastrointestinal Disorders System Organ Class occurring at ≥1% study subjects – Extended Dosing Safety Set and Study 033 Safety Population

Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)		**Placebo** (n=295)[1]	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)	
	Extended Dosing Safety Set (n=825)	**Study 033 Subjects Only** (n=492)	**Extended Dosing Safety Set** (n=295)	**Extended Dosing Safety Set** (n=309)	**Study 033 Subjects Only** (n=162)
Subjects with any TEAE within Gastrointestinal Disorders SOC	281 (34.1%)	178 (36.2%)	96 (32.5%)	133 (43.0%)	66 (40.7%)
Diarrhea	105 (12.7%)	89 (18.1%)	93 (3.1%)	33 (10.7%)	32 (19.8%)
Nausea	50 (6.1%)	34 (6.9%)	6 (2.0%)	18 (5.8%)	15 (9.3%)
Abdominal pain	49 (5.9%)	20 (4.1%)	33 (11.2%)	35 (11.3%)	10 (6.2%)

Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)** (n=825)		**Placebo** (n=295)[1]	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)	
	Extended Dosing Safety Set (n=825)	**Study 033 Subjects Only** (n=492)	**Extended Dosing Safety Set** (n=295)	**Extended Dosing Safety Set** (n=309)	**Study 033 Subjects Only** (n=162)
Vomiting	31 (3.8%)	24 (4.8%)	5 (1.7%)	11 (3.6%)	9 (5.6%)
Constipation	20 (2.4%)	3 (0.6%)	8 (2.7%)	19 (6.1%)	4 (2.5%)
Abdominal pain upper	16 (1.9%)	4 (0.8%)	9 (3.1%)	7 (2.3%)	2 (1.2%)
Gastroesophageal reflux disease	14 (1.7%)	13 (2.6%)	1 (0.3%)	6 (1.9%)	3 (1.9%)
Dyspepsia	13 (1.6%)	3 (0.6%)	13 (4.4%)	13 (4.2%)	3 (1.9%)
Gastritis	13 (1.6%)	6 (1.2%)	8 (2.7%)	2 (0.6%)	-
Dental caries	9 (1.1%)	1 (0.2%)	10 (3.4%)	6 (1.9%)	1 (0.6%)
Enteritis	7 (0.8%)	-	6 (2.0%)	10 (3.2%)	-
Gingivitis	6 (0.7%)	1 (0.2%)	4 (1.4%)	2 (0.6%)	-
Toothache	6 (0.7%)	2 (0.4%)	10 (3.4%)	12 (3.9%)	2 (1.2%)
Hemorrhoids	5 (0.6%)	5 (1.0%)	1 (0.3%)	3 (1.0%)	2 (1.2%)
Abdominal discomfort	4 (0.5%)	-	2 (0.7%)	4 (1.3%)	-

[1]*Study 033 did not have a placebo arm.*

Gastrointestinal disorders SMQ

SMQ for 'Gastrointestinal nonspecific inflammation and dysfunctional conditions' did not reveal any additional TEAEs at ≥1%. The percentage of subjects experiencing TEAEs in this SMQ from the Extended Dosing Safety Set was similar across treatment groups (TQ ACR 32.5%; Placebo 32.1%; MQ 37.5%). In Study 033, similar findings were noted (overall TEAEs TQ ACR 33.5% and MQ 36.4%).

Food Effect

The PK study between the current tablet and prior capsule TQ formulations was only conducted under fed conditions. The ISS dataset does not provide information on whether subjects were fed or fasted prior to TQ administration.

Reviewer comment: *In the population studied, the TQ ACR is associated with gastrointestinal effects. TEAEs which should be reflected in labeling include 'abdominal pain', 'abdominal pain upper', 'constipation', 'diarrhea', 'dyspepsia', 'gastritis', 'gastroesophageal reflux disease', 'nausea', and 'vomiting'. There is inadequate data to comment on the comparative safety profile of TQ when administered with or without food.*

9.15.7 Hepatobiliary

Hepatobiliary effects associated with TQ exposure were investigated due to known safety concerns with MQ. In the labeling for CQ/hydroxy-CQ and MQ, concerns for hepatobiliary effects are noted in the Precautions and Adverse Reactions section (Table 73).

Hepatobiliary TEAEs

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

Hepatobiliary TEAEs in the Investigations SOC are summarized in Table 69.

As described in Table 113, there were 6 subjects in the TQ ACR group who discontinued due to ALT elevations. All the subjects were in Study 045, which excluded study participation if laboratory values were outside of those listed in the study's entry criteria (ALT >60 U/L). In addition, subjects with non-serious changes in ALT, including some with ALT values below 60 U/L were grounds for withdrawal in Study 045. Peak ALT values for the withdrawn subjects in Study 045 are listed: Subject (b) (4) (51 U/L); Subject (b) (6) (ALT 82 U/L); Subject (b) (6) (ALT 47 U/L); Subject (b) (6) (68 U/L); Subject (b) (6) (145 U/L); and Subject (b) (6) (ALT 61 U/L).

Hepatic Disorders SMQ

An SMQ for hepatic disorders revealed an overall incidence of TEAEs in the TQ ACR group (2.4% [20/825]). See Table 113. An SMQ for 'Biliary disorders' and 'Drug related hepatic disorders-comprehensive search' did not identify any additional TEAEs from the hepatic disorders SMQ.

The TEAE incidence of 'alanine aminotransferase increased' was 1.5% in the TQ ACR. An analysis of subjects enrolled in Study 033 revealed TEAEs only in the MQ group (1 subject each; 'liver function test abnormal' and 'cytomegalovirus hepatitis'), with zero TEAEs in the TQ group.

An SMQ for 'Biliary disorders' and 'Drug related hepatic disorders-comprehensive search' did not identify any additional TEAEs from the hepatic disorders SMQ.

Table 113: TEAEs within the Hepatic Disorders SMQ – 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=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Subjects with any TEAE within Hepatic Disorders SMQ	20 (2.4%)	16 (5.4%)	13 (4.2%)
Alanine aminotransferase increased	12 (1.5%)	6 (2.0%)	4 (1.3%)
Hyperbilirubinemia	5 (0.6%)	4 (1.4%)	2 (0.6%)
Blood bilirubin increased	2 (0.2%)	1 (0.3%)	3 (1.0%)
Jaundice cholestatic	1 (0.1%)	0	-

Dictionary Derived Term Number of subjects (%)	**TQ 200 mg daily for 3 days then 200 mg weekly (ACR)** (n=825)	**Placebo** (n=295)	**MQ 250 mg daily for 3 days, then 250 mg weekly** (n=309)
Blood bilirubin abnormal	1 (0.1%)	4 (1.4%)	3 (1.0%)
Alanine aminotransferase abnormal	1 (0.1%)	1 (0.3%)	1 (0.3%)
Liver function test abnormal	-	0	1 (0.3%)
Cytomegalovirus hepatitis	-	0	1 (0.3%)

Hy's Law

Hy's Law can be used to provide information on the potential hepatotoxicity of a drug.[1] There were no subjects who met the criteria for Hy's Law in the entire ISS, including TQ exposed subjects.

In the entire ISS safety population, there were two subjects who met Hy's Law laboratory criteria (b) (6). Both subjects were enrolled in the dose ranging Study 047. Subject (b) (6) received PQ. Case narrative for the one subject who received TQ, Subject (b) (6), follows.

- *Subject (b) (6):* This was a 23 year old Asian male with non-severe *P. vivax* malaria who had ALT, AST and bilirubin values of 33 U/L, 37 U/L, and 71.8 µmol/L at baseline. He received a single TQ dose of 600 mg. The patient experienced TEAEs of 'alanine aminotransferase increased' and 'aspartate aminotransferase increased' of severe and moderate intensity, respectively, on Study Day 8. These TEAEs lasted for 22 days and resolved. Maximum ALT was 249 U/L and maximum AST was 189 U/L. ALT levels improved (Day 10: 142 U/L, Day 14: 116 U/L), however remained elevated through the end of the study.

Reviewer comment: *In the population studied, it does not appear that TQ ACR was associated with hepatotoxicity. There was a single case of a subject who met laboratory criteria for Hy's Law; however, the contribution of P. vivax infection to observed findings cannot be excluded.*

9.1.6. Safety Analyses by Demographic Subgroups

9.1.6.1 Age

Pediatrics

In the entire ISS safety population, there were 290 pediatric subjects exposed to study drug with all but one child age ≥12 to <18 years of age.

There was one 4-year-old child exposed to TQ (Study 054, TQ 600 mg daily and then 300 mg weekly). The remainder of the pediatric subjects (n=223) were exposed to TQ of various doses. Of the 223 pediatric subjects exposed to TQ, 216 (96.9%) were enrolled in Study 006, all 12 to 17 years of age. TQ dosing regimens included the following: single dose only (Studies 036 and 047); 3-day loading dose regimens (Studies 006 and 043); a 2-week regimen (Study 047); and loading doses followed by extended weekly dosing (Studies 030 and 045). There were 46 TQ-exposed pediatric subjects who withdrew from the study for the following reasons: 'protocol deviation' (n=24), 'insufficient therapeutic effect' (n=12), 'adverse experience' (n=4), 'lost to follow-up' (n=5), and 'unknown' (n=1). There were 4 TQ pediatric subjects with SAEs. SAEs included 'abortion' (n=3) and 'unintended pregnancy' (n=2).

There were 2 pediatric subjects exposed to MQ 50 mg, both in Study 030. These 2 subjects were withdrawn from the study due to insufficient therapeutic effect. None had an SAE.

There were 64 pediatric subjects exposed to placebo (n=62 Study 006; n=1 Study 030; n=1 Study 045). There were 23 pediatric placebo-exposed subjects who withdrew from the study for the following reasons: 'protocol deviation' (n=8), 'insufficient therapeutic effect' (n=12), 'adverse experience' (n=3). Four of these subjects experienced SAEs including 'abortion' (n=1), 'abortion spontaneous' (n=1), 'hematemesis' (n=1), 'induced abortion failed' (n=1), 'intentional overdose' (n=1), and 'unintended pregnancy' (n=3).

Study 006

Further safety analyses were conducted on the 278 pediatric subjects enrolled in Study 006, entitled '*Dose Down Range Placebo Controlled Double-Blind Study of Oral TQ SB-252263 (WR 238605) for Prophylactic Efficacy, Safety and Tolerance in Subjects Resident in a Malarious Area of Gabon'*. Adolescent subjects received TQ loading doses of 25 mg, 50 mg, 100 mg, or 200 mg daily for 3 days. Follow-up assessments were conducted at pre-specified intervals up to Day 70 after study medication was stopped. There were no deaths. Ten subjects were withdrawn from the study due to the adverse event, 'unintended pregnancies'. There were 3 serious adverse events considered unrelated to study drug: 'injury', 'hematemesis', and 'vulvar disorder'.

While on-treatment, 24 subjects (7.2%) in the TQ group and 6 subjects (7.2%) in the placebo group had TEAEs (Table 114). During follow-up, 147 subjects (44.3%) in the TQ group and 28 subjects in the placebo group had TEAEs. The most frequent TEAE during the on-treatment period was 'headache' (TQ: 0 to 3.5%; Placebo 2.4%). During the follow-up period, the most frequent TEAEs were fever, headache, abdominal pain, and infection. Abdominal pain occurred more frequently in the TQ 50 mg, 100 mg, and 200 mg groups (10.5%, 7.3%, and 11.9%, respectively), than in the placebo group (2.4%). No clinically relevant changes in laboratory parameters were noted.

Table 114: Study 006 - Most frequently reported adverse events (≥2% of subjects on-treatment; ≥3% subjects during follow-up) - Safety population

Adverse Experience	Treatment Group				
	Tafen 25 mg N=80	Tafen 50 mg N=86	Tafen 100 mg N=82	Tafen 200 mg N=84	Placebo N=83
On-treatment					
At least 1 AE	6 (7.5%)	9 (10.5%)	3 (3.7%)	6 (7.1%)	6 (7.2%)
Headache	0	3 (3.5%)	1 (1.2%)	2 (2.4%)	2 (2.4%)
Fever	0	1 (1.2%)	0	2 (2.4%)	0
Dizziness	2 (2.5%)	2 (2.3%)	0	0	0
Abdominal pain*	1 (1.3%)	1 (1.2%)	0	1 (1.2%)	1 (1.2%)
Fever	0	1 (1.2%)	0	2 (2.4%)	0
Pruritus	2 (2.5%)	0	0	0	0
Follow-up					
At least 1 AE	28 (35.0%)	36 (41.9%)	43 (52.4%)	40 (47.6%)	28 (33.7%)
Fever	11 (13.8%)	14 (16.3%)	17 (20.7%)	14 (16.7%)	12 (14.5%)
Headache	9 (11.3%)	14 (16.3%)	13 (15.9%)	11 (13.1%)	13 (15.7%)
Abdominal pain	4 (5.0%)	9 (10.5%)	6 (7.3%)	10 (11.9%)	2 (2.4%)
Infection	6 (7.5%)	2 (2.3%)	7 (8.5%)	4 (4.8%)	3 (3.6%)
Unintended pregnancy	1 (1.3%)	1 (1.2%)	2 (2.4%)	2 (2.4%)	3 (3.6%)
URTI	1 (1.3%)	5 (5.8%)	0	1 (1.2%)	1 (1.2%)

Data source: Tables 15.1.1, 15.1.2 in Section 13; Listing 15.1.1 in Appendix D

* Although abdominal pain did not fulfil the stated criteria for inclusion in the table it was added because it was one of the most frequently occurring adverse experiences overall in the on-treatment period.

Source: NDA 210607 Clinical Study Report Study 006, Table 27.

Reviewer comment: *No conclusion can be made regarding the safety of the TQ ACR in the pediatric population. The TQ doses pediatric subjects received in Study 006 consist of a three-day regimen. Toxicities occurring with continuous dosing may be different. In addition, frequencies of adverse events with respect to mg/kg dosing could be informative in future pediatric studies. Please refer to the Clinical Pharmacology Section for a review on the PK/PD aspects of Study 006.*

Geriatric Subjects

There were 3 subjects ≥65 years in the ISS Safety Population. One subject (b) (6) received placebo, and 2 subjects (b) (6) received TQ (100 mg or ACR). None of the subjects experienced a TEAE.

Reviewer comment: *No conclusion can be made regarding the safety of the TQ ACR in the geriatric population age 65 and over due to insufficient sample size.*

9.1.6.2 Sex

Selected TEAEs by sex in the Extended Dosing Safety Set are summarized in Table 115. Although these subjects were exposed to the TQ ACR, meaningful comparisons are difficult to make because of varying demographic enrollment for each study. For example, in Study 033, 22 (3.4%) of the 644 subjects enrolled were female, with 14 of these subjects exposed to TQ. Furthermore, assessments for specific TEAEs, such as keratopathy and retinal changes, were only conducted in selected studies.

Table 115: Selected Treatment Emergent Adverse Events by Sex – Extended Dosing Safety Set

Body System or Organ Class/ Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)		Placebo (n=295)		MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	
	Female (n=133)	Male (n=692)	Female (n=111)	Male (n=184)	Female (n=55)	Male (n=254)
Subjects with any selected TEAE	70 (52.6%)	338 (48.8%)	53 (47.7%)	77 (41.8%)	33 (60%)	128 (50.4%)
Blood and lymphatic system disorders						
Hemolytic anemia	1 (0.8%)	1 (0.1%)	-	-	-	-
Anemia	8 (6.0%)	2 (0.3%)	7 (6.3%)	-	1 (1.8%)	-
Eye disorders						
Keratopathy	-	68 (9.4%)*	-	-	-	-
Retinal disorder	-	2 (0.3%)	-	-	-	1 (0.4%)
Visual impairment	-	3 (0.4%)	1 (0.9%)	-	1 (1.8%)	-
Night blindness	1 (0.8%)	1 (0.1%)	-	-	-	1 (0.4%)
Visual acuity reduced	1 (0.8%)	1 (0.1%)	-	-	-	-
Vision blurred	2 (1.5%)	1 (0.1%)	-	2(1.1%)	-	1 (0.4%)
Conjunctivitis	9 (6.8%)	15 (2.2%)	8 (7.2%)	10 (5.4%)	5 (9.1%)	8 (3.1%)
Gastrointestinal disorders						
Nausea	12 (9.0%)	38 (5.5%)	3 (2.7%)	3(1.6%)	5 (9.1%)	13 (5.1%)
Abdominal pain	15 (11.3%)	34 (5.1%)	9 (8.1%)	24 (13.0%)	12 (21.8%)	23 (9.1%)
Vomiting	4 (3.0%)	27 (3.9%)	3 (2.7%)	2 (1.1%)	2 (3.6%)	9 (3.5%)
Diarrhea	9 (6.8%)	96 (13.9%)	3 (2.7%)	6 (3.3%)	-	33 (12.9%)
Investigations						
Blood bilirubin abnormal	-	1 (0.1%)	1 (0.9%)	3 (1.6%)	1 (1.8%)	2 (0.8%)
Blood bilirubin increased	-	2 (0.3%)	-	2 (0.3%)	1 (1.8%)	2 (0.8%)
Blood creatinine abnormal	-	1 (0.1%)	-	-	-	1 (0.4%)
Blood creatinine increased	-	2 (0.3%)	-	2 (0.3%)	-	2 (0.8%)
Hematocrit abnormal	-	-	1 (0.9%)	-	-	-
Hematocrit decreased	-	-	1 (0.9%)	-	-	-
Hematocrit increased	-	-	-	0 (0.0%)	-	1 (0.4%)
Hemoglobin decreased	-	3 (0.4%)	-	3 (0.4%)	-	-
Liver function test abnormal	-	-	-	-	-	1 (0.4%)
Alanine aminotransferase abnormal	1 (0.8%)	-	-	1 (0.5%)	-	1 (0.4%)
Alanine aminotransferase increased	1 (0.8%)	11 (1.6%)	-	6 (3.3%)	1 (1.8%)	3 (1.2%)
Glomerular filtration rate decreased	2 (1.5%)	3 (0.4%)	1 (0.9%)	1 (0.5%)	-	-
Nervous system disorders						
Somnolence	-	2 (0.3%)	1 (0.9%)	0	-	1 (0.4%)
Lethargy	1 (0.8%)	23 (3.3%)	-	-	-	11 (4.3%)
Visual field defect	1 (0.8%)	-	-	-	-	-
Dizziness	4 (3.0%)	18 (2.7%)	8 (7.2%)	0	10 (18.2%)	7 (2.8%)
Headache	48 (36.1%)	130 (18.8%)	43 (38.7%)	51 (27.7%)	24 (43.6%)	68 (26.8%)
Psychiatric disorders						
Insomnia	3 (2.3%)	7 (1.0%)	1 (0.9%)	2 (1.1%)	1 (1.8%)	-

**All subjects were in Study 033, which predominantly enrolled White males.*

9.1.6.3 Racial Subgroups

Selected TEAEs by race in the Extended Dosing Safety Set are summarized in Table 116. Only Black or African American and White race categories are shown because of the low numbers of

subjects in other race categories. Although these subjects were exposed to the TQ ACR, meaningful comparisons are difficult to make because of varying demographic enrollment for each study. For example, in Study 033, 10 (1.6%) of the 644 subjects enrolled were non-White, with 8 of these subjects exposed to TQ. Furthermore, assessments for specific TEAEs, such as keratopathy and retinal changes, were only conducted in selected studies.

Table 116: Selected Treatment Emergent Adverse Events by Race – Extended Dosing Safety Set

Body System or Organ Class/ Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)		Placebo (n=295		MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	
	Black or African American (n=278)	White (n=526)	Black or African American (n=266)	White (n=26)	Black or African American (n=147)	White (n=160)
Subjects with any selected TEAE	124 (44.6%)	277 (52.7%)	109 (41%)	19 (73.1%)	80 (54.4%)	80 (50.0%)
Blood and lymphatic system disorders						
Anemia	10 (3.6%)	-	7 (2.6%)	-	1 (0.7%)	-
Hemolytic anemia	2 (0.7%)	-	-	-	-	-
Eye disorders						
Conjunctivitis	17 (6.1%)	7 (1.3%)	18 (6.8%)	-	11 (7.5%)	2 (1.3%)
Night blindness	1 (0.4%)	1 (0.2%)	-	-	1 (0.7%)	-
Vision blurred	1 (0.4%)	2 (0.4%)	-	-	-	1 (0.6%)
Keratopathy	-	68 (12.9%)*	-	-	-	-
Retinal disorder	-	2 (0.4%)	-	-	-	1 (0.6%)
Visual acuity reduced	-	2 (0.4%)	-	-	-	-
Visual impairment	-	3 (0.6%)	1 (0.4%)	-	-	1 (0.6%)
Gastrointestinal disorders						
Abdominal pain	28 (10.1%)	21 (4.0%)	33 (12.4%)	-	25 (15.6%)	10 (6.3%)
Diarrhea	9 (3.2%)	93 (17.7%)	6 (2.3%)	3 (11.5%)	1 (0.7%)	32 (20.6%)
Nausea	7 (2.5%)	42 (8.0%)	4 (1.5%)	2 (7.7%)	3 (2.0%)	15 (9.4%)
Vomiting	1 (0.4%)	30 (5.7%)	3 (1.1%)	2 (0.7%)	2 (1.4%)	9 (5.7%)
Investigations						
Alanine aminotransferase increased	12 (4.3%)	-	6 (2.3%)	-	4 (2.7%)	-
Hemoglobin decreased	3 (2.4%)	-	1 (0.4%)	-	-	-
Blood bilirubin increased	2 (1.1%)	-	1 (0.4%)	-	3 (2.0%)	-
Blood creatinine increased	2 (1.1%)	-	1 (0.4%)	-	2 (1.4%)	-
Glomerular filtration rate decreased	2 (1.1%)	3 (0.6%)	1 (0.4%)	1 (3.8%)	-	-
Alanine aminotransferase abnormal	1 (0.4%)	-	1 (0.4%)	-	1 (0.7%)	-
Blood bilirubin abnormal	1 (0.4%)	-	4 (1.4%)	-	3 (2.0%)	-
Blood creatinine abnormal	1 (0.4%)	-	-	-	1 (0.7%)	-
Hematocrit abnormal	-	-	1 (0.4%)	-	-	-
Hematocrit decreased	-	-	1 (0.4%)	-	-	-
Hematocrit increased	-	-	1 (0.4%)	-	1 (0.7%)	-
Liver function test abnormal	-	-	-	-	-	1 (0.6%)
Nervous system disorders						
Headache	81 (29.1%)	94 (17.9%)	75 (28.2%)	17 (65.4%)	63 (42.9%)	28 (17.5%)
Dizziness	14 (5.0%)	7 (1.3%)	6 (2.3%)	2 (7.7%)	15 (10.2%)	2 (1.3%)

Body System or Organ Class/ Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)		Placebo (n=295		MQ 250 mg daily for 3 days, then 250 mg weekly (n=309)	
	Black or African American (n=278)	White (n=526)	Black or African American (n=266)	White (n=26)	Black or African American (n=147)	White (n=160)
Lethargy	1 (0.4%)	23 (4.4%)	-	-	-	11 (6.9%)
Somnolence	1 (0.4%)	1 (0.2%)	1 (0.4%)	-	1 (0.7%)	-
Visual field defect	-	1 (0.2%)	-	-	-	-
Psychiatric disorders						
Insomnia	-	10 (1.9%)	2 (0.8%)	1 (3.8%)	-	1 (0.6%)

*All subjects were in Study 033, which predominantly enrolled White males.

9.1.7. Specific Safety Studies/Clinical Trials

The Applicant submitted a 120-day Safety Update Report on 11 April 2018. The Applicant reports one clinical trial in progress, protocol 60PH04 entitled 'Multisite, Randomized, Double Blind, Placebo-Controlled Study to Assess the Long-Term Safety of TQ' under IND 129656. Per the Applicant, as of the end of March 2018, 40 subjects were randomized and are still undergoing treatment. No serious adverse events have been reported. Subjects continue to be enrolled.

9.1.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

In the population studied, there was limited data to assess potential issues related to human carcinogenicity or tumor development and no conclusions can be drawn.

Pediatrics and Assessment of Effects on Growth

See Section 9.6.1.1 regarding safety explorations in the pediatric population. No studies of TQ exposure and effects on growth were conducted by the Applicant.

Pregnancy, Lactation, and Females and Males of Reproductive Potential

Pregnant women were excluded from TQ clinical trials. Per the Applicant, as of October 2014, there were a total of 25 pregnancies reported in association with TQ clinical studies, 18 of which were in subjects who had received TQ.

Outcomes of these 18 subjects were reported by the Applicant as follows:

- Four had uncomplicated pregnancies, with uncomplicated deliveries of healthy offspring. Three of these subjects had first trimester TQ exposure, while the fourth

conceived at approximately 6 weeks after the last TQ dose.
• Two had spontaneous abortions that occurred in the first trimester and were considered unrelated to TQ.
• 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.

No preclinical studies were conducted to determine if TQ is excreted in breast milk.

The Division of Pediatrics and Maternal Health (DPMH) provided input regarding pregnancy, lactation as well as males and females of reproductive potential. The following are excerpts from the DPMH review. See review by Jane Liedtka, M.D., in DARRTS, dated 23 May 2018, Reference ID: 4267093.

Pregnancy

The major issue of concern is the potential for hemolysis in a G6PD-deficient fetus (which theoretically can occur even in the presence of a G6PD normal mother). Given that the concern is a theoretical one that has not actually been demonstrated, DPMH recommended the following:

1. A Warning for embryofetal toxicity
2. A recommendation for pregnancy testing prior to administration of TQ
3. A recommendation for contraception use in females of reproductive potential during administration of TQ and for 6 half-lives after dosing is completed (in this case 15 days X 6 = 90 days).

Lactation

There is no information available regarding the presence of TQ in human or animal milk. Only recently (in 2018) results of studies on PQ in human milk were published which document that PQ is very poorly excreted into human milk and levels were undetectable in infants[15, 16]. TQ is a larger molecule than PQ (464 vs 259) and has very high protein binding (>99%) which would suggest it is even less likely to be excreted in significant amounts into human milk. However, if it is present even in small amounts, the very long half-life (15 days) raises the possibility of TQ accumulating in the infant's plasma.

With regard to breastfeeding, if the full-term infant has normal levels of G6PD upon testing, breastfeeding can be considered, keeping in mind that with the long half-life of TQ means whatever exposure does occur will not be resolved for almost 3 months even with a one-time exposure. If G6PD levels for the infant are unavailable, or if the infant is premature or G6PD-deficient, breastfeeding is not recommended unless long term serial laboratory monitoring of the infant's blood parameters can be performed.

Females and Males of Reproductive Potential

Animal studies demonstrated "slight" changes in viable fetuses (decreased by 15% per the pharmacology/toxicology reviewer) but these were seen in the context of maternal toxicity and are unlikely to be relevant to humans. There are no human data regarding the effect of TQ on fertility.

Because of concerns about embryofetal toxicity due to a G6PD-deficiency in the fetus, DPMH is recommending pregnancy testing prior to administration for sections 2 and 8.3. Contraception for women during and for 3 months (15-day half-life x 6) after exposure is recommended for the same reason.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

In the Overdosage sections of labeling for PQ, MQ and CQ/h-CQ, gastrointestinal, cardiovascular, hematologic and neurologic events are noted (Table 117).

Table 117: Labeling: Overdosage Section for PQ, MQ, and CQ/hydroxy-CQ

Label Section	**PQ Label** *(updated 20 July 2017)*	**MQ Label** *(updated 12 September 2016)*	**CQ/ Hydroxy-CQ label** (CQ updated 11 April 2017)
Overdosage	*Symptoms of overdosage of PQ phosphate include abdominal cramps, vomiting, burning epigastric distress, central nervous system and cardiovascular disturbances, including cardiac arrhythmia and QT interval prolongation, cyanosis, methemoglobinemia, moderate leukocytosis or leukopenia, and anemia. The most striking symptoms are granulocytopenia and acute hemolytic anemia in G6PD deficient patients. Acute hemolysis occurs, but patients recover completely if the dosage is discontinued.*	Symptoms and Signs *In cases of overdosage with MQ, the symptoms mentioned under ADVERSE REACTIONS may be more pronounced.* Treatment *Patients should be managed by symptomatic and supportive care following MQ overdose. There are no specific antidotes. Monitor cardiac function (if possible by ECG) and neuropsychiatric status. Provide symptomatic and intensive supportive treatment as required.*	Chloroquine is very rapidly and completely absorbed after ingestion. Toxic doses of chloroquine can be fatal. As little as 1 g may be fatal in children. Toxic symptoms can occur within minutes. These consist of headache, drowsiness, visual disturbances, nausea and vomiting, cardiovascular collapse, shock and convulsions followed by sudden and early respiratory and cardiac arrest. Hypokalemia has been observed with arrhythmias in cases of intoxication. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation

			and/or arrest.

Based on studies with doses above 200 mg, symptoms of TQ overdose may include gastrointestinal TEAEs (abdominal pain, nausea, and diarrhea), as well as neurologic AEs (headache, dizziness, and somnolence). Hematologic TEAEs (such as methemoglobinemia) may occur with higher doses (greater than 200 mg) or prolonged exposure. In addition, symptoms and signs of overdose are expected if normal TQ doses are administered to G6PD deficient individuals. According to the Applicant, as of January 2017, there were no reported cases of TQ overdose.

Reviewer comment: *When evaluating for signs and symptoms of overdosage, the population receiving higher doses than the TQ ACR was relatively small.*

The Overdosage section of labeling states that hemoglobin decline and methemoglobinemia may be encountered in an overdose..

Drug Abuse Potential

Non-clinical or clinical evidence to date does not suggest that TQ has the potential for abuse liability.

Withdrawal and Rebound

Not applicable.

9.1.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

TQ has not been marketed in any country. On 20 July 2018, TQ was approved for the treatment /radical cure of *P. vivax* under NDA 210795.

Expectations on Safety in the Postmarket Setting

In addition to the ongoing Study 60PH04, the Applicant is required to conduct a study to better evaluate the following safety concerns previously discussed: ophthalmic, hematologic, and psychiatric.

9.2. Integrated Assessment of Safety

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 in the population studied.

Although there were 825 subjects exposed to the TQ ACR in the Extended Safety Set , only 529 subjects were exposed to the TQ ACR for greater than or equal to 23 weeks. This database is relatively small to detect potential low-frequency adverse events, particularly for a prophylaxis indication.

Key safety findings identified during the review include:

- *Ophthalmic*: TQ ACR is associated with reversible vortex keratopathy (corneal deposits) in the studies which conducted ophthalmic evaluations (Study 033, 057 and 058). In these studies, the corneal deposits resolved within one year after drug cessation (except for two subjects lost to follow-up). Although no changes in vision were reported; the risk of adverse effects on vision and on 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 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 is higher.

- *Neurologic*: The TQ ACR is associated with headache, lethargy, dizziness, vertigo/tinnitus, and myalgia. 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 33%) was numerically higher than the placebo group (31%), while fall/dizziness/lightheadedness were higher with TQ ACR than 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 with TQ ACR.

- *Psychiatric*: The TQ ACR is associated with psychiatric adverse reactions. In the Extended Dosing Safety Set, psychiatric adverse reactions were reported in 3.9% (32/825) subjects receiving TQ ACR. Specifically, 21/825 (2.5%) experienced sleep symptoms including abnormal dreams, insomnia, nightmares, and sleep disorder. In Study 033, the overall incidence of subjects experiencing Psychiatric adverse reactions in the TQ ACR group (5.1%)

was numerically higher than in the MQ group (4.3%). Sleep disturbances (including abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism) in Study 033 were similar in the TQ ACR (3.5%) and MQ groups (3.7%). 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 with TQ ACR. The safety of TQ ACR in individuals with underlying psychiatric conditions cannot be ascertained because these subjects were excluded from the clinical trials. There were three subjects with an underlying psychiatric illness undisclosed at the time of enrollment who received 350 to 500 mg of TQ for up to 3 days, doses different than the TQ ACR and experienced psychosis approximately 1 to 3.5 weeks after exposure. This is notable given the mean half-life of TQ is 16.5 days (range 10.8 – 27.3 days).

- *Gastrointestinal*: TQ ACR is associated with gastrointestinal adverse reactions, notably diarrhea, nausea, vomiting, and abdominal pain. In Study 033, the incidence of diarrhea, nausea, vomiting and abdominal pain in the TQ ACR was numerically lower than in the MQ group. The safety profile of TQ when administered without food has not been assessed in the development program.

- *Hepatobiliary:* In the population studied, the TQ ACR was not associated with hepatobiliary toxicity. No subjects met Hy's Law criteria in the entire ISS safety population.

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

10 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was held on 26 July 2018. The Anti-Microbial Drugs Advisory Committee was requested to vote on two questions.

1. VOTE: Has the applicant provided substantial evidence of the effectiveness of TQ for the prevention of malaria in adults for up to 6 months of continuous dosing?

a. If yes, please provide any recommendations concerning labeling.
b. If no, what additional studies/analyses are needed?

There were 11 yes votes, 2 no votes, and 0 abstentions.

In general, the Committee felt that the efficacy data were consistent across all the studies (key and supportive), despite the fact that these were legacy studies and there was no access to the source data for the two key efficacy studies. Specific comments included the fact that data for semi-immune and non-immune populations were consistent.

Two Committee members commented on the relatively small number of subjects who received TQ ACR for greater than 23 weeks and recommended that a larger study should be carried out.

The Committee members encouraged the Agency to mandate studies for various population subgroups including pediatrics (<18 years), geriatrics (≥65 years), low BMI and high BMI. Committee members recommended obtaining more data for efficacy for *P. ovale* and *P. malariae*, and follow-up for post-exposure prophylaxis and relapses.

2. VOTE: Has the applicant provided adequate evidence of the safety of TQ for the prevention of malaria in adults for up to 6 months of continuous dosing?

a. If yes, please provide any recommendations concerning labeling.
b. If no, what additional studies/analyses are needed?

There were 9 yes votes, 4 no votes, and 0 abstentions.

All Committee members felt strongly that postmarketing studies and/or surveillance should be mandated to evaluate neurologic, psychiatric, and hematologic adverse events.

In general, Committee members who voted yes felt that the data were adequate; however, neurologic and psychiatric adverse effects were a concern. Specific comments included the need to ensure ophthalmic, neurologic, psychiatric, and hematologic effects are appropriately labeled. In addition, the label should note limited safety data with longer term use (only 529 subjects were exposed to the TQ ACR for >23 weeks). In addition, the label should note that data in subjects <18 years and ≥65 years are lacking.

In general, Committee members who voted no felt that the safety database was small for a prophylactic indication. More information is needed on safety, especially ocular, hematologic, neurologic and psychiatric adverse effects at the proposed dose and duration, and perhaps longer to reflect intended use in military populations. Committee members felt that is was difficult to assess whether TQ will behave like PQ or MQ. One committee member recognized the need for a new malaria prophylactic drug, but not the urgency, and recommended additional studies to better evaluate safety prior to approval.

One Committee member felt that TQ, recently approved (20 July 2018) for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria, could potentially be used off-label for the prophylaxis if the current NDA is not approved; and opportunities for post-marketing surveillance for safety would be lost.

Additionally, Committee members recommended a postmarketing surveillance study with FDA input. They recommended using an existing large database so the Applicant will know in advance how long it will take to acquire information. In addition, some committee members recommended a large study/trial to evaluate safety measuring 6 month outcomes with observed adherence and active monitoring for neurologic, psychiatric, and hematologic adverse events.

11 Pediatrics

The Division agreed to an initial Pediatric Study Plan with full deferral for the 0 to 17-year-old population. See IND 129656, submission dated 06 Oct 2017 and NDA 210607, Module 1.9.4.

(b) (4)

12 Labeling Recommendations

12.1. Prescribing Information

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
4. Contraindications	• G6PD deficiency • (b) (4)	• Addition of unknown status to the G6PD contraindication • (b) (4) • Addition of contraindication for breastfeeding of G6PD deficient infant or infant with unknown G6PD status • Addition of contraindication for patients with known hypersensitivity • Addition of contraindication for history of psychotic disorders and current psychotic symptoms
5. Warnings and Precautions	• (b) (4) • • •	• Hemolytic Anemia • G6PD Deficiency in Pregnancy and Lactation • Methemoglobinemia • Psychiatric Effects • Hypersensitivity Reactions
6. Adverse Reactions	(b) (4)	• Presentation of Adverse reactions in the active control and placebo controlled studies separately. • Addition of psychiatric and ocular adverse events description as well as hematologic abnormalities
14. Clinical Trials	(b) (4)	• Study 043 and 045 presented as primary efficacy trials • Supportive trial 033 and TQ-2016-02

12.2. Patient Labeling

A Medication Guide was developed as a risk mitigation strategy.

13 Risk Evaluation and Mitigation Strategies (REMS)

No REMS were issued for this application.

13.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

13.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

13.3. Recommendations on REMS

Not applicable.

14 Postmarketing Requirements and Commitments

PREA PMR:

1. Conduct a randomized, active comparator study to evaluate the safety, tolerability, and pharmacokinetics of ARAKODA for the prophylaxis of malaria in children from birth to 18 years of age.

The timetable submitted on August 03, 2018, specifies that this study will be conducted according to the following schedule:

Draft Protocol Submission: 12/2020

Final Protocol Submission: 11/2021

Study Completion: 12/2024

Final Report Submission: 06/2025

2. Conduct study 60PH04 to assess ophthalmic adverse reactions, entitled "Multisite, Randomized, Double Blind, Placebo-Controlled Study to Assess the Long-Term Safety of Tafenoquine".

The timetable submitted on August (b) (4), 2018, specifies that this study will be conducted according to the following schedule:

Final Protocol Submission: Submitted

Study Completion: 06/2022

Final Report Submission: 01/2023

The following are 505 (o) safety PMR's to evaluate the signals of serious risks of ophthalmic, psychiatric, and hematologic adverse reactions.

3. Conduct an observational study to evaluate safety, including neurologic, psychiatric and hematologic adverse reactions, in patients taking ARAKODA (tafenoquine) for the prophylaxis of malaria.

The timetable submitted on August (b) (4) 2018, specifies that this study will be conducted according to the following schedule:

Draft Protocol Submission:12/2018

Final Protocol Submission: 12/2020

Interim Study Reports: 12/2021

12/2022

12/2023

12/2024

Study Completion: 12/2025

Final Report Submission: 12/2026

The following is a CMC PMC:

4. Conduct studies of ARAKODA to identify an optimal QC dissolution method and acceptance criteria for the finished drug product.

Draft Protocol Submission: 11/08/2018

Final Protocol Submission: 02/08/2019

Interim Report Submission: 08/08/2019

Study Completion: 11/08/2019

Final Report Submission: 2/8/2020

15 Appendices

15.1. References

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15.2. Financial Disclosure

List of Clinical Investigators

Study Number	Investigator/Subinvestigator
006	Investigator Prof Dr. Peter G Kremsner
030	Investigator Jose Stoute, MD
033	Investigator Lt Col P Nasveld MD Subinvestigator Lt Col Leonard Brennan MD Subinvestigator Lt Col Peter Leggat MD Subinvestigator Lt Col Mike Edstein PhD Subinvestigator Maj Scott Kitchener MD Subinvestigator Maj Ivor Harris BVSc Subinvestigator Lt Mark Reid BSc
043	Investigator Dr. G. Dennis Shanks, MD, MPH, LTC, MC (USAMRU-K) Investigator Dr. A. J. Oloo MB, ChB, M.Med, D.T.M.H. (KEMRI)
044	Investigator Major Douglas Walsh, MD Subinvestigator Chirapa Eamsila
045	Investigator Dr Braden R Hale, MD, MPH Subinvestigator Eileen Franke Villasante Subinvestigator Fred Binka Subinvestigator Alex Nazzar Subinvestigator Rexford Oduro Subinvestigator Kojo Koram
047	Investigator Dr. Sornchai Looareesuwan Investigator Dr. Srivicha Krudsood Subinvestigator P. Wilairatana Subinvestigator D. Walsh Subinvestigator D.G. Heppner Subinvestigator R. Brueckner Subinvestigator D. Kyle Subinvestigator D. Tang Subinvestigator W. Milhous Subinvestigator B. Schuster
049	Investigator MAJ Peter Nasveld MBBS BSc Med Subinvestigator LT COL Mike Edstein PhD Subinvestigator MAJ Scott Kitchener MBBS MPH Subinvestigator Lt Bruce Russell BSc
058	Investigator Prof Sornchai Looareesuwan

Source: NDA 210607 SN56 Clinical Information Amendment, Table 2.

