Ms Lyn Beverley
Committee Secretary
Senate Foreign Affairs, Defence and Trade References Committee

Dear Ms Beverley

Thank you for the opportunity to respond to Mr. McCarthy's comments. Given the time constraints and in the interests of brevity I am limiting my comments to three key points. It is acceptable if this response is published.

Mr. McCarthy asserts, in essence, that all quinolines cause permanent brain lesions, that "tafenoquine is more neurotoxic than mefloquine", and that the non-clinical toxicology package presented to regulators was insufficient. We feel that our original letter of July 31st, and the submissions of independent scientists, adequately present the literature and data showing why this is not the case. However, we wish to draw your attention to the FDA presentation slides from 60P's advisory committee in which the Agency stated publicly that the toxicology package submitted adequate, there was not evidence of neurotoxicity like earlier 8-aminoquinolines (plasmocid), and that further non-clinical studies would not be helpful (see Slide 76 of 122, in attached document).

Mr. McCarthy states that our key safety publication for the approved ARAKODA dose (Novitt-Moreno et al, attached) is "fraudulent". In good faith, we do not understand why he would say this. As we also stated in our response to Dr. Quinn, the key factual findings of this paper, a 5.1% incidence of psychiatric events (regardless of relatedness to study drug) in the ADF Timor deployment and a small (approx. 1%) increase in psychiatric events amongst civilians taking tafenoquine versus placebo, is exactly what the FDA reported in their backgrounder for the 60P advisory committee meeting (see p45, attached) and/or reflected in the U.S. prescribing information for ARAKODA (see p7, attached). The FDA audited the ADF studies as part of their review of our dossier.

Mr. McCarthy's assertion that 60P has no interest in further evaluating the safety profile of ARAKODA is disappointing and false. Prior to marketing approval in the U.S., 60P and its partners committed to conducting a long-term study in which the safety and tolerability of the drug is being evaluated following 12 months exposure (current safety database is six months). This study will take several years and is being conducted at considerable expense. This study includes, as secondary endpoints, specific and validated neuropsychiatric assessments to monitor those events which were elevated in incidence in the ADF Timor deployment (general psychiatric events, insomnia and motion sickness/dizziness). Since we attribute the higher incidence of such effects to the operational environment, not tafenoquine, we expect a similarly low incidence of psychiatric events to be reported in the placebo and tafenoquine arms of this study. More details of the study can be found at www.clinicaltrials.gov (reference number NCT03320174). Additional studies in pediatric subjects and travelers are being planned with regulatory input from FDA.

Overall, 60P's position, supported by the data cited in this and two other letters to the Committee and in the testimony of independent scientists, is that tafenoquine does not meaningfully increase the risk of psychiatric events in a civilian population, and that there is

no evidence that the approved dose of ARAKODA causes permanent brain lesions or increases the risk of severe psychiatric adverse events. We hope the Committee is able to find a way to get Australian veterans the resources and medical care they deserve without attributing blame to an important new tool for global malaria eradication.

Geoffrey S. Dow
CEO/Chairman
60 Degrees Pharmaceuticals LLC
1025 Connecticut Ave NW, Suite 1000
Washington, DC 20036
United States

FDA Introductory Comments

NDA 210607: Tafenoquine for the prevention of malaria

Antimicrobial Drugs Advisory Committee Meeting

July 26, 2018

Yuliya Yasinskaya, MD

Medical Team Leader, Division of Anti-Infective Products

FDA

Introduction

- NDA 210607: Tafenoquine tablet, 100mg
- Applicant: 60 Degrees Pharmaceuticals
- NDA granted priority review
- Currently approved drugs for malaria prophylaxis:
  - Atovaquone/proguanil
  - Doxycycline
  - Mefloquine
  - Primaquine

Indication

Prevention of Malaria in Adults for up to 6 months of Continuous Dosing

Anticipated Clinical Regimen (TQ-ACR) Dosing

- 200 mg dose (two 100 mg tablets) daily for 3 days prior to travel to a malarious area
- 200 mg dose (two 100 mg tablets) weekly while in malarious area
- 200 mg dose (two 100 mg tablets) once within a week after return from a malarious area