Clinical Study Number: 030
Clinical Study Name: A Randomized, Double Blind, Placebo Controlled Evaluation of Weekly Tafenoquine (WR 238605/SB252263) Compared to Mefloquine for Chemosuppression of Plasmodium falciparum in Western Kenya

Was a list of clinical investigators provided?	Yes [X]	No [ ] (If no, please explain.)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes [ ]	No [ ] (If no, provide details.)
Is a description of the steps taken to minimize potential bias provided:	Yes [ ]	No [ ] (If no, provide additional information.)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: see *financial disclosure due diligence*	Yes X	No [ ] (If no, provide explanation.)

Clinical Study Number: 033
Clinical Study Name: 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

Was a list of clinical investigators provided?	Yes [X]	No [ ] (If no, please explain.)
Total number of investigators identified: 7		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes [ ]	No [ ] (If no, provide details.)
Is a description of the steps taken to minimize potential bias provided:	Yes [ ]	No [ ] (If no, provide additional information.)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: see *financial disclosure due diligence*	Yes X	No [ ] (If no, provide explanation.)

Clinical Study Number: 043
Clinical Study Name: Evaluation of Weekly tafenoquine (SB 252263 / WR 238605) Compared to Placebo for Chemosuppression of Plasmodium falciparum in Western Kenya

Was a list of clinical investigators provided?	Yes [X]	No [ ] (If no, please explain.)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes [ ]	No [ ] (If no, provide details.)
Is a description of the steps taken to minimize potential bias provided:	Yes [ ]	No [ ] (If no, provide additional information.)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: see *financial disclosure due diligence*	Yes X	No [ ] (If no, provide explanation.)

Clinical Study Number: 045
Clinical Study Name: 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

Was a list of clinical investigators provided?	Yes [X]	No [ ] (If no, please explain.)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes [ ]	No [ ] (If no, provide details.)
Is a description of the steps taken to minimize potential bias provided:	Yes [ ]	No [ ] (If no, provide additional information.)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: see *financial disclosure due diligence*	Yes X	No [ ] (If no, provide explanation.)

Clinical Study Number: 057
Clinical Study Name: 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.

Was a list of clinical investigators provided?	Yes [X]	No [ ] (If no, please explain.)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes [ ]	No [ ] (If no, provide details.)
Is a description of the steps taken to minimize potential bias provided:	Yes [ ]	No [ ] (If no, provide additional information.)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: see *financial disclosure due diligence*	Yes [ ]	No [ ] (If no, provide explanation.)

Clinical Study Number: TQ-2016-01
Clinical Study Name: A Phase 1, Single-Dose, Open-Label Study of Tafenoquine in Healthy Adults to Compare the Pharmacokinetic Parameters of the Proposed Marketed 2X 100 mg Tafenoquine Tablets to the Pharmacokinetic Parameters of Tafenoquine 200 mg Capsules used during Previous Clinical Trials

Was a list of clinical investigators provided?	Yes [X]	No [ ] (If no, please explain.)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes [ ]	No [ ] (If no, provide details.)
Is a description of the steps taken to minimize potential bias provided:	Yes [ ]	No [ ] (If no, provide additional information.)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: see *financial disclosure due diligence*	Yes [ ]	No [ ] (If no, provide explanation.)

Clinical Study Number: TQ-2016-02
Clinical Study Name: A randomized, double-blinded, placebo-controlled study in healthy, non-immune adults to determine the schizonticidal activity of tafenoquine after challenge with *Plasmodium falciparum* blood stage parasites

Was a list of clinical investigators provided?	Yes [X]	No [ ] (If no, please explain.)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes [ ]	No [ ] (If no, provide details.)
Is a description of the steps taken to minimize potential bias provided:	Yes [ ]	No [ ] (If no, provide additional information.)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: see *financial disclosure due diligence*	Yes [ ]	No [ ] (If no, provide explanation.)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Summary of Bioanalytical Method Validation and Performance

Table 1 describes the summary of the bioanalytical methods used for quantification of TQ in human plasma (See **Table 2** for details). The analytical method validation and performance are acceptable.

Table 1. Summary of Bioanalytical Methods for Quantification of Tafenoquine

Analytical Method	Matrix	Validated Range	Study Number
HPLC-MS/MS	Plasma	2 to 500 ng/mL	15
HPLC-MS/MS	Plasma	2 to 500 ng/mL	06, 22 and 40
HPLC-MS/MS	Plasma	0.815 to 408 ng/mL	51
HPLC with (b) (4)	Plasma	0.815 to 408 ng/mL	52
HPLC-MS/MS	Plasma	2 to 500 ng/mL	TQ-2016-01
HPLC-MS/MS	Plasma	5 to 1000 ng/mL	TQ-2016-02

Table 2. Validation Reports for Quantification of Tafenoquine in Human Plasma (Adapted from Applicant's Bioanalytical Methods Summary)

Study 15

Parameter	Requested Information
Analytical Validation Study Number & Location	Method validation report: report-sb-252263-rsd-1013vc-1
Short Description of the Method	LC/MS/MS
Biological Matrix	Human plasma
Analyte	Tafenoquine
Internal Standard	[$^{2}H_{4}$, ^{15}N] SB-252263 (tafenoquine)
Calibration Concentrations	2, 8, 200, 500 ng/mL
Lower Limit of Quantification	2 ng/mL
QC Concentrations	2, 5, 10, 20, 50, 100, 200, 500 ng/mL
Intra-Assay Precision	6.46% (LLOQ)
Intra-Assay Accuracy	-3.69 (LLOQ) Only average bias reported
Inter-Assay Precision	4.38% (LLOQ)
Inter-Assay Accuracy	-3.69 (LLOQ) Only average bias reported
Long-Term Stability of the Working Solution (Observed % Change)	Not reported
Short Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Not reported
Long Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Not reported
Post-Preparative stability (Observed % Change)	Not reported
Freeze-Thaw Stability (Observed % Change)	-8.87%
Dilution Integrity	Not reported

Study 006 and 40

Parameter	Requested Information
Analytical Validation Study Number & Location	Method validation report: study-sb-252263-rsd-101csx-1
Short Description of the Method	HPLC/MS/MS
Biological Matrix	Human plasma
Analyte	Tafenoquine
Internal Standard	[$^{2}H_4$, ^{15}N] tafenoquine
Calibration Concentrations	2, 20, 200, 500 ng/mL
Lower Limit of Quantification	5 ng/mL
QC Concentrations	5, 10, 20, 50, 100, 200, 400, 500 ng/mL
Intra-Assay Precision	5.84% (LLOQ)
Intra-Assay Accuracy	2.00 (LLOQ) Only average bias reported
Inter-Assay Precision	7.32% (LLOQ)
Inter-Assay Accuracy	2.00 (LLOQ) Only average bias reported
Long-Term Stability of the Working Solution (Observed % Change)	Not reported
Short Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Not reported
Long Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Not reported
Post-Preparative stability (Observed % Change)	Not reported
Freeze-Thaw Stability (Observed % Change)	Not reported
Dilution Integrity	Not reported

Study 51

Parameter	Requested Information
Analytical Validation Study Number & Location	Bioanalytical report: *report-WR5-P94-7*
Short Description of the Method	HPLC with fluorescence detection
Biological Matrix	Human plasma and whole blood
Analyte	Tafenoquine
Internal Standard	(b) (4)
Calibration Concentrations	2, 8, 200, 500 ng/mL 0, 0.815, 1.63, 3.26, 6.52, 12.2, 24.5, 48.9, 97.8, 204, and 408 ng/mL plasma 0, 1.91, 3.82, 7.64, 14.3, 28.7, 57.4, 95.7, 191, and 383 ng/mL whole blood
Lower Limit of Quantification	0.815 ng/ml WR 238,605 (free base) in plasma 1.91 ng/ml WR 238,605 (free base) in blood
QC Concentrations	4.0, 20.0, 50.7, 151 ng/mL Precision 1, 2, 4, 8. 15. 25. 50. 100, 200 , 400 ng/mL Accuracy
Intra-Assay Precision	2.2 to 16.9%
Intra-Assay Accuracy	3.83 to 11.0%
Inter-Assay Precision	5.25 to 7.86%
Inter-Assay Accuracy	3.18 to 10.5%
Long-Term Stability of the Working Solution (Observed % Change)	Not reported
Short Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Not reported
Long Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Plasma 4 months at <-20°C (% change not reported) Blood samples 1 month at <-20°C (% change not reported)
Post-Preparative stability (Observed % Change)	Not reported
Freeze-Thaw Stability (Observed % Change)	Not reported
Dilution Integrity	Not reported

Study 52

Parameter	Requested Information
Analytical Validation Study Number & Location	Method validation report: *Study Report No. 13 (section 4.2.2.1)*
Short Description of the Method	HPLC with fluorescence detection
Biological Matrix	Human plasma and whole blood
Analyte	Tafenoquine
Internal Standard	(b) (4)
Calibration Concentrations	0 to 408 ng/mL Plasma 0 to 383 ng/mL Blood
Lower Limit of Quantification	0.815 ng/ml WR 238,605 (free base) in plasma 1.91 ng/ml WR 238,605 (free base) in blood
QC Concentrations	1.63, 20.4, 81.5, and 163 ng/mL for plasma 3.82, 19.1, 76.5, and 143 ng/mL for blood
Intra-Assay Precision	5.44% to 9.07% for plasma 7.69% to 9.15% for blood
Intra-Assay Accuracy	- 4.68% to 31.7% for plasma - 22.7% to -5.86% for blood
Inter-Assay Precision	6.64% to 8.70% for plasma 2.94% to 7.75% for blood
Inter-Assay Accuracy	Not reported
Long-Term Stability of the Working Solution (Observed % Change)	Not reported
Short Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Not reported
Long Term Solution in Biological Matrix at Room Temperature (Observed % Change)	134 days 0.3% to 4.3% plasma stored at <-20°C 62 days -10.1% to 2.0% blood stored at <-20°C
Post-Preparative stability (Observed % Change)	Not reported
Freeze-Thaw Stability (Observed % Change)	Not reported
Dilution Integrity	Not reported

Study TQ-2016-01

Parameter	Requested Information
Analytical Validation Study Number & Location	Method validation report: *report-4003710* *report-4003710a* (long term stability amendment)
Short Description of the Method	LC-MS-MS
Biological Matrix	Human plasma
Analyte	Tafenoquine
Internal Standard	Tafenoquine-D_5
Calibration Concentrations	2.00, 4.00, 10.0, 50.0, 100, 250, 450 and 500 ng/mL
Lower Limit of Quantification	2.00 ng/mL
QC Concentrations	LLOQ 2.00 ng/mL, low 6.00 ng/mL, medium 50 ng/mL, high 400 ng/mL and very high (dilution) 2500 ng/mL
Intra-Assay Precision	1.7-2.7% (LLOQ sample)
Intra-Assay Accuracy	2.0-9.5% (LLOQ sample
Inter-Assay Precision	3.7% (LLOQ sample)
Inter-Assay Accuracy	5.0% (LLOQ sample)
Long-Term Stability of the Working Solution (Observed % Change)	Not done.
Short Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Mean -2.0 % (24 hours)
Long Term Solution in Biological Matrix at Room Temperature (Observed % Change)	Mean -0.8 % (8 days at -20°C) Mean -3.3 (99 days at -20°C)
Post-Preparative stability (Observed % Change)	Mean -4.0% (104 hours, 4°C)
Freeze-Thaw Stability (Observed % Change)	Mean -2.8% (5 cycles, -20°C)
Dilution Integrity	Precision 2.5% Accuracy (bias) 0.4%

Study TQ-2016-02

Parameter	Requested Information
Analytical Validation Study Number & Location	Method validation report and bioanalytical report are included in section 16.1.10 of the CSR *TQ-2016-02*
Short Description of the Method	LC-MS-MS
Biological Matrix	Human plasma
Analyte	Tafenoquine
Internal Standard	Tafenoquine-D_3
Calibration Concentrations	5.00, 10.0, 20.0, 50.0, 200, 500, 1000 ng/mL
Lower Limit of Quantification	5.27 ng/mL (mean)
QC Concentrations	5.00, 6.00, 40.0. 400, 800 ng/mL
Intra-Assay Precision	2.98 to 14.21% (n=6)
Intra-Assay Accuracy	-6.08 to 17.43% (n=6)
Inter-Assay Precision	12.42% (LLOQ)
Inter-Assay Accuracy	5.34% (LLOQ)
Long-Term Stability of the Working Solution (Observed % Change)	-1.30% (-80°C for 41 days)
Short Term Solution in Biological Matrix at Room Temperature (Observed % Change)	-13.94% (6.00 ng/mL, 4 days)
Long Term Solution in Biological Matrix at Room Temperature (Observed % Change)	-3.75% (6.00 ng/mL, -80°C)
Post-Preparative stability (Observed % Change)	-5.82% (6.00 ng/mL, 4°C in LC-MS autosampler for 4 days)
Freeze-Thaw Stability (Observed % Change)	-9.11% (6.00 ng/mL, 4 freeze/thaw cycles, -80° C to RT
Dilution Integrity	Not reported

15.3.2. Population Pharmacokinetic Analysis

A population PK analysis of tafenoquine (TQ) was conducted by Applicant using data from 10 clinical studies including Study 50, 51, 52, 53, 54, 14, 15, 33, 44 and 58.

Study 50 was a Phase 1, placebo-controlled, single dose escalation study in healthy volunteers under a fasted condition with a TQ dose range of 16 to 600 mg. A total of 80 male subjects were enrolled in the study and 45 of them were included in the PK dataset. The PK samples were collected before dosing and at 4, 8, 12, 24, 48, 72, 96, and 168 hours after dose. For six higher dose groups (250, 300-600 mg), additional PK samples were collected on Days 16, 23, 30, and 37.

Study 51 was a Phase 1, placebo-controlled, single and multiple dose study in healthy volunteers under a fasted condition with TQ doses of 200, 400, or 600 mg weekly for 10 weeks. A total 30 male subjects and 6 female subjects were enrolled in the study and 25 of them (N=4 for females) were included in the PK dataset. The PK samples were collected on Day 1 and at Week 10 before dosing and at 2, 4, 6, 8, 12, 16 and 24 h postdose. Trough blood samples were drawn predose (weekly) prior to Week 2 through 9 and at weeks 12, 14, 16, 18, and 20.

Study 52 was a Phase I, single dose study in healthy volunteers under a fasted condition with TO doses of 100, 200, or 400 mg. A total of 18 male subjects were enrolled in the study and all of them were included in the PK dataset. PK samples were collected before dosing and at 0.5, 1, 2, 4, 8, 10, 12, 14, 18, 24, 28, 48, 96, 168, 216, 384, 552, 720, and 1056 hours postdose.

Study 53 was a Phase 1, placebo-controlled, challenge study in healthy volunteers under a fasted condition with a TQ dose of 600 mg one day before sporozoite inoculation. A total of 4 male subjects and 2 female subjects were enrolled in the study and 4 of them (N=2 for females) were included in the PK dataset. PK samples were collected before dosing and at 5, 7, 12, 28, and 42 days after dosing on Day 1.

Study 54 was a Phase 1, placebo-controlled, challenge study in healthy volunteers with a TQ dose of 600 mg on Day -3 and -2 before sporozoite inoculation (Day 0), then 300 mg on Day 3, 10 and 17 and 24. A total of 12 male subjects were enrolled in the study and 10 of them were included in the PK dataset. PK samples were collected before dosing on Day 17 and Before dosing on Day 24 and at 26, 31, 38, 45, and 59 days after dosing on Day 24.

Study 14 was a Phase 1, bioavailability study of 3 oral formulations in healthy volunteers with a TQ dose of 400 mg QD for 3 days. A total of 43 male subjects, 15 female subjects were enrolled in the study and all of them were included in the PK dataset. Blood samples were collected on Day 1 before dosing and up to 96 h post dose. Further blood samples were collected on an ambulatory basis on days 6, 7 and 8 and in weeks 4, 6, 8, 10, 12, 14, 16 and 18.

Study 15 was a Phase 1, drug-drug interaction study in healthy volunteers with a TQ dose of 400 mg QD for 3 days under the fed condition. A total of 20 male subjects and 14 female subjects were enrolled and all of them were included in the PK dataset. Blood samples were collected up to 96 hours and thereafter at 2-week intervals after the first dose of TQ.

Study 33 was a Phase 3, placebo-controlled study in nonimmune Australian army with a TQ dose of 200 mg QD for 3 days, and then 200 mg weekly. A total of 632 male subjects and 22 female subjects were enrolled in the study and 491 of them (N=14 for females) were included in the PK dataset. PK samples were collected on Day 2, Week 4, 8, 16, and 26.

Study 44 was a Phase 2, placebo-controlled study in nonimmune royal Thai army with a TQ dose of 400 mg QD for 3 days, and then 400 mg monthly. A total of 205 male subjects were enrolled in the study and 135 of them were included in the PK dataset. PK samples were collected blood samples at about 8, 24, 48 and 56 hours after the last loading dose and then every 3 to 4 days up until the first monthly dose. After each monthly dose, samples were collected at about 8 hour, mid-month and prior to next dose. Following the last monthly dose samples were collected at about 4, 8, 12 and 24 hours and then every 3 to 4 days for 2 months.
Study 58 was a Phase 2, active-controlled study in patients with P. vivax with TQ doses of 400 mg QD for 3 days or 600 mg QD for 1 day. A total of 120 subjects were enrolled in the study and 46 of them (N=9 for females) were included in the PK dataset. PK samples were collected daily for Day 0-7, Day 12-20, and Day 28-30.
The demographics of subjects in the population PK dataset is summarized in **Table 1**.

Table 1. Demographic Summary of Subjects used in the Population PK Analysis

Baseline Characteristic	Statistic	All Subjects	Male	Female
Number of Subjects	n (%)	866	808 (93.3%)	58 (6.7%)
Age (years)	Mean	27.8	27.1	37.2
	SE	0.28	0.25	1.68
	Median	25.0	25.0	35.0
	Min,Max	18.0,60.0	18.0,60.0	19.0,60.0
Race				
Asian or Oriental	n (%)	181 (20.9%)	172 (19.9%)	9 (1.0%)
Black or African	n (%)	26 (3.0%)	21 (2.4%)	5 (0.6%)
Caucasian/White	n (%)	626 (72.3%)	582 (67.2%)	44 (5.1%)
Hispanic	n (%)	31 (3.6%)	31 (3.6%)	-
Other	n (%)	2 (0.2%)	2 (0.2%)	-
Food				
No	n (%)	92 (10.6%)	86 (9.9%)	6 (0.7%)
Yes	n (%)	774 (89.4%)	722 (83.4%)	52 (6.0%)
Weight (kg)	Mean	75.0	75.9	62.4
	SE	0.47	0.48	1.37
	Median	75.0	76.0	62.3
	Min,Max	43.0,135.0	43.0,135.0	43.0,88.0

Source: Applicant's population PK report, Page 91, Table 16-4

A one-compartment PK model with first order absorption and elimination rate constants was selected as the structural model. Body weight and age were identified as covariates of apparent clearance (CL/F) and body weight and food was identified as covariates of apparent volume distribution (V/F). The parameter estimates of final model are listed in **Table 2**.

Table 2. Population PK Parameters of Final PK Model

Parameters (Units)	Final Estimate	Bootstrap 95% CI		Between-individual Variability [a]
		Lower	Upper	
$CL/F\ (L/hr) = \theta_{CL} \times (WT/75)^{\theta_{CL\text{-}WT}} \times (AGE/25)^{\theta_{CL\text{-}AGE}}$				23.6%
θ_{CL}	4.17	4.080	4.230	
$\theta_{CL\text{-}WT}$	0.552	0.474	0.637	
$\theta_{CL\text{-}AGE}$	-0.200	-0.267	-0.138	
$V/F\ (L) = \theta_{V} \times (WT/75)^{\theta_{V\text{-}WT}} \times (\theta_{V\text{-}FOOD})^{FOOD}$				24.1%
θ_{V}	2470	2340	2630	
$\theta_{V\text{-}WT}$	0.781	0.652	0.901	
$\theta_{V\text{-}FOOD}$	0.822	0.761	0.861	
Ka (1/hr)	0.359	0.321	0.384	54.1%

Source: Applicant's population PK report, Page 62, Table 12-5

The goodness of fit is plotted in **Figure 1**. The results show the prediction has a good agreement with observations.

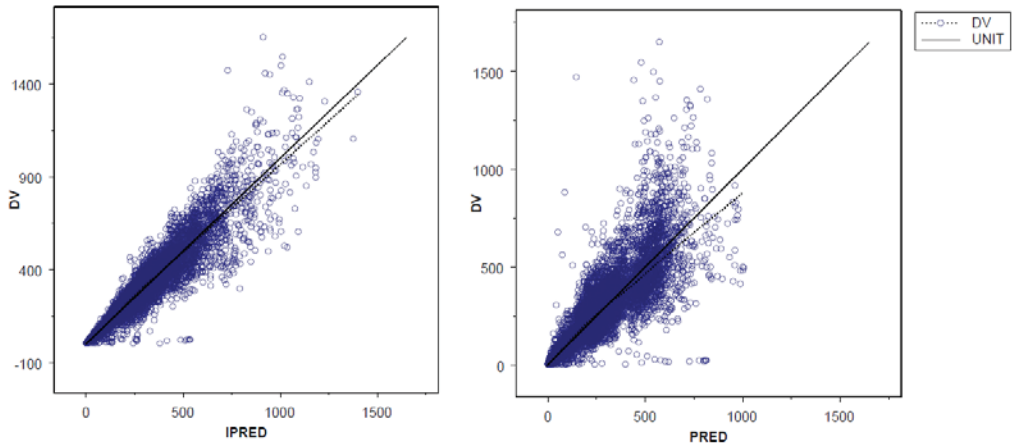


Figure 1. Goodness of Fit Plot

Source: Applicant's population PK report, Pages 44 and 45, Figures 8-1 and 8-2

The visual predictive check plot is shown in Figure 2. The result suggests the adequacy of final PK model to reproduce a majority of TQ concentrations over the course of several dose levels.

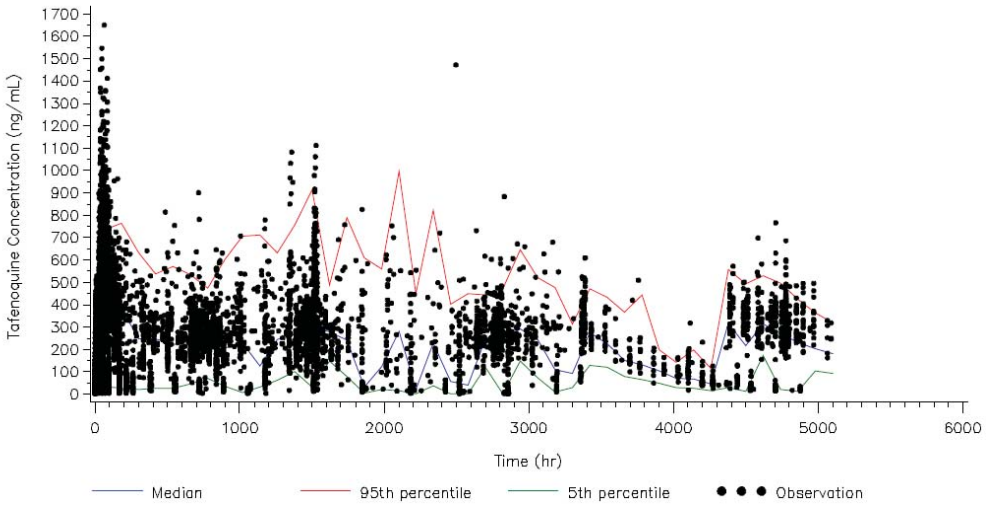


Figure 2. Visual Predictive Check

Source: Applicant's population PK report, Pages 44 and 45, Figures 8-1 and 8-2

Reviewer's comments: The Reviewer verified the population PK model developed by Applicant and the population PK model appears to be reasonable. The impact of covariates on exposure was evaluated. The mean estimate of CL/F for an individual with a median age of 25 years in the lowest body weight (43 kg) could be as low as 0.74-fold of the average CL/F. The mean estimate of CL/F in the highest body weight (135 kg) could be as large as 1.38-fold of the average CL/F. The mean estimate of CL/F for an individual with a median body weight of 75 kilograms in the younger age category (18 years) could be 1.07-fold of the average CL/F. The mean estimate of CL/F in the older age category (60 years) could be 0.84-fold of the average CL/F. It may be more appropriate to add the food effect on relative bioavailability than on V/F.
There was insufficient bioanalytical information for Study 50. Therefore, the PK data from Study 50 was excluded from the Reviewer's population PK analysis. The result was consistent with Applicant's result. The population PK model suggested that no dose adjustment is needed in any known subpopulation based on the intrinsic patient factors such as body weight, gender, age, and race.

15.3.3. Review of Individual Study Reports

The following clinical pharmacology related individual studies were reviewed. The study report names on the actual report itself and that provided by the Applicant are both indicated in the Study No. below.

Study No.	Study information
1016RS/DI99340	In vitro plasma protein binding in the rat, dog and man
1016V2/DI99078	In vitro blood cell partitioning and the in vitro plasma protein binding in the rat, dog and man
RSD-101GZN/DD99222	A comparison of the metabolism of tafenoquine between preclinical species and man
2014N212406/XS-0517	In vitro evaluation of tafenoquine as inhibitors for transporters
RSD-101HD5	In vitro evaluation of tafenoquine as inhibitors of human CYP enzymes
2011 N114285	In vitro evaluation of tafenoquine as inducer of human CYP3A4
OPT-2017-089	Assessment of tafenoquine as an inhibitor of human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 mediated transport
OPT-2017-090	Assessment of tafenoquine as a substrate of human BCRP, P-gp, OATP1B1 and OATP1B3 mediated transport
SB252263/052	Pharmacokinetics, pharmacodynamics, safety and tolerance of a single oral dose of tafenoquine
SB252263/015	An open-label study to determine the effect of tafenoquine on the PK of desipramine in healthy volunteers
SB252263/040	Evaluation of the effect of tafenoquine on the metabolism of multiple Cytochrome P-450 substrates
TQ-2016-01	A phase 1, single-dose, open-label study of tafenoquine in healthy adults to compare the PK parameters of the proposed marketed 2X 100 mg tafenoquine tablets to the PK parameters of tafenoquine 200 mg capsules used during previous clinical trials
TQ-2016-02	A randomized, double-blinded, placebo-controlled study in healthy, non-immune adults to determine the schizonticidal activity of tafenoquine after challenge with plasmodium falciparum blood stage parasites
51	A multiple dose safety, tolerance and PK study of tafenoquine when given to healthy male and female subjects
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 No.: 1016RS/DI99340

A Preliminary Investigation of the I*n Vitro* Plasma Protein Binding of [14C]SB-252263 (Tafenoquine) in the Rat, Dog and Man

Date(s): September 16, 1999 to January 26, 2000
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Test facility: (b) (4)

METHODS
Pooled plasma was obtained from the male rat (Sprague-Dawley), dog (Beagle) and human (three healthy male volunteers). Total protein and albumin levels for each sample were determined prior to use to ensure they were within normal range. The *in vitro* plasma protein binding of [14C]SB-252263 was investigated in each species at target concentrations of 500 and 2000 ng free base/mL by equilibrium dialysis against isotonic PBS at approximately *37* °C over 5 hours. The radiochemical purities of both the stock solution used for spiking and the dialyzed plasma samples from each species were determined by radio-HPLC, to determine the stability of [14C]SB-252263 over the duration of the experiment and the error intervals of the protein binding.

Results
Reviewer Comment: While initial plasma concentrations were close to those targeted, the recovery of total radioactivity was approximately 80% at equilibrium. The investigator suggests this is likely due to non-specific binding to the dialysis cells and/or membranes and should not affect the quoted values for plasma protein binding at equilibrium.

The plasma and PBS concentrations of [14C]SB-252263 at equilibrium and the corresponding human *in vitro* plasma protein binding of [14C]SB-252263 is shown in **Table 1**.

Table 1. In Vitro Plasma Protein Binding of [14C]SB-252263 in Human Plasma

Initial plasma conc. (ng fb/mL)	Equilibrium plasma conc. (dpm/g)	Mean equilibrium plasma conc. (dpm/g)	Equilibrium PBS conc. (dpm/g)	CF	% bound	Mean % bound
456	96829 98461	97645	593	1.41	99.57	99.50 +/- 0.06
	96387 98487	97437	69	1.33	99.46	
	96397 96259	96328	692	1.32	99.46	
1822	379096 377487	378292	1769	1.27	99.63	99.72 +/- 0.13

	392686 391712	392199	1693	1.28	99.66	
	373850 373917	373883	622	1.33	99.88	

Volume shift correction factor (CF) = equilibrium plasma weight x (initial total weight/equilibrium total weight)
Source: NDA 210607

Reviewer Comment: In several samples, the equilibrium plasma concentrations were lower than the expected maximum plasma concentrations of SB-252263 noted in clinical and toxicology studies (400 and 3,000 ng/mL, respectively). The investigator was unable to determine the extent of plasma protein binding at concentrations significantly lower than those reporter (~370 ng/mL) due to limits on analytical sensitivity. The investigator proposes that the linearity of plasma protein binding from 370 to 1500 ng/mL can be extrapolated to these lower plasma concentrations.

The radiochemical purity of the compound in the stock spiking solution was found to be ~ 97%. Radio-HPLC of the dialyzed plasma samples showed that the radiochemical purity was reduced to ~ 87 and 82%, in rat and dog, respectively, suggesting some instability of the [14C]SB-252263 during the experiment. In dialyzed human plasma, the estimated radiochemical purity was ~ 94%, indicating little or no degradation over the 5 hour dialysis.

Reviewer Comment: Less than 0.5% of the total radioactivity (either SB-252263 or impurities/degradation products) were found to be unbound to plasma proteins. Therefore, the estimates of in vitro plasma protein binding are thought to be only marginally affected despite the low radio-chemical purities of the dialyzed plasmas.

Reviewer Assessment: The plasma protein binding of [14C]SB-252263 was very high (>99.5 %) with no evidence of difference between species.

Study No.: 1016V2/ DI99078

A Preliminary Investigation of the *In Vitro* Blood Cell Partitioning and the *In Vitro* Plasma Protein Binding of SB-252263 (Tafenoquine) in the Rat, Dog and Man

Date(s): March 1, 1999 to March 25, 2009
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Test facility: [redacted] (b) (4)

METHODS

The *in vitro* blood: plasma partitioning of SB-252263 was determined in blood from each species at target concentrations of 100, 250 and 1000 ng free base/mL, after approximately 10 and 60 min mixing at ~37C. Blood was obtained from male rats (Sprague-Dawley), one male dog (Beagle) and one female human volunteer. The *in vitro* plasma protein binding of SB-252263 was investigated in each species at target concentrations of 250, 1000 and 5000 ng free base/mL by equilibrium dialysis against PBS (phosphate buffered saline) over 5 hours at ~ 37C. Pooled plasma was obtained from male rats (Sprague-Dawley), dog (Beagle) and three healthy male volunteers.

Concentrations of SB-252263 in blood, plasma and PBS were determined by LC/MS/MS following protein precipitation, as appropriate. The lower limit of quantification (LLQ) was 5 ng/mL and 1 ng/mL for a 50 uL aliquot of blood/plasma and PBS, respectively.

Results:

The *in vitro* blood cell association of SB-252263 in humans is detailed in **Table 1.**

Table 1. In Vitro Blood Cell Association of SB-252263 in Humans

Target blood conc (ng fb/mL)	Time (min)	Mean [B] (ng fb/mL)	Mean [P] (ng fb/mL)	H	% BCA	[B]:[P] conc. Ratio
100	10	76.4	51.7	0.40	59	1.5
	60	74.6	51.4	0.40	59	1.5
250	10	211.2	159.0	0.40	54	1.3
	60	235.0	153.2	0.40	61	1.5
1000	10	879.8	619.6	0.40	58	1.4
	60	843.3	653.1	0.40	54	1.3
			Mean +/- SD		57 ± 3	**1.4 ± 0.1**

[P] = measured concentration of SB-252263 in plasma
H = haematocrit, as determined by packed cell volume
% BCA = % association of SB-252263 with blood cells
The mean [B] and [P] results above represent the means of duplicate determinations
Source: NDA 210607

The plasma protein binding could not be accurately determined as the PBS concentrations were non-quantifiable at all 3 plasma concentrations.

REVIEWER ASSESSMENT: While a similar mean blood:plasma concentration ratio was noted in dog and man, it was significantly higher in rats. *In vitro* plasma protein binding could not be accurately determined in this study.

Study No.: RSD-101GZN/DD99222

A Comparison of the Metabolism of SB-252263 between Preclinical Species and Man
Date(s): June 22, 1999 to October 23, 2000
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Clinical Site: Glaxosmithkline Drug Metabolism and Pharmacokinetics, The Frythe, Welwyn, Herts, UK

OBJECTIVE(S):

- To investigate the metabolites of SB-252263 (tafenoquine) in human urine and plasma
- To provide information on the likely routes of metabolism of SB-252263 in rat, dog and man using *in vitro* systems

METHODS

Human urine (predose and 48-72 h after the first dose) and plasma (predose, 60 and 84 h after the first dose) were obtained from clinical study 252263/014 where human volunteers received an oral dose of 400 mg free base of SB-252263-AX for each of three consecutive days, with food. HPLC-MS and HPLC with fluorescence detection were used to investigate possible metabolite structures in these samples.

[^{14}C] SB-252263-AX was incubated with human hepatocytes (10 uM) and rat, dog and human microsomes (10 uM or 1 mM).

RESULTS

At least 18 drug-related components were detected in human urine, resulting from O-demethylation, O-dearylation, deamination, N-dealkylation, oxidation, N-carbamylation, acetylation and glucuronide conjugation pathways. O-dearylation and O-demethylation were the two most common pathways. Drug-related material identified in human urine is consistent with the metabolites identified in rat and dog studies.
Unchanged SB-252263 was the only significant drug-related component detected in human plasma by HPLC-MS and HPLC with fluoresence detection.

Reported data is derived from a single experiment where [^{14}C] SB-252263-AX was incubated with human hepatocytes for 24 hours. Radioassay of a 24 hour cell extract indicated that 39% of the drug-related material was associated with the human hepatocytes. A further 61% was recovered in the medium making a total of 100% recovery of drug-related material in the cells plus medium. All radio- peaks detected in the hepatocyte medium by radio-HPLC were also detected in the no-cell control. Cell extracts at 24 hours contained only unchanged SB-252263.

No significant loss of drug-related material was observed following radioassay of all microsome incubations or extractions. Only unchanged SB-252263 was detected in rat, dog, human and denatured microsomes by radio-HPLC.

Reviewer comment: The Sponsor suggests that long term hepatocyte incubations are not ideal for studying the metabolism of SB-252263 due to the low rates of metabolism coupled with insolubility of SB- 252263 in the absence of BSA, cell death at 50 uM and instability of SB-252263 on extraction and in light.

REVIEWER ASSESSMENT: Drug-related material identified in human urine mainly resulted from O-dearylation and O-demethylation. Unchanged SB-252263 was the only significant component detected in human plasma. The cross-species metabolism or enzymology of SB-252263 could not be adequately determined in *in vitro* systems.

STUDY NO.: 2014N212406/XS-0517

***In Vitro* Evaluation of Tafenoquine as Inhibitors for OCT2, MATE1 and MATE2-K**

Date(s): 14 March 2014– 16 June 2014
Sponsor: GlaxoSmithKline R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)

OBJECTIVES

To evaluate the ability of TQ to act as an inhibitor of the following transporters: organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporters 1 and 2-K (MATE1 and MATE2-K).

METHODS

Human embryonic kidney 293 (HEK293) cells expressing OCT2, MATE1 or MATE2-K (HEK293 cells transfected with a vector containing human OCT2, MATE1 or MATE2-K cDNA) and control cells (HEK293 cells transfected with vector only) were used. [^{14}C]Metformin was used as the Probe Substrate for OCT2, MATE1 and MATE2-K. Cimetidine was used as a positive control inhibitor for OCT2, MATE1 and MATE2-K. Quinidine was used as a positive control inhibitor for OCT2. Transporter expressing HEK293 cells and control cells were incubated with Hanks' Balanced Salt Solution (HBSS) solutions containing [^{14}C]metformin and TQ, cimetidine or quinidine. The adsorption of TQ was investigated on the assay plate with TQ concentration of 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 40 and 50 µM. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to measure the concentration of TQ in the incubation solution. The mean observed concentration was treated as the actual concentration just after the incubation and was used for calculation of IC50 values. [^{14}C]Metformin radioactivity was measured by Liquid scintillation counter (LSC).

Calculation of Uptake Amount and Cleared Volume (OCT2, MATE1 and MATE2-K):

Uptake amount and cleared volume were calculated using the following equations:

[OCT2 and MATE1]:

$$\text{Uptake amount (dpm/well)} = \text{Radioactivity in cell lysate (dpm)} \times \frac{500\ (\mu L)}{300\ (\mu L)}$$

(conversion was made for the update amount in original 500 µL cell lysates when only 300 µL cell lysates was assayed)

[MATE2-K]:

$$\text{Uptake amount (dpm/well)} = \text{Radioactivity in cell lysate (dpm)} \times \frac{700\ (\mu L)}{500\ (\mu L)}$$

(conversion was made for the update amount in original 700 µL cell lysates when only 500 µL cell lysates was assayed)

Cleared volume (µL/mg protein)

$$= \frac{\text{Uptake amount (dpm/well)}}{\text{Protein amount (mg protein/well)} \times \text{Initial concentration (dpm/µL)}}$$

Calculation of Inhibitory Effects:

Inhibitory effects were calculated using the equation shown below from the cleared volume of expressing and control cells for test articles and positive control inhibitors:

$$\%\ \text{of control} = \frac{D - C}{B - A} \times 100$$

A: Cleared volume into control cells in the absence of TQ or a positive control inhibitor

B: Cleared volume into expressing cells in the absence of TQ or a positive control inhibitor

C: Cleared volume into control cells in the presence of TQ or a positive control inhibitor

D: Cleared volume into expressing cells in the presence of TQ or a positive control inhibitor

The percentage of control was rounded off to one decimal place.

Calculation of IC50 Value:

The IC50 value was calculated using the equation shown below from the relationship between percentage of control and test article or inhibitor concentration:

$$\% \text{ of control} = C + \frac{D - C}{1 + (x/IC_{50})^{b}}$$

where

D: Upper limit of the percent of control

C: Lower limit of the percent of control or fixed as zero

x: Test article or inhibitor concentration

b: slope

The IC50 value was calculated using Phoenix WinNonlin 6.1 (Certara). The IC50 value was expressed to three significant figures and represented as the mean ± SE.

Calculation of Adsorption Ratio

The adsorption ratio was calculated from the following equation using Microsoft Office Excel 2003 (Microsoft) and rounded off to one decimal place.

$$\text{Adsorption ratio (\%)} = 100 - \frac{\text{Concentration after incubation (nM)}}{\text{Concentration before incubation (nM)}} \times 100$$

RESULTS AND CONCLUSIONS

The active uptake of [^{14}C]metformin (as a substrate in OCT2, MATE1 and MATE2-K transfected cells) was clearly observed, and the positive control inhibitors for each transporter were found to inhibit the transporter activities as expected in each assay.

The inhibitory effects and IC_{50} of TQ and positive inhibitors on OCT2, MATE1 and MATE2-K are summarized in Table 1.

Table 1: Summary of Results: Inhibitory Effects of TQ and Probe Inhibitors on Human Transporters

Isoform	Substrate	Test article or typical inhibitor	IC_{50} (μM) [a]	Percent of control at highest concentration (%)
OCT2	Metformin	SB-252263	0.282 ± 0.064	3.4
		Cimetidine	43.2 ± 11.6	4.9
MATE1	Metformin	SB-252263	1.99 ± 0.30	6.2
		Cimetidine	0.508 ± 0.044	5.4
MATE2-K	Metformin	SB-252263	0.632 ± 0.279	5.8
		Cimetidine	8.86 ± 1.61	3.0

a: Average data obtained from triplicate samples for each test article or typical inhibitor concentration were used to calculate IC_{50} values. Each value represents the mean ± SE.

SB-252263: TQ

The adsorption ratio of TQ to the assay plate was determined. After incubation in HBSS (pH 7.4 or pH 8.5) for 2 or 5 min, the adsorption ratios were 35.9% to 78.7% or 39.7% to 85.2%, respectively. In consideration of the actual concentration of TQ during the incubation, the Table 1 reported IC_{50} values could be 4-7 lower and were calculated to be 0.0419 ± 0.0126 µM for OCT2, 0.435 ± 0.024 µM for MATE1, and 0.170 ± 0.073 µM for MATE2-K.

REVIEWER'S ASSESSMENT

As shown in Table 2, when the values of IC_{50} are used 'as is', the $C_{max,u}$/IC50 ratios are lower than the guidance recommended cutoff values (0.1 for OCT2 and 0.02 for MATEs), suggesting that TQ is unlikely to inhibit these transporters at the clinical dosing regimen. However, after correcting the nonspecific binding of TQ to the assay plate, the corrected $C_{max,u}/IC_{50}$-C ratios using the adjusted lower IC_{50} values are higher than the guidance recommended cutoff values. Thus, at the clinical dosing regimen, TQ is likely to be an inhibitor of OCT2, MATE1, and MATE2-K. The Applicant stated that TQ may inhibit OCT2, MATE1, and MATE2-K transporters in the kidney, which could lead to increased exposure of the medication that these transporters excrete.

The Clinical Pharmacology review team concluded that at the clinical dosing regimen, TQ may inhibit OCT2, MATE1, and MATE2-K transporters.

Table 2. Summary of IC_{50} Values and Estimated Cmax,u/IC_{50} Ratios for Human OCT2, MATE1 and MATE2-K Transporters

Transporter isoforms	OCT2	MATE1	MATE2-K
Mean IC_{50} (µM)	0.282	1.99	0.632
Mean IC_{50}-C (µM)[a]	0.0419	0.435	0.170
Cmax,u/IC_{50}ratios	0.037	0.0053	0.016
Cmax,u/IC_{50}-C ratios[b]	0.25	0.024	0.062

[a]: Mean IC_{50}-C: Mean IC_{50} values corrected by the non-specific binding of TQ in the tested system; values were reported by the Applicant from Study 2014N212406

[b]: The Applicant reported a 99.5% protein binding of TQ; the unbound fraction of TQ in plasma (fu,p) was set to 1% (fu,p = 0.01) if protein binding was experimentally determined to be < 1% per the in vitro DDI draft guidance; to calculate C_{max} in µM, mean C_{max} ≈ 496 ng/mL (Study 15, where 400 mg TQ is administered once daily for 3 days to attain a pseudo steady state), MW=463.5 g/mol as free base, resulting in an unbound C_{max} value of 0.0107 µM

STUDY NO.: RSD-101HD5

An In Vitro Evaluation of the Inhibitory Potential of Tafenoquine on Human Cytochrome P450 Enzymes

Date(s): 15 September 1999– 12 December 2000
Sponsor: GlaxoSmithKline R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)
Analytical Site:

OBJECTIVES

To determine the potential of TQ to inhibit the major cytochrome P450 enzymes (CYP) (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11) in human liver microsomes.

METHODS

TQ was supplied as the hydrogen succinate salt. Enzyme activities, presented in **Table 1**, were measured, using probe substrates, in the presence and absence of TQ.

Human liver microsomes (HLM) was used in this study. The pooled HLM sample was prepared from nine individual samples. This pooled sample was used in the determination of the Ki values and as the "medium-activity" HLM sample for all the metabolism-dependent experiments. In designing the various experiments, the kinetic constants, Km and Vmax, determined for a different pooled HLM sample (prepared from seven individuals) were used to select the probe substrate concentrations and incubation conditions.

In Part 1, the ability of TQ to directly and reversibly (metabolism-independent) inhibit the major cytochrome P450 enzymes in a pooled human liver microsomal sample was evaluated and the corresponding inhibitory constants (Ki values) were calculated.

In Part 2, the ability of TQ to act as a reversible metabolism-dependent inhibitor and as an irreversible or quasi-irreversible metabolism-dependent inhibitor of the CYP450 enzymes listed was investigated using two individual HLM samples and the pooled HLM sample.

Table 1 lists the human CYP450 enzyme activities, using probe substrates, that were evaluated in the assessment of the metabolism-independent and metabolism-dependent inhibitory potentials of TQ.

Table 1. Measurement of Human CYP450 Enzyme Activities by Using Probe Substrates

Cytochrome P450 Enzyme	Activity Measured
CYP1A2	7-Ethoxyresorufin *O*-dealkylation
CYP2A6	Coumarin 7-hydroxylation
CYP2C8	Paclitaxel 6α-hydroxylation
CYP2C9	Diclofenac 4′ –hydroxylation
CYP2C19	*S*-Mephenytoin 4′ –hydroxylation
CYP2D6	Dextromethorphan *O*-demethylation
CYP2E1	Chlorzoxazone 6-hydroxylation
CYP3A4/5	Testosterone 6β-hydroxylation
CYP3A4/5	Midazolam 1′-hydroxylation
CYP3A4/5	Nifedipine oxidation
CYP4A9/11	Lauric acid 12-hydroxylation

RESULTS AND CONCLUSIONS

Table 2 lists the Ki values determined for CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 (three different probe substrates evaluated), and CYP4A9/11 using the pooled HLM sample.

Table 2. In Vitro Inhibition of CYP P450 Enzyme Activities in Human Liver Microsomes by Tafenoquine

Cytochrome P450 enzyme	Activity measured	Metabolism-independent				Metabolism-dependent[c]
			IC50 (uM)			
		Ki[a] (uM)	Individual[b]	Mean	Type of inhibition	Reversible/Irreversible
CYP1A2	7-Ethoxyresorufin *O*-dealkylase	5.2	12, 18, 18	16	mixed	no effect observed
CYP2A6	Coumarin 7-hydroxylase	7.1	6.9, 6.6, 6.5	6.7	noncompetitive	no effect observed
CYP2C8	Paclitaxel 6α-hydroxylase	8.8	6.0, 6.3, 9.3	7.2	noncompetitive	no effect observed
CYP2C9	Diclofenac 4′-hydroxylase	1.8	5.5, 4.5, 4.5	4.8	mixed	no effect observed
CYP2C19	*S*-Mephenytoin 4′-hydroxylase	54	Not determined[d]	-	competitive	no effect observed
CYP2D6	Dextromethorphan *O*-demethylase	15	20, 21, 20	20	noncompetitive	no effect observed
CYP2E1	Chlorzoxazone 6-hydroxylase	81	Not determined[d]	-	noncompetitive	no effect observed
CYP3A4/5	Testosterone 6β-hydroxylase	1.6	2.9, 3.3, 4.1	3.4	competitive	no effect observed
CYP3A4/5	Midazolam 1′-hydroxylase	7.2	8.4, 8.5, 8.8	8.6	noncompetitive	no effect observed
CYP3A4/5	Nifedipine oxidase	10	7.6, 8.1, 10	8.6	noncompetitive	no effect observed
CYP4A9/11	Lauric acid 12-hydroxylase	18	27, 28, 27	27	noncompetitive	no effect observed

Note: Values were calculated using the average data obtained from duplicates for each incubation condition. The Ki and IC50 values were calculated using GraFit software with simple weighting.
a: Determined using the pooled microsomal sample.
b: Values obtained from microsomal samples with low, medium and high activity, respectively, for the selected enzyme
c: Evaluated using the pooled microsomal sample and two individual microsomal samples.
d: Not determined since inhibition was weak.

The in vitro incubation of TQ with human liver microsomal (HLM) preparations in the presence of specific probe substrates demonstrated that SB- 252263 has the potential to inhibit several human cytochrome P450 enzymes.

- In human liver microsomes, TQ was a significant inhibitor of CYP1A2, CYP2A6, CYP2C8, CYP2C9, and CYP3A4/5. For CYP3A4/5, the degree of inhibition varied with the probe substrate used. The most pronounced inhibition was on the activities of diclofenac 4¢-hydroxylase (Ki 1.8 uM) and testosterone 6b-hydroxylase (Ki 1.6 uM).
- TQ was a moderate inhibitor of CYP2D6 and CYP4A9/11, and a weak inhibitor of CYP2C19 and CYP2E1.
- There was no evidence for metabolism-dependent inhibition of the evaluated CYP450 enzymes.

REVIEWER'S ASSESSMENT

Study RSD-101HD5 determine the inhibitory effects and Ki values of TQ on the major cytochrome P450 enzymes (CYP) (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11) in human liver microsomes. One drawback of the study design is a lack of appropriate strong inhibitors as positive controls, which is recommended by the following FDA guidance: In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies (October 2017). However, the potential of TQ to inhibit the CYP enzymes was further evaluated in clinical studies. In general, we concur with the Applicant's results from this study.

STUDY NO.: 2011 N114285

Activation of Human PXR by Tafenoquine, SB-252263-AX

Date(s): 21 February 2011– 29 March 2011
Sponsor: GlaxoSmithKline R&D Ware, Hertfordshire, UK
Testing Site: GlaxoSmithKline Medicines Research Centre, Herts, SG1 2NY, UK
Analytical Site: (b) (4)

OBJECTIVES

To examine the ability of TQ, SB-252263-AX to activate the human Pregnane-X-Receptor (PXR).

METHODS

The human hepatoma cell line (HEPG2) is used as a host cell. These cells are transfected with full length human PXR and a reporter gene construct containing the upstream regulatory sequence of CYP3A4 (containing the binding sites for PXR) linked to a luciferase reporter gene.Activation of human PXR by a compound is expressed as a percentage of that achieved with rifampicin (10 µM) positive control. When a full dose response curve is achieved, the pEC50 value can be calculated. If a full dose response curve is not achieved, the pEC50 value is reported as "< -logmax concentration tested".

Interpretation of Results:

% Max	pEC_{50}	Interpretation
0%	<	No response
<30%		Weak response
30 -70%		Moderate response
>70%	<	PXR activation at high concentrations only
>70%	value	PXR activation with some potency

RESULTS AND CONCLUSIONS

Table 1 shows the activity of TQ against hPXR. TQ was much less potent than the standard agonist, rifampicin, when run at the same time.

Within the 0.001-50µM concentration range of this investigation, TQ failed to trigger a response, and only on one occasion out of 11 did the maximum response reach 30% of that achieved with rifampicin (10 µM), the positive control. Therefore, the quoted pEC50 is <4.3. However, it was observed that at the two highest concentrations (50µM and 16.6µM), TQ had an apparent toxic effect upon the cells.

Table 1. Activity of TQ against hPXR

Compound	pEC50 (Mean) ± StdDev	N	Max Response (% Mean) ± StdDev	N
SB-252263-AX	<4.3	7	16.5 ± 9.3	11*
SKF-39973	6.2 ± 0.2	21	111.2 ± 22	21

*SB-252263-AX was tested 11 times. On one occasion, it failed to fit a curve but the max response was reported, on 10 occasions data was reported with a modifier. On 7 occasions out of 11, data was reported as <4.3, on 3 occasions data was reported as <5.26 (as the last two points were excluded due to toxicity of the compounds at high concentration).

SB-255563-AX=TQ; SKF-39973=Rifampicin

REVIEWER'S ASSESSMENT

We concur with the conclusion from this study that TQ did not induce CYP3A4 in PXR transfected hepatocytes.

Study No.: OPT-2017-089

Assessment of Tafenoquine as an Inhibitor of Human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 Mediated Transport

Date(s): September 19 – October 14, 2017
Sponsor: 60 Degrees Pharmaceuticals LLC, 1025 Connecticut Ave NW, Suite 1000, Washington DC, 20036 United States
Study Site: (b) (4)

List of Abbreviations:

A → B	Apical to Basal
ABC	ATP binding cassette
B → A	Basal to Apical
BCRP	Breast Cancer Resistance Protein
BSA	Bovine Serum Albumin
MDCK	Madin-Darby Canine Kidney
MDR	Multi-Drug Resistance
OAT1	Organic Anion Transporter 1
OAT3	Organic Anion Transporter 3
OATP1B1	Organic Anion Transporting Polypeptide 1B1
OATP1B3	Organic Anion Transporting Polypeptide 1B3
P-gp	P-glycoprotein

Papp Apparent Permeability
SLC Solute Carrier

Objectives: The purpose of this study is to determine the IC50 of TQ against the transport mediated by human BCRP, P-gP, OAT1, OAT3, OATP1B1 and OATP1B3.

Methods and Data Analysis: The methodology is discussed briefly in this individual study report (ISR). A summary of experimental conditions is described in **Table 1**.
Prior to conducting the study, a separate experiment was carried out using the same TQ concentration used in this study in the presence of either 0.1% bovine serum albumin (BSA) or 4% BSA, to assess any non-specific binding to assay apparatus. The recoveries ranged from 45.3% - 90.7% with 0.1% BSA and 52.7% - 85.5% with 4% BSA. Therefore, 0.1% BSA was selected as the condition to be used in this transporter study.

The transport of each substrate was determined by radiometric detection. The net transporter mediated substrate uptake and percent inhibition for OAT1, OAT3, OATP1B1 and OATP1B3 transporters were determined as per the formulae in the study protocol and provided in the report. The apparent permeability (Papp), Efflux Ratio (ER), Net basal (B) to apical (A) flux (B → A), and percent inhibition for BCRP and P-gp were also determined and are summarized in the study report. The IC50 was determined or estimated for OAT1, OAT3, OATP1B1, OATP1B3, BCRP and P-gp.

Table 1. Summary of the Test System, Probe Substrate, Reference Inhibitor, Test Article Concentration and Incubation Conditions.

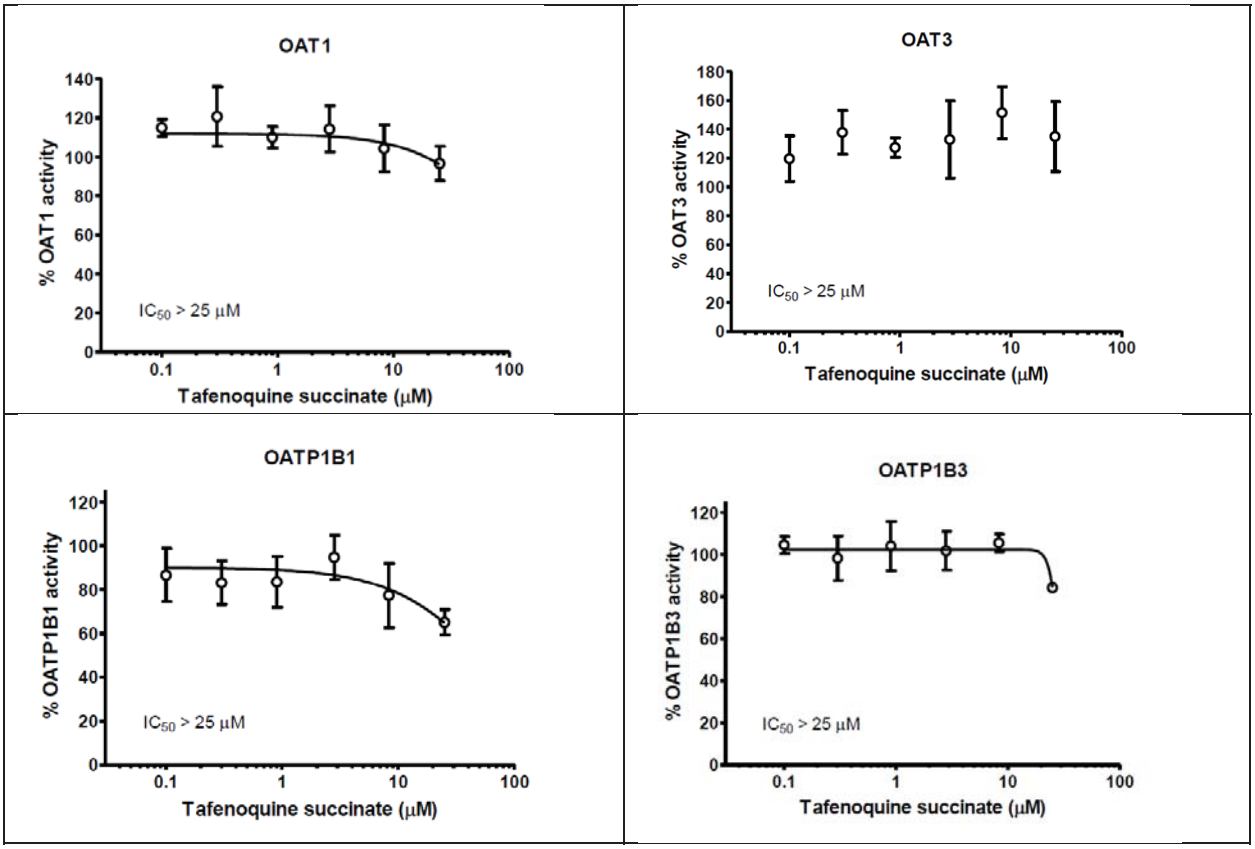
Test System	1. MDCK-II cells expressing human transporter OAT1, OAT3, OATP1B1, OATP1B3, or BCRP 2. MDCK-II control cells transfected with a control vector (GFP) 3. MDCK-II stable cells expressing P-gp (MDR1)
Probe Substrate (positive control for transport)	1. OAT1: 2 µM [^{3}H]-p-aminohippurate 2. OAT3: 10 µM [^{3}H]-p-aminohippurate 3. OATP1B1: 2 µM [^{3}H]-estradiol-17β-D-glucuronide 4. OATP1B3: 2 µM [^{3}H]-CCK-8 5. BCRP: 2 µM [^{3}H]-prazosin 6. P-gp: 100 nM [^{3}H]-quinidine
Reference Inhibitor (Positive Control for Inhibition)	1. OAT1: 100 µM probenecid 2. OAT3: 100 µM probenecid 3. OATP1B1: 100 µM rifampicin 4. OATP1B3: 100 µM rifampicin 5. BCRP: 1 µM Ko143 6. P-gp: 3 µM elacridar
Test Article Concentration(s)	25, 8.3, 2.8, 0.9, 0.3, 0.1, 0 µM (total of 7 including zero), in the presence of 0.1% BSA
Pre-incubation Time (min)	15 for OAT1, OAT3, OATP1B1 and OATP1B3 30 for BCRP and P-gp
Incubation Time (min)	5 for OAT1, OAT3, OATP1B1, OATP1B3 90 for BCRP and P-gp
Notes	Assay controls will be run under normal conditions, test article assays will contain 0.1% BSA.

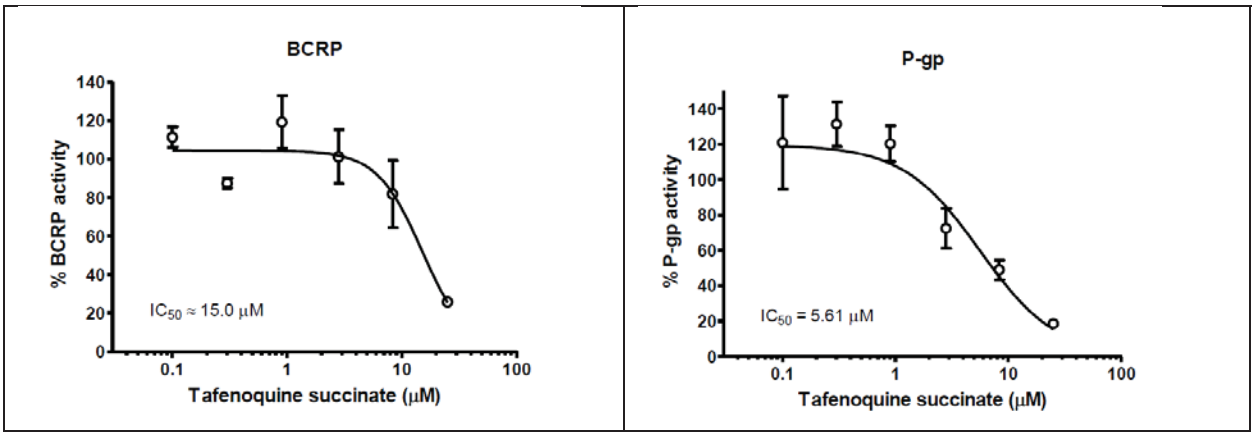
Results:

The Applicant reports that there was <50% inhibition observed at any concentration of TQ for OAT1, OAT3, OATP1B1, and OATP1B3 and therefore, TQ IC50 values are > 25 µM for OAT1, OAT3, OATP1B1, and OATP1B3 -mediated transport as seen in **Figure 1.** For BCRP, only one concentration showed >50% inhibition, so the IC50 value was only estimated rather than determined as per the Applicant. For BCRP, the maximum inhibition seen was 74.1% at 25 µM TQ and the IC50 is estimated to be 15.0 µM (**Figure 1**). The maximum inhibition of P-gp was 81.3% at the highest TQ concentration studied, and the IC50 was estimated to be 5.61 µM (**Figure 1**).

The Applicant also states that the positive controls for both the transport assays and the inhibition assays satisfied the respective control criteria as per the study protocol.
The reviewer has summarized the probe substrate(s) and control inhibitor(s) information that were employed for the determination of IC50 of TQ against the transport mediated by the SLC, BCRP, and P-gp transporters in **Table 2 and 3**.

Figure 1. Determination of IC50 of TQ against the Transport Mediated by Human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 Mediated Transport





Note: Data represent the mean and standard deviation of triplicate samples.

Table 2. Summary of Probe Substrate and Control Inhibitor for the Determination of IC50 of TQ against the Transport mediated by SLC Transporters

Transporter	Control Inhibitor	Probe Substrate	Cellular Accumulation (transporter) (pmol/min/cm^2)	Cellular Accumulation (control) (pmol/min/cm^2)	Net Transporter Mediated Cellular Accumulation (pmol/min/cm^2)	Inhibition (%)
OAT1	100 µM Probenecid	2 µM p-aminohippurate	0.367 ± 0.0192	0.0345 ± 0.0157	0.332 ± 0.0192	91.0 ± 0.519
OAT3	100 µM probenecid	10 µM p-aminohippurate	0.197 ± 0.0146	0.181 ± 0.0141	0.0156 ± 0.0146	97.3 ± 2.55
OATP1B1	100 µM rifampicin	10 µM estradiol-17-β-D glucuronide	0.105 ± NA	0.130 ± 0.0249	-0.0249 ± NA	101 ± NA
OATP1B3	100 µM rifampicin	2 µM CCK-8	0.0902 ± 0.0133	0.0533 ± 0.00981	0.0369 ± 0.0133	98.1 ± 0.689

Note: Data represent the mean and standard deviation of triplicate samples.
NA: Not available.

Table 3. Summary of Probe Substrate and Control Inhibitor for the Determination of IC50 of TQ against the Transport mediated by BCRP and P-gp Transporters

Transporter	Control Inhibitor	Probe Substrate	Papp B->A (x10^{-6} cm/s)	Papp A->B (x10^{-6} cm/s)	Mean Net B->A flux (pmol/hr/cm^2)	Efflux ratio (Papp B->A)/(Papp A->B)	Inhibition (%)
BCRP	1 µM Ko143	2 µM prazosin	10.3 ± 1.05	10.70 ± NA	-0.051 ± 0.126	0.960 ± 0.0978	100 ± 0.890
P-gp	3 µM elacridar	*0.1 µM quinidine*	17.5 ± 0.241	9.09 ± 3.59	0.0505 ± 0.00145	1.93 ± 0.0265	84.2 ± 0.451

Note: Data represent the mean and standard deviation of triplicate samples.
NA: Not available.

Reviewer Comments: In the study report, the Applicant has not explicitly provided the IC50 values of probe substrate or control inhibitor used in the study. In addition, the study report included the results but did not provide conclusions of this study regarding the inhibitory potential of TQ against the transport mediated by these transporters. As applicable, based on

the recommendations in the FDA guidance: In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies (October 2017), the reviewer performed these assessments to determine the inhibitory potential of TQ for these transporters and determined that at the proposed clinical dosing regimen, TQ is unlikely to inhibit OAT1, OAT3, OATP1B1, OATP1B3, BCRP and P-gp.

Following are the calculations for the transporters (BCRP and P-gp), where IC50 value were estimated or determined in this study.

For BCRP and P-gp, if the Igut/IC50 ≥ 10, then the investigational drug has the potential to inhibit these transporters (As per the FDA Guidance stated earlier, October 2017).

Note: Igut = dose of inhibitor/250 mL.
Note: IC50 for BCRP and P-gp from this study are reported to be 15.0 µM and 5.61 µM respectively.

In case of BCRP, for a dose of 200 mg of TQ based on the clinical dosing regimen, the Igut/IC50 = 0.11, which is less than 10, thus TQ is unlikely to inhibit BCRP.

And for P-gp, for a dose of 200 mg of TQ based on the clinical dosing regimen, the Igut/IC50 = 0.3, which is less than 10, so TQ is unlikely to inhibit P-gp.

The Applicant reports that there was <50% inhibition observed at any concentration of TQ for OAT1, OAT3, OATP1B1, and OATP1B3 and therefore, TQ IC50 values are > 25 µM for OAT1, OAT3, OATP1B1, and OATP1B3 -mediated transport. Based on this data, TQ is unlikely to inhibit these transporters at the clinical dosing regimen.

Reviewer's Assessment/Conclusions: Study OPT-2017-089 determined the inhibitory potential of TQ on human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 mediated transport. Overall, the study results are acceptable to the reviewer. At the clinical dosing regimen of 200 mg/day x 3 days, followed by 200 mg weekly of TQ, TQ is unlikely to inhibit human BCRP, P-gp, OAT1, OAT3, OATP1B1 and OATP1B3 mediated transport.

Study No.: OPT-2017-090

Assessment of Tafenoquine as a Substrate of Human BCRP, P-gp, OATP1B1 and OATP1B3 Mediated Transport

Date(s): 19 September 2017 through 30 October 2017
Sponsor: 60 Degrees Pharmaceuticals LLC, 1025 Connecticut Ave NW, Suite 1000, Washington DC, 20036 United States
Study Site: (b) (4)

Final Report: 6 November 2017

List of Abbreviations:

A → B	Apical to Basal
ABC	ATP binding cassette
B → A	Basal to Apical
BCRP	Breast Cancer Resistance Protein
MDCK	Madin-Darby Canine Kidney
MDR	Multi-Drug Resistance
OATP1B1	Organic Anion Transporting Polypeptide 1B1
OATP1B3	Organic Anion Transporting Polypeptide 1B3
P-gp	P-glycoprotein
Papp	Apparent Permeability

Objectives: To determine whether TQ is transported by human BCRP, P-gp, OATP1B1 and OATP1B3.

Methods: The methodology are discussed very briefly in this individual study report (ISR). A summary of experimental conditions is described in **Table 1**.

Prior to conducting the study, a separate experiment was carried out using the same TQ concentrations used in this study in the presence of either 0.1% BSA or 4% BSA, to assess any non-specific binding to assay apparatus. The recoveries ranged from 45.3% - 90.7% with 0.1% BSA and 52.7% - 85.5% with 4% BSA. Therefore, 0.1% BSA was selected as the condition to be used in the transporter study.

The transport of each substrate was determined by radiometric detection. The transport of test article was determined by LC/MS/MS. The net transporter mediated substrate uptake and percent inhibition for OATP1B1 and OATP1B3 transporters were determined as per the formulae in the study protocol and are provided in the report. The apparent permeability (Papp), Efflux Ratio (ER), Net basal (B) to apical (A) flux (B → A), and percent inhibition for BCRP and P-gp were also determined and are summarized in the study report.

Table 1. Summary of the Test System, Probe Substrate, Reference Inhibitor, Test Article Concentration, and Incubation Time

Test System	1. MDCK-II cells expressing human transporter OATP1B1, OATP1B3, or BCRP 2. MDCK-II control cells transfected with a control vector (GFP) 3. MDCK-II stable cells expressing P-gp (MDR1)
Probe Substrate (positive control for transport)	1. OATP1B1: 2 µM [^{3}H]-estradiol-17β-D-glucuronide 2. OATP1B3: 2 µM [^{3}H]-CCK-8 3. BCRP: 2 µM [^{3}H]-prazosin 4. P-gp: 100 nM [^{3}H]-quinidine
Reference Inhibitor (Positive Control for Inhibition)	1. OATP1B1: 100 µM rifampicin 2. OATP1B3: 100 µM rifampicin 3. BCRP: 1 µM Ko143 4. P-gp: 3 µM elacridar
Test Article Concentration(s) for Transporter Assays	All conditions below are to be run with 0.1% BSA 1. 0.1 µM 2. 0.5 µM 3. 5 µM 4. 0.5 µM + reference inhibitor for each transporter
Pre-incubation Time (min)	15 for OATP1B1 and OATP1B3 30 for BCRP and P-gp
Incubation Time (min)	5 for OATP1B1, OATP1B3 90 for BCRP and P-gp
Notes	Assay controls will be run under normal conditions, test article assays will contain 0.1% BSA.

Results:

At 0.1 µM, 0.5 µM, and 5 µM of TQ, less than 2-fold difference of uptake was observed in transporter-transfected cells compared to control cells for OATP1B1 and OATP1B3 (**Figure 1**). Incubation of TQ at 0.5 µM in the presence of prototypical reference inhibitors for these transporters did not alter TQ uptake (< 2-fold). Therefore, the Applicant concluded that TQ does not appear to be a clinically relevant substrate as defined by regulatory guidance documents for human OATP1B1 or OATP1B3 under these study conditions.

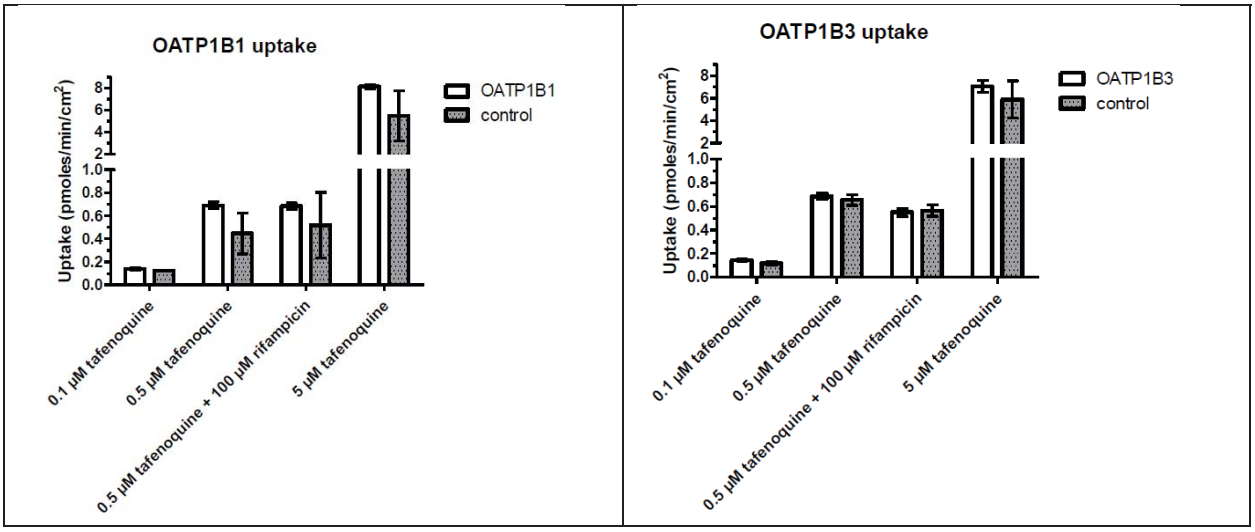
For BCRP, results for each concentration except the 5 µM TQ in the B->A direction were below the limit of quantitation (BLQ) of 0.0197 (**Figure 2**). Hence, no conclusions are reported based on these data.

For P-gp, results for each concentration except the 0.5 and 5 µM TQ in the B->A direction were BLQ (**Figure 2**). Thus, no conclusions are provided based on these data.

The mass balance in the BCRP and P-gp assays varied between 8.55% - 102%.

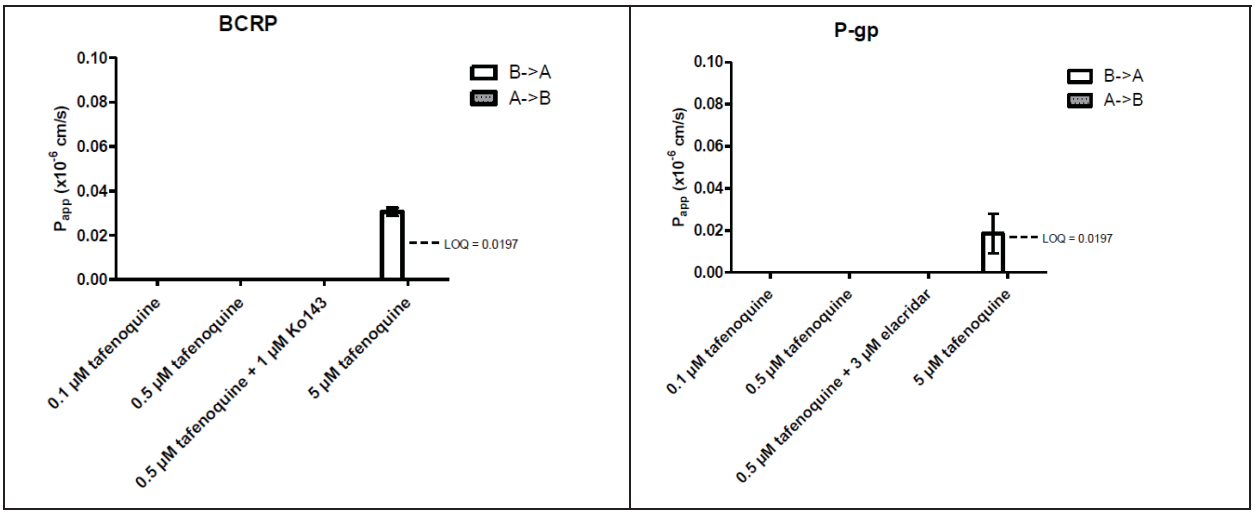
Reviewer Comments: The concentration in the B->A direction for 0.5 µM TQ in case of P-gp is not described in Figure 2. As per the Table 2 provided in the study report, this value reported is 0.226 ± NA (not available).

Figure 1. Transport of TQ in MDCK Cells Expressing Human OATP1B1 and OATP1B3



Note: Data represent the mean and standard deviation of triplicate samples.

Figure 2. Transport of Tafenoquine in MDCK Cells Expressing Human BCRP and P-gp



Note: Data represent the mean and standard deviation of triplicate samples.

Reviewer's Assessment: Study OPT-2017-090 determined the potential of TQ as a substrate of human BCRP, P-gp, OATP1B1 and OATP1B3 mediated transport. The reviewer concurs with the Applicant's results and conclusions from this study that TQ is unlikely to be a substrate of OATP1B1 and OATP1B3. It was inconclusive from this study as to whether TQ is a substrate of P-gp and BCRP mediated transport.

STUDY NO.: SB252263/052

Pharmacokinetics, Pharmacodynamics, Safety and Tolerance of a Single Oral Dose of WR 238605 Succinate/Tafenoquine

Date(s): September 1993 – December 1993
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Clinical Site: Walter Reed Anny Medical Center, Walter Reed Army Institute of Research, Fort Detrick, MD
Analytical Site: (b) (4)

METHODS

Study SB252263/052 was an open-label study to assess the pharmacokinetics, pharmacodynamics, safety and tolerance of WR 238605 Succinate in healthy adult male volunteers. Subjects were randomly divided into 3 phases corresponding to the three ascending dose levels (100, 200 and 400 mg base). Subjects fasted after midnight and received the drug at about 0800 on day 0 with 6-8 ounces of water.

The capsule(s) of WR 238605 (tafenoquine) succinate used in the study was manufactured by the (b) (4)

PK Sample Collection**:** Twenty blood and plasma samples were obtained up to 44 days in all subjects.

Analytical Methods: Pharmacokinetic samples were analyzed for WR 238605 succinate by validated HPLC. This assay had a sensitivity of 1 ng/ml for plasma and 2 ng/ml for blood, with both intra- and inter-day coefficients of variation of <10%.

RESULTS

Pharmacokinetic analysis was performed on the plasma drug concentrations using non-compartmental (**Table 1**) and compartmental (**Table 2**) methods, in which concentration data were analyzed using a one-compartment model with first order absorption and elimination. Both demonstrated linear kinetics at the doses studied, with a t_{max} of 12 hours, an elimination half-life of two weeks, and a large volume of distribution suggested of extensive tissue distribution. Blood and calculated RBC concentrations were 2.0 and 3.4 times higher than corresponding plasma concentrations.

Table 1. Noncompartmental Parameter Estimates of WR 238605 (Mean ± SD)

	*T_{max} (hr)	AUC_{total}	C_{max}	$T_{1/2}$ (hr)	CL/F (L/hr)	V_{ss}/F (L)	Absorption time	Residence Time
100 mg	23.9 (12.2 – 24.3)	18.02 ± 2.61	46.7± 12.6	336 ± 40	5.65 ± 0.86	2729 ± 654	5.0 ± 1.5	480 ± 58
200 mg	12.2 (12.00 – 54.3)	39.55 ± 4.25	96.5 ± 12.2	340 ± 70	5.11 ± 0.57	2445 ± 465	5.7 ± 1.6	482 ± 90
400 mg	12.2 (12.0 – 54.3)	82.76 ± 17.51	183.8 ± 29.9	363 ± 44	5.01 ± 1.04	2557 ± 421	5.9 ± 2.5	516 ± 61
Mean±SD	-	N/R	N/R	346 ± 51	5.26 ± 0.85	2577±506	5.5±1.9	492±69

N/R: not reported, *-Median and range ()

Reviewer Comment: For the dose of 200 mg TQ, the median T_{max} was 12.3 hours. This median value is similar to what was reported in a previous ascending dose study. Although the median T_{max} value is around 12 hours for the 200 and 400 mg cohorts, the T_{max} range is considerably large, i.e., 12.00 – 54.3. As per the study investigator, this could be a reflection of the assay or biological variability.