Development Program

- Five randomized, double-blind efficacy/safety trials evaluated TQ-ACR:
  - Three trials compared TQ-ACR to placebo in semi-immune population
    - 043
    - 045
    - 030
  - Single trial compared TQ-ACR to mefloquine in non-immune military deployed to East Timor (033)
  - Single challenge study in healthy volunteers (TQ2016-02)
- Ophthalmic/renal safety study (057)

Efficacy

- In two trials 043 and 045, TQ-ACR was superior to placebo for the protective efficacy (PE) endpoint in all randomized subjects
  - Study 043, week 15: Parasitemia: Placebo 91.9%, TQ-ACR 24.6%. PE: 73.3%, 95%CI (54.0, 84.5), $p < 0.001$
  - Study 045, week 12: Parasitemia: Placebo 93.6%, TQ-ACR 26.9%. PE: 71.3%, 95%CI (55.8, 81.4), $p < 0.001$
  - Source data for studies 043 & 045 not available for FDA audit
- In trial 033, TQ-ACR was compared to mefloquine (MQ) for the prophylactic success at 26 weeks
  - TQ-ACR 96.1% vs MQ 96.9%, difference -0.78%, 95%CI (-3.71%, 3.57%)
  - Attack rate is unknown, NI margin cannot be justified
  - Supportive
- In trial 030 TQ-ACR was compared to placebo and MQ was positive control
  - Initial erroneous slide reading; Blinded re-read
  - Not a concern for efficacy
- In malaria challenge trial (TQ2016-02) TQ-ACR was superior to placebo
  - Success: TQ 100%, placebo 0%, $p < 0.0005$

Safety

- In five Phase 2/3 trials, 825 healthy subjects were exposed to TQ-ACR, 529 of them received TQ-ACR for the proposed duration of 6 months
  - Hemolysis
  - Methemoglobinemia
  - No QT prolongation potential of greater than 20 msec
  - Psychiatric adverse reactions (sleep disturbances), serious psychiatric adverse reactions primarily in patients with underlying psychiatric history
  - Ocular safety findings (keratopathy)

Outline for the Day

- Presentations by the Applicant
- Presentations by the FDA
  - **Efficacy** by Xianbin Li, Ph.D.
  - **Nonclinical findings** by Owen McMaster, Ph.D.
  - **Safety** by Sheral Patel, M.D.
- Clarifying Questions
- Lunch
- Open Public Hearing
- Questions to the committee

Question 1

- Has the applicant provided substantial evidence of the effectiveness of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing?
  - If yes, please provide any recommendations concerning labeling.
  - If no, what additional studies/analyses are needed?

Question 2

- Has the applicant provided adequate evidence of the safety of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing?
  - If yes, please provide any recommendations concerning labeling.
  - If no, what additional studies/analyses are needed?

U.S. FOOD & DRUG ADMINISTRATION

Efficacy Evaluation of Tafenoquine in the Prophylaxis of Malaria

Xianbin Li
Statistical Reviewer
Division of Biometrics IV

Introduction

- Indication: prophylaxis of malaria in adults for a period of up to 6 months.
- Dosage:
  - A loading dose of 200 mg, once daily for 3 days before travelling to a malarious area
  - A maintenance regimen of 200 mg once weekly while in the malarious area
  - 200 mg one time in the week following exit from the malarious area

Introduction

- 3 placebo-controlled trials:
  - Study 043: Placebo-controlled studies in **semi-immune** subjects
  - Study 045: Placebo-controlled studies in **semi-immune** subjects
  - TQ-2016-02: Placebo-controlled challenge study in **non-immune** subjects
- These trials provide evidence of TQ efficacy.

Introduction

- Two additional studies reviewed:
  - Study 033: Active-controlled study in non-immune subjects – difficult to interpret
  - Study 030: Placebo-controlled studies in semi-immune subjects – did not show an effect of TQ
    - Positive control also did not show effect
    - Possible slide reading errors
    - Not pointing to evidence against TQ

Study 043: Study Design

- Phase IIb, placebo-controlled, single-center study in Kenya (*P. falciparum* malaria).
- Healthy subjects received a 3-day presumptive course of halofantrine to eliminate any existing *Plasmodium* parasitemia.