Table 2. Population Pharmacokinetic Parameters of WR 238605

	Cl/f (L/h)	V/f (L/kg)	Ka (hr^{-1})	Tlag (h)
Estimate	5.32	34.8	0.31	0.46
SEE	0.23	0.96	0.03	0.02
SEE as % CV	4.30	2.77	10.71	4.11
Inter-individual Variability (%)	14.6	10.9	45.3	7.6

SEE =Standard Error of the Estimate

Reviewer Comment: In this study, WR 328605 was best described by a one-compartment model. In some individuals, peak concentrations were under-predicted; however, a 2-compartment model did not significantly improve the fits. The Sponsor recognizes the limitations of obtaining population PK parameters from a small homozygous cohort of eighteen healthy male subjects.

REVIEWER ASSESSMENT: TQ appeared to have dose proportional kinetics and a half-life of approximately 2 weeks.

STUDY NO.: SB252263/015

An open-label study to determine the effect of TQ on the plasma pharmacokinetic profile of desipramine in healthy male and female volunteers

Date(s): 26 July 1999 – 4 November 1999
Sponsor: (b) (4)
Testing Site: (b) (4)

Analytical Site:
Sample Analysis Date(s): 26 August 1999 and 9 September 1999

METHODS

Study Design:

The study consisted of two treatment sessions; in the first treatment session, following an overnight fast, each subject received a single oral dose of desipramine 100 mg on Day 1 followed by a 7-day washout.

In the second treatment session, each subject received TQ 400 mg QD for 3 days from Day 8, 9 and 10, followed by an overnight fast prior to administration of a single oral dose of desipramine 100 mg, 12 hours after the last dose of TQ (i.e. in the morning of Day 11). Each dose of TQ was administered with food in the evening.

Assessments

Pharmacokinetic Assessments: Blood samples (~ 2.5 mL) for the determination of plasma concentrations of desipramine were collected pre-dose (0 hours), at 1 hour intervals until 10 hours post-dose, and at 12, 14, 24, 32, 48, 72 and 96 hours post-dose both on Days 1 and 11.

On the evening of Day 8, 9 and 10, a pre-dose blood sample was collected prior to the administration of TQ was administered for determining the minimum plasma concentration (Cmin). In addition, blood samples were collected pre- dose and at 24, 36, 60, 84 and 108 hours after the last dose of TQ, corresponding to 12, 24, 48, 72 and 96 hours after dosing with desipramine. Additional 2.5 mL samples were collected at bi-weekly intervals after the last (third) dose of TQ for 8 weeks, and a final sample was collected 9 weeks after the last dose of TQ.

Desipramine and TQ plasma concentration time data were analyzed by non-compartmental analysis. The reported sample times are the actual times of sample collection.

Analytical Methods: The analytical method, matrix, and lower limit of quantification (LLQ) values are summarized in **Table 1**. Plasma samples were assayed for desipramine using a method based on solvent extraction followed by gas chromatography using (b) (4)

(b) (4) Quality control (QC) samples were assayed with each batch of samples against separately prepared calibration standards. Plasma samples were assayed for TQ using LC/MS/MS method.

Table 1. Bioanalytical Methods Summary

Analyte	Matrix	LLQ
Desipramine	Plasma	0.5 ng/mL
Tafenoquine	Plasma	2 ng/mL

Reviewer Comment: The bioanalytical methods are acceptable.

RESULTS AND CONCLUSIONS

Pharmacokinetic Results: The plasma concentration-time profiles of desipramine when administered alone and when administered with TQ appear similar. A summary of the PK parameters for desipramine alone and coadministration with TQ are presented in **Table 2.**

Table 2. Geometric Mean (CVb%) Desipramine Pharmacokinetic Parameters

Regimen		C_{max} (ng/mL)	T_{max}# (h)	$AUC_{(0-\infty)}$ (ng.h/mL)	T½ (h)
Desipramine Alone	Mean	27.5	7.00	955	22.5
	SD	11.7	3.00 – 14.1	1115	14.5
Desipramine +	Mean	28.3	7.00	891	19.9
Tafenoquine	SD	11.7	3.00-10.00	979	10.4

= Tmax (median & range)

The statistical analyses provided the following overall comparison of $AUC_{(0-\infty)}$ and C_{max} between regimens for desipramine can be seen in **Table 3**.

Table 3. Summary of Results of Statistical Analysis of Primary Pharmacokinetic Parameters Comparison for Desipramine alone and Desipramine with Tafenoquine

Parameter	Comparison^	Ratio or Difference	90% C.I.*	CV% (within)
$AUC_{(0-\infty)}$	C : A	0.94	(0.89, 1.00)**	11.7
C_{max}	C : A	1.04	(0.98, 1.10)	11.1

^ A : Desipramine alone; C : Desipramine + Tafenoquine

* Adjusted 90 % confidence interval (to account for the interim analysis)

** Confidence Interval 0.999 is rounded to 1.00

The arithmetic mean (SD) PK parameter estimates for TQ after administration of the last (third) 400 mg dose are summarized in **Table 4**. The C_{max} for TQ ranged from 240 to 967 ng/mL.

Table 4. Arithmetic Mean Pharmacokinetic Parameter Estimates for TQ

Parameter (units)	Mean (SD)
$AUC_{(0-\infty)}$ (µg.h/mL)	275 (80)
C_{max} (ng/mL)	496 (162)
T_{max} (h)*	24.0 (0.0-84.0)
$T_{1/2}$ (h)	436 (95)

*Median (range)

Reviewer Comment: In this study, the TQ C_{max} ranged from 244 to 967 ng/mL with a mean C_{max} of 496 ng/mL, which overlapped with C_{max} values following three consecutive once daily oral doses of 400 mg TQ observed in other studies.

REVIEWER'S ASSESSMENT

Based on the findings from this study, it appears that TQ is not an inhibitor of CYP2D6, and thus, is unlikely to affect the metabolism of other drugs that undergo biotransformation by CYP2D6.

STUDY NO.: SB252263/040

Evaluation of the Effect of Tafenoquine on the Metabolism of Multiple Cytochrome P-450 Substrates

Date(s): 25 July 2005– 21 November 2005
Sponsor: GlaxoSmithKline (GSK) R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)
Analytical Site:
Sample Analysis Date(s): Could not locate this information from the CSR

OBJECTIVES

Primary

To characterize the effect of dosing of TQ on the pharmacokinetics (PK) of a single oral dose of enzyme substrates midazolam (CYP3A4), flurbiprofen (CYP2C9) and caffeine (CYP1A2) in healthy volunteers.

RATIONALE

The purpose of this study was to investigate the in vivo potential for TQ to interact with substrates of CYP2C9, 3A4 and 1A2. Due to the long half-life of TQ, ranging from 15 – 35 days, the study was not designed as a randomized crossover study. To achieve relevant therapeutic concentrations of the drug during the study period, a loading dose was administered of TQ. The study utilized this approach, thereby achieving a pseudo steady state after only 3 days of dosing.

METHODS

Study Design: This was an open-label, two-period, non-randomized, crossover study. Each subject participated in 2 study sessions (**Table 1**) separated by a washout period of at least 7 days.

Table 1. Study Medication Administration Schedule

Session 1		
Study Day	**Study Drug, Dose**	
1	Midazolam, 5 mg	
2	"Multi-drug cocktail"	Flurbiprofen, 50 mg
		Caffeine, 200 mg
Session 2		
Study Day	**Study Drug, Dose**	
1-2	Tafenoquine 400 mg	
3	Tafenoquine 400 mg; Midazolam, 5 mg	
4[1]	"Multi-drug cocktail"	Flurbiprofen, 50 mg
		Caffeine, 200 mg
1. Tafenoquine was not coadministered with the multi-drug cocktail on Day 4 of Session 2.		

TQ was administered under fed condition in this study.

TQ (capsule) in this clinical study was supplied by (b) (4) Midazolam (solution), flurbiprofen (tablet), and caffeine (tablet) were supplied by the (b) (4) and the manufacturers for these were (b) (4) respectively.

Assessments

Pharmacokinetic Assessments: Nine blood samples (~2 mL) were collected for midazolam/1'-hydroxymidazolam PK analyses on Day 1 of Session 1 and Day 3 of Session 2 at designated times up to 24 hours post-dose.

Nine blood samples (~5 mL) for caffeine/paraxanthine and flurbiprofen PK analyses were collected on Day 2 of Session 1 and Day 4 of Session 2 at designated times up to 24 hours post-dose.

Pre-dose blood samples (~2.5 mL) were collected for TQ PK analysis on Days 1, 3, and 4 of Session 2.

Urine samples for 4'-hydroxyflurbiprofen PK analysis were collected on Day 2 of Session 1 and Day 4 of Session 2 just prior to 8 hour timepoint.

The following nomenclatures are used to describe the regimens administered during this clinical study and to perform the calculation on their geometric means.

Regimen A1: Midazolam 5 mg

Regimen A2: Flurbiprofen 50 mg, Caffeine 200 mg

Regimen B2: Midazolam 5 mg, TQ 400mg

Regimen B3: Flurbiprofen 50 mg + Caffeine 200 mg (post administration of TQ 400 mg)

Analytical Methods: PK samples were analyzed by validated HPLC-MS/MS. The assays were validated over the relevant concentration range. The performance of the bioanalytical methods is acceptable.

RESULTS AND CONCLUSIONS

Pharmacokinetic Results: A summary of the midazolam, 1'-Hydroxymidazolam, caffeine, paraxanthine, flurbiprofen and 4'-hydroxyflurbiprofen PK parameters along with the ratios of 1'Hydroxymidazolam/Midazolam and paraxanthine/caffeine are presented in **Table 2, 3**, **4, 5, 6, 7, 8, and 9** respectively. The ratio of the primary and secondary PK parameters for the substrates of CYP3A4 (midazolam), CYP1A2 (caffeine), and CYP2C9 (flurbiprofen) with and without TQ are presented in **Table 10** and **11**.

Table 2. Geometric Mean (CVb%) Midazolam Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	CL/F (L/hr)	Cmax (ng/mL)	tmax (hr)[1]	t½ (hr)
1	1	Midazolam 5 mg	77.5 (25.8)[2]	69.5 (28.0)[3]	64.8 (26.0)[2]	17.9 (48.4)[3]	0.53 (0.25-4.00)[3]	3.04 (40.6)[2]
2	3	Tafenoquine 400 mg + Midazolam 5 mg	68.5 (35.7)[2]	61.7 (35.8)[3]	73.5 (36.0)[2]	17.3 (38.7)[3]	0.50 (0.25-2.02)[3]	2.99 (51.6)[2]

1. Median (range)
2. N = 22
3. N = 25

Table 3. Geometric Mean (CVb%) 1'-Hydroxymidazolam Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	CL/F (L/hr)	Cmax (ng/mL)	tmax (hr)[1]	t½ (hr)
1	1	Midazolam 5 mg	27.3 (41.8)[2]	22.0 (45.7)[3]	182 (41.2)[2]	6.66 (67.2)[3]	0.55 (0.25-4.00)[3]	2.49 (23.7)[2]
2	3	Tafenoquine 400 mg + midazolam 5 mg	21.6 (28.0)[2]	17.3 (35.5)[3]	231 (27.8)[2]	6.48 (39.1)[3]	0.50 (0.25-2.00)[3]	2.00 (38.6)[2]

1. Median (range)
2. N = 11; t½ and therefore AUC(0-∞) could only be determined in both sessions for 11 subjects.
3. N = 25

Table 4. Geometric Mean (CVb%) 1'-Hydroxymidazolam/Midazolam Ratios

Session	Day	Regimen	AUC(0-∞) Ratio	AUC(0-t) Ratio
1	1	Midazolam 5 mg	0.324 (28.6)[1]	0.317 (37.1)[2]
2	3	Tafenoquine 400 mg + midazolam 5 mg	0.283 (31.4)[1]	0.280 (40.4)[2]

1. N = 11; t½ and therefore AUC(0-∞) could only be determined in both sessions for 11 subjects.
2. N = 25

Table 5. Geometric Mean (CVb%) Caffeine Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	CL/F (L/hr)	Cmax (ng/mL)	tmax (hr)[1]	t½ (hr)
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	37177 (40.0)[2]	34759 (37.9)[2]	5.38 (40.1)[2]	4929 (21.9)[2]	1.00 (0.5-2.00)[2]	5.13 (35.1)[2]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	37675 (40.9)[2]	35245 (38.2)[2]	5.31 (40.9)[2]	4671 (24.2)[2]	0.79 (0.48-2.00)[2]	5.31 (32.1)[2]

1. Median (range)
2. N = 24

Table 6. Geometric Mean (CVb%) Paraxanthine Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-t) (ng·hr/mL)	Cmax (ng/mL)	tmax (hr)[1]
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	17733 (25.2)[2]	1161 (21.3)[2]	8.00 (4.08-12.08)[2]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	18522 (28.1)[2]	1187 (21.0)[2]	8.00 (4.00-12.0)[2]

1. Median (range)
2. N = 24

Table 7. Geometric Mean (CVb%) Paraxanthine/Caffeine Ratios

Session	Day	Regimen	Concentration (8 hours post-dose) Ratio	Metabolic [AUC(0-t)] Ratio
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	0.626 (37.5)[1]	0.510 (20.5)[1]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	0.646 (37.2)[1]	0.526 (22.0)[1]

1. N = 24

Table 8. Geometric Mean (CVb%) Flurbiprofen Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-∞) (µg·hr/mL)	AUC(0-t) (µg·hr/mL)	CL/F (L/hr)	Cmax (µg/mL)	tmax (hr)[1]	t½ (hr)
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	39.5 (30.9)[2]	37.2 (28.7)[2]	1.27 (30.8)[2]	6.69 (24.7)[2]	2.00 (0.5-4.00)[2]	5.09 (29.5)[2]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	44.5 (31.3)[2]	41.5 (28.3)[2]	1.13 (31.3)[2]	6.53 (29.5)[2]	2.00 (0.5-6.07)[2]	5.88 (23.4)[2]

1. Median (range)
2. N = 24

Table 9. Arithmetic Mean (95% CI) Free 4'-Hydroxyflurbiprofen Formation Clearance

Session	Day	Regimen	CLform (mL/hr)
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	21.5 (13.7, 29.4)[1]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	15.8 (8.83, 22.8)[1]

1. N = 23

Table 10. Summary of Results of Statistical Analysis of Primary Pharmacokinetic Parameters

Parameter	Comparison of Interest	Point Estimate	90% CI	CVw%
Midazolam				
AUC(0-∞) (ng•hr/mL)[1]	B2 : A1	0.88	(0.83, 0.94)	12.1
AUC(0-t) (ng•hr/mL)[1]	B2 : A1	0.89	(0.84, 0.94)	12.1
Flurbiprofen				
AUC(0-∞) (µg•hr/mL)[1]	B3 : A2	1.13	(1.09, 1.16)	6.7
AUC(0-t) (µg•hr/mL)[1]	B3 : A2	1.11	(1.07, 1.16)	7.7
Total 4'-hydroxyflurbiprofen				
Formation clearance (mL/hr)[1]	B3 : A2	0.85	(0.77, 0.94)	19.6
Caffeine				
AUC(0-∞) (ng•hr/mL)[1]	B3 : A2	1.01	(0.98, 1.05)	7.4
AUC(0-t) (ng•hr/mL)[1]	B3 : A2	1.01	(0.98, 1.05)	7.2
Paraxanthine/caffeine plasma AUC ratio[1]	B3 : A2	1.03	(0.99, 1.07)	8.0
Paraxanthine/caffeine plasma 8 h Concentration ratio[1]	B3 : A2	1.03	(0.98, 1.09)	10.4

1. Point estimate represents the ratio of the adjusted geometric means between regimens

Regimen A1: Midazolam 5 mg
Regimen A2: Flurbiprofen 50 mg, Caffeine 200 mg
Regimen B2: Midazolam 5 mg, Tafenoquine 400mg
Regimen B3: Flurbiprofen 50 mg + Caffeine 200 mg (post administration of Tafenoquine 400 mg)

Table 11. Summary of Results of Statistical Analysis of Secondary Pharmacokinetic Parameters

Parameter	Comparison of Interest	Point Estimate	90% CI	CVw%
Midazolam				
Cmax (ng/mL)[1]	B2 : A1	0.97	(0.83, 1.13)	32.0
t½ (hr)[1]	B2 : A1	0.98	(0.89, 1.08)	18.8
CL/F (L/h)[1]	B2 : A1	1.13	(1.06, 1.21)	12.3
tmax (hr)[2]	B2 - A1	0.00	(-0.25, 0.23)	
1'-Hydroxymidazolam				
AUC(0-t) (ng•hr/mL)[1]	B2 : A1	0.78	(0.71, 0.87)	20.9
Cmax (ng/mL)[1]	B2 : A1	0.97	(0.80, 1.18)	40.8
tmax (hr)[2]	B2 - A1	-0.13	(-0.75, 0.13)	
1-Hydroxymidazolam/ Midazolam AUC(0-∞)[1]	B2 : A1	0.87	(0.78, 0.98)	15.14
1-Hydroxymidazolam/ Midazolam AUC(0-t)[1]	B2 : A1	0.88	(0.79, 0.98)	22.43
Flurbiprofen				
Cmax (µg/mL)[1]	B3 : A2	0.98	(0.91, 1.04)	13.9
t½ (hr)[1]	B3 : A2	1.15	(1.10, 1.21)	9.1
CL/F (L/h)[1]	B3 : A2	0.89	(0.86, 0.92)	6.7
tmax (hr)[2]	B3 - A2	0.50	(0.00, 1.25)	
Caffeine				
Cmax (ng/mL)[1]	B3 : A2	0.95	(0.89, 1.01)	13.6
t½ (hr)[1]	B3 : A2	1.03	(0.99, 1.08)	8.8
CL/F (L/h)[1]	B3 : A2	0.99	(0.95, 1.02)	7.4
tmax (hr)[2]	B3 - A2	0.00	(-0.01, 0.03)	

1. Point estimate represents the ratio of the adjusted geometric means between regimens
2. Point estimate represents median difference between regimens

Regimen A1: Midazolam 5 mg
Regimen A2: Flurbiprofen 50 mg, Caffeine 200 mg
Regimen B2: Midazolam 5 mg, Tafenoquine 400mg
Regimen B3: Flurbiprofen 50 mg + Caffeine 200 mg (post administration of Tafenoquine 400 mg)

REVIEWER'S ASSESSMENT

Based on the findings from this study, there is no clinically significant effect of TQ on the PK of substrates of CYP3A4, CYP1A2, and CYP2C9.

STUDY NO.: TQ-2016-01

A Phase 1, Single-Dose, Open-Label Study of Tafenoquine in Healthy Adults to Compare the Pharmacokinetic Parameters of the Proposed Marketed 2X 100 mg Tafenoquine Tablets to the Pharmacokinetic Parameters of Tafenoquine 200 mg Capsules used during Previous Clinical Trials

Date(s): 6 March 2017 – 31 May 2017
Sponsor: 60 Degrees Pharmaceuticals
Study Site:
Analytical Site: (b) (4)

Sample Analysis Date(s): 7 June 2017 to 19 June 2017
Date of Report: 6 July 2017

OBJECTIVES

The primary objective of this study was to compare the pharmacokinetic (PK) parameters in subjects administered a single 200 mg dose of the new clinical formulation, TQ 100 mg tablets (2 x 100 mg), to historic PK parameter values for the 200 mg capsules used in previous TQ clinical trials.

RATIONALE

The comparability of the PK parameters between the to be marketed (TBM) TQ 100 mg tablet to that of TQ 200 mg capsule when administered under fed conditions would serve as a bridge to the previously conducted clinical pharmacology study data with the capsule formulation and safety and efficacy data from the clinical studies, including the pivotal and supporting efficacy studies, where the 200 mg capsule formulation was used. In majority of clinical studies, TQ was administered as a capsule formulation with food.

METHODS

Study Design: This is a single dose PK bridging study comparing the PK of the TBM TQ 100 mg tablet to 200 mg capsule product PK data from Study 22 under fed conditions. Study 22 was a parallel single dose food effect study of capsule formulation that consisted of 20 fasted and 20 fed subjects. Study 22 showed that there was increased exposure to TQ when the drug was given with food. The Applicant stated that to optimize oral absorption and possibly reduce variability, this current study TQ-2016-01 utilized a similar FDA high-fat meal as the historic study. Sample size power calculations by the Applicant suggested that 60 or more completed subjects would be needed for this current study. It is also important to note that in most pivotal clinical studies that the Applicant has submitted in this NDA, TQ was administered following the administration of a meal or a snack as per the relevant clinical study reports (CSR) submitted by the Applicant.

The comparison of the two formulation under the same study was not possible due to the safety issues related to the use of (b) (4) in the manufacturing of the capsule formulation of TQ that was used in majority of the clinical studies. The TBM 100 mg tablet formulation does not use (b) (4) Thus, due to the inability to study both capsule and tablet within the same clinical study, the Applicant's proposal to make cross study comparison of the PK of the TBM 100 mg tablet to the 200-mg capsule from Study 22 was allowed by the Agency.

To minimize the noise to the extent possible between the two studies, efforts were made by the Applicant to keep various aspects of this clinical study with tablet formulation as similar as possible to Study 22. Inclusion criteria were selected to match subject age, weight, and gender to that in Study 22.

On Day 1, a single dose of 2 x 100 mg TQ tablets was administered once with 180 mL of room temperature water and within 5 minutes after ingestion of the FDA high fat meal.

Reviewer Comment: In this study, TQ tablets were administered with 180 mL of water to match the volume of water with which TQ capsules were administered in Study 22.

Assessments

Pharmacokinetic Assessments: PK samples following the administration of TQ tablets were collected at the following time points: 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 48, 72, 96, 144, 336, 504, 672, 840, 1008, 1176 and 1334 hrs. The PK sampling time points were consistent with the sampling schema from Study 22.

Although the weight and range of weights for the subjects in both studies were similar, the parameters of C_{max} and the AUCs were adjusted by the Applicant to a 70-kg subject for comparison purposes.

C_{max} and AUC_{∞} were LN-transformed for comparisons of the two products. For this parallel designed study, a two-one-sided t-test (TOST) procedure was utilized to construct 90% confidence intervals (CI) for ratios of geometric means.

Analytical Methods: Plasma samples for TQ concentration determination were analyzed using a validated LC/MS/MS method. Conditions and specifications for the TQ LC-MS/MS method for the present study were based on the procedures utilized in the historic Study 022. As the results from this clinical study were compared with those of Study 022, analytical performance was compared between previous and current procedures based on validation reports prior to the start of the current study.

The analytical method and performance related metrics are summarized in **Tables 1 and 2**.

Table 1. Precision and Bias for Analytical Procedures for Study 022

	LLOQ[a]	[b]Low	Middle	High
Tafenoquine Plasma Concentration	5 ng/mL	20 ng/mL	200 ng/mL	500 ng/mL
Average Within Run Precision (CV%)	5.84	4.56	2.17	2.19
Between Run Precision (CV%)	7.32	2.48	2.31	1.21
Average Bias (%)	2.00	4.38	1.54	2.91

[a] Lower limit of quantitation.
[b] Low, middle and high concentration standards.

Table 2. Precision and Bias for Analytical Procedures for Current Study

	LLOQ[a]	Low[b]	Middle	High
Tafenoquine Plasma Concentration	2 ng/mL	6 ng/mL	50 ng/mL	400 ng/mL
Range Within Run Precision (CV%)	1.7 - 2.7	0.9 - 3.6	0.5 - 1.4	1.2 - 20.5
Range Within Run Bias (%)	2.0 - 9.5	-1.0 - 4.7	-0.4 - 3.6	-1.0 - 5.0
Between Run Precision (CV%)	3.7	3.4	1.9	11.9
Between Run Bias (%)	5.0	2.5	1.6	1.0

[a] Lower limit of quantitation.
[b] Low, middle and high concentration standards.

Reviewer Comment: Overall, based on the information in Table 1 and 2 above, along with the reported QC parameters from day-to-day performance of the assay as per the bioanalytical report for this study, the reviewer finds the bioanalytical methods to be acceptable.

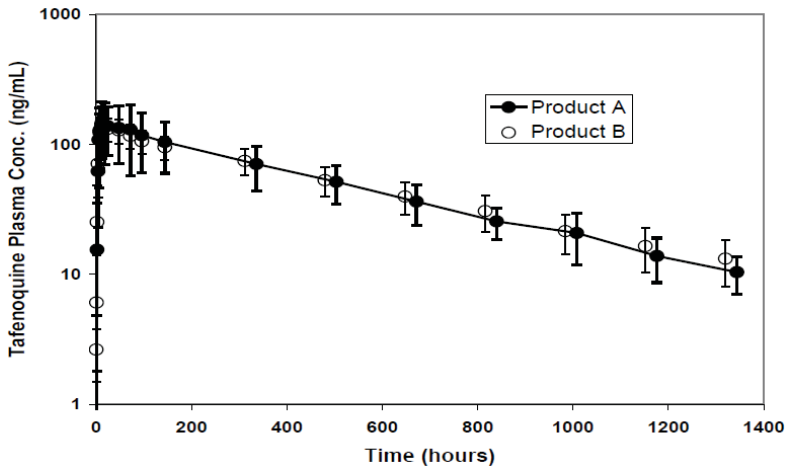
Additionally, a consult was sent to Office of Study Integrity and Surveillance (OSIS) to request the inspection of the PK bioanalytical lab for this study, and OSIS recommendation was that an on-site inspection of the analytical facility is not necessary and the data is acceptable.

RESULTS AND CONCLUSIONS

Study Population: A total of 65 out of the 70 subjects involved in this study were included in the PK analysis. Five subjects were withdrawn from the study due to violation of protocol requirements and data from these 5 subjects were not included in the PK analysis.

Pharmacokinetic Results: Log-linear plot of mean TQ plasma concentrations with SDs are presented in **Figure 1** .

Figure 1. Log-Linear Plot of Mean (±SD) TQ Plasma Concentration Following Oral Administration of 200 mg as the TQ Capsule (Product A) and Tablet (Product B) Formulations



Reviewer Comment: The mean plasma concentration vs. time profiles for TQ tablets and capsules are superimposable.

The relevant PK parameters for comparison of TQ products are provided in **Table 3 and 4.**

Table 3. Pharmacokinetic Comparison of TQ Tablets (Test) and Capsules (Reference)

Parameter		TBM Tablets Geometric Least Squares		Tafenoquine Capsule Geometric Least Squares		Ratio of Geometric Least Squares Mean (Test/Reference %)	90% CI of Mean Ratio
		n	Mean	n	Mean		
C_{max}	(ng/mL)	65	147	20	151	96.7	86.2 - 108.5
t_{max}	(hr)	65	15.8	20	17.8		
AUC_{∞}	(hr*µg/mL)	65	70.1	20	66.6	105.3	94.1 - 117.8

The % CV for C_{max} and AUC_{∞} for the TQ tablets are 20.7 % and 24.6 % respectively, whereas that for the TQ capsules are 50.4 % and 34.8 % respectively. The median tmax for the TQ tablets is 14 hours and ranged from 6.05 to 72 hours. The median tmax for the TQ capsules is 14 hours and ranged from 5.63 to 144 hours. The mean t1/2 for the TQ tablets was approximately 16 days and ranged from 10.83 days to 27.25 days. The mean t1/2 for the TQ capsules was approximately 15.54 days and ranged from 11.83 days to 20.16 days.

When adjusted to 70 kg body weight, the ratios of geometric means and 90% confidence intervals for C_{max} and AUC_{∞} were 97.8 (88.3 - 108.3) and 106.4 (95.5 – 118.6) respectively.

The Applicant concludes that the administration of 2 x 100 mg TQ tablets is bioequivalent to administration of the earlier 200 mg capsule Study 22.

Reviewer Assessment: Based on the results above, C_{max}, T_{max} and AUC_{∞} are comparable between the TQ tablets and capsule when administered with food, which confirms an exposure bridge.

The reviewer choses to differ from the Applicant using the term 'bioequivalent' to describe the results of this study. The reviewer would instead like to state that when administered with food, the PK parameters between the to-be-marketed 2 x 100 mg TQ tablets and TQ 200 mg capsules from Study 022 are comparable.

STUDY NO.: TQ-2016-02

A Randomized, Double-Blinded, Placebo-Controlled Study in Healthy, Non-Immune Adults to Determine the Schizonticidal Activity of Tafenoquine after Challenge with *Plasmodium Falciparum* Blood Stage Parasites

Date(s): 12 January 2017 – 31 March 2017
Sponsor: 60 Degrees Pharmaceuticals (60P)
Study Site(s): (b) (4)

Analytical Site: (b) (4)

Sample Analysis Date(s): 7 June 2017 to 19 June 2017
Date of Report: 20 July 2017

OBJECTIVES

Primary: To evaluate the schizonticidal activity of TQ administered orally against challenge with blood stage *Plasmodium falciparum* (*P. falciparum*) in healthy, non-immune adult participants.

Secondary: 1. To characterize the pharmacokinetic/pharmacodynamic (PK/PD) relationship between TQ concentration and Malaria Failure, defined as a participant with a quantitative polymerase chain reaction (qPCR) parasitemia of > 5,000 asexual blood stage parasites/mL accompanied by a clinical symptom score of > 6 OR parasitemia of > 5,000 asexual blood stage parasites/mL and increasing 2-fold within 48 hours.

2. To evaluate the safety and tolerability of TQ in healthy, non-immune participants and following challenge with blood stage *P. falciparum.*

METHODS

Study Design: This was a randomized, double-blinded, placebo-controlled study undertaken in healthy men and women with no previous exposure to malaria infection. The induced blood stage malaria (IBSM) challenge model (Engwerda et al, 2012; McCarthy et al, 2011) was used to assess the schizonticidal activity of TQ against challenge with blood stage *P. falciparum*. A total of 16 healthy volunteers were randomized to receive TQ or placebo in a 6:2 ratio for enough time to reach steady state (in the TQ group) comparable to that achieved with the proposed clinical regimen, after which blood stage parasites were administered and the volunteers were monitored for parasitemia by quantitative polymerase chain reaction (qPCR).

Participants received either TQ 200 mg, as 2 x 100 mg of the to-be-marketed tablet formulation, or placebo, as 2 matching tablets.

TQ 200 mg or placebo was administered once per day via the oral route to participants after their normal breakfast (participants were allowed to consume their normal breakfast before the study medication administration). Food, water and other beverages were not permitted for 60 minutes prior to dosing (the Applicant defines this as relative fasted state). TQ/placebo tablets were given with 240 mL of water after which time a fasting state was maintained by participants for an additional 60 minutes. Dosing occurred for three consecutive days (Days 1-3, the “loading dose”) and was followed, 7 days later, by another 200-mg dose of TQ or placebo, given under the same conditions (on Day 10).

Participants returned to the study site on Day 13 and were inoculated intravenously with erythrocytes containing approximately 2800 viable *P. falciparum* malaria parasites.

Participants returned to the site for daily clinical evaluation and blood sampling for TQ PK and qPCR assessment of parasitemia. Assessment of parasitemia occurred from Day 17 until the time that the qPCR demonstrated positivity for malaria, or, if qPCR remained negative, until approximately Day 32.

Following demonstration of positivity by qPCR, participants were to attend twice daily visits to the site for clinical assessment and blood sampling for qPCR. If qPCR results were negative over a 48 hour period or <5000 asexual blood stage parasites/mL and stable, then subsequent qPCR sampling reverted to 3 times per week until commencement of Riamet® (artemether/lumefantrine) treatment, with scheduling made at the Investigator's discretion. The results of the clinical evaluation and qPCR were used to ascertain attainment of the treatment threshold for initiation of early Riamet® therapy.

All participants received a standard course of antimalarial therapy with Riamet® on Day 32 or earlier in the event of Malaria Failure.

Assessments

Pharmacokinetic Assessments: PK samples were collected at the following time points: pre-dose on Day 1, Day 2, Day 3, and Day 10; pre-Blood stage *P. falciparum* challenge (BSPC) inoculum on Day 13; then on Day 20, Day 29 and Day 34/EOS (End of Study). After BSPC inoculum, PK sample time points were varied to correlate with qPCR collection days, at the discretion of the Investigator, with documentation of the actual date/time of the PK sample in the electronic case report form (eCRF).

Pharmacodynamic Assessments: Quantification of parasitemia in blood samples was determined by qPCR and was undertaken by the Queensland Pediatric Infectious Diseases Laboratory (QPID)

Reviewer Comment: In this Individual Study Review, the reviewer will provide an assessment only on the PK/PD aspects of this study. The Clinical Pharmacology Reviewer defers the assessment of the exploratory efficacy objective/s from this study to the Statistical Reviewer for this NDA. The reviewer also defers to the Microbiology reviewer's assessment on the adequacy of the analytical method for quantification of parasitemia by qPCR.

Analytical Methods: Plasma samples for TQ concentration determination were analyzed using a validated LC/MS/MS method. The lower limit of quantitation and upper limit of quantitation for the bioanalytical method were 5 ng/mL and 1000 ng/mL respectively.

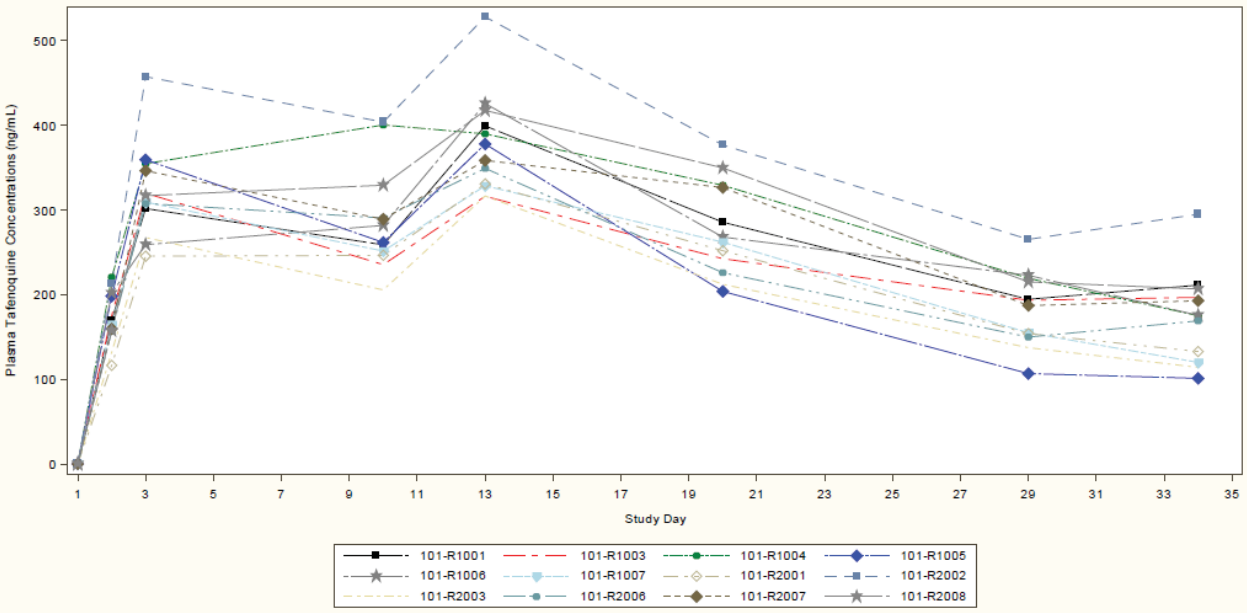
Reviewer Comment: Overall, based on the review of performance metrics reported by the Applicant in the relevant bioanalytical and method validation reports, the reviewer deems the bioanalytical methods to be acceptable.

RESULTS AND CONCLUSIONS

Study Population: The intention to treat (ITT) population was the primary population for analyses of TQ PK. All participants were considered eligible to be included in the ITT analysis population. TQ concentration-time data from 12 treated participants was included in the PK analysis. PK samples from 4 placebo participants were collected and analyzed to establish dosing compliance.

Pharmacokinetic Results: The individual plasma concentrations of TQ across time are presented in **Figure 1**.

Figure 1. Linear Plot of Individual TQ Plasma Concentrations over Time following Oral Administration of 200 mg of TQ Tablets QD on Days 1 through 3 and at Day 10



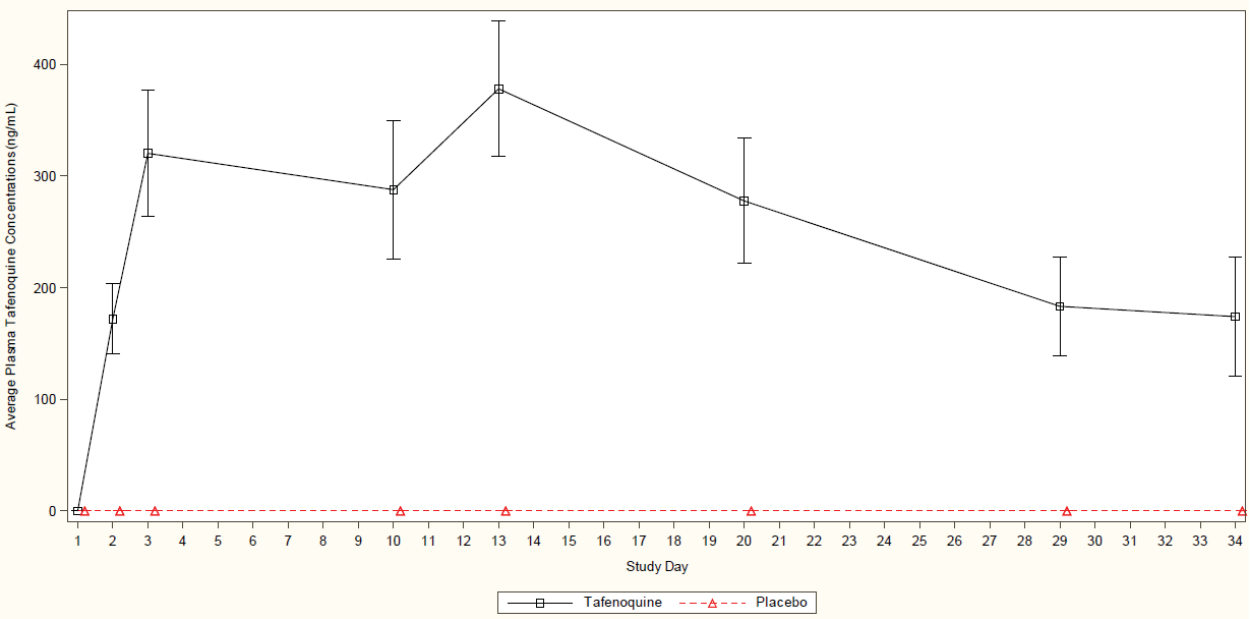
Note: Below limit of quantification (BLOQ) is replaced by 0
Source: Applicant's clinical study report, Page 2388, Listing 16.2.5.5

Reviewer Comment: The individual plasma concentration of TQ for up to Day 20 appear to be approximately 200 ng/mL or greater, following which they begin to slowly decline over time. During Days 29 through 34, approximately 2 weeks following the last dose of TQ tablet, the TQ concentrations were still approximately 100 ng/mL or greater in majority of the study participants.

The mean (pooled treatment group) plasma concentrations of TQ across time are presented in **Figure 2**. In the TQ group, pre-dose mean plasma levels and associated standard deviation were 172.02 ± 31.58 ng/mL at Day 2, which increased to 320.35 ± 56.40 ng/mL on Day 3. Mean plasma levels were 287.81 ± 61.75 ng/mL on Day 10, 7 days after the last administered loading dose. Plasma levels increased following administration of the final, post-loading dose on Day 10, with mean TQ concentrations on the day of parasite inoculation assessed to be 378.14 ±

60.63 ng/mL. Thereafter, the circulating TQ levels in plasma appear to be greater 80 ng/mL, which the Applicant claims is the threshold plasma drug concentration reported to be protective against breakthrough malaria infection (Edstein 2003). A slow decline in plasma levels occurred until the last sampling time point at EOS, with mean plasma levels of 277.76 ± 56.21 ng/mL on Day 20, 183.33 ± 44.30 ng/mL on Day 29 and 174.12 ± 53.50 ng/mL at EOS. As per the Applicant, low variability (CV<25.0%) was observed for plasma concentrations of TQ across individuals at all-time points except for the EOS assessments, where CV was 30.7%.

Figure 2. Linear Plot of Mean Plasma TQ Concentration Over Time following Oral Administration of 200 mg TQ Tablets or Placebo QD on Days 1 through 3 and at Day 10



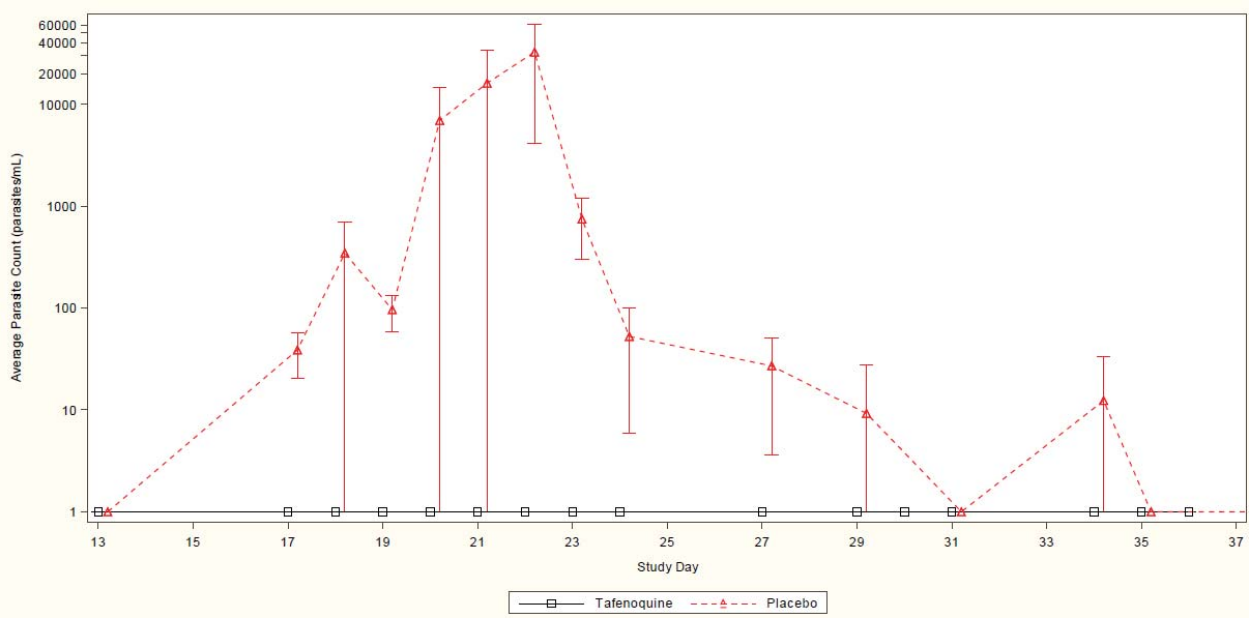
Note: BLOQ is replaced by 0
Source: Applicant's clinical study report, Page 133, Listing 16.2.5.5

Pharmacodynamic Results: The semi-log plot of mean parasite count over time for both TQ and placebo can be seen in **Figure 3**. The induced blood stage malaria (IBSM) challenge model demonstrated the predicted pattern of parasitemia in placebo participants following inoculation. Post BSPC inoculum on Day 13, mean parasite counts increased from below limit of quantification (BLQ) at the malaria monitoring visit on Day 17 (38.8 ± 18.34 parasites /mL) to 345.8 ± 352.16 parasites/mL on Day 18, and peaked at 32452.5 ± 28336.76 parasites/mL on Day 22. Riamet® was administered to all placebo participants due to the emergence of parasitemia that met the criteria for initiation of rescue treatment. In the placebo group, this occurred in one participant on Day 21 and in all other placebo participants on Day 22. Following antimalarial treatment, clearance of blood-stage parasites occurred within 48 hours of initiation of therapy (by Day 34) in all placebo participants.

In contrast to the placebo administration, the oral administration of 200 mg TQ tablet; QD on Days 1 through 3 and at Day 10, appeared to prevent symptomatic blood-stage infection following *P. falciparum* exposure in these malaria- naïve healthy volunteers. Post BSPC

inoculum, *P. falciparum* parasites were detected by qPCR in placebo participants only, as evident in **Figure 3**.

Figure 3: Semi-log Plot of Mean (SD) Parasite Count (Estimated Parasites/mL) over Time following Oral Administration of 200 mg TQ Tablets or Placebo QD on Days 1 through 3 and at Day 10



Note: BLOQ is replaced by 0
Source: Applicant's clinical study report, Page 319, Listing 16.2.6.1

No TQ participant met the criteria for early initiation of Riamet® rescue therapy; all participants received antimalarial treatment at the EOS, as mandated in the clinical protocol.

The Applicant states that the findings from this IBSM challenge study supports the proposed clinical dosing regimen (200 mg/day x 3 days, followed by 200 mg weekly) for TQ and that target trough TQ concentrations of 80 ng/mL or higher are achieved throughout the study duration, resulting in protection of non-immune individuals from a symptomatic breakthrough infection.

From this study, the Applicant concludes that the TQ steady state drug concentrations achieved with the dosing regimen employed in this study (i.e, 200 mg "loading dose" for 3 consecutive days (Days 1-3), and followed by another 200-mg dose of TQ or placebo 7 days later (Day 10)) were completely effective (100.0% prophylactic efficacy) against challenge with approximately 2800 *P. falciparum* blood stage parasites in the IBSM model in healthy, non-immune adults. The Applicant further adds that the results from this study suggests that after challenge in the field by *P. falciparum* sporozoites, parasites that escape TQ parasiticidal activity in the liver will be killed by TQ in the blood.

Reviewer Comment: Based on the results of this study, the reviewer concurs with the Applicant regarding the adequacy of the dosing regimen employed in this study against P. falciparum blood stage parasites in healthy, non-immune adults (i.e, 200 mg "loading dose" for 3 consecutive days (Days 1-3), and followed by another 200-mg dose of TQ or placebo 7 days later (Day 10)). However, it is unknown if the Applicant's proposed minimum target trough TQ plasma concentration of 80 ng/mL from this study is appropriate to generalize to the population at-large due to the limited number of participants in this study. As only one dose was studied and the response rate was high, the distribution or range of steady-state trough drug concentrations and their relationship to efficacy are not evaluable from this study.

References:

Engwerda CR, Minigo G, Amanate FH, et al. Experimentally induced blood stage malaria infection as a tool for clinical research. Trends Parasitol 2012; 28(11): 515-21. doi: 10.1016/j.pt.2012.09.001.

McCarthy JS, Sekuloski S, Griffin PM, et al. A pilot randomized trial of induced blood-stage Plasmodium falciparum infections in healthy volunteers for testing efficacy of new antimalarial drugs. PloS One 2011; 6(8): e21914.

Edstein MD, Kocisko DA, Walsh DS, et al. Plasma concentrations of tafenoquine, a new long-acting antimalarial agent in Thai soldiers receiving monthly prophylaxis. Clin Infect Dis 2003; 37: 1654-1658. doi: 10.1086/379718.

STUDY NO.: 51

Study Title: A Multiple Dose Safety, Tolerance and Pharmacokinetic Study of TQ When Given to Healthy Male and Female Subjects

Date(s):	20 April 1995 through 29 November 1995
Sponsor:	60 Degrees Pharmaceuticals/ US Army Medical Research
Study Site:	(b) (4)
Analytical Site:	
Sample Analysis Date(s):	26 July 1995 through 07 June 1996
Date of Report:	30 July 1997

OBJECTIVES

To evaluate the safety, tolerability and Pharmacokinetics (PK) of TQ following multiple ascending once weekly doses for 10 weeks in healthy male and female subjects.

METHODS

Study Design:

This was a randomized, double-blind, placebo controlled study to evaluate the safety and tolerance of weekly oral doses of TQ capsules. A total of 36 healthy adult male and female subjects (age 23 – 46 years old) participated in this study. Three doses of TQ capsules were studied; 200 mg, 400 mg, or 600 mg administered once weekly for 10 weeks, in the morning under fasting conditions. In each dose group, eight subjects were randomized to receive TQ and four received a placebo. Each subsequent dose group only began weekly dosing after the previous group had tolerated their dosing for 5 weeks.

Assessments

Pharmacokinetic Assessments: Blood samples (~ 5 mL) were collected pre-dose on Day 1 (prior to Dose 1) and at Week 10 (prior to Dose 10) and at 2, 4, 6, 8, 12, 16 and 24 hours (h) post dose for evaluation of plasma concentrations of TQ. Following the Dose 10, additional blood samples were collected at weeks 12, 14, 16, 18, and 20. Trough blood samples were drawn pre-dose (weekly) prior to Doses 2 through 9.

Analytical Methods: Plasma samples for TQ concentration determination were analyzed using a validated assay based on extraction followed by HPLC with fluorescence detection. The lower limit of quantitation (LLQ) was 1.0 ng/mL.

Reviewer Comment: Overall, based on the review of performance metrics reported by the Applicant in the bioanalytical and method validation reports, the reviewer deems the bioanalytical methods to be acceptable.

RESULTS AND CONCLUSIONS

Study Population: Plasma concentrations of TQ were quantifiable in all subjects in all dose groups. One subject (Subject (b) (6) who was randomized to receive placebo received active medication on Day 1 of the study. Conversely, Subject (b) (6) appeared to have received placebo on Day 1 even though he was allocated to receive active drug. Subsequently, both subjects appeared to receive the dose to which they were allocated. Day 1 PK data for Subject (b) (6) were included in the summary of PK results. As there were no concentration-time data for Subject (b) (6) on Day 1 and the terminal half-life following the last dose could not be determined (the concentration-time profile was erratic and did not decline over the 7-week sampling period), the data for this subject were not included in the PK analysis. Only Day 1 PK data for Subjects (b) (6) were included in the analysis, as these subjects withdrew from the study prior to week 6 and week 10, respectively.

Reviewer Comment: The reviewer believes that the aspects reported above were appropriately dealt with during the PK analysis and would not affect the overall findings and/or conclusions from this study.

Pharmacokinetic Results: The comparison of PK parameters following the administration of single and multiple dose of 200 mg, 400 mg, or 600 mg TQ are presented in **Table 1**. The PK of TQ following Day 1 and Week 10 doses were approximately dose proportional between 200 and 400 mg**.** The Applicant reported that only negligible increases and/or no increases were in observed AUC and C_{max} between 400 and 600 mg, which they believed to be possibly due to a high incidence of vomiting and diarrhea in the 600-mg dose.

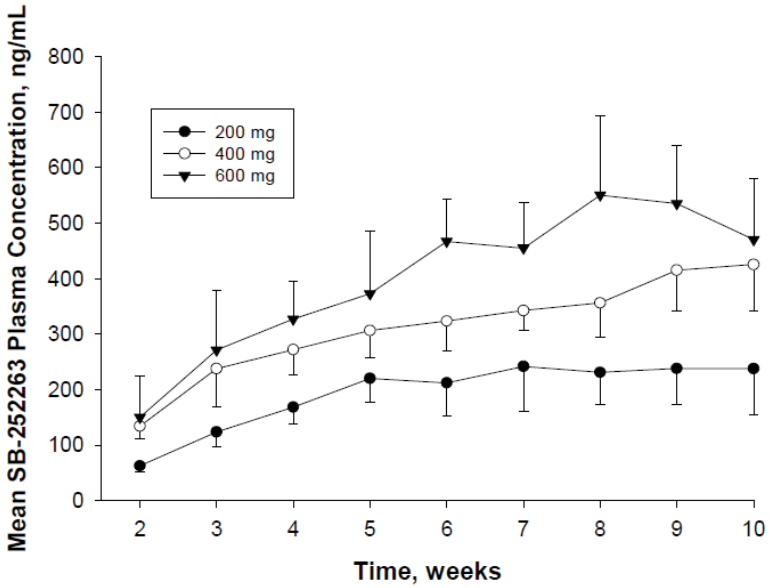
Table 1. Mean (SD) Pharmacokinetic Parameters for TQ (n=8/dose group)

Dose (mg)	AUC(0-1 wk) (ug.h/mL)		Cmax (ng/mL)		Tmax* (h)		T1/2 (d)
	Day 1	Week 10	Day 1	Week 10	Day 1	Week 10	Week 10
200	13.2 (1.9)	56.0 (18.4)	106 (20)	455 (456)	12.0 (8.0-24.0)	7.0 (0.0-24.0)	15.7 (2.0)
400	27.8 (4.9)	82.1^ (14.2)	249 (74)	783** (196)	12.0 (4.0-24.0)	12.0** (6.0-24.0)	20.0^ (3.5)
600	30.9 (13.7)	78.3^ (8.4)	252 (132)	707^ (159)	9.0 (4.0-24.0)	7.0^ (4.0-12.0)	28.8^ (5.0)

* Median (range) ** n=7 ^ n=6

The mean $T_{1/2}$ values ranged from approximately16 to 29 days following 10 weeks of dosing, with an apparent increase in mean $T_{1/2}$ from 200 mg to 600 mg. The mean trough concentrations over the 10-week duration can be seen in **Figure 1**. Trough concentrations of TQ between 1 and 10 weeks showed that steady-state was achieved in the 10-week period, with steady state achieved at around 5 weeks for the 200-mg dose cohort.

Figure 1. Mean Tafenoquine Trough Concentrations, Repeated Dose Administration over 10 Weeks



Note: Error bars are standard deviation

Based on mean $AUC_{(0\text{-}1\ wk)}$ and C_{max} data for the 200 and 400 mg dose groups, an accumulation ratio of approximately 3.2 to 4.4 was observed (**Table 2**). Accumulation ratio was not calculated for the 600 mg dose.

Table 2. Observed Accumulation Ratios for TQ

Dose (mg)	Observed Accumulation Ratio (Ro)	
	AUC(0-1 week)	Cmax
200 (n = 8)	4.30	4.39
400 (n = 7)	3.21[a]	3.42

[a] n = 6

The Applicant concludes that mean $AUC_{(0\text{-}1\ week)}$ and C_{max} increased only up to 400 mg dose of TQ, whereas Tmax did not. The Applicant also concluded that the loss of dose proportionality for doses > 400 mg (i.e., 600 mg) may be attributable to high incidence of vomiting and diarrhea for this dose and therefore reduced absorption of TQ.

REVIEWER'S ASSESSMENT/CONCLUSIONS

The reviewer agrees with the Applicant's conclusion regarding dose proportionality at the 200 mg and 400 mg dose of TQ capsules. Regarding the highest capsule dose of 600 mg, the assessment regarding dose proportionality are considered inconclusive due to the higher than usual incidences of vomiting and diarrhea in this cohort of 8 subjects. Steady state trough concentrations of TQ were reached with the 200 mg once weekly dose regimen (proposed clinical regimen) by approximately Week 5 (35 days). Following 10 weeks of dosing with 200 mg once weekly, plasma accumulation of TQ appeared to be substantial, as evidenced by a mean accumulation ratio of approximately 4.4. This extent of plasma accumulation is to be expected, given the mean $T_{1/2}$ of 16 days with the 200 mg once weekly dose regimen.

STUDY NO.: 006

Dose Down Range Placebo Controlled Double-Blind Study of Oral TQ for Prophylactic Efficacy, Safety and Tolerance in Subjects Resident in a Malarious Area of Gabon

Date(s):	16 March 1999 – 16 June 1999
Sponsor:	60 Degrees Pharmaceuticals (SmithKline Beecham as per the Clinical Study Report (CSR))
Study Site:	(b) (4)
Analytical Site:	
Sample Analysis Date(s):	2 September 1999 – 9 November 1999

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Date of Report: 6 February 2002

OBJECTIVES

Primary Objective(s): To determine the prophylactic efficacy of a range of 3-day loading doses of oral TQ in comparison to placebo in malaria prophylaxis.

Secondary Objective(s): To assess safety and tolerability of a range of 3-day loading doses of oral TQ.

METHODS

Study Design:

This was a placebo-controlled double-blind, parallel group, single-center study of malaria prophylaxis carried out in a malarious area of Gabon. Subjects who met the study entry criteria were treated with halofantrine 250 mg once daily (QD) for 3 days with food to clear any existing parasitemia. Four days after the clearance period, a total of 415 subjects free from malaria parasitemia were randomized to receive either TQ 25 mg, 50 mg, 100 mg or 200 mg or placebo QD for 3 days. TQ or placebo were given as a capsule formulation that was matched for shape, weight and color. The study treatment was administered following ingestion of a meal by the subjects. Subjects remaining free from plasmodia species (spp) after study treatment attended 10 weekly follow-up assessments.

Reviewer Comment: Additional details regarding the food/meal that halofantrine and study medications are administered with are not described in the CSR for this study.

Assessments

Efficacy Parameters: The primary efficacy variables were time to malaria parasitemia in thick blood smear and protective efficacy (PE) of TQ at 49 days. The secondary efficacy variables were PE of TQ at 42 and 70 days, and clinical response (successful or unsuccessful) per the Investigator's clinical opinion. This was termed 'clinical outcome' in the protocol and case report form (CRF).

Reviewer Comment: In this Individual Study Review (ISR), the reviewer will provide the assessment only on the PK aspects of this study. The reviewer defers to the Clinical Reviewer assessment regarding the adequacy of Applicant's safety, and tolerability assessment from Study 006.

Pharmacokinetic Assessments: Blood samples for determination of plasma TQ concentrations were collected 7 and 14 days after the first dose of double blind medication. Summary statistics of TQ concentrations on each day were determined by dose.

Analytical Methods: Plasma samples were assayed for TQ using a validated LC/MS/MS method. The lower limit of quantification (LLQ) and upper limit of quantification (ULQ) of the bioanalytical method was 5.00 ng/mL and 500 ng/mL respectively.

Reviewer Comment: Overall, based on the review of performance metrics reported by the Applicant in the relevant bioanalytical and method validation reports, the reviewer deems the bioanalytical methods to be acceptable.

RESULTS AND CONCLUSIONS

Study Population: A total of 327 (78.8 %) out of 415 subjects that were randomized to receive the study medication completed the study. A summary of reasons for withdrawal from the study are shown in **Table 1**.

Reviewer Comment: It is worth noting in Table 1 that around 14 % of subjects that received 25 mg of TQ or placebo had to be withdrawn from the study due to the loss of prophylactic efficacy. There was no withdrawal associated with loss of prophylactic efficacy in the 200 mg and 50 mg dose cohort and only one subject (~ 1 %) had to be withdrawn due to the loss of prophylactic efficacy in the 100-mg dose cohort.

Table 1. Reason for Study Conclusion: Intention-To-Treat Population (Number (%) of Subjects)

Study Conclusion Reason	Treatment Group				
	Tafen 25 mg N=80	Tafen 50 mg N=86	Tafen 100 mg N=82	Tafen 200 mg N=84	Placebo N=83
Completed Study*	61 (76.3%)	73 (84.9%)	61 (74.4%)	74 (88.1%)	58 (69.9%)
Reason for Withdrawal					
Adverse experience**	2 (2.5%)	1 (1.2%)	2 (2.4%)	2 (2.4%)	3 (3.6%)
Loss of prophylactic efficacy†	11 (13.8%)	0	1 (1.2%)	0	12 (14.5%)
Protocol deviation††	5 (6.3%)	9 (10.5%)	16 (19.5%)	8 (9.5%)	10 (12.0%)
Lost to follow-up	1 (1.3%)	3 (3.5%)	2 (2.4%)	0	0
Total Withdrawn	19 (23.8%)	13 (15.1%)	21 (25.6%)	10 (11.9%)	25 (30.1%)

Data source: Table 13.3.2 in Section 11; Listing 13.3 in Appendix B

* Subjects were considered to have completed the study if they satisfied all study entry criteria, completed the three day prophylactic course and attended all the follow-up visits.

** Includes subjects [redacted] (b) (6) who were withdrawn due to an adverse experience on the Conclusion page but not the Adverse Events page of the CRF. All withdrawn due to unintended pregnancy/abortion.

† Signs and symptoms of malaria appeared after first follow-up (Day 7)

†† Including non-compliance.

Source: Applicant's Clinical Study Report, Page 55, Table 7, Tafen: Tafenoquine

Pharmacokinetic Results: Plasma concentration data were obtained in nearly all (322/332) TQ treated subjects. A summary of the mean concentration data for TQ on Days 14 and 28 (i.e., 7 and 14-days post first dose randomized medication) is presented in **Table 2** below.

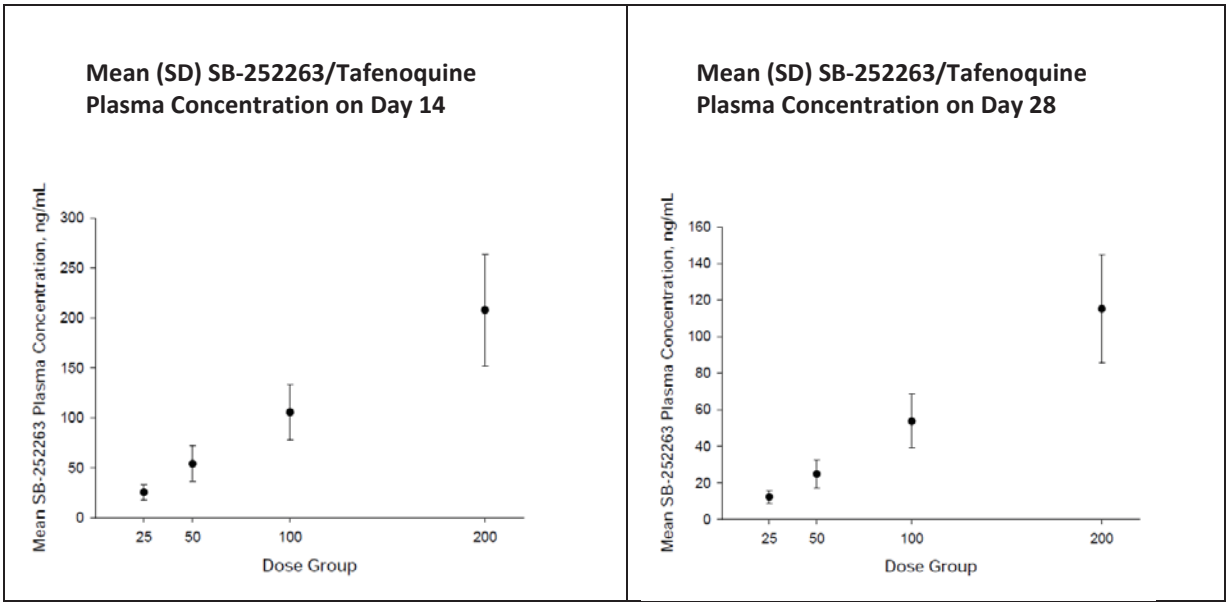
Table 2. Mean (SD) TQ Plasma Concentrations (ng/mL) on Days 14 and 28

	Treatment Group			
Day	Tafen 25 mg N=75	Tafen 50 mg N=81	Tafen 100 mg N=82	Tafen 200 mg N=78
Day 14	25.6 (7.7)	54.1 (18)	106 (28)	208 (56)
Day 28	12.3 (3.5)	24.8 (7.6)	53.7 (14.8)	114 (32)

Source: Applicant's Clinical Study Report, Page 80, Table 36, Tafen: Tafenoquine

TQ concentrations decreased on average 2-fold between Days 14 and 28 for all dose groups which is consistent with the 2-3-week half-life ($T_{1/2}$) reported for TQ in adult volunteers from the single and multiple dose studies. Mean plasma concentrations increased in an approximately dose proportional manner (**Figure 1**) with increasing dose from 25 to 200 mg on both days of sampling.

Figure 1. Mean TQ Plasma Concentrations on Day 14 and 28 following Administration of 25 mg, 50 mg, 100 mg and 200 mg TQ Capsules



Source: Applicant's Clinical Study Report, Page 109 and 111

Based on the results of this study, the Applicant concludes that TQ provided prolonged protection against malaria infection using a three-day loading dose regimen in this 12-20-year-old study population. The Applicant further adds that at 10 weeks, a 200-mg three-day dosing regimen provided 100% protective efficacy, with lower levels of protective efficacy at lower doses of TQ.

REVIEWER'S ASSESSMENT/CONCLUSIONS

Based on the review of the PK aspects in this study, the reviewer concludes that the observed $T_{1/2}$ of around 2-3 weeks for the TQ 200 mg capsule in this 12-20-year-old study population were consistent with that reported for TQ 200 mg capsule in other adult volunteer study subjects. The reviewer also agrees with the Applicant's conclusion regarding dose proportionality at TQ doses of 25 to 200 mg.

15.4. Clinical Microbiology

15.4.1. Summary of in vitro studies

The studies supporting the activity of TQ against the laboratory strains as well as clinical isolates of the asexual blood stage parasites and gametocytes of *P. falciparum* and/or *P. vivax* are summarized in Tables 1A, 1B, and 1C, respectively.

Table 1A: In vitro activity of TQ against the laboratory strains (asexual parasites) of *P. falciparum*

Experimental design (Reference)	Strain (Clone)	IC_{50} µM (µg/mL*)
Cultures were incubated for 48 hours, ^{3}H-hypoxanthine added and cultures incubated for additional 18-20 hours. (Study Report WRPD1)	W2[a]	1.13 (0.66)
	D-6[b]	0.15 (0.09)
Cultures were incubated for 48 hours, ^{3}H-hypoxanthine added and cultures incubated for additional 18-20 hours. (Vennerstrom et al., 1999)	NIG59	0.69 (0.40)
	NIG9171	0.20 (0.12)
	D6[b]	1.47 (0.85)
	W2[a]	0.22 (0.13)
	TM91C235	0.06 (0.03)
	WR75-235	0.12 (0.07)
	TM91C40	0.29 (0.17)
	Average	0.48 (0.28)
Testing performed by the WHO microtest for determination of *P. falciparum* drug sensitivity. (Russell et al., 2003)	K1[c]	(7.00)
Cultures incubated for 72 hours and activity measured by incorporation of ^{3}H-hypoxanthine. (Adjalleya et al., 2011)	NF54	4.44 (2.58)
Cultures incubated for 72 hours and stained with 4',6-diamidino-2-phenylindole (DAPI). The plates were left for at least 4 hours before imaging on the Opera QEHS microplate confocal imaging system (PerkinElmer, Australia). DNA spot analysis was performed and the number of infected red blood cells provided as the output. (Duffy and Avery, 2013)	3D7	5.60 (3.26)
Asynchrous culture of blood stage parasites incubated with the drug for 48 hours and SYBR Green I dye was added and cultures incubated for 1 hour to allow DNA intercalation. The growth (fluorescence) was measured at 538 nm using a Spectra GeminiEM plate reader. (Gorka et al., 2013)	HB3[d]	2.19 (1.27)
	Dd2[e]	2.09 (1.22)

[a] W-2: Indochina clone is resistant to the antimalarial drugs CQ, pyrimethamine sulfadoxine and mefloquine
[b] D-6: Sierra Leone clone is susceptible to CQ, pyrimethamine and sulfadoxine but resistant to MQ
[c] K1: Resistant to CQ, pyrimethamine and sulfadoxine.
[d] HB3: Honduras, CQ-sensitive
[e] Dd2: Indochina, CQ-resistant*

Table 1B: In vitro activity of TQ against the clinical isolates (asexual parasites) of *P. falciparum* and *P. vivax*

Experimental design (Reference)	Source	IC_{50} µM (µg/mL)	
		Mean	Range
P. falciparum			
The test was based on the standard WHO in vitro micro-test technique that is based on measuring the drug-dependent inhibition of schizont maturation. The number of schizonts (3 nuclei) per 200 asexual parasites counted microscopically. After 24 hours of incubation, the cultures harvested and a thick film prepared from each well and stained with Giemsa. (Ramharter et al., 2002) Note: The region in Thailand is thought to harbor the most resistant forms of falciparum malaria in the world (high degree of resistance to CQ and antifolates, and reduced sensitivity to MQ and quinine.	Isolates from Thailand (n=43)	0.21 (1.22)	Not available
Clinical isolates collected in 1999 from malaria patients from Libreville (Gabon, Central Africa), Dielmo and Ndiop (Senegal, West Africa), and Djibouti (East Africa). Cultures incubated for 42 hours and growth measured by incorporation of ^{3}H-hypxanthine. (Pradines et al., 2006)	Isolates from Gabon (n=87)	4.62 (2.69)	0.6–33.1 (0.35-19.25)
	Isolates from Senegal (n=53)	5.06 (2.94)	0.5–20.7 (0.29-12.04)
	Isolates from Djibouti (n=22)	2.68 (1.56)	0.9-9.7 (0.52-5.64)
	Average (N=162)	4.43 (2.58)	0.5–33.1 (0.29-19.25)
Isolates collected from three sentinel sites in Ghana (Cape Coast, Hohoe and Navrongo, representing three distinct eco-epidemiological zones). Cultures with and without drug incubated for 72 hours and the activity measured by the SYBR Green 1-fluorescent based method. 63 isolates were collected from each region; > 85% of the 189 isolates were successfully cultured (n = approximately 160). (Quashie et al., 2013)	Isolates from Hohoe	0.11 (0.06)	0.03-2.72 (0.02-1.59)
	Isolates from Navrongo	0.05 (0.03)	0.03-0.14 (0.01-0.08)
	Isolates from Cape Coast	0.16 (0.09)	0.03-4.9 (0.02-2.85)
	Average (N ~ 160)	0.94 (0.55)	0.03-4.9 (0.02-2.85)
P. vivax			
Leucocytes were removed from 2 mL of whole blood parasitized with 1,000 to 50,000 ring stage *P. vivax* parasites/µL, cells washed and resuspended to a hematocrit of 40% in AB^{+} human serum; 50 µL of blood serum mixture (4% hematocrit) was incubated with different concentrations of TQ and other drugs until ≥50% of the ring stage parasites had matured to schizonts (24 to 36 hours). Smears were prepared, stained with Romanowsky stain and the number of normal schizonts per 200 asexual stage parasites counted. (Russell et al., 2003)	Isolates from Mae Sod malaria clinic, Thailand; patients successfully treated with CQ n =34).	(9.74)	

Table 1C: The activity of TQ against gametocytes of *P. falciparum* and *P. vivax*

Experimental design (Reference)	Strain (Clone)	IC_{50} µM (µg/mL)
P. falciparum		
Micronutrients were limited in culture for gametocyte induction. This was followed by incubation with N-acetyl glucosamine to eliminate asexual parasites and gametocytes magnet-purified and incubated with different concentrations (0.5X, 1X, and 5X the mean IC_{50} value obtained against asexual blood stage parasites) of TQ and other drugs for a 3-day duration initiated on Days 2, 5, 8, or 11 (corresponding to stages I and II, III, IV, and V). The activity was measured relative to the luciferase signal emitted by untreated gametocyte controls cultured in parallel. Drug-specific effects (represented as means ± SEM) were calculated for up to 12 days after the beginning of treatment at Day 0. The results show that both TQ and PQ were effective in inhibiting gametocyte development during early stages (I and II); however, TQ was not active against the late stages (mature gametocytes) at any of the concentrations tested whereas PQ was effective against the late stages (mature gametocytes) at the highest concentration tested i.e., 5X the IC_{50} value against the asexual parasites. (Adjalleya et al., 2011)	NF54 ($NF54^{pfs48/45}$, $NF54^{pfs16}$ and $NF54^{mal8p1.16}$ – 3 transgenic lines expressing stably integrated gametocyte-specific GFP-luciferase reporters)	Not determined
Activity of TQ was measured against the early and late gametocytes by high throughput screening assays. (Duffy and Avery, 2013)	NF54 ^{Pfs16}	Early gametocytes: 4.8 (2.79) Late gametocytes: 4.6 (2.68)
P. vivax		
Drug activity was determined by assessing oocyst and sporozoite development within the mosquitoes. Mosquitoes (*Anopheles dirus*) were fed for 30 minutes on 1 mL of blood, collected from patients, living in Western Thailand and had gametocytes in the blood. All unengorged mosquitoes were removed; engorged mosquitoes were maintained on a 5% sugar solution. At 4, 8, 11, and 16 days post-infection, mosquitoes were fed on uninfected mice that were administered different doses of TQ and other drugs, IP, 90 minutes prior to feeding of mosquitoes. All engorged mosquitoes were followed, by phase contrast microscopy, for the presence of oocysts in the midgut and sporozoites in the salivary gland on Days 10 and 21, respectively. The results show that TQ at a dose of 100 mg/kg was most effective when mosquitoes were fed on Day 4. TQ was effective in inhibiting sporozoite development at a dose of ≥25 mg/kg; PQ was not effective in inhibiting sporozoite development under the experimental conditions tested. (Ponsa et al., 2003)	Clinical isolates from patients living in Western Thailand (number of subjects not specified)	Not determined

References (Publications and Study Reports):

Adjalleya SH, Johnston GL, Li T, Eastman RT, Ekland EH, Eappen AG, Richman A, Sim BKL, Lee MCS, Hoffman SL, and Fidock DA. 2011, Quantitative assessment of *Plasmodium falciparum* sexual development reveals potent transmission blocking activity by methylene blue. *PNAS* 108: E1214-1223.

Duffy S and Avery VM. 2013, Identification of inhibitors of *Plasmodium falciparum* gametocyte development. *Malaria J* 12: 408 (https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-12-408).

Gorka AO, Jacobs LM, and Roepe PD. 2013, Cytostatic versus cytocidal profiling of quinolone drug combinations via modified fixed-ratio isobologram analysis. *Malaria J* 12: 232 (http://www.malariajournal.com/content/12/1/332).

Ponsa N, Sattabongkot J, Kittayapong P, Eikarat N, and Coleman RE. 2003, Transmission-blocking activity of tafenoquine (WR-238605) and artelinic acid against naturally circulating strains of *Plasmodium vivax* in Thailand. *Am J Trop Med Hyg* 69 (5): 542-547.

Pradines B, Mamfoumbi MM, Tall A, Sokhna C, Koeck J-L, Fusai T, Mosnier J, Czarnecki E, Spiegel A, Trape JF, Kombila M, and Rogier C. 2006, In Vitro activity of tafenoquine against the asexual blood stages of *Plasmodium falciparum* isolates from Gabon, Senegal, and Djibouti. *AAC* 50 (9): 3225-3226.

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, and Koram KA. 2013, A SYBR Green 1-based *in vitro* test of susceptibility of Ghanaian *Plasmodium falciparum* clinical isolates to a panel of anti-malarial drugs. *Malaria J* 12:450 (http://www.malariajournal.com/content/12/1/450).

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

Russell BM, Udomsangpetch R, Rieckmann KH, Kotecka BM, Coleman RE, and Sattabongkot J. 2003, Simple In Vitro Assay for determining the sensitivity of *Plasmodium vivax* isolates from fresh human blood to antimalarials in areas where *P. vivax* is endemic. *AAC* 47 (1): 170-173.

Study Report no. WRPD1: WRAIR *in vitro* screen for intrinsic anti-malarial activity.

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.

15.4.2. Summary of in vivo studies (animal models)

Summary of in vivo studies supporting the activity of TQ against different stages of *Plasmodium* species infecting rodents (Table 2A), nonhuman primates (Table 2B) and humans (Table 2C).

Table 2A: The activity of TQ in mice infected with sporozoites or parasitized erythrocytes of the rodent *Plasmodium* species

***Plasmodium* species/ strain (Reference)**	**Study summary**
Infected with sporozoites: Pre-exposure and post-exposure prophylaxis (Causal prophylaxis)	
P. berghei yoelii (Study report no. SGRD-UWM-B3)	Swiss ICR/HA strain of mice were infected with the sporozoites and treated with TQ 4 hours prior to challenge; mice were followed until Day 30. All untreated mice died between Days 7 and 15. The results show that TQ at a dose of ≥8 mg/kg administered S/C or orally was effective in preventing parasitemia and curing mice.
P. berghei - Luciferase expressing (Marcsisin et al., 2014)	C57BL/6 WT, CYP2D KO mice and humanized/CYP 2D6 knock-in mice were infected IV with 10^4 luciferase-expressing sporozoites (90% – 100% viability). Treatment with TQ was initiated one day prior to sporozoite inoculation (Day -1) for 3 days. D-Luciferin potassium salt, the luciferase substrate, was intraperitoneally inoculated into mice at a concentration of 200 mg/kg 15 min before luminescence analysis. All mice were followed for the progress of infection at 24, 48 and 72 hours by IVIS using the Xenogen IVIS-200 Spectrum (b) (4) IVIS instrument. Blood stage parasites were measured up to Day 31 post-inoculation by flow cytometry. Disease progression in both liver and blood was analogous in the WT, CYP2D KO and humanized/CYP 2D6 knock-in mice. TQ at a dose of 3 mg/kg was effective in preventing infection (liver and blood) in wild type mice but not in CYP 2D KO and humanized/CYP 2D6 knock-in mice thereby suggesting that replacing the CYP 2D gene cluster with human CYP 2D6 was not sufficient to fully restore the activity of TQ. However, at 2-times the higher dose, TQ was effective in preventing infection in liver as well as blood in 4/5 CYP2D KO/CYP 2D6 knock-in mice thereby suggesting that TQ is active in the presence of the CYP 2D gene cluster.
P. berghei transgenic ANKA strain - luciferase-expressing (Li et al., 2014)	C57BL/6 mice infected IV with 5 x 10^4 transgenic *P. berghei* sporozoites expressing the bioluminescent reporter protein luciferase. The viability of the sporozoites ranged between 87 and 100%. Oral treatment with different doses of TQ or PQ, by intragastric feeder, was initiated one day prior to sporozoite inoculation for 3 days. Mice were followed for the spread of infection by in vivo imaging system (IVIS) using Spectrum instrument at 24, 48, and 72 hours post sporozoite inoculation. For IVIS, the mice were administered 150 mg/kg luciferin, IP, and 3 minutes later, mice were anesthetized and positioned ventral side up in the IVIS, set to measure the abdominal area at the location of the liver from whole body imaging. In addition, blood stage infection was analyzed between Days 5 and 30 by flow cytometry. In untreated mice, the mean luminescence of liver increased approximately 17-fold from 24 to 48 hours (liver stage of *P. berghei* is 48 hours); at 72 hours, whole body luminescence was observed that was about 4-fold higher than at 48 hours suggesting that majority of the increase in luminescence observed was produced by blood stage parasites. This is consistent with the known 48-hour duration of the liver stage of *P. berghei* malaria model where parasites invade erythrocytes after the rupture of liver schizonts 48 hours post inoculation. In mice treated with TQ for 3 days (at a dose of ≥5 mg/kg) or PQ (at a dose of ≥25 mg/kg), no luminescence was observed, during the observation period, Also, no parasites were detected in the blood by flow cytometry.

***Plasmodium* species/ strain (Reference)**	**Study summary**
	A single dose of TQ (5 mg/kg) administered on Days -1 was protective in curing mice; however, when administered on Day 0, 4 of the 5 mice were not cured. A single dose of PQ (25 mg/kg) administered on Day-1 or 0 was not effective in curing mice.
P. berghei transgenic ANKA - luciferase-expressing (Milner et al., 2016)	C57BL/6 WT and CYP2D KO mice were infected with 10^4 sporozoites (viability 87-100%). Experimental design was same as summarized above (Marcsisin et al., 2014) except that treatment with TQ was initiated either on Day -1, 0 and/or 1. Also, asexual parasitemia and gametocyte count was performed on blood smears in addition to flow cytometry. The results show that in both WT and CYP2D KO mice, TQ, at a dose of 20 mg/kg, was effective in suppressing the IVIS signal when administered at Day -1, 0, and/or Day +1 of sporozoite inoculation. No parasites (asexual and gametocytes) were observed in the blood; no recrudescence was reported in any of the mice. Lower doses of TQ were less effective. PQ was not effective when administered on Day-1 prior to challenge.
P. y. yoelii (Study report no. WRPD2)	ICR/HA Swiss mice were infected IP, with 2.5 x 10^5 sporozoites and treatment with a single dose of TQ (80 mg/kg) was administered either S/C or orally on Day -21, Day-14, or Day -7. Blood smears were examined between Days 6 and 13 PI. The results suggest that TQ was effective in reducing parasitemia when administered 7 or 14 days prior to challenge; administration of TQ 21 days prior to challenge was less effective. 2 to 3 of the mice died in each of the groups which appears to be due to toxicity of the drug.
P. y. nigeriensis (Study report no. SGRD-UWM-B2)	TQ at a dose of 30 and 100 mg/kg administered S/C to CFW Swiss mice, 2 hours post challenge with 2.5 x 10^5 sporozoites (injected IP), was effective in suppressing parasitemia. Results not shown.
Infected with sporozoites: Radical cure	
P. berghei ANKA (WRAIR report)	C57BL/6 wild type and CYP2D KO mice were infected IV with 10^4 luciferase-expressing sporozoites (87% – 100% viability). A single dose of treatment with TQ or PQ was administered orally, on Day 4 PI. Mice were monitored by imaging for up to 72 hours and for 30 days by flow cytometry (parasitemia-asexual stages) and microscopy [asexual and sexual (gametocytemia) parasites] to assess the effect of treatment on erythrocytic infections. Disease progression in both liver and blood was analogous in the WT and CYP2D KO mice. Following IV sporozoite inoculation (Day 0), the presence of a liver stage infection was detected at 24h and 48h followed by an erythrocytic infection at 72h in both WT and CYP2D KO mice. Mortality or euthanasia due to morbidity occurred within approximately one week following infection. TQ (25 mg/kg) and PQ (40 mg/kg) were effective in reducing the development of parasitemia including gametocytemia in both WT and CYP2D KO mice.
P. berghei transgenic ANKA - luciferase-expressing (Milner et al., 2016)	C57BL/6 WT and CYP2D KO mice were infected with 10^4 sporozoites (viability 87-100%). Experimental design same as summarized above for the prophylactic study except that treatment was with 25 mg/kg dose of TQ on day 4 post-inoculation. The results show that both in WT and CYP2D KO mice, TQ, at a dose of 20 mg/kg, was effective in suppressing parasitemia. No parasites (asexual and gametocytes) were observed in the blood of 4 of the 5 mice. Lower doses of TQ were less effective. PQ was not effective when administered on Day 4 post challenge.
Infected with parasitized erythrocytic: Suppressive activity	

***Plasmodium* species/ strain (Reference)**	**Study summary**
P. berghei ANKA (Coleman et al., 1992)	ICR mice were infected with 10^6 parasitized erythrocytes and treated with TQ (25 mg/kg), IP, on Day 4 PI when gametocytes were most prevalent. Blood smears were prepared every other day for up to 18 days PI. All untreated mice died between Days 6 and 10 PI; mean parasitemia was as high as 49% on Day 8 PI. Macrogametocyte and microgametocyte rates in the control mice peaked on Day 4 PI at 0.30 and 0.13%, respectively. Gametocyte rates decreased rapidly following this peak, and gametocytes were not observed after Day 6 PI. Treatment with TQ increased survival time to >18 days. There was no effect on asexual parasites; macrogametocyte and microgametocyte rates increased on Day 8 PI (four days after treatment) and remained high for the remainder of the duration of the study. Sporontocidal activity was evaluated by allowing *Anopheles stephensi* mosquitoes to feed on *P. berghei*-infected mice for 15 minutes, 90 min after treatment with the drug. Mosquitoes were dissected either on Day 10 or 20-22 after infection to assess oocyts in the midgut or sporozoites in the salivary glands, respectively. Although there was no effect of TQ on ookinete, retarded development of oocysts as well as reduction in the number of oocyst and sporozoites was reported in the mosquitoes fed on TQ treated mice compared to the untreated mice. PQ was more effective in abolishing the development of the parasite within the mosquitoes.
P. berghei KEG 173 (Study report no. SGRD-UWM-B1)	ICR/HA Swiss mice were infected with 4 x 10^7 parasitized erythrocytes and treated IP, with a single dose of TQ on Day 3 PI when parasitemia is approximately 10-15%. Untreated mice died within 6 to 8 days. The results show that TQ, between doses of 20 and 160 mg/kg, was effective in improving survival.
WT-wild type; KO-knockout; PI-post-infection; S/C-subcutaneously; IP-intraperitoneally; IV-intravenously	

Table 2B: Summary of nonclinical studies supporting activity of TQ in nonhuman primates infected with *Plasmodium* species (*P. cynomolgi* and *P. fragile*) other than those infecting humans

***Plasmodium* species/ strain (Reference)**	**Study summary**
Infected with sporozoites (Causal prophylaxis)	
P. cynomolgi / NS (Milhous et al 1998)	Rhesus monkeys (*Macaca mulatta*) were infected with the sporozoites of *P. cynomolgi*. TQ doses of 0.1, 0.316 and 1.0 mg/kg/day were administered, in combination with CQ, for 7 days. However, the time of initiation of therapy was not specified. The authors state that CD_{50}s of 0.172 mg/kg/day demonstrated TQ to be 7.4 times more active than PQ as a tissue schizonticide. In another experiment, animals were challenged with sporozoites on Day 0 and drug was administered orally on Day -1, 0, and +1. Patency was successfully prevented with TQ at daily oral doses of 0.1, 0.316, 1.0 and 1.78 mg/kg. The causal prophylactic activity of the calculated ED_{50} of 0.124 mg/kg/day was 10.5 times more effective than PQ against pre-erythrocytic stages.
P. cynomolgi / M (DiTusa et al., 2014)	Rhesus monkeys were infected IV with $4.7x10^4$ to $6x10^5$ sporozoites of *P. cynomolgi*. Animals were treated orally for 3 days (Days -0, 0, +1) with TQ and other drugs. Efficacy was evaluated by blood smears in which parasitemia on thick and thin smears was assessed daily from Day 7 through Day 21, then 3 times per week for 4 weeks, then twice per week until Day 100 after the last day of treatment. Causal prophylaxis was defined as the absence of parasitemia up to Day 100 post-inoculation. The results show that TQ at a dose of 0.95 mg/kg was not effective in curing the animals although patency was delayed by 2 to 3 days. A higher dose (6 mg/kg) of TQ was effective in curing the monkeys. The number of monkeys in each group is small (n=2).
P. cynomolgi bastianelli (Study report no. WRPD3)	Rhesus monkeys were infected IV with sporozoites (inoculum concentration not specified) and treated orally with TQ on Days -1, 0, and 1. Blood smears are examined from Day 7 until Day 70 to observe patency. Primary peak parasitemia was obtained 7-10 days after patency in untreated control monkeys. Preliminary experiments were conducted using 0.95 mg/kg administered on Days -2, -1 or 0 of sporozoite challenge. Patency was successfully prevented in only one animal which had been given the drug on Day 0. This single dose regimen was increased to 2.84 mg/kg and administered on Day -5, -3 and 0 with patency successfully prevented on Days 0 (2 of 2 monkeys) and -3 (1 of 2 monkeys). The compound was tested at higher doses in subsequent experiments and a single dose of 5.68 mg/kg found to be fully protective when administered 3 days prior to sporozoite challenge. TQ prevented patency in 2 of 2 animals at 1.78 mg/kg/day, 2 of 2 animals at 1.0 mg/kg/day, 7 of 7 animals at 0.316 mg/kg/day, 1 of 7 animals at 0.10 mg/kg/day, and none of the 4 animals at 0.0316 mg/kg/day. TQ exhibits causal prophylactic activity with a calculated ED_{50} of 0.124 mg/kg/day x three days. This represents activity 10.5 times higher than PQ against pre-erythrocytic stages.
Infected with sporozoites (Radical cure)	
P. cynomolgi bastianelli (Study report no. SEATO 338)	Rhesus monkeys (*Macaca mulatta*) were infected with 10^6 sporozoites. A rapidly rising parasitemia developed after a 7-9 day prepatent period. TQ in combination with CQ were administered for 7 days, by nasogastric intubation, when the rising parasite count exceeded $5000/mm^3$ (typically Days 10-12). Blood smears were prepared daily through Day 20 and every 2 days thereafter. If there was no relapse within 20 days of the initial clearance of parasitemia, parasitemia was followed for an additional 80 days. If there was no relapse within this period, the experiment was terminated and the monkey was considered "cured".

***Plasmodium* species/ strain (Reference)**	**Study summary**
	The results show that tissue schizonticidal cures were achieved at dosages of 0.1, 0.316 and 1.0 mg/kg/day for 7 consecutive days by oral administration in combination with a completely suppressive blood schizonticidal regimen of CQ. TQ was effective against the persistent tissue stages of the parasite with a calculated CD_{50} of 0.172 mg/kg/day x 7 days. TQ was 7.4 times more active than PQ as a tissue schizonticide. PQ diphosphate cured 90% of monkeys, under the experimental conditions tested, when administered at a dose of 1.3 mg/kg per day for 7 days (1.0 mg/kg free base) in combination with CQ.
P. cynomolgi / NS (Study report no. SGRD-UWQ-J)	Rhesus monkeys were infected IV with $0.9x10^6$ – $3.3x10^6$ sporozoites. Administration of the test drug was initiated the day after the initial parasitemia reached 5000/mm^3 for 7 days. Parasitemia was determined in each monkey by blood smears, two times prior to inoculation, daily from Day 6 post-inoculation until 20 days after the last dose administered, then twice weekly until negative parasitemia was found for 100 days post treatment. During relapses or recrudescences of parasitemia, blood smears were made daily. Monkeys in which parasitemia was cleared by the drug, but then reappeared, were treated with CQ phosphate, orally, at a dose of 10 mg/kg for 7 days whether or not CQ was included in the original regimen. Any monkey that developed parasitemia after the CQ treatment were considered relapses and terminated from the study. The number of monkeys in each group were small (n=2). The results show that tissue elimination of the malarial parasite occurred in some of the monkeys treated with a single dose of ≥3.5 mg/kg TQ. Treatment with a single lower dose (1.75 mg/kg) of TQ in combination with CQ for 7 days was 100% effective in eliminating both blood and tissue forms of the parasites.
P. cynomolgi bastianelli (Dow et al., 2011)	Rhesus monkeys (*Macaca mulatta*) were infected with 10^6 sporozoites of *P. cynomolgi bastianelli* and blood smears prepared daily between Days 6 and 21 post-inoculation to measure parasitemia. Patency was consistently observed in all animals on Day 8. Oral treatment (by intra-gastric feeding tube) with TQ was initiated for 1 – 3 days, once parasitemia of 5000/µL blood was reached. After study Day 21, if blood smears remained negative, they were monitored 3 days/week for 4 weeks and then twice weekly until 100 days post treatment, after which the animals were radically cured i.e., elimination of both blood and liver stages. The results show that TQ alone at a dose of 6 mg/kg/day for 3 days was effective in conferring radical cure; lower doses of TQ were not effective in suppressing parasitemia. However, lower doses of TQ in combination with CQ were effective in conferring radical cure. CQ decreased parasite clearance time to 3 days when co-administered with TQ at 2 mg/kg/day for three days. At lower doses of TQ, CQ administered after initial TQ failure eventually resulted in radical cure. These data suggest that CQ compensates for the poorer blood schizonticidal effects of lower TQ doses. Anti-relapse activity of the minimum curative dose of TQ alone and in combination with CQ was determined. For this, 6 monkeys were administered TQ (0.6 mg/kg/day × 3 days) alone or in combination with CQ (24 mg/kg/day × 3 days) after a 10-day course of IM quinine to eliminate blood stage parasites (loading dose of 40 mg/kg base and followed by 20 mg/kg twice daily for 10 days; total dose 420 mg/kg) shown in pilot studies to eliminate blood stage parasites. All monkeys were negative by blood smear at the time of TQ and TQ/CQ dosing. The primary endpoint of the study was the proportion of radical cures observed in each group. The results show that radical cures were achieved in 6 of 6 monkeys administered TQ alone (0.6 mg/kg/day for three days) and 6 of 6 monkeys given TQ at the same dose combined with CQ (24

***Plasmodium* species/ strain (Reference)**	**Study summary**
	mg/kg/day for three days) following quinine treatment. Thus, the anti-relapse activity of 1.8 mg/kg TQ is not dependent on co-administration with CQ.
Infected with parasitized erythrocytes (suppressive activity)	
P. cynomolgi/B (Puri and Dutta, 2003)	Rhesus monkeys were infected IV with 10^5 parasitized erythrocytes and blood smears prepared daily to determine parasitemia. Oral treatment with TQ was initiated for 7 days when parasitemia reached approximately 5000/mm^3. Monkeys were followed until Day 70 after the end of treatment. Monkeys, which did not show recrudescence through Day 70, were recorded as cured. Monkeys, which developed recrudescence within 30 days after the end of treatment, were retreated with another drug or the next higher dose of the same drug upon attaining the required parasitemia level. It is noted that there was a rise in parasitemia 24 to 48 hours after the first dose. The results show that treatment with TQ at doses of 0.32 mg/kg/day and 1 mg/kg/day was effective in clearing parasitemia. However, recrudescence occurred in all the monkeys treated with the 0.3 mg/kg/day dose and 3 of the 12 monkeys treated with the 1 mg/kg/day dose. The highest dose (3.2 mg/kg/day) tested was effective in clearing parasitemia and no recrudescence was observed up to Day 70. PQ, at the same doses was not effective, in preventing recrudescence.
P. fragile/Ceylon (Puri and Dutta, 2003)	Experimental design was same as summarized above except that TQ treatment was initiated when parasitemia reached approximately 2000/mm^3. It is noted that there was a rise in parasitemia 24 to 48 hours after the first dose. The results show that treatment with 0.32 mg/kg/day was effective in clearing parasitemia; however, recrudescence occurred in all the monkeys. A dose of 1 mg/kg/day was effective in clearing parasitemia in all monkeys; recrudescence occurred in one of the 11 monkeys. The highest dose (3.2 mg/kg/day) tested was effective in clearing parasitemia and no recrudescence was observed up to Day 70. PQ, at the same doses was not effective, in preventing recrudescence.
NS-Not specified; IM=intramuscular; CD_{50}=50% curative dose	

Table 2C: Activity of TQ in nonhuman primates infected with parasitized erythrocytes (suppressive activity) of *Plasmodium* species (*P. falciparum* and *P. vivax*) that infect humans

***Plasmodium* species/ strain (Reference)**	**Study summary**
P. falciparum Uganda Pala Alto and the Vietnam Smith (DAMD 17-82-C-2186)	Panamanian monkeys (*Aotus trivirgatus*), were infected IV with 5 x 10^6 parasitized erythrocytes of either of the two *P. falciparum* strains (monkey adapted): • Uganda Pala Alto strain (sensitive to CQ and quinine, RIII resistant to pyrimethamine). • Vietnam Smith strain (RIII resistant to CQ, pyrimethamine and quinine). TQ was administered by gastric intubation for 3 days; time of treatment initiation was not specified. Giemsa stained blood smears were prepared daily to evaluate parasitemia. Once parasitemia had cleared, blood films were made and examined twice weekly until a total of 100 negative days had been recorded. If recrudescence occurred, blood films were obtained daily. The results show variability in response to treatment with TQ, amongst the different monkeys, against the two strains of *P. falciparum*. At a dose of ≥4 mg/kg for 3 days TQ was effective in reducing parasitemia; however, doses of ≥16 mg/kg were more effective in clearing primary infections and recrudescence.
P. vivax / Chesson (DAMD 17-82-C-2186, 1983)	Experimental design was same as summarized above for *P. falciparum*; Chesson strain used for infection was sensitive to CQ, pyrimethamine, and quinine. The results show variability in activity of TQ. At a dose between 1.0, 4.0, 16.0, and 32.0 mg/kg for 3 days, TQ was effective in reducing parasitemia. However, cures were reported at a dose of ≥16 mg/kg for 3 days.
P. vivax / AMRU-1 (Cooper et al., 1994)	Splenectomized *Aotus* monkeys were infected IV with 5 x 10^5 parasitized erythrocytes of a CQ resistant (AMRU-1) strain of *P. vivax* that was adapted in monkeys and previously isolated from an Australian Army serviceman who acquired the infection in Papua New Guinea. Thick and thin blood smears were prepared daily to measure parasitemia. All the six monkeys were parasitemic by Day 7 post-inoculation. When the infections were established, with parasite densities >500/mm^3, the monkeys were treated orally with TQ (3 monkeys were administered 0.8 mg base/kg/d for 3 days and 3 received 3.2 mg base/kg/d for 3 days). The results show that the activity of TQ was slow and higher dose of TQ was more effective in decreasing parasitemia. Recrudescence was observed on Day 107 in one monkey treated with the low dose of TQ; this monkey had the slowest clearance of the parasites.
P. vivax / AMRU-1 (Obaldia et al., 1997)	Rhesus monkeys were infected IV with 5 x 10^6 erythrocytic parasites of a CQ resistant stain (AMRU 1) of *P. vivax*. The experimental design was same as summarized above (Cooper et al., 1994). The results show that treatment with TQ at a dose of 3 mg/kg for 3 days was effective in suppressing parasitemia; however, recrudescence occurred between Days 15 and 25. Higher doses (9 and 36 mg/kg) of TQ were effective in curing animals. Low dose (0.9 mg/kg) TQ in combination with CQ (30 mg/kg) were suppressing parasitemia but animals were not cured. CQ alone was not effective.

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15.4.3. Parasitological assessments

Parasitological assessments were based on either blood smears or by PCR.

A: Parasitological assessment by blood smears

Parasitological assessments, based on blood smears for subjects enrolled in Studies 030, 033, 043 and 045, include identification of *Plasmodium* species and measurement of parasitemia by Giemsa stained thick and/or thin blood smears (Table 1A).

Table 1A: Parasitological assessments by blood smears in clinical studies 030, 033, 043 and 045 to evaluate prophylaxis of TQ

Study ID	Details of the method and quality control
030	***Blood smears:*** Duplicate thick and thin smears prepared using EDTA blood. Asexual stage parasites and gametocytes counted in 200 high power fields reported as the number of parasites per 500 white blood cells. If the slide obviously contained parasites, only 50 fields may have been counted. Duplicate smears were read by two separate microscopists blinded to the others' results. A 3rd reader was assigned to collate the results of the two readers. In the event of a positive/negative discordance in readings of the two microscopists, a third microscopist was utilized (senior technician). The third "tie breaker" slide reading was used to confirm positive or negative parasitemia from the initial slide that was reported negative. ***Quality control (QC):*** QC slides were stained to make sure stain is appropriate and that the colors are distinctive. The slides were scanned for the presence of debris. QC slides were read each day staining occurred. ***Discrepancies in results:*** The results of the slide readings from Kenya and the re-reads from US Navy's Naval Medical Research Unit (NARU-2) were compared and discrepancies identified by the Applicant (b) (4) Subsequently, number of the discrepant slides plus a selection of positive slides, were shipped to Professor (b) (4) for morphological assessment of any parasites found. The Applicant states that *only 19* of 113 (16.8%) "positive" Kenyan slides were, in fact, positive for malaria parasites. This was due to lack of training, experience and/or motivation, inadequate supervision, and inadequate microscopes or microscopic illumination.
033	***Blood smears:*** Thick and thin blood films, prepared from the venous blood sample or by finger prick, and stained with Giemsa. For subjects presenting at any time during the prophylactic phase with signs and symptoms suggestive of malaria, blood smears were to be read immediately by microscopists at the study site. In these cases, serial confirmatory slides were to be taken and read over at least 3 consecutive days following the onset of signs and symptoms until *Plasmodium* spp. were identified or an alternative diagnosis was made. All slides were read separately by two microscopists, each of whom was 'blinded' to other reader's result. A total of 200 high-power fields were viewed before a sample was declared negative. However, where symptoms were present, more than 200 fields were read to confirm the diagnosis if necessary. Parasite counts were expressed per 500 white cell counts. In the case of a disagreement between Reader I and Reader 2 on the reading of a slide, the slides were to be read by a third microscopist (the 'Arbitrator'). The Arbitrator reading was taken as final. **QC: For internal quality control,** the quality of each prepared thick and thin film was assessed at the time of microscopic examination. Any slide that was inadequately spread, fixed or stained was prepared again until a slide of an acceptable standard was produced. Before staining a second set of thick and thin films, the factors influencing the quality of smears such as the pH of the buffer,

Study ID	Details of the method and quality control
	quality of the stain and staining time were considered. External quality assurance **was performed at** (b) (4)
043	Thick and thin smears, prepared from blood collected by finger prick, were Giemsa stained and asexual parasites counted per 200 white blood cells. A blood slide was considered negative after an examination of at least 200 oil immersion fields. All slides were read by two microscopists who were blinded to one another's readings. If both microscopists agreed that a given slide was positive, a second sample was to be quickly obtained from the subject for a confirmatory, thick film. If the two microscopists agreed that the second, confirmatory thick film was positive, then that subject was to be classified as a prophylactic failure. Subjects whose first slide was positive but whose confirmatory smear was negative within 24 to 72 hours were not counted as a prophylactic failure and continued to receive study medication. Disagreements on either the first or confirmatory slides between the two microscopists were to be adjudicated by the senior technologist present.
045	Thick and thin blood films were prepared in duplicate, from blood collected by finger prick, and transported to the laboratory on the day of collection. Thick blood films were Giemsa stained and read by a field (junior) microscopist. Parasitemia with *Plasmodium* sp. was defined as at least one asexual stage parasite per 200 fields read at 1000x magnification and results recorded either as positive for the appropriate species, questionably positive [if findings were not typical of a positive smear but were possibly consistent with 'drug-affected' parasites (i.e. bare nuclei, abnormal appearing cytoplasm)], or negative. Questionably positive smears were recorded as negative for the primary efficacy analysis. Positive films were read by a second field microscopist and, when possible as a QC step, were to be checked by the senior investigator on site. In practice, approximately half of the positive smears were checked by the principal investigator (Braden Hale). A prophylaxis failure, for the purposes of the primary endpoint, was defined as a subject where both field microscopists readings were positive for at least one malarial blood smear – a 'single positive' blood smear. Confirmed parasitemia was defined as two consecutive positive blood smears, as read by two field microscopists. All routine slides from were archived at the (b) (4) Slides read as positive at least once were stored as source data in zip-lock bags with desiccation granules to prevent deterioration. The duplicate slides were saved unstained for later confirmation if required and in case slide boxes were lost or damaged. Field (junior) microscopists were required to pass an examination in the assessment of malarial smears.

B: Parasitological assessment by PCR

For Study TQ-2016-02, parasitological assessments were based on real time 18S quantitative (q) PCR for the detection of *P. falciparum*. The PCR assay was performed at (b) (4) Clinical specimens were tested in the same laboratory.

The assay targeted three specific sites on 18S rRNA gene across the genome of *P. falciparum* (chromosome 1, 11 and 13) and utilized a fluorescent TaqMan hydrolysis probe to detect template accumulation in a PCR reaction. The calibrator used was produced using a ring-stage

synchronous culture of the *P. falciparum* 3D7 strain with red blood cells containing a single ring stage parasite. The concentration of template used as the calibrator in clinical trials was calculated using ethidium bromide stained culture counted using fluorescence-activated cell sorting (FACS) and estimated to be 3.1909 x 10^6 parasites/mL. Six ten-fold dilutions ranging from 10^6 to 10^1 of this calibrator formed the standard that was used to create the standard curve each time testing of clinical specimens was performed. Also, testing of two negative controls (water or uninfected human blood nucleic acid extracts) were included for testing each time. Calibrator material was stored in uninfected human blood nucleic acid extract at -80°C. Each qPCR run included the standard curve and two negative controls with study samples.

DNA was extracted from 2 mL of whole blood with EDTA, using QIAamp DNA Mini kit, and stored at -80°C until PCR reactions performed. A known concentration of equine herpes virus (EHV) was added to each specimen to monitor the efficiency and reliability of the extraction process (assay control). The PCR primers and cycling conditions used were as follows:
The reaction mix consisted of the Quantitect Probe PCR Mix (b) (4) and the following primers and probe:

- Forward primer (PerFAL F): 5'-CTTTTGAGAGGTTTTGTTACTTTGAGTAA-3' (10 pmol)
- Reverse primer (PerFAL R): 5'-TATTCCATGCTGTAGTATTCAAACACA-3' (10 pmol)
- Probe (PerFAL-Pr): 5'-FAM-TGTTCATAACAGACGGGTAGTCATGATTGAGTTCA-BHQ1-3'(4 pmol)

Evaluation of extraction and amplification efficiency to monitor for the presence of inhibitors was routinely assessed through inclusion of an Equine Herpes virus (EHV) control and EDTA containing blood; use of some of the analytical inhibitors, such as heparin, was avoided.

The parameters assessed to ensure the suitability of the method for the intended use of the assay include reportable range, limit of detection (LoD), precision (intra-assay variability and inter-assay variability), specificity, accuracy, reference interval, assay controls, and stability. Some of the parameters to support the Applicant's context of use are summarized in Table 1B.

Table 1B: Summary of the parameters assessed and performance of the PCR assay to support the context of use.

Parameter assessed	Details	Results
Reportable range (the range over which the laboratory can establish the accuracy of the instrument or test system measurement response)	Nine standards (32, 64, 160, 319, 638, 3191, 31909, 319090 and 3190900 parasites/mL), run on three consecutive days with seven technical replicates (21 replicates for each concentration level in total except for the 319090 parasites/mL standard, where 22 replicates were included) and the negative control.	The quantification cycle (Cq) was between 3.19 x 10^6 and 3.19 x 10^1 estimated parasites/mL of whole blood. Variability in mean Cq values was low and met the acceptance criteria (CV <15%).
Limit of detection (analytical sensitivity i.e., the lowest template concentration that	• Assay standards from 34 runs were performed during a pilot clinical study in healthy volunteers exposed to malaria infection. Serial dilutions of the calibrator material (nucleic acids extracted from 3.19 x 10^6 *P. falciparum* parasites/mL were	The data support ULoQ to be 3.19 x 10^6 estimated parasites/mL in whole blood. The data supports LLoQ and LoD to be equivalent i.e., 111

Parameter assessed	Details	Results
could be consistently detected in ≥95% of malaria infected blood samples tested with acceptable precision)	performed to prepare assay standards spiked into a matrix consisting of uninfected human genomic DNA extracts (human genomic DNA obtained from whole blood from volunteers without malaria); the spiked samples reflected the observed range of parasitemia in IBSM clinical studies. Replicates (n=7) of each spiked concentration as well as negative controls (n = 7–9; uninfected human blood/genomic DNA extract) were analyzed from assays conducted over 3 days by the same operator using the same lot of reagents. The results, by probit analysis, showed that a 100% detection rate for all standard concentration levels >64 parasites/mL. The detection rate dropped to 27% at the lowest standard level tested (6 parasites/mL). The estimate of LoD was determined as 134 (95% CI 70, 472) parasites/mL. • A dilution series of 9 rather than 6 spiked sample controls of known concentration, with greater representation at the lower parasite/mL range were tested.	estimated parasites/mL in whole blood.
Precision [Repeatability (intra-assay variability) and reproducibility (inter-assay variability) and intermediate precision (intra-laboratory variations i.e., different days, different technicians, and different equipment.)].	*Intra-assay variability:* A dilution series (same as that used for determining reportable range) of the *P. falciparum* 3D7 strain ring-stage synchronous culture calibrator material was used and run on 3 different days with 7 technical replicates and the negative control. *Inter-assay variability:* A dilution series (same as that used for determining intra-assay variability) was prepared. In addition, two negative controls and clinical samples were analyzed. Overall, testing included 661 qPCR runs across 11 clinical studies and 20 cohorts. As the calibration methods for the assay were refined between 2012-2013, the data were analyzed for clinical studies conducted between 2012 to 2015 and separately for studies conducted from 2013 to 2015. Acceptance criteria for intra- and inter-assay variability were mean values to have CV <15%, except at LLoQ, where CV <20%. *Intra-laboratory variability:* Based on comparison of results from assays run in real time and those run on the same samples retrospectively to derive malaria parasitemia and slope values for estimation of parasite multiplication and clearance rates. This was based on data from 16 clinical studies.	*Intra-assay and inter-assay variability:* The applicant states that negative controls were found to be PCR positive on rare occasions; when this occurred, whole runs were re-analyzed. The false negative results were ascertained to be due to operator error, unstable reagents and contamination. This is acceptable as the negative controls were negative for the assay runs when clinical specimens were tested. False negatives were recorded at the lowest two standard concentrations; detection of 32 and 64 estimated parasites/mL failed in 9 (43%) and 4 (19%) replicates tested, respectively. Mean Cq and intra-assay SD increased inversely as concentration of the standard decreased, with SD, pooled for all standards, of 0.456. % CV was low (<2% for all standard levels except 64 estimated

Parameter assessed	Details	Results
		parasites/mL, where CV=2.25%) and met the acceptance specifications defined for this parameter. By linear regression parameter estimates, the mean Cq values and inter-assay SD was shown to increase inversely with decreased concentration of standards for both datasets; an overall SD was 0.754 for studies conducted between 2012-2015 and an SD of 0.658 for studies conducted 2013 - 2015. Relative variability (% CV) was low (<3%) and stable across the entire range of parasite/mL levels represented in the assay standard curve. Acceptance specifications were met. *Intra-laboratory variability:* Both parasitemia values and parasite multiplication and clearance rate estimates were consistent between the retrospectively performed and daily assays.
Specificity (Ability of an assay to detect only the intended target in the presence of components that may be expected to be present)	The primer and probe sequences of the *P. falciparum* 18S rRNA nucleic acid target were compared to sequences available on publicly accessible databases (BLAST, NCBI; https://blast.ncbi.nlm.nih.gov/Blast.cgi). Also, confirmed positive blood samples for *P. vivax, P. malariae,* and *P. ovale* from the field or experimental cultures were tested. The results calculated as the percentage of negative *P. falciparum* samples that were correctly identified as negative by the QPID qPCR assay. Interference due to substances present in human blood samples (specifically heparin and hemoglobin) that might potentially interfere with/inhibit the PCR reaction was minimized by using EDTA. Note: Cross-reactivity with pathogens, especially protozoans such as *Babesia*, was not measured.	*In-silico* analysis revealed the QPID qPCR assay is specific only to the *P. falciparum* 18S rRNA gene (100% maximum identity/100% coverage) and no cross-reactivity was observed with other malaria species or human genomic DNA. No cross-reactivity was observed with the three human malaria species (*P. vivax, P. malariae,* and *P. ovale*) suggesting specificity of the *P. falciparum* specific qPCR assay.
Accuracy [Closeness of the agreement between the results of a single measurement	The samples tested were part of an EQC study conducted among 5 laboratories. The comparison was made between parasitemia based on microscopy and qPCR completed in Vietnam - 357 samples from 22 subjects were analyzed.	All 357 samples were positive by both microscopy and PCR; however, qPCR results were lower on average (5.57 log10 units) compared to those

Parameter assessed	Details	Results
and the true value of the analyte - International Organization for Standardization (ISO-2003)].	*Note*: The results of EXQ are less relevant for the Study TQ-2016-02 as the testing of clinical specimens was performed in the same laboratory where the assay was standardized.	reported by microscopy (5.82 log10 units). Lower parasitemia count was thought to be due to loss of sample integrity occurring because of the delay in analysis of samples, after storage, transport and additional processing of samples, compared to results obtained in real time with microscopy and the external qPCR method performed in Vietnam and other laboratories. No false negative results were obtained.
Reference interval	Samples from healthy, malaria naïve subjects tested.	No cross-reactivity with human genomic DNA was reported. The reference interval for the general population who do not have malaria is defined as not detected or negative. All measured template values, including those below the LoD, were recorded for research purposes. Values below the level of detection are reported as <LoD for diagnostic purposes.
Assay controls (This is to assure appropriate amplification)	All samples were spiked with EHV.	Assay amplification was appropriate
Stability	Internal standards were routinely prepared every 4-8 months from frozen stocks, stored at -80°C in low-bind DNA tubes to prevent nucleic acid degradation. The temperature of the -80°C freezers was monitored and recorded.	Stability of internal assay standards prepared fresh after storage at -80°C in low-bind DNA tubes showed a mean difference in Cq values between old and new standards of -0.03 (95% CI -0.23, 0.17; p=0.75; paired samples t-test) supporting good consistency in performance over time.
LLoQ-lower limit of quantitation; ULoQ-upper limit of quantitation; SD-standard deviation; EQC-external quality control; EHV-equine herpes virus.		

The performance of the qPCR assay based on the parameters measured does support the specificity of the assay for *P. falciparum* and quantitating the parasites in blood. The upper and lower limits of quantitation was determined to be 3.19 x 10^6 estimated parasites/mL and 111 estimated parasites/mL, respectively, in whole blood. The lower limit of quantitation was established as equivalent to the LoD. Although estimated parasite <111/mL were detected by

the assay, there was variability and the detection rate dropped. The external quality control assurance study showed that qPCR results were lower on average (5.57 log10 units) in the Applicant's laboratory compared to those reported by microscopy (5.82 log10 units) and PCR in the laboratory in Vietnam and other laboratories. Lower parasitemia count was thought to be due to loss of sample integrity occurring because of the delay in analysis of samples, after storage, transport and additional processing of samples, compared to results obtained in real time with microscopy and the external qPCR method in Vietnam and other laboratories. The results of external quality control are less concerning for the Study TQ-2016-02 as the testing of clinical specimens was performed in the same laboratory where the assay was standardized.

The applicant had proposed an endpoint to measure efficacy based on the following criteria:

> qPCR parasitemia of >5,000 asexual blood stage estimated parasites/mL accompanied by a clinical symptom score of >6 OR parasitemia of >5,000 estimated asexual blood stage parasites/mL and 2-fold increase within 48 hours.

The data supporting the threshold of >5,000 asexual blood stage estimated parasites/mL for evaluating efficacy was not available for review. However, the assay does support the criteria for subjects to be diagnosed as parasitemic or aparasitemic based on LoD as well as comparing the alteration in parasite count at different time intervals.

16 Division Director (Clinical)

Concur with the review team's assessment.

17 Office Director (OAP)

Concur with the review team's assessment.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY F DIBERNARDO
08/08/2018

EDWARD M COX
08/08/2018

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT # 11726

Consultant Reviewer:	Gregory M. Dubitsky, MD Medical Officer Division of Psychiatry Products
Consultation Requestor:	Sheral Patel, MD Medical Officer Division of Anti-Infective Products
Subject of Request:	NDA 210607/Arakoda (tafenoquine) Tablets
Date of Request:	June 18, 2018
Date Received:	June 18, 2018
Desired Completion Date:	July 2, 2018

I. Background

The Division of Anti-Infective Products (DAIP) is reviewing NDA 210607 for the administration of Arakoda (tafenoquine) tablets in the prevention of malaria in patients (b) (4) A related drug approved for the prophylaxis of malaria is mefloquine, which was approved as Larium in 1989. Serious psychiatric adverse effects were associated with mefloquine and led to a boxed warning to highlight this risk. Psychiatric adverse reactions have included anxiety, paranoia, depression, hallucinations, suicidal ideation, and completed suicide.

DAIP requested that the Division of Psychiatry Products (DPP) provide its assessment of the safety of tafenoquine from a psychiatric perspective. I completed a consultative review on May 18, 2018, that determined the incidence of psychiatric adverse events (AEs) from patients in five clinical trials who were treated with the proposed regimen of tafenoquine. Three of the five trials excluded patients with a history of a psychiatric disorder. None of these trials systematically assessed psychiatric symptoms. Findings from my review included the following:

- the largest trial was a randomized, double-blind, mefloquine-controlled study of malaria prophylaxis in Australian Defense Force (ADF) soldiers who were deployed on a peacekeeping mission to East Timor (Study 33). In this study, there was a slightly higher incidence of any psychiatric AE among patients in the tafenoquine arm (5.5% of 492 patients) compared to the mefloquine arm (4.9% of 162 patients).

- in a randomized, double-blind, placebo-controlled study conducted in civilians and non-deployed military personnel in the U.S. and U.K. (Study 57), the incidence of any psychiatric AE was approximately the same (about 5%) in the tafenoquine and placebo treatment arms. This study was much smaller than Study 33 (81 vs. 492 patients on tafenoquine) and had a much lower completion rate (65% vs. 96%).
- in the pool of the remaining three trials (Studies 30, 43, and 45, all conducted in Africa), the incidence of any psychiatric AE was highest in the mefloquine arm (2.0% of 147 patients), lowest in the placebo arm (0.4% of 256 patients), and exactly between those two groups in the tafenoquine arm (1.2% of 252 patients).
- in the pool of all five trials, the incidence of any psychiatric AE was slightly higher among the 825 tafenoquine-treated patients compared to the 309 mefloquine-treated patients (4.1% vs. 3.6%) and much higher than among the 295 placebo-treated patients (1.0%).
- among tafenoquine-treated patients in these five trials, there was one serious psychiatric AE (alleged poisoning to attempt suicide in a Kenyan male with marital problems) and one dropout due to depression in a soldier from Study 33. One mefloquine-treated patient dropped out due to severe anxiety. No placebo patients had a serious psychiatric AE or dropped out for such an event.
- among patients in other trials, three patients with a history of psychotic illness experienced a psychotic episode after receiving a higher than proposed dose of tafenoquine.

I concluded that, in so far as there were no deaths or other serious psychiatric AEs that could be attributed directly to tafenoquine exposure, tafenoquine appeared to be reasonably safe for up to six months of continuous dosing from a psychiatric standpoint. However, there are two significant limitations to this conclusion. First, there was no systematic monitoring for psychiatric symptoms during any of the five safety studies and, therefore, the reported psychiatric AE rates may substantially underestimate the true incidence. Second, the database was not sufficiently large to confidently rule out the risk of serious psychiatric AEs that might occur at a low rate comparable to reported rates with mefloquine (1/607 to 1/20,000). In addition, I noted that the risk of any psychiatric AE with tafenoquine appeared to be roughly comparable to that with mefloquine based on reporting rates from Study 033 and the pool of the five key studies.

DAIP held a Late Cycle Meeting (LCM) with the Applicant on June 12, 2018. During this meeting, the Applicant presented a series of slides to clarify their perspective on the psychiatric AEs observed during the tafenoquine development program. DAIP has again requested consultation with DPP for any comments regarding psychiatric AEs or labeling based on the Applicant's slide presentation.

II. Material Reviewed

I reviewed the following materials in completing this review:

- Applicant's slides presented at the LCM and submitted on June 19, 2018 (NDA 210607 Sequence #0062). These slides are provided as an attachment to this review.
- Applicant's response to DPP recommendations for psychiatric safety monitoring in an ongoing study (NDA 210607 Sequence #0063).
- Adverse Event and Medical History Analysis Datasets (ADAE.xpt and ADMH.xpt) (NDA 210607 Sequence #0001).

III. Review of Clinical Data

I reviewed the 43 slides presented by the Applicant and have comments on the following slides.

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/s/

GREGORY M DUBITSKY
06/26/2018

MITCHELL V Mathis
06/26/2018

Date: May 24, 2018
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Team Leader
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Gregory DiBernardo, Regulatory Project Manager, Division of Anti-Infective Products
Subject: Renal safety of tafenoquine

Background

Tafenoquine is an 8-aminoquinoline antimalarial agent that is an analog of primaquine, an approved antimalarial agent.[1] On December 8, 2017, the Division of Anti-infective Products (DAIP) received an NDA for tafenoquine for the prophylaxis of malaria in adults for up to 6 months of continuous dosing. In preclinical rodent studies, tafenoquine was associated with proximal tubular necrosis and dilation that was believed to be related to hemolysis. Because of the potential for renal toxicity with tafenoquine, data from Study 033, one of the key clinical trials in support of the proposed indication, was reviewed by a panel of clinical nephrologists who recommended additional renal testing for some trial subjects. In addition, the applicant conducted an additional study, Study 057, to assess the renal safety of tafenoquine. DAIP has requested input from the Division of Cardiovascular and Renal Products on the renal safety of tafenoquine in these studies and comment on whether renal monitoring is warranted for patients taking tafenoquine.

Materials Reviewed

1. Clinical Study Reports for Trials 033 and 057
2. Draft prescribing information for tafenoquine
3. Summary of Clinical Safety
4. Integrated Summary of Safety
5. Prescribing information for primaquine and mefloquine
6. Select subject laboratory values

Study 033

Overview of Study Design

Study 033 was a randomized, double-blind, double-dummy study to evaluate safety, tolerability, and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria. The first phase was a "prophylactic phase" in which 654 healthy male and female Australian Defence Force (ADF) soldiers aged 18 to 55 years deployed to East Timor were randomized 3:1 to tafenoquine 200 mg (n=492) or mefloquine 250 mg (n=162) each dosed daily for three days then weekly. Subjects were excluded for any clinically significant medical history, concurrent conditions, or laboratory tests. Subjects who completed 26 weeks of treatment then entered a 24-week "relapse follow-up phase." At the end of the deployment, subjects randomized to mefloquine received primaquine 15 mg bid x 14 days. Subjects randomized to tafenoquine received placebo.

Study visits occurred at Weeks 4, 8, 16, and 26, and 12 weeks after the end of treatment. Serum creatinine was assessed at screening, on Day 2, and at each study visit. It is not clear whether urinalysis or urine protein was assessed regularly.

[1] To our knowledge, renal toxicity has not been described for primaquine.

Renal Results

Baseline Characteristics and Disposition

The mean age of subjects in the tafenoquine group was 25.4 (±5.3) years. The mean baseline serum creatinine was 1 mg/dL. A total of 96% of tafenoquine and 97% of mefloquine subjects completed the trial.

Renal Findings

As shown in Table 1, mean serum creatinine increased slightly from baseline in both groups with the greatest increase in mean serum creatinine in the tafenoquine group, 16.2 umol/L (0.18 mg/dL; standard deviations not provided), seen between Weeks 2 and 6. More subjects in the tafenoquine group had an increase from baseline in serum creatinine of >25% at some timepoints during the study including at the final visit (11.3% vs. 7.1%). The differences had resolved by the follow-up visit (6.0% vs. 8.2%). Of note, mefloquine is not known to have renal toxicity.

Table 1: Change from baseline in serum creatinine

Creatinine							
	Base-line (umol/L)	Days 0-10	2-6 weeks	7-12 weeks	13-21 weeks	22-30 weeks	Follow-up
Mean change in creatinine from baseline							
Tafenoquine	88.7	6.1	16.2	13.2	9.6	12.1	7.0
(N)	479	475	474	477	468	454	454
Mefloquine	88.7	5.3	10.7	8.0	5.0	8.8	6.7
(N)	156	152	155	156	155	151	152
Percentage subjects with creatinine increased from baseline value (+25%)							
Tafenoquine	n/a	5.4% 26/480	18.9% 92/487	16.3% 80/490	8.7% 42/481	11.3% 53/467	6.0% 28/467
Mefloquine	n/a	6.5% 10/155	9.4% 15/160	8.1% 13/161	10.0% 16/160	7.1% 11/156	8.2% 13/158

Source: Applicant, Clinical Study Report for Study 033, Table 42.

Reviewer's comment: It is not clear whether the observed increases in serum creatinine >25% above baseline were transient or persistent.

No renal adverse events were reported during the study.

Additional Renal Follow-up

After Study 033 ended, a panel of clinical nephrologists reviewed the renal data and "concluded that, while tafenoquine did not seem to be nephrotoxic, there was a trend towards increased creatinine values during treatment that warranted further investigation." As a result, 183 (147 tafenoquine and 36 mefloquine subjects) of 246 subjects with a serum creatinine ≥0.23 mg/dL above baseline at the end of the prophylactic and/or follow-up phase underwent additional testing. This accounted for 98% of subjects who were still in the ADF and were not serving overseas. Subjects with a confirmed 1) creatinine above the upper limit of normal, 2) creatinine ≥0.03 mmol/L (0.34 mg/dL) above baseline, or 3) "significant urinalysis finding" defined as greater than "trace" proteinuria on follow-up were to be referred to a nephrologist.

According to the applicant, no subject had a creatinine value above the upper limit of normal. Two tafenoquine (b) (6) and one mefloquine subject had a persistent creatinine elevation of ≥0.03 mmol/L (0.34 mg/dL). Five tafenoquine (b) (6) and two mefloquine subjects had persistent "clinically significant urinalysis" findings. These ten subjects were referred for

renal evaluation. "All subjects referred for renal work-up were examined by a clinical nephrology consultant, who performed whatever follow-up assessments they felt to be necessary. In all cases the subjects were found not to have suffered long term chronic renal injury." The applicant provided the creatinine results for these subjects (see appendix). Although there is some variability in creatinine readings, there are no obvious trends suggesting a progressive decline in renal function. We could not locate narratives of these cases or information regarding any additional evaluation performed by the clinical nephrology consultant.

Study 057

Study Design

Overview

Study 057 was a randomized, double-blind, placebo-controlled study to evaluate the renal and ophthalmic safety and tolerability of tafenoquine in 120 healthy males and females aged 18 to 55 years with no history of renal disease or abnormal renal function test results at screening. Subjects were randomized 2:1 to tafenoquine 200 mg (n=81) or matching placebo (n=39) once daily for 3 days then once weekly for 24 weeks total. The primary renal endpoint was the mean change from baseline in iothalamate GFR assessed at 24 weeks. The primary analysis was a non-inferiority analysis with a margin of -15% of the mean iothalamate GFR value at baseline for all subjects, which was calculated to be -0.247 mL/s/1.73m^2 (or 14.8 mL/min/1.73m^2).

Reviewer's comment: It is not clear how the non-inferiority margin was selected. A decline in GFR of ~15 mL/min/1.73 m^2 over 6 months would be a large decline if it reflected an irreversible loss of renal function.

Renal Monitoring

Study visits occurred at screening, baseline, Days 1 and 2, Weeks 3, 6, 12, 18, and 24, and 12 weeks after the end of treatment. Serum creatinine, urinalysis, urine protein to creatinine ratio, and urine microscopy were assessed at each visit. Iothalamate GFR was measured at baseline, Week 12, and Week 24.

If creatinine increased by ≥0.3 mg/dL from baseline to any post-baseline visit, an additional sample was to be taken within three days. If there was greater than trace proteinuria or hematuria on urinalysis, the test was to be repeated twice more. If the repeat serum creatinine remained ≥0.3 mg/dL above baseline or the proteinuria or hematuria persisted for three measurements, iothalamate GFR was to be measured.

During treatment, subjects with a decrease in iothalamate GFR of ≥20% but <25% were to have a repeat measurement within 1 week. If iothalamate GFR was decreased by ≥25% from baseline at any point, study drug was to be held and the measurement was to be repeated. If the repeat iothalamate GFR was decreased from baseline by ≥20%, then treatment was to be permanently discontinued and the subject was withdrawn from the study.

Analysis Populations

The "safety population" included all subjects who received at least one dose of study medication.

The "renally evaluable population" included all subjects in the safety population who "were compliant with study medication and did not violate any aspect of the protocol to an extent that could affect the assessment of renal function." "Compliant" was defined as taking all scheduled loading doses and missing no more than five maintenance doses.

The "modified observed case dataset" included data for subjects with iothalamate GFR measures at both baseline and Week 24 and subjects who discontinued study medication for renal safety issues. For the latter subjects, the iothalamate GFR measurement at the time of treatment discontinuation was carried forward. This dataset excluded patients without an iothalamate GFR measurement at Week 24 who did

not withdraw for renal safety reasons. The analysis also excluded any male subject with a GFR >180 mL/min and any female subject with a GFR >155 mL/min.

Subjects were analyzed according to the medication they received, rather than what they were randomized to.

Analyses of renal endpoints and data used the "renally evaluable population" and "modified observed case dataset."

Renal Results

Disposition

Only 53/81 (65.4%) tafenoquine and 29/39 (74.4%) of placebo subjects completed the study. Nearly all subjects were withdrawn for the reason "other" which includes "withdrawn consent, spurious renal data, poor compliance, lost to follow-up, and 'incorrect subject technique'", "protocol deviation (including noncompliance)", or lost to follow-up.

Reviewer's comment: Many subjects did not complete the study. Reasons for premature discontinuation included "spurious renal data" and "incorrect subject technique," which may reflect difficulties with performing assessments of measured GFR; however, we could not locate details regarding the nature of these discontinuations.

Baseline Characteristics

The mean age of the subjects was 33.9 (±10.1) years. The mean baseline iothalamate GFR was 98.8 mL/min.

Endpoint Analyses

As shown in Table 2, the 95% confidence interval for the treatment difference ranges from -10 mL/min (i.e., a greater decline in renal function in the tafenoquine group) to 2.7 mL/min (i.e., a greater decline in renal function in the placebo group).

Table 2: Mean change in GFR from baseline to Week 24 – Renally Evaluable Population, Modified Observed Case Dataset

	Tafenoquine n=81	**Placebo n=39**	**Treatment Difference (95% CI)**
Subjects included in analysis	50 (62%)	23 (59%)	
Adjusted mean change (mL/min)	1.4	5.0	-3.7 (-10, 2.7)

Source: Adapted from Clinical Study Report for Study 057, Table 18.

The applicant conducted sensitivity analyses for the primary endpoint ("Worst Case Analysis," "Safety Population") that confirmed the primary endpoint finding. In addition, the applicant provided the results of secondary endpoints based on change in iothalamate GFR (i.e., change in GFR from baseline to Week 12, percentage change in GFR from baseline to Weeks 12 and 24) that are similar to the primary endpoint results.

Reviewer's comment: There is substantial missing data with only ~60% of randomized study subjects contributing to the analyses, rendering the results largely uninterpretable.

Subjects with Decreases in GFR/Increases in Serum Creatinine

The applicant identified four subjects in the tafenoquine group with a ≥20% decrease in iothalamate GFR: one at Week 12, one at Week 18, and two at Week 24. No subjects had a decline of this magnitude in the placebo group. The applicant provided brief narratives for the four tafenoquine subjects as follows:

Subject [redacted] was a 22 year-old man with a baseline iothalamate GFR of 170.9 mL/min and serum creatinine of 1.1 mg/dL who started tafenoquine on [redacted]. At Week 12, his GFR was 108 mL/min and his serum creatinine was 1.3 mg/dL. The GFR measurement was repeated and was 124.4 mL/min. Treatment was withdrawn on [redacted] per protocol. There was no associated proteinuria, albuminuria, or active urinary sediment. The case was reviewed by the IDMC who felt the baseline GFR value was likely inaccurately high. "The nephrology service cleared the subject."

Subject [redacted] was a 45 year-old woman with a baseline iothalamate GFR of 123 mL/min who started tafenoquine on [redacted] At Week 12, her GFR was 97 mL/min and her serum creatinine was 0.8 mg/dL. Urine blood was '+' at Week 12 but no subsequent urinalysis data were available. One week later, her GFR was 96 mL/min and serum creatinine was 0.8 mg/dL. Tafenoquine was discontinued per protocol. The subject was asymptomatic. At Week 18, her GFR was 68 mL/min and serum creatinine remained 0.8 mg/dL. The investigator thought it was unlikely that she had a decreased GFR related to study drug and cited "variability of GFR measurements as a possible cause." "The subject remained well and declined further follow-up." Because of questions regarding the validity of the results, samples were retested and showed GFR values of 118 mL/min, 105 mL/min, and 102 mL/min at baseline, Week 12, and Week 13, respectively. The final GFR value was 89 mL/min. The renal IDMC reviewed the results and did not consider them significant.

Subject [redacted] was 39 year-old man with a baseline iothalamate GFR of 122.9 mL/min who started tafenoquine on [redacted] On [redacted] his GFR was 104.3 mL/min. On [redacted] his GFR was 90.6 mL/min. There were no concurrent changes in serum creatinine, and the subject was "medically well." The IDMC reviewed the case and noted that the baseline renal clearance values were 169.4, 95.9 and 122.9 mL/min and that the first value was likely spuriously elevated, making subsequent study values appear to be decreased.

Subject [redacted] was a 48 year-old man with a baseline iothalamate GFR of 137.7 mL/min and serum creatinine of 0.9 mg/dL who started tafenoquine on [redacted]. He had decreases in GFR of 17%, 22%, and 32% at Weeks 12, 24 (6 days after the last dose, GFR 107.3 mL/min), and at the follow-up visit 12 weeks after the last dose, respectively. The serum creatinine was 0.9 at both baseline and Week 24. The only "clinically significant urinalysis finding" reported was urine blood at Week 12. Repeat urinalysis at Week 12 and Weeks 18 and 24 did not show blood. The subject was referred to a nephrologist for evaluation but "refused any additional renal follow up." "The IDMC agreed that there were no concerns about this subject."

Three subjects in the tafenoquine group [redacted] and one in the placebo group had an increase in serum creatinine from baseline of at least 0.3 mg/dL. The applicant provided the following information on the tafenoquine subjects:

Subject [redacted] had a 35.4% increase from baseline in serum creatinine to a value of 1.1 mg/dL at Week 3 associated with a 21.4% *increase* in iothalamate GFR.

Subject [redacted] had a 35.4% increase from baseline in serum creatinine to a value of 1.3 mg/dL at Week 12 associated with a 3.4% decrease in GFR. The serum creatinine was the same at the following visit (timing not specified.)

Subject [redacted] had a 0.35 mg/dL increase from baseline in serum creatinine to a value of 1.23 mg/dL at Week 6. GFR was not measured at this visit.

The applicant defined an "F2" change in serum creatinine as an increase of >125% above baseline. According to the applicant, "at any visit, 13 (18.8%) subjects receiving tafenoquine and 5 (15.6%) subjects receiving placebo had elevated serum creatinine outside the F2 range (OS Table 7.15). At most post-Baseline time points, the incidence of elevated creatinine meeting the F2 criteria was greater in the tafenoquine group than in the placebo group." We were unable to locate the referenced table in the submission.

Changes in Urine Parameters
The applicant defined "clinically significant urinalysis finding" as urine protein, blood, or glucose >trace or urine RBC/hpf>0. Such findings were identified at Week 24 in two (3.6%) tafenoquine and three (11.5%) placebo subjects. According to the applicant, no meaningful changes in renal function were seen in those subjects who had corresponding creatinine/GFR data.

"An elevated microalbumin/creatinine ratio was observed throughout the study in an appreciably greater proportion of subjects receiving tafenoquine than those receiving placebo (DS Table 8.11)." We were unable to locate the referenced table in the submission. It is not clear what the applicant considered to be an "elevated" microalbumin/creatinine ratio.

Adverse Events
An adverse event of "Glomerular filtration rate decreased" was reported for five (6.2%) tafenoquine and two (5.1%) placebo subjects. All events were classified as serious for unclear reasons, but were reported as mild in severity. The event resulted in study drug discontinuation for two (2.5%) tafenoquine subjects per protocol-defined stopping rules. The narratives for four of the tafenoquine subjects (b) (6) are provided above. The remaining narrative is as follows:

> *Subject* (b) (6) was a 30 year-old woman with a baseline iothalamate GFR of 114.6 mL/min and serum creatinine of 0.8 mg/dL who started tafenoquine on (b) (6), she had an uninterpretable GFR measurement. The measurement was repeated on (b) (6) 10 days after discontinuation of study drug, and showed a GFR of 73.8 mL/min. Her serum creatinine at Week 24 was 0.7 mg/dL. Urinalysis showed 1+ blood and trace to 1+ protein around this time but the subject had recently been menstruating. The subject was asymptomatic. The case was discussed with a nephrologist who felt it was implausible that the GFR result represented a true decline in renal function. The measurement was repeated on (b) (6) and the GFR was 131.6 mL/min and urine protein and blood were negative. The renal IDMC reviewed the case and concluded that the GFR decrease was implausible given that there was no change in serum creatinine.

Trial Conduct
According to the Clinical Study Report, the Renal IDMC made several recommendations regarding the conduct of the study in March 2005 including 1) "to implement the analysis of all GFR samples in the US laboratory"; 2) "to implement the analysis of creatinine for all GFR serum and urine samples from that point onwards"; 3) "to review data anomalies and take appropriate action"; 4) "to clarify GFR inclusion criteria to allow correction for body surface area when considering Baseline GFR values 75-80 mL/min"; 5) "to clarify protocol procedures to allow for repeat GFR measurements before permanent discontinuation of study subjects due to suspected spurious GFR data"; and 6) "to review all SAE reports and clarify them in accordance with the reviews described, as well as the urinalysis results. All other cases of reported GFR decrease were to be reviewed to determine if any met the criteria for an SAE." It is not clear what the basis was for these recommendations, but they suggest that there may have been concerns with trial conduct and data quality.

Other Data
The applicant conducted an in vitro assessment of the effect of tafenoquine on the renal transporters

MATE1, MATE2-K, and OCT2, and "tafenoquine was found to be a more potent inhibitor of these renal transporters than the positive control, cimetidine (Study XS-0517)."

Consult Questions

1. From a renal perspective, is tafenoquine reasonably safe for use for up to 6 months of continuous dosing?
2. What renal monitoring, if any, should be conducted for individuals on tafenoquine prophylaxis for up to 6 months of continuous dosing?
3. Please provide labeling recommendations based on your review of the renal safety data.

DCRP Response:
Based on our review of the analyses and information provided, we find it difficult to answer these questions. Our assessment of the data is as follows:

- *In Studies 033 and 057, the applicant identified several subjects with elevations in serum creatinine and/or decreases in GFR. We note that the applicant has not provided details regarding these cases, and the data provided are not presented in a clear and comprehensive manner; however, none of the referenced cases appear to represent intrinsic renal injury. Several of the cases were reviewed by nephrologists and/or a renal IDMC who concurred with this assessment. Although the applicant notes that a greater number of tafenoquine subjects had an elevated urinary albumin/creatinine ratio during the study, no additional details are provided, and it is not clear that these changes were clinically relevant.*
- *In Study 057, which was intended to assess renal safety, the 95% confidence interval for the treatment difference between tafenoquine and placebo on the mean change in iothalamate GFR from baseline to Week 24 ranges from -10 mL/min (i.e., a greater decline in renal function in the tafenoquine group) to 2.7 mL/min (i.e., a greater decline in renal function in the placebo group). Only ~60% of randomized subjects contributed to this analysis. Also, based on recommendations made by the renal IDMC in March 2005, there appear to have been questions regarding trial conduct. As such, we find these results to be largely uninterpretable.*
- *In Study 33, a small increase in mean serum creatinine was observed in both treatment arms. Generally speaking, aside from causing intrinsic renal injury, drug-induced changes in creatinine can result from a hemodynamic effect, a change in production of creatinine, interference with the creatinine assay, or interference with the renal tubular secretion of creatinine. It is not clear whether the subjects, who were deployed soldiers, could have had other exposures that led to a mean increase in creatinine levels in the study through a hemodynamic effect or through a change in the production of creatinine (e.g., changes in climate, diet, or physical exertion) or whether tafenoquine is likely to interfere with the creatinine assay. We note that in vitro studies show that tafenoquine inhibits the renal transporters MATE1, MATE2-K, and OCT2. These data suggest that tafenoquine could increase serum creatinine through inhibition of renal tubular secretion of creatinine; however, the trial data were not analyzed in a way that allows us to determine whether tafenoquine leads to elevations in serum creatinine that follow the expected time course of such an effect (i.e., an early increase, a plateau, and a decrease with treatment discontinuation). We would also want to know whether the in vitro data suggest that the reported effects on renal transporters would be expected to occur at clinically relevant exposures. We defer to clinical pharmacology on this issue. We note that Study 057 included both serum creatinine and measured GFR, which ideally could help sort out this issue (i.e., drugs that inhibit the tubular secretion of creatinine cause an increase in serum creatinine without a corresponding change in measured GFR); however, as noted above, we question the integrity of these data and, therefore, question whether there is utility in conducting additional analyses of this trial.*

Appendix: Creatinine values for tafenoquine subjects referred for nephrology evaluation

Subject	Visit	Creatinine (mg/dL)	Reason for Follow-up
(b) (6)	Screening	0.90	Elevated creatinine
	Loading	1.13	
21 year-old male	Week 6	1.36	
	Week 10	1.13	
	Week 16 (follow-up)	1.13	
(b) (6)	Screening	0.90	Elevated creatinine
	Loading	1.13	
26 year-old male	Week 5	1.36	
	Week 10	1.24	
	Week 17	1.24	
	Week 30 (follow-up)	1.36	
	Follow-up Week 10	1.24	
(b) (6)	Screening	1.02	Urinalysis
	Loading	1.13	
25 year-old male	Week 5	1.13	
	Week 8	1.24	
	Week 16	1.36	
	Week 26	1.13	
	Follow-up Week 11	1.24	
(b) (6)	Screening	0.90	Urinalysis
	Loading	0.90	
20 year-old male	Week 4	1.02	
	Week 9	1.02	
	Week 16	1.02	
	Week 28 (follow-up)	1.13	
	Follow-up Week 9	1.13	
(b) (6)	Screening	0.90	Urinalysis
	Loading	1.13	
22 year-old female	Week 5	1.24	
	Week 10	0.90	
	Week 17	1.02	
	Week 28 (follow-up)	1.13	
	Follow-up Week 11	1.02	
(b) (6)	Screening	1.33	Urinalysis
	Loading	1.41	
33 year-old male	Week 5	1.23	
	Week 8	1.05	
	Week 17	1.17	
	Week 28 (follow-up)	1.10	
	Follow-up Week 11	1.32	
(b) (6)	Screening	1.21	Urinalysis
	Loading	1.19	
26 year-old male	Week 5	1.41	
	Week 10	1.09	
	Week 17	1.09	
	Week 28 (follow-up)	1.11	
	Follow-up week 11	1.70	

Source: Applicant, 16.2.8 Listings of Individual Laboratory Measurements by Patient

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/s/

KIMBERLY A SMITH
05/24/2018

ALIZA M THOMPSON
05/24/2018

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05/24/2018

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT # 11713

Consultant Reviewer:	Gregory M. Dubitsky, MD Medical Officer Division of Psychiatry Products
Consultation Requestor:	Sheral Patel, MD Medical Officer Division of Anti-Infective Products
Subject of Request:	NDA 210607/Tafenoquine
Date of Request:	April 24, 2018
Date Received:	April 24, 2018
Desired Completion Date:	May 22, 2018

I. Background

The Division of Anti-Infective Products (DAIP) is reviewing NDA 210607 for the administration of tafenoquine succinate tablets in the prevention of malaria in patients (b) (4) This application was resubmitted on December 8, 2017, after a Refuse-to-File action and has been granted priority review status. An Advisory Committee (AC) meeting is scheduled for July 26, 2018, to discuss this NDA.

Tafenoquine is an analog of primaquine, which is approved for prophylaxis against malaria. Tafenoquine has not been marketed in any country. The proposed treatment regimen for tafenoquine is a loading dose of 200 mg/day for 3 days, followed by 200 mg/week for up to 6 months while in a region where malaria is endemic, and ending with a single dose of 200 mg in the week after exiting the region.

A related drug approved for the prophylaxis of malaria is mefloquine, a 4-quinolinemethanol, which was approved as Larium in 1989 under NDA 19591.[1] A risk of serious neuropsychiatric adverse effects associated with mefloquine, which became apparent only in the postmarketing phase, mandated a boxed warning to highlight this risk in 2013. Mefloquine labeling states psychiatric adverse reactions have ranged from anxiety, paranoia, and depression to hallucinations and psychotic behavior, which may occur early in the course of treatment. Suicidal ideation and suicide have been reported. Symptoms have

[1] Larium was withdrawn from the U.S. market in 2011. However, mefloquine is currently available in generic formulations.

been reported to continue for months or years after mefloquine has been stopped. Mefloquine should not be prescribed for prophylaxis in patients with active depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders and should be used with caution in patients with a history of depression. During prophylactic use, the emergence of psychiatric symptoms such as acute anxiety, depression, restlessness, or confusion suggest a risk for more serious reactions and mefloquine should be discontinued in these cases.

A Danish registry study retrospectively profiled acute psychiatric adverse events in 73 subjects who reported side effects associated with mefloquine between January 1996 and August 2000.[2] Substantial percentages of subjects had recurring nightmares (59%), anxiety (55%), phobic anxiety (51%), depression (44%), acute psychotic symptoms (15%), and hypomania or mania (6%).

Various mechanisms for the neuropsychiatric adverse effects of mefloquine have been suggested including inhibition of cholinesterase enzymes that results in increased stimulation of post-synaptic cholinergic neurons, effects on neuron cell polarity, and interference with extracellular signaling by blocking adenosine receptors.[3]

In view of the serious psychiatric reactions associated with mefloquine, DAIP has requested that the Division of Psychiatry Products (DPP) provide its assessment of the safety of tafenoquine from a psychiatric perspective.

II. Material Reviewed

I referred to the following materials in completing this review:

NDA 210607/Sequence #0001 (submitted August 21, 2017)

- Integrated Summary of Safety.
- Summary of Clinical Safety.
- Clinical Study Reports for Studies 030, 033, 043, 045, and 057.

NDA 210607/Sequence #0017 (submitted February 7, 2018)

- ISS Analysis Datasets adae.xpt and addm.xpt.

IND 129656/Sequence #0006

- Protocol for Study 60PH04.

[2] Ringqvist A, et al. Acute and long-term psychiatric side effects of mefloquine: A follow-up on Danish Adverse Event Reports. Travel Medicine and Infectious Disease 2015;13:80-88.
[3] Grabias B and Kumar S. Adverse neuropsychiatric effects of antimalarial drugs. Expert Opinion on Drug Safety 2016;15(7):903-910.

III. Review of Clinical Data

A. Clinical Studies

Tafenoquine has been studied in more than 25 clinical trials, including seven Phase 2 and Phase 3 studies in malaria prophylaxis and one renal and ocular safety trial in healthy volunteers.

Given the proposed treatment regimen for malaria prophylaxis, i.e., 200 mg/day for 3 days followed by 200 mg/week for up to 6 months, the 5 trials listed in Table 1 are the most relevant for the evaluation of clinical safety. These trials all used a randomized, double-blind, parallel group design.

Table 1: Trials Most Relevant to the Evaluation of Clinical Safety

Trial	Treatment Arms	TX Duration
030	• Tafenoquine 200 mg/day x3, then 200 mg/week • Mefloquine 250 mg/day x3, then 250 mg/week • Placebo	12 weeks[4]
033	• Tafenoquine 200 mg/day x3, then 200 mg/week • Mefloquine 250 mg/day x3, then 250 mg/week	26 weeks
043	• Tafenoquine 400 mg/d x3, then placebo/week • Tafenoquine 200 mg/d x3, then 200 mg/week • Tafenoquine 400 mg/d x3, then 400 mg/week • Placebo	15 weeks
045	• Tafenoquine 25 mg/d x3, then 25 mg/week • Tafenoquine 50 mg/d x3, then 50 mg/week • Tafenoquine 100 mg/d x3, then 100 mg/week • Tafenoquine 200 mg/d x3, then 200 mg/week • Mefloquine 250 mg/day x3, then 250 mg/week • Placebo	12 weeks
057	• Tafenoquine 200 mg/d x3, then 200 mg/week • Placebo	23 weeks

B. Study Pooling

Studies 033 and 057 approximated the maximum proposed tafenoquine treatment duration (26 weeks). I considered Study 033 to be the primary source of safety data.

I considered Study 057 to be a secondary source of safety data because it was much smaller than Study 033 (81 vs. 492 patients treated with tafenoquine) and

[4] Although Study 030 was intended to be a 24-week trial, the mean exposures for all treatment groups were less than 10 weeks. Only 26% of patients in the tafenoquine group were exposed to drug for longer than 12 weeks. (See pages 65 and 94 of the Study Report.) Thus, I am considering this trial to have a nominal duration of only 12 weeks.

the completion rate was substantially lower in Study 057 compared to Study 033 (65% vs. 96% in the tafenoquine treatment arms).

Study 033 was conducted in Australian Defense Force (ADF) soldiers who were deployed on a peacekeeping mission to East Timor between October 2000 and April 2001 whereas Study 057 was intended to evaluate renal and ocular safety and was conducted in civilians in the U.S. and U.K. and non-deployed military personnel in the U.S.

I considered the pool of Studies 030, 043, and 045 to be another secondary source of data because the treatment duration was considerably shorter than the proposed maximum duration (12 to 15 weeks vs. 26 weeks) and this study pool was smaller than Study 033 (252 vs. 492 patients in the tafenoquine group). These trials were performed in sub-Saharan Africa: Studies 030 and 043 were conducted in Kenya and Study 045 was conducted in Ghana. For Studies 043 and 045, only the tafenoquine 200 mg treatment arms were analyzed because this dose was proposed for clinical use.[5]

C. Psychiatric Exclusion Criteria

Psychiatric exclusion criteria differed somewhat among the 5 studies selected for analysis, as shown in Table 2 below. Specifically, the 3 trials with a mefloquine control arm excluded individuals with a history of a psychiatric disorder, in accordance with current labeling for mefloquine.

Table 2: Psychiatric Exclusion Criteria

Trial	Exclusionary 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.

D. Psychiatric Rating Scales

Importantly, none of the 5 trials utilized a rating scale during treatment to assess psychiatric symptoms such as depression, anxiety, psychosis, insomnia, or suicidal ideation. This fact should be kept in mind in reviewing the adverse event (AE) reporting rates from these trials because lack of systematic monitoring for psychiatric symptoms likely resulted in underestimation of the actual incidence of these events.

[5] The other two Phase 2/3 trials in malaria prophylaxis (Studies 006 and 049) were not included in this pool because tafenoquine was administered for only 3 days in these studies.

E. Coding of Psychiatric AEs

I examined all AEs, regardless of body system, listed in the ISS adverse event dataset (adae.xpt) to 1) determine the accuracy of coding the reported event (AETERM) to the MedDRA-preferred term (AEDECOD) for psychiatric AEs and 2) to detect any psychiatric AEs not categorized under the Psychiatric Disorders body system (AEBODSYS).

I found the accuracy of coding reported terms to preferred terms for psychiatric AEs to be satisfactory. There were 5 AEs considered psychiatric in nature that were not classified under the Psychiatric Disorders body system:

- "psychomotor hyperactivity" and "amnesia" were classified under Nervous System.
- "irritability" and "feeling jittery" were classified under General Disorders and Administration Site Conditions.
- "intentional overdose" was classified under Injury, Poisoning, and Procedural Complications.

These adverse event terms were included in my analysis of psychiatric AEs.

In addition, certain closely related preferred terms were combined into common terms for purposes of analysis and are noted as such in the following section. For example, the occurrences of AEs coded to "depression" and "depressed mood" were combined under the term "depression" for purposes of computing the reporting rate of depression.

F. Incidence of Psychiatric AEs

<u>Methodology</u>

I used the following methodology to calculate reporting rates of psychiatric AEs. Reporting rate numerators were determined from the adverse event dataset adae.xpt using JMP version 11.1.1. Multiple occurrences of the same event in the same patient were counted only once. AEs for patients not included in the safety population (denoted by SAFFL=N) and AEs not flagged as treatment-emergent (denoted by TEAEFL=N) were excluded from these calculations. AEs were enumerated by the actual treatment received (as indicated by the variable TRT01A). The reporting rate denominators were the safety population sample sizes reported in the Clinical Study Reports.

<u>Reporting Rates of Psychiatric AEs</u>

My calculated reporting rates of psychiatric AEs for the primary safety Study 033 are displayed in Table 3 below.

Table 3: Psychiatric AE Reporting Rates (n (%)) Study 033		
Adverse Event	**Taf 200[6] N=492**	**Mefloquine[7] N=162**
Abnormal Dreams[8]	7 (1.4%)	3 (1.9%)
Agitation	2 (0.4%)	0
Amnesia	1 (0.2%)	0
Anxiety[9]	4 (0.8%)	0
Depression	1 (0.2%)	1 (0.6%)
Euphoric Mood	2 (0.4%)	0
Insomnia	8 (1.6%)	1 (0.6%)
Somnambulism	0	1 (0.6%)
Any Sleep Symptom[10]	17 (3.5%)	6 (3.7%)
Any Psychiatric AE	27 (5.5%)	8 (4.9%)

Reviewer's Comment: Because the types of reactions associated with mefloquine cover a wide spectrum, a comparison of the incidence of any psychiatric AE is of primary interest. The percentage of patients with any psychiatric AE was slightly higher in the tafenoquine group than in the mefloquine group.

The inclusion of a placebo control would have been useful in ascertaining the contribution of tafenoquine and mefloquine to these events as opposed to other factors such as the stress of military deployment to a potentially hazardous area. The Applicant attempted to address this concern by comparing AE rates among deployed soldiers from Study 033 with the rates in non-deployed subjects from the pool of Studies 030, 043, 045, and 057, all of whom were treated with the proposed tafenoquine treatment regimen.[11] In their analysis, the rate of any psychiatric AE in Study 033 was about 2.5-fold higher than in the non-deployed subjects (5.1% vs. 2.1%); this difference is statistically significant (p=0.04, 2-tailed Fisher's exact test).

I don't find this finding surprising given the increased levels of stress likely experienced by deployed ADF soldiers who are separated from their families and living in an isolated, potentially hostile area. But these soldiers were randomized in a 3:1 ratio to tafenoquine or mefloquine. The stress burden and propensity to develop a psychiatric reaction related to stress or factors other than the study drug should have been similar between the two treatment groups. Had a placebo arm been included in this study and demonstrated a risk of any psychiatric AE

[6] Tafenoquine 200 mg/day x3, then 200 mg/week.
[7] Mefloquine 250 mg/day x3, then 250 mg/week.
[8] Includes abnormal dreams and nightmares.
[9] Includes anxiety disorder, panic attack, and stress.
[10] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.
[11] Table 50 in the Summary of Clinical Safety.

comparable to the drug arms, I could conclude that the observed rates were not likely attributable to either drug. Also, consider that if mefloquine had conferred additional risk (as one might expect based on previous mefloquine experience) to an underlying level of stress present in both groups, the mefloquine rate would have been appreciably higher than the tafenoquine rate. This was not the case. As it stands, the risk of a psychiatric AE among tafenoquine-treated soldiers appears to be comparable or slightly higher than the risk among mefloquine-treated soldiers.

My calculated reporting rates for psychiatric AEs in the placebo-controlled Study 057 and in the pool of Studies 030, 043, and 045 are shown in Tables 4 and 5, respectively.

Table 4: Psychiatric AE Reporting Rates (n (%)) Study 057

Adverse Event	Taf 200 N=81	Placebo N=39
Depression[12]	2 (2.5%)	0
Insomnia	2 (2.5%)	2 (5.1%)
Any Psychiatric AE	4 (4.9%)	2 (5.1%)

Table 5: Psychiatric AE Reporting Rates (n (%)) Studies 030, 043, & 045

Adverse Event	Taf 200 N=252	Placebo N=256	Mefloquine N=147
Anxiety[13]	1 (0.4%)	0	2 (1.4%)
Insomnia	0	1 (0.4%)	0
Loss of Libido	0	0	1 (0.7%)
Suicide Attempt	1 (0.4%)	0	0
Any Sleep Symptom[14]	1 (0.4%)	1 (0.4%)	0
Any Psychiatric AE	3 (1.2%)	1 (0.4%)	3 (2.0%)

In the pool of all 5 trials, the percentage of patients who experienced any psychiatric AE was slightly higher in the tafenoquine group (4.1% (34/825)) than in the mefloquine group (3.6% (11/309)) and considerably higher than in the placebo group (1.0% (3/295)).

Reviewer's Comment: In the pool of Studies 030, 043, and 045, the incidence of any psychiatric AE among tafenoquine-treated patients is midway between the placebo and mefloquine rates. In the pool of all 5 studies, the tafenoquine rate of

[12] Includes depression and depressed mood. One patient with depression also had an AE of bipolar disorder the same day, which is not enumerated separately here.
[13] Includes anxiety and neurosis.
[14] Includes insomnia and sleep disorder.

psychiatric AEs is significantly higher than the placebo rate (p=0.008) and not significantly different from the mefloquine rate (p=0.736). The mefloquine and placebo rates differ in the trend range of statistical significance (p=0.056). As in Study 033, this finding suggests that the risk of a psychiatric AE with tafenoquine therapy is comparable to that with mefloquine.

Serious Psychiatric AEs and Psychiatric AEs Resulting in Dropout

From these 5 trials, one tafenoquine-treated patient experienced a serious psychiatric AE:

- Subject (b) (6) in Study 043 was a 24 year old Kenyan male with a history of malaria who, on Study Day 9, became intoxicated with ethanol and, according to his family, "took a poison" to attempt suicide, apparently due to marital problems. Tafenoquine treatment was stopped and he was hospitalized. The event was considered resolved 2 days later.

There was also one tafenoquine-treated patient from Study 033 who dropped out due to a psychiatric AE:

- Subject (b) (6) was a 28 year old male with a history of head trauma and malaria who experienced moderately depressed mood on Study Day 24. Tafenoquine was discontinued and he was treated with paroxetine. The depression was considered resolved 87 days later.

Neither patient had a medical history of a psychiatric disorder.

Among mefloquine-treated patients in these 5 trials, one mefloquine-treated patient (Study 030 Subject (b) (6)) dropped out because of severe anxiety on Study Day 3. Cannabis use was suspected. Diazepam was administered and the event resolved after 4 days.

Among placebo-treated patients in these 5 studies, no patient had a psychiatric AE that led to dropout or was considered severe or serious.

I also searched for any psychiatric AE that was considered serious or severe among the other dose arms of Studies 043 and 045 and the remainder of the studies in the ISS.[15] Four patients with serious events were identified: 3 received tafenoquine and one received placebo. These events are summarized below.

Tafenoquine

- Subject (b) (6) was a 23 year old male who experienced paranoid ideation and hallucinations 25 days after receiving tafenoquine 400

[15] Other ISS trials were Studies 003, 006, 014, 015, 022, 040, 047, 049, 050, 051, 052, 053, 054, 058, and 933.

mg/day x 3 days. It was discovered that this subject had a past history of psychosis.

- Subject (b) (6) was a 22 year old male who received a single dose of tafenoquine 350 mg and experienced an acute psychotic episode 3 weeks later. This subject had a history of 2 psychiatric hospitalizations.
- Subject (b) (6) was a 30 year old male who received a single dose of tafenoquine 500 mg and experienced a psychotic episode one week later. It was discovered that he had a history of schizophrenia.

Placebo

- Subject (b) (6) was a 16 year old female who received placebo and had an unintended pregnancy. She took an overdose of chloroquine in an attempt to induce an abortion.

Reviewer's Comment: The psychiatric histories of the 3 tafenoquine-exposed subjects apparently were unknown at the time of study enrollment. Tafenoquine has a half-life of 17 days, according to the Applicant's labeling. Thus, the onset of a drug-related event a few weeks after the last dose is plausible. These cases suggest that tafenoquine may increase the risk of exacerbation in patients with a history of psychiatric illness and contraindication in such patients is advisable.

Dose-Response

Because Studies 043 and 045 had multiple tafenoquine dose arms, I examined the incidence of psychiatric AEs in these two trials for evidence of a dose-response relationship. In Study 043, only 3 patients had a psychiatric AE: two patients in the tafenoquine 200 mg weekly arm and one patient in the 400 mg weekly arm. In Study 045, no patient experienced a psychiatric adverse event.

IV. Conclusions and Recommendations

Responses to the specific questions posed by DAIP are provided below.[16]

1. **From a psychiatric perspective, is tafenoquine reasonably safe to use for up to 6 months of continuous dosing?**

   DPP Response: In so far as there were no deaths from psychiatric causes or serious psychiatric AEs that can be attributed directly to tafenoquine exposure in the safety database, tafenoquine appears to be reasonably safe for up to 6 months of continuous dosing from a psychiatric standpoint. However, there are two significant limitations in assessing the psychiatric safety of tafenoquine from these data.

[16] Although the Consultation Request to DPP asks about both neurological and psychiatric safety, DAIP was informed that DPP will address only psychiatric safety and advised to consult the Division of Neurology Products to evaluate neurological safety.

First, there was no systematic monitoring for psychiatric symptoms during any of the 5 key safety studies reviewed above. Although it seems likely that serious and severe psychiatric AEs were detected and documented, many non-serious or less severe psychiatric symptoms may have been missed and, thus, the apparent psychiatric AE rates presented above may substantially underestimate the true incidence. For example, abnormal dreams and insomnia have been reported to occur in greater than 10% of prophylactic users of mefloquine.[17] This is much higher than the rate seen in the mefloquine-treated patients in Study 033, where 3.7% of patients reported any sleep symptom. This suggests that detection of psychiatric AEs in these studies was not adequate.

Second, only 825 patients received the proposed dose of tafenoquine for any duration and, of these, 596 patients received the proposed dose for 24 weeks in the 5 analyzed clinical trials.[18] While the absence of an adverse event from this experience provides some measure of assurance that the event has a true incidence not greater than 0.5% (1/200) with 6 months of exposure, serious psychiatric AEs at a lower rate may not have been occurred in this sample. Consider that the estimated incidence of serious neuropsychiatric AEs with mefloquine has been reported to range from 1/607 to 1/20,000.[19] Assuming the highest mefloquine incidence rate, a sample size of 1800, with no serious psychiatric AEs in this sample, would be required to nominally rule out this level of risk with tafenoquine.

In sum, although there are no clear data indicating a major psychiatric risk that would preclude approval of tafenoquine, the accuracy of the apparent psychiatric AE incidence rates is questionable and the sample size is not sufficient to confidently rule out the risk of serious psychiatric AEs that might occur at a low rate comparable to that of mefloquine.

2. What psychiatric monitoring, if any, should be conducted for individuals on tafenoquine prophylaxis for up to 6 months of continuous dosing?

DPP Response: The risk of any psychiatric AE with tafenoquine appears to be roughly comparable to that with mefloquine based on reporting rates from Study 033 and the pool of the 5 key studies examined above. In view of the psychiatric risk associated with mefloquine, I recommend that clinicians actively query patients at each visit for the occurrence of a wide spectrum of psychiatric symptoms including suicidal thoughts, depressed mood, anxiety or nervousness, trouble sleeping, nightmares or vivid

[17] Nevin RL and Croft AM. Psychiatric effects of malaria and anti-malarial drugs: historical and modern perspectives. Malar J 2016;15:332. DOI 10.1186/s12936-016-1391-6.
[18] Table 4 in the ISS.
[19] Chen LH, et al. Controversies and Misconceptions in Malaria Chemoprophylaxis for Travelers. JAMA 2007;297(20):2251-2263.

dreams, hallucinations, and delusional thoughts. As part of a Risk Evaluation and Mitigation Strategy (REMS), a checklist of relevant psychiatric symptoms could be devised with advice on referring the patient for psychiatric examination and discontinuing tafenoquine therapy.

3. Please provide labeling recommendations based on your review of the psychiatric safety data.

DPP Response: I have the following high-level recommendations, from a psychiatric perspective, for tafenoquine labeling:

- Highlights – the absence of observed serious psychiatric AEs attributable directly to tafenoquine thus far may be due to the absence of a substantial risk or a patient sample that is too small to observe the infrequent to rare occurrence of these AEs with tafenoquine. Although the data from Study 033 and the pool of the 5 key studies above suggest a risk comparable to that of mefloquine, I am reluctant to recommend a boxed warning without reports of serious psychiatric AEs that can be reasonably attributed to drug. Although a boxed warning for tafenoquine could, in principle, be based on the its relationship to mefloquine, the data to support such a relationship are unclear at this time.
- Section 4 - because there were some serious psychiatric adverse events in patients with a history of psychiatric illness who took tafenoquine and a role for tafenoquine in those cases cannot be ruled out with reasonable certainty, it is recommended that labeling contraindicate use in patients with a history of psychiatric illness in a fashion consistent with current mefloquine labeling.
- Section 5 - a Warning regarding psychiatric AEs seems appropriate based on the above findings with tafenoquine, which suggest a psychiatric risk comparable to that of mefloquine.[20] The Warning should include the recommendation for monitoring for psychiatric symptoms, as discussed above, and consideration of stopping the drug and referring the patient for a psychiatric evaluation if these events emerge.
- Section 6 – the labeling of AEs should be based on Study 033, with a listing of clinically important psychiatric AEs from other ISS studies. I strongly recommend the inclusion of a caveat to inform the prescriber that systematic monitoring of psychiatric AEs was not conducted in these trial and, therefore, the reported AE rate may significantly underestimate the true incidence of these events in these trials.

[20] Per 21 CFR 201.57(c)(6)(i), a Warning statement does not require that a causal relationship have been definitively established, only reasonable evidence that a clinically significant hazard is causally associated with a drug.

- Section 17 - advise the prescriber to discuss the range of psychiatric side effects possible with tafenoquine and instruct the patient to promptly report any such effects.
- the Medication Guide should inform the patient of the possibility of the range of possible psychiatric side effects with tafenoquine treatment with advice to contact the prescriber if they occur.

4. What postmarketing requirements are recommended from a psychiatric perspective?

DPP Response: To better characterize the common psychiatric AE profile of tafenoquine, a placebo-controlled study of tafenoquine with systematic monitoring for psychiatric AEs and using the proposed dosing regimen should be performed. Such a trial should enroll at least 300 subjects per arm to permit detection of AEs occurring at a rate of 1% or higher. The following psychiatric rating instruments are recommended, with assessments no less frequently than each month:

- Beck Depression Inventory (BDI) for depressive symptoms.
- Beck Anxiety Index (BAI) for symptoms of anxiety.
- Brief Psychiatric Rating Scale (BPRS) for psychotic symptoms such as hallucinations and delusions.
- Pittsburgh Sleep Quality Index (PSQI) to monitor for sleep disturbance.
- Columbia-Suicide Severity Rating Scale (C-SSRS) to detect suicidal ideation or behavior.
- Prospective daily log to record nightmares and bad dreams.[21]

To detect serious psychiatric AEs occurring at a frequency under 1%, a more practical approach would be a registry for patients who are treated with tafenoquine.

Another potential source of postmarketing safety data for evaluating serious psychiatric AE incidence in Phase 4 would be the FDA Sentinel program, using data from a large electronic healthcare database.

5. Please provide an outline of additional information needed to assess potential psychiatric adverse reactions that could be obtained from the ongoing ophthalmologic safety study in healthy volunteers (Study 60PH04) through a protocol amendment based on your review of the data submitted by the Applicant.

[21] See: Robert G and Zadra A. Measuring nightmare and bad dream frequency: impact of retrospective and prospective instruments. J Sleep Res 2008;17:132-139.

DPP Response: Study 60H04 is a single-site, randomized, double-blind, placebo-controlled study to assess the long-term safety of tafenoquine, including ophthalmic safety, in 600 healthy volunteers. Subjects are randomized in a 1:1 ratio to receive either 1) a loading dose of tafenoquine 200 mg/day for 3 consecutive days followed by 200 mg weekly for 51 weeks or 2) placebo throughout. Subjects who complete treatment and have ongoing eye abnormalities or other AEs then enter a 24-week follow-up phase. Specific psychiatric assessments consist of the following:

- Mini International Neuropsychiatric Interview (MINI) performed during screening and at Weeks 12, 24, and 52. Assessments continue during the follow-up period if a disorder is found at Week 52.
- Leeds Sleep Evaluation Questionnaire (LSEQ) performed on Day 1, and at Weeks 4, 12, 24, and 52.

The monitoring frequency in this trial may be adequate for evaluating slowly evolving conditions, such as ophthalmic abnormalities, but it is not adequate for assessing psychiatric AEs, which can evolve quickly and depend on retrospective recall to document experiences accurately. Assessing patients every 12 to 28 weeks is too infrequent to produce reliable data regarding psychiatric AEs. The visit frequency should be increased to at least monthly if this trial is to produce useful data on psychiatric AEs. Also, because the study is already ongoing, the patient sample size will be well below 300, which is very unlikely to permit detection of rare serious psychiatric AEs such as those observed with mefloquine.

The LSEQ is an acceptable instrument for assessing trouble falling asleep, sleep quality, wakefulness following sleep, and behavior after awakening.

The MINI is useful as a diagnostic screening tool to identify individuals with psychiatric disorders but is not adequate for monitoring the emergence of psychiatric symptoms. The instruments listed under Question 4 are recommended for monitoring instead of the MINI.

Thank you for your consultation request. Please do not hesitate to contact me if you have further questions regarding this review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY M DUBITSKY
05/18/2018

MITCHELL V Mathis
05/18/2018

Medical Officer's Consult Review of NDA 210607
Ophthalmology

NDA 210607

Submitted date: December 8, 2017
Consult Request: December 19, 2017
Review completed: April 27, 2018

Product Name: **Arakoda (tafenoquine succinate) tablets, for oral use**

Applicant: **60 Degrees Pharmaceuticals, LLC**

Cross Referenced IND: **129656**

Consult Request: The Division of Anti-Infective Products requests your expert opinion on the ophthalmic safety of tafenoquine. This NDA is a resubmission after a refuse-to-file. The resubmission date is December 8, 2017. The Applicant has requested Priority Review and this request is under review. The proposed indication for tafenoquine is prophylaxis of malaria in adults for up to 6 months of continuous dosing.

1) We request your review and comments on the ophthalmologic safety results for tafenoquine in Study 057 in folder M5 (there is no dataset).
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Study 057 was initiated following the finding of vortex keratopathy in military personnel taking tafenoquine prophylaxis for up to 6 months in Study 033. Study 057 is a randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, specifically renal and ophthalmic effects of tafenoquine 200 mg daily for 3 days and then weekly for a total of 6 months in healthy volunteers in the United States. This study was conducted under the Army (b) (4) and the applicant has right of reference.

2) We also ask for your review and comments on the ophthalmologic findings in Study 033 (folder M5), section 2.1.5.5 Ophthalmic Effects in the Summary of Clinical Safety (folder M2), and Summary of Ophthalmologic Evaluations in Clinical Studies of Tafenoquine (folder M5, ISS).

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3) Please provide labeling recommendations based on your review of the ophthalmology data. A draft labeling can be located at
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Questions:
1) From an ophthalmologic perspective, is tafenoquine reasonably safe for use for up to 6 months of continuous dosing?
2) What ophthalmologic monitoring, if any, should be conducted for individuals on tafenoquine prophylaxis?

EDR link NDA 210607: \\CDSESUB1\evsprod\NDA210607\0001
EDR link to Resubmission: \\CDSESUB1\evsprod\NDA210607\0009

Reviewer's Comment: *Comments in this review are limited to areas of ophthalmologic concern.*

NDA Organization

Module 1.14 contains proposed product labeling.

Module 2.7.4 Summary of Clinical Safety contains a summary of ophthalmic adverse events and discussion in subsection 2.1.5.5.

Module 5.5.5.3 ISS Integrated Summary of Safety (ISS), ISS Report Body, contains a summary of ophthalmic adverse events and discussion in subsection 10.5.

As part of Module 5.5.5.3 ISS Integrated Summary of Safety (ISS) is a document titled, "Summary of Ophthalmologic Evaluations in Clinical Studies of Tafenoquine." This document organizes the various summary documents on procedures performed during tafenoquine clinical trials and provides meeting minutes from independent data review board findings of results of these studies.

Study 033

Study 033 was a randomized, double-masked, Phase 3 study (IND 38,503) to evaluate the safety, tolerability and effectiveness of tafenoquine (TQ) and mefloquine(MQ) for the prophylaxis of malaria (*P. falciparum* and *P. vivax*).

The study was divided into 2 phases. The first phase ('prophylactic phase') consisted of a 26-week (± 4 weeks) period where subjects received prophylactic study medication. Subjects were randomized in a ratio of 3:1 to receive TQ (N=492) or MQ (N=162). Subjects received a loading dose of either TQ 200mg/day or MQ 250mg/day for 3 days, followed by study treatment (TQ 200mg or MQ 250mg) once-weekly for the remainder of their deployment. Those subjects who completed the prophylactic phase then entered a 24- week 'relapse follow-up phase.' This consisted of an initial 12-week safety follow-up phase at the beginning of which subjects followed a supervised 14-day double-blind PQ (15mg bid) or PQ placebo dosing regimen (whereby those who took MQ during the prophylactic phase received PQ 15mg bid, whereas those who had taken TQ received PQ placebo bid), and then a further 12-week period to look for relapse of malaria.

Detailed ophthalmic assessments were performed in a sub-group of 98 study participants (77 TQ; 21 MQ) who underwent the following ophthalmic examination at baseline:

- Best-corrected visual acuity (Snellen chart).
- Visual field tests (Amsler grid).
- Color vision (Ishihara test).
- Physical examination (fundoscopy; corneal examination).

No subjects had clinically significant abnormalities at baseline. However, due to the observation of corneal deposits (vortex keratopathy) in a large proportion of TQ-treated subjects (69/74; 93%) compared with 0/21 of MQ-treated subjects at the end of the prophylactic phase, a wider range of ophthalmic tests for post-treatment assessment was added than had been planned in the protocol. The additional ophthalmic assessments were:

- Humphrey Perimetry (visual field test).
- Color Vision Standard Pseudoisochromatic Plates 2 (SPP-2).
- Color Vision Farnsworth-Munsell 100 hue test (FM-100).

- Digital retinal photography and digital corneal photography as part of the physical examination
- Fundus Fluorescein Angiogram (FFA) was performed in subjects in whom possible retinal findings had been observed.

Per the applicant, there were no notable changes from baseline or differences between the treatment groups in visual field tests (Amsler Grid and Humphrey Perimetry), visual acuity (Snellen chart) or color vision (Ishihara, SPP2, FM-100).

Subjects with corneal deposits were followed up beyond the scheduled 12-week follow-up. At each follow-up visit, corneal deposits were noted to have improved, with all subjects having resolved within 1 year of stopping study medication.

Table 2 Follow-Up of Vortex Keratopathy in Tafenoquine-Treated Subjects Following Six-Months of Prophylactic Treatment.

	End of Prophylaxis	3 Months FU	6 Months FU	12 Months FU
No. of subjects with vortex keratopathy	69/74 (93.2%)	32/74 (43.2%)	6/74 (8.1%)	0
No. subjects with vortex keratopathy resolved	N/A	37/69 (53.6%)	63/69 (91.3%)	69/69 (100%)

Fundoscopy examinations were carried out on 86 subjects at the 3-month post-treatment follow-up visit. These examinations were not masked because the examinations were carried out with the knowledge that corneal deposits were present and no baseline data were available for comparison. Abnormalities were reported (e.g., granularity/pigmentation of retinal pigment epithelium [RPE], hard drusen) in 27/69 (39%) of TQ subjects and 4/17 (24%) of MQ subjects.

Table 3 Fundoscopy results

	Baseline		End of Treatment (6 months)		3 Months FU	
	TQ	MQ	TQ	MQ	TQ	MQ
Normal	72/74	21/21	43/74 (58%)	15/21 (71%)	42/69 (61%)	13/17 (76%)
Granularity/RPE/Hard Drusen	0/74	0/21	21/74 (28%)	2/21 (10%)	9/69 (13%)	2/17 (12%)
Granularity/RPE with normal limits	0/74	0/21	9/74 (12%)	3/21 (14%)	8/69 (12%)	1/17 (6%)
Hard Drusen	2/74	0/21	1/74 (1%)	1/21 (5%)	10/69 (14%)	1/17 (6%)
			p=0.32 [1]		p=0.27 [1]	

1. Note: p-value for difference in proportions with normal results between treatment groups at the visit

Fundus Fluorescein Angiogram (FFA) was performed on 14 TQ subjects and 1 MQ subject in whom possible retinal findings had been observed of these 4/14 (29%) subjects in the TQ group and 1/1 (100%) subject in the MQ group were considered to have abnormal findings.

Table 4 Fundus Fluorescein Angiogram

	End of Treatment (6-Months)		3-Months FU	
	TQ	MQ	TQ	MQ
Abnormal	2/8 (25%)	1/1 (100%)	4/14 (29%)	1/1 (100%)

Reviewer's Comments:

The vortex keratopathy see with TQ in Study 033 appeared benign and fully reversible by Month 12 of follow-up.

Pseudochromatic color plates (e.g. Ishihara) are not generally recommended for use as an estimate of acquired color loss or central visual dysfunction. They do not assess blue/yellow deficiencies which are the most common acquired defects.

The applicant asserts that their expert ophthalmology advisory board concluded that the lack of baseline retinal photography data meant that the relevance of the retinal findings (observed on fundoscopy and fundus fluorescein angiograms) could not be ascertained. These subjects were recruited from the Australian Army when on deployment to East Timor. This population would not be expected to have granularity/pigmentation of retinal pigment epithelium [RPE] or hard drusen at baseline, end of treatment or after 3month follow-up fundoscopic examinations.

The presence of these retinal findings indicates a potential problem with the quality of the fundoscopic examinations and/or their interpretation or potential drug effect.

Study 057

This was a double-blind, placebo-controlled, Phase 1 safety study in healthy volunteers designed to assess ophthalmic and renal safety of TQ over 6 months. A total of 120 healthy volunteers (from US or UK) were randomized to receive either TQ 200 mg or placebo daily for 3 days followed by once-weekly dosing for 23 weeks. Ophthalmic assessments were conducted at Weeks 3, 6, 12, 18 and 24 of the treatment period and at 12 and 24 weeks after the end of the treatment.

The following tests were conducted at screening/baseline and at various timepoints throughout treatment and during the follow up period:

- Corneal and retinal digital photograph
- Macular function assessment (visual field evaluation using Amsler grid and Humphrey perimetry; Macular Stress Test)
- Best corrected visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] high-contrast acuity),
- Color vision assessment with standard (Pseudoisochromatic Plates [PIP] plates) and specialised (L'Anthony 40 hue) color plates, and the City University color vision test (Color Assessment & Diagnostics [CAD]).
- Night vision assessment (Forward Light Scatter Test [FLST], Low Contrast Visual Acuity [LCVA], Mesopic Contrast Threshold [MCT] and Scotopic Contrast Threshold [SCT]).

At screening, 10/70 (14%) of subjects randomized to TQ and 7/32 (22%) of subjects randomized to placebo had evidence of keratopathy in either eye. During the study, 15/70 (21%) of subjects receiving TQ and 4/32 (13%) of subjects receiving placebo developed keratopathy in 1 or both eyes; all of the cases in the placebo group and 60% of the cases in the TQ group emerged during the first 12 weeks of the study. Treatment emergent keratopathy resolved in either eye by Week 6 of the study in approximately 73% of the evaluable subjects receiving TQ and 100% of the evaluable subjects receiving placebo. All cases of keratopathy among subjects receiving TQ resolved by Week 48.

The only observed retinal abnormalities were at the 12-Week post-treatment Follow-Up Visit. At this visit, 1 subject receiving TQ had a single area of retinal hyperpigmentation. This was not associated with a decrement in visual acuity, foveal sensitivity, or visual field and did not change 11 months after cessation of therapy. One placebo subject had a retinal abnormality in the left eye that resolved within 2 months. No retinal abnormalities were reported at any other visit for either treatment group.

Table 5 **Subjects With Retinal Changes In Either Eye In Study 057**

	Screening	End of Treatment (Week 24)	Week 36 FU
TQ 200mg weekly	0/69	0/56	1/57
Placebo	0/32	0/26	1/27

Of the 2 subjects with retinal changes, the subject receiving TQ failed 1 of the 4 macular function tests, and the subject receiving placebo passed all 4 macular function tests.

An ophthalmic Independent Data Monitoring Committee (IDMC) concluded that no retinal abnormalities were found in either treatment group during the dosing phase of the study. However, they also stated that there were not enough data to completely rule out potential retinal toxicity associated with TQ use and recommended that a conservative way to evaluate ocular changes in a future study would be to use the following tests/techniques:

- Best corrected visual acuity.
- Photopic contrast acuity.
- Red-green and yellow-blue color vision thresholds.
- Humphrey automated perimetry with the 10-2 test.
- Complete eye examination, including indirect ophthalmoscopy through a dilated pupil, and retinal photographs.

Reviewer's Comments:

It is not clear why subjects with keratopathy at screening were included in this trial.

The presence of retinal findings not seen at screening indicates a potential problem with the quality of the fundoscopic examinations and/or their interpretation or a potential drug effect.

Study 058

This was a randomized, active-control, double-masked, double-dummy, Phase 2 study conducted at a single center in Thailand, in which all subjects received both active and placebo study medication to compare the efficacy of TQ versus CQ plus PQ (CQ + PQ) in the treatment of blood stage parasites and hypnozoites in *P. vivax*-infected patients.

Seventy subjects were randomized to receive either 400mg TQ for 3 days or 1500mg CQ over 3 days (600mg on Days 1 and 2; 300mg on Day 3) followed by 15mg PQ daily for 14 days.

Ophthalmic safety was assessed in all subjects using the following tests at baseline, Day 28 and at the Day 90 visit:

- Macular Function Tests:
- Amsler Grid, Humphrey 10-2 Visual Field, Macular stress test, High contrast visual acuity (HCVA) – ETDRS chart, Color vision – PIP [Pseudochromatic color plates (e.g., Ishihara)] plates & Lanthony 40 hue
- Digital Photography:
- Corneal and retinal digital photographs.

Fourteen of 44 subjects (32%) receiving TQ had corneal AEs of keratopathy, compared with none of the subjects in the CQ+PQ group. All 14 AEs of keratopathy (12 reported at Day 28 and 2 reported at Day 90) were mild in intensity and per the applicant did not impact the vision of the subjects. Six of the keratopathies reported at the Day 28 ophthalmic assessment had resolved by the Day 90 visit, another 2 subjects were lost to follow-up prior to the Day 90 assessment, while the remaining 4 were reported as ongoing. The 4 ongoing keratopathies and the 2 first reported at the Day 90 assessment did not require further follow-up as they were all mild in intensity and did not impact the vision of the subjects.

Nine subjects receiving TQ and 1 subject receiving CQ+PQ had abnormal results at Day 28 indicating retinal changes from baseline that were considered clinically significant and reported as AEs (retinopathy) by the investigator. The retinal changes resolved in 1 of the subjects in the TQ arm by the Day 90 assessment. In the other 9 subjects (8 TQ and 1 CQPQ) the retinal changes were still present at the Day 90 assessment. One additional subject receiving TQ had an abnormal result at the Day 90 assessment indicating retinal changes from baseline that were considered clinically significant by the investigator and reported as an AE (retinopathy). All retinal changes detected at the Day 90 assessment did not require further follow-up as they were all mild in intensity and did not impact the vision of the subjects.

Table 6 Summary of Retinal Examination Results by Visit

Assessment Day	Result	TQ		CQ+PQ	
		Left Eye	Right Eye	Left Eye	Right Eye
		n (%)	n (%)	n (%)	n (%)
Screening	n	46	46	24	24
	Normal	45 (97.8)	45 (97.8)	23 (95.8)	23 (95.8)
	Abnormal	1 (2.2)	1 (2.2)	1 (4.2)	1 (4.2)
Day 28	n	44	44	24	24
	Normal	35 (79.5)	36 (81.8)	22 (91.7)	22 (91.7)
	Abnormal	9 (20.5)	8 (18.2)	2 (8.3)	2 (8.3)
Day 90	n	37	37	22	22
	Normal	29 (78.4)	30 (81.1)	21 (95.5)	21 (95.5)
	Abnormal	8 (21.6	7 (18.9)	1 (4.5)	1 (4.5)

An Independent Data Monitoring Committee, which included 2 ophthalmic experts, reviewed all data for all subjects up to the Day 28 assessment. Both ophthalmic experts concurred that there was no difference in visual function tests between the 2 groups. The IDMC also had no major concerns regarding findings in the digital photographs of the corneas or retinas and agreed that the eye findings did not raise undue concern since visual function did not change

A masked review of the retinal digital photographs was conducted at the Fundus Photograph Reading Center, University of Wisconsin, following completion of the study. For the review the photographs were graded independently for hyperpigmentation (RPE deposits), RPE atrophic changes and for other notable changes (including optic nerve or vascular abnormalities).

The findings of the IDMC and blinded review of the digital retinal photographs were confirmed by a study-specific Ophthalmology Advisory Board, which consisted of 4 ophthalmologists who 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 TQ.

Reviewer's Comments:

The vortex keratopathy see with TQ in Study 058 was not followed to resolution in all subjects; four subjects had ongoing keratopathy at last examination and two subjects were lost to follow-up. These subjects should have been followed to resolution of the keratopathy.

Pseudochromatic color plates (e.g. Ishihara) are not generally recommended for use as a gross estimate of acquired color loss and central visual dysfunction. They do not assess blue/yellow deficiencies which are the most common acquired defects.

The presence of abnormal retinal findings (reported as "retinopathy") indicates a potential problem with the drug product or the quality of the fundoscopic examinations and/or their interpretation. The expert ophthalmology panels did not conclude that retinal findings were absent; they concluded that the findings were not expected to impact vision. It is not clear how they arrived at this conclusion.

Study TAF106491

This was a 2-part Phase 1 study designed to assess the safety, tolerability, and pharmacokinetics of concomitant TQ and CQ in healthy subjects and to evaluate whether there is a clinically significant drug interaction between TQ and CQ.

Part 1 was a pilot study in 12 subjects to evaluate the safety, tolerability, and pharmacokinetics of the co-administered regimen using lower doses of CQ. Once this regimen was seen to be well-tolerated, Part 2 was initiated to evaluate clinically relevant doses of both drugs with a larger number of subjects to assess safety and drug interaction. TQ and CQ were co-administered to reflect the maximum combination dose investigated in *P. vivax*- infected subjects: CQ 600mg on Day 1, CQ 600mg/TQ 450mg on Day 2 and CQ 300mg/TQ 450mg on Day 3. Fifty-eight subjects were randomly assigned to treatment groups: 20 each in the CQ and TQ groups, and 18 in the CQ + TQ group.

Ophthalmic safety was assessed in all subjects by the following tests conducted at screening and at Day 28 and Day 56:

- Best corrected LogMAR visual acuity
- Color vision testing – Lanthony 40 hue
- Humphrey 10-2 visual field
- Digital retina photography
- Mesopic contrast threshold
- Slit lamp examination of the cornea with digital corneal photography at baseline. Digital corneal photography were to be performed at follow up visits (i.e., Day 28 and Day 56) only if corneal abnormalities (e.g., vortex keratopathy) were noted during the slit lamp examination.

One TQ subject in Part 2 had decreased acuity from baseline at Day 28; this had reversed by Day 56 (logMAR scores of -0.1, 0.3, and 0). One CQ+TQ subject in Part 1 had decreased acuity from baseline at Day 28; this had partially reversed by Day 56 (logMAR scores of 0.2, 0.5, and 0.3). Neither of these 2 subjects had retinal abnormalities identified from the independent grading of photos or reported eye-related AEs or had keratopathy. Per the applicant, the color perception results and visual field tests were similar between treatment groups.

With the exception of 1 CQ+TQ subject with new but not clinically significant keratopathy in 1 eye at Day 56 follow-up, there was no treatment emergent keratopathy. This subject showed no functional changes.

Reviewer's Comments:

Vortex keratopathy was seen in one CQ+TQ subject in one eye at Day 56; it would be uncommon to see drug-related keratopathy in one eye following systemic administration of these drugs for three days.

Study TAF112582

This is a 2-part, multi-center, double-masked, double-dummy, parallel group, randomized, active control study. Part 1 was a Phase 2b dose-ranging study that completed in March 2013, whereas Part 2 is a pivotal Phase 3 study scheduled to commence in April 2014.

Part 1 enrolled 329 subjects. Eligible subjects were randomized to 1 of 6 treatment groups:

- 600, 600, 300mg CQ (Day 1 to 3) + 50mg TQ single dose (Days 1 or 2); (N=55).
- 600, 600, 300mg CQ (Day 1 to 3) + 100mg TQ single dose (Days 1 or 2); (N=57).
- 600, 600, 300mg CQ (Day 1 to 3) + 300mg TQ single dose (Days 1 or 2); (N=57).
- 600, 600, 300mg CQ (Day 1 to 3) + 600mg TQ single dose (Days 1 or 2); (N=56).
- 600, 600, 300mg CQ (Day 1 to 3) + 15mg PQ once-daily for 14 days (Days 2 to 15); (N=50).
- 600, 600, 300mg CQ only regimen (Days 1 to 3); (N=54).

Following randomization, the study consisted of a treatment period of 14 days. Subjects stayed in the clinic and received directly observed therapy for Days 1 to 3, and were treated as outpatients for the remainder of the study. Subjects were followed up to Day 180.

The following ophthalmic assessments were carried out during in-patient stay prior to randomization:

- Best corrected visual acuity and color vision was assessed by standard methods.
- Humphrey 10-2 visual field in order to determine the threshold sensitivity of specific loci in the central retina, detection and definition of relative or absolute scotomas.
- Slit lamp examination of the cornea (to document and grade any corneal deposits) and retina.
- Retinal digital photography for the documentation of changes in the retinal morphology.

Repeat eye examinations were conducted at Day 29, Day 90 and Day 180 (only if Day 90 examination was abnormal), as well as at study withdrawal.

There were no reports or observations of keratopathy from the 93 subjects who underwent ophthalmic investigations (61/93 received TQ+CQ co-administration). No change from baseline was observed on review of visual acuity, slit lamp, and fundus photograph data. With the exception of 4 subjects who were reported with post-baseline changes in the results of their Humphrey visual field test there were no clinically meaningful changes or treatment-associated trends across the population cohorts in any of the other visual field or retinal tests. These 4 subjects had a shift from normal to abnormal in their Humphrey perimetry assessment on day 29 or 90, which had resolved by day 180.

A GSK ophthalmologist conducted an unblinded review of all ophthalmic data from this study. It was noted that for all of the visual fields reported to be abnormal in these subjects, the test-taking parameters, as assessed by the machine, were poor and unreliable.

Reviewer's Comments:

Vortex keratopathy was not seen in any subject after two systemic dosing (single dose or once-daily dosing for 14 days or once daily dosing for three days).

This GSK Summary Report does not specify what standard methods were utilized to measure color vision in Study TAF112582.

It is not clear why a GSK ophthalmologist conducted an unblinded review of all ophthalmic data from this study.

Reports from the GSK Worldwide Clinical Safety Database

(b) (4)

[redacted]

Reviewer's Comments:

Case narratives are presented.

1) *The vortex keratopathy reported in 5 subjects (Study 33) resolved completely after discontinuation of TQ.*

2) *A 22 year-old male developed periorbital cellulitis (study 30).*

3) *A 29-year-old male developed viremia (Study 33). 15 days after the first dose, the patient developed sudden onset of severe headache and blurred vision followed by rigor. The patient was reported to have had a two-day history of upper respiratory tract symptoms and sore throat. The patient was also noted to be lethargic and drowsy. Relevant test results included a negative malaria and Dengue screen. The patient was diagnosed with viremia.*

4) *A 19 year-old male developed a retinal disorder (Study 33). The patient did not experience any visual disturbances whilst receiving treatment with study medication. On* [redacted], *at the six month ophthalmological assessment, 16 days after the last dose, the following changes from baseline were found: visual acuity was unaltered, color vision was reduced by one Ishihara plate, and formal Amsler assessments were normal. On* [redacted], *a visual examination of the retina revealed minimal to moderate pigmentation of the macula, though it was within normal limits. A single pinpoint area of hyperfluorescence (a retinal pigment epithelium window defect) was observed at the edge of the foveal avascular zone of the left eye. No leakage of dye was noted and the area appeared to correspond to a drusen noted on color photography. The patient was asymptomatic. The patient was diagnosed as having retinal changes.*

5) *A 38-year-old male experienced a foreign body in the eye with pain (Study 45). This 2/18/14 submission does not include discussion of Study 45. On* [redacted], *18 days after the last dose, the patient experienced pain in the left eye due to an "intraocular foreign body." The "intraocular foreign body" was removed and the patient was treated for the event with ceftriaxone and topical antibiotics. The event resolved on an unspecified date. Note: it is unlikely that this patient had an intraocular foreign body – it is more likely he had a corneal foreign body.*

6) *A 23-year-old male developed a retinal disorder (Study 33). Following the six month treatment period, angiogram of the left eye revealed several perifoveal pinpoint areas of hyperfluorescence, which appeared early in the examination and persisted through to the late frames. There was also mild fluorescein leakage in several of these spots. An angiogram of the right eye was normal. Other ophthalmological assessments revealed corneal deposits. Visual acuity had improved from baseline and was 6/5, 6/5. Colour vision was unaltered from baseline, and formal Amsler assessments were normal. Visual examination revealed granulation of the retinal pigment epithelium (left eye only), indicating retinal changes. The patient was asymptomatic at this time, and had not experienced any visual disturbances while receiving treatment with study medication. The patient did not receive any treatment for the event. A repeat angiogram on* [redacted] *did not reveal any changes to the patient's condition. The most recent information received on* [redacted], *reported that the event was ongoing and owing to the nature of the event, was unlikely to resolve.*

7) *A 45-year-old female developed a visual field defect (Study 057). On* [redacted], *approximately three weeks after starting treatment with investigational product, the subject developed a mild reduction in visual field. A Humphreys visual field analyzer 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 investigational product was discontinued due to this event on* [redacted] *and the subject was withdrawn from the study. The subject received no treatment for this event. The event resolved on* [redacted] *approximately six weeks after onset.*

DTOP Summary statement regarding narratives: *the most common serious adverse event reported was vortex keratopathy. There were two reports of "retinal disorder" in subjects following six months of TQ therapy; these cases are unresolved. There was a single case of VF defect after three weeks of therapy; this case resolved.*

GlaxoSmithKline (GSK) and the Medicines for Malaria Venture (MMV) CONCLUSIONS

The potential for retinopathy with CQ in long-term use is acknowledged, but the proposed short-term dosing regimen for CQ (co-administered with TQ) in Phase 3 is identical to that used in the Phase 2b study, TAF112582, where no ophthalmic effects were observed. Consequently, GSK/MMV considers the risk of retinopathy with TQ+CQ use in Phase 3 to be very low.

On the advice of the 2009 Ophthalmic Advisory Board, an evaluation strategy was developed which was considered to be proportionate to the perceived risk and which would enable integration of new ophthalmic data with the existing ophthalmic safety database for TQ. As part of this strategy, it is proposed (b) (4)

Reviewer's Comments:

After reviewing the summary data in the GSK/MMV Summary Review of Ophthalmology Data, DTOP does not agree that (b) (4) *subjects on TQ collected in Phase 3 trials would be adequate to assess the level of ophthalmic risk.* (b) (4) *could only be expected to detect adverse events which occurred at a 3% adverse event rate or greater; we believe that the seriousness of potential retinal adverse events warrants additional evaluation. We would recommend that the applicant assess at least 300 subjects to adequately assess the level of ophthalmic risk.*

As noted throughout this review for several of the studies, the presence of retinal findings not seen at screening indicates a potential problem with the quality of the fundoscopic examinations and/or their interpretation or potential drug effect.

Planned Clinical Trial: Protocol No. 60PH04:

60° Pharmaceuticals LLC, is conducting the following clinical protocol, Protocol No. 60PH04: A Single Site, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Long-term Safety of Tafenoquine, under IND 129656. The objective is to assess the ophthalmic safety of tafenoquine after 12 months of exposure versus placebo in 600 healthy volunteers using Spectral Domain Optical Coherence Tomography (SD-OCT) and Quantitative Fundus Auto Fluorescence (qFAF).

This protocol was reviewed by DTOP and comments provided on 9/1/2017. The sponsor agreed to incorporate the Agency's comments for this protocol.

Status of 60PH04 as of January 2018:

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SUMMARY DTOP RECOMMENDATIONS

1) After reviewing the summary data in the GSK/MMV Summary Review of Ophthalmology Data, DTOP does not agree with the applicant that 100 subjects on TQ collected in Phase 3 trials would be adequate to assess the level of ophthalmic risk. One Hundred (100) subjects could only be expected to detect adverse events which occurred at a 3% adverse event rate or greater; we believe that the seriousness of potential retinal adverse events warrants additional evaluation. We would recommend that the applicant assess at least 300 subjects to adequately assess the level of ophthalmic risk.

   As noted throughout this review for several of the studies, the presence of retinal findings not seen at screening indicates a potential problem with the quality of the fundoscopic examinations and/or their interpretation or potential drug effect.

2) 60° Pharmaceuticals LLC, is conducting the following clinical protocol, Protocol No. 60PH04: A Single Site, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Long-term Safety of Tafenoquine, under IND 129656. The objective is to assess the ophthalmic safety of tafenoquine after 12 months of exposure versus placebo in 600 healthy volunteers using Spectral Domain Optical Coherence Tomography (SD-OCT) and Quantitative Fundus Auto Fluorescence (qFAF).

   This protocol was reviewed by DTOP and comments provided on 9/1/2017. The applicant/sponsor agreed to incorporate the Agency's comments for this protocol.

3) Provided that 60° Pharmaceuticals LLC, commits to adequately completing and reporting Protocol No. 60PH04: A Single Site, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Long-term Safety of Tafenoquine to the Agency, there is adequate safety data contained within this application to permit approval of the drug product with revisions to the proposed labeling. These proposed revisions are noted in track changes in the labeling attached to this review. The ophthalmic section in its entirety is recommended to read:

   <u>Ocular Adverse Reactions</u>
   Vortex keratopathy was reported in 21-93% of tafenoquine subjects in the studies which included ophthalmic evaluations (study 33 and study 57 and study 58). The keratopathy resolved within one year after drug cessation. Retinal abnormalities were also noted in <1% of tafenoquine subjects.
   A total of 7 serious treatment related adverse events (SAEs) were reported in tafenoquine-treated subjects in the studies which included ophthalmic evaluations. There were 5 serious reports of keratopathy and two serious reports of retinal disorders.

Questions:

1. From an ophthalmologic perspective, is tafenoquine reasonably safe for use for up to 6 months of continuous dosing?

   DTOP Response: Yes. Tafenoquine reasonably safe for use for up to 6 months of continuous dosing provided the suggested revisions regarding ophthalmic findings are made to the proposed labeling.

2. What ophthalmologic monitoring, if any, should be conducted for individuals on tafenoquine prophylaxis?

   DTOP Response: Ophthalmologic monitoring is not recommended provided the applicant commits to adequately completing and reporting Protocol No. 60PH04: A Single Site, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Long-term Safety of Tafenoquine to the Agency. Upon completion of the trial, the data can be reviewed for reassessment of the need for ophthalmic monitoring.

William M. Boyd, M.D.
Clinical Team Leader

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
05/04/2018

WILEY A CHAMBERS
05/04/2018