Study 043: Study Design

- Then randomized into one of the 4 groups:
  - TQ load only: 400 mg x 3 days
  - TQ low dose: 200 mg x 3 days, then weekly for 10-15 weeks
  - TQ high dose: 400 mg for 3 days, then weekly for 10-15 weeks
  - Placebo
- Visits: Day 1 of loading doses, then weekly (including additional 4 weeks of follow-up).

Study 043: Study Design

- Key Inclusion Criteria
  - Healthy subjects (male or female)
  - Age of 18-55 years
- Key Exclusion Criteria
  - Any cardiovascular, liver, neurologic, or renal functional abnormality
  - Use of antimalarial drugs within 2 weeks of study initiation
  - G6PD deficiency

Study 043: Primary Endpoint

- **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.

Study 043: Analysis Populations

- Applicant: “ITT efficacy” (intent-to-treat: clearance treatment + loading dose + at least one weekly dose) and “Efficacy” populations (ITT+ at least one on-therapy smear).
- FDA: “**All randomized population**” (all randomized subjects).

Study 043: Analysis Method

- **Protective efficacy (PE)** at Week 15, where PE was defined as:

$$PE = \frac{I_{placebo} - I_{drug}}{I_{placebo}} = 1\text{-}RR$$

0: no protection. 1: 100% protection.

Study 043: Statistical Methods

- No adjustment for multiple comparisons.
- FDA used Bonferroni method with type I error adjusted to 0.05/3=0.017.
- Chi-square test for parasitemia proportion comparison.
- 98.3% confidence intervals (CI).

Study 043: Baseline Characteristics

	Placebo (N=62)	TQ Load only (400 mg) (N=64)	TQ Low Dose (200 mg) (N=61)	TQ High Dose (400 mg) (N=62)
Randomized	62	64	61	62
Males, n(%)	34 (55%)	38 (59%)	42 (69%)	37 (60%)
Mean age (yrs)	32.3	32.1	33.5	31.7

Only had limited data

Study 043: Efficacy Results, 15 weeks

	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, n(%)	57 (91.9)	26 (40.6)	**15 (24.6)**	11 (17.7)
Actual	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)
Adverse event (AE)	0	1	**1**	0
Loss to Follow-up (FU)	2	7	**1**	3
Protocol Deviation	1	2	**6**	2
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

Study 043: Efficacy Results

- The majority of the subjects with observed parasitemia (99% or 78/79) were infected with *P. falciparum*.
- *P. malariae* parasites were only detected in one subject in the TQ load only group.

Study 043: Efficacy Results, 15 weeks

Parasitemia, n/N(%)	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)

Single race, single center, no weight data

Study 043: Conclusion

- This study demonstrated the efficacy of TQ 200 mg, compared with the placebo group.

Study 045: Study Design

- A Phase II/III, placebo-controlled trial of multiple doses in Ghana.
- Prior to study drug administration, subjects received an 18-day antimalarial radical cure treatment.

Study 045: Study Design

- Then randomized (2:2:2:2:2:1) to one of the groups: TQ 25, 50, 100, 200 mg, placebo and a mefloquine (MQ) group.
- Treatment: loading dose for 3 days + 12 weekly doses.
- Visit: Day 1 of loading doses, and then weekly (including 4 weeks of follow-up phase).

Study 045: Study Design

- Inclusion Criteria
  - Subjects in good general health
  - Males aged 18 to 60 and females aged 50 to 60 to exclude women in reproductive ages
- Exclusion Criteria: Very similar to Study 043.

Study 045: Primary Endpoint

- **Parasitemia** by Week 12: the first occurrence of malaria infection as documented by a single positive blood smear from both field microscopists.

Study 045: Analysis Populations

- Applicant: **Full data set** - all subjects who completed the radical cure phase successfully, were randomized, completed the loading dose, received at least one dose of weekly prophylactic medication, and had at least one efficacy assessment.
- FDA: **Safety data set** - all randomized subjects who completed the radical cure phase successfully and started the randomized treatment.

Study 045: Analysis Method

- CI for PE calculated.
- No control for multiple comparisons pre-specified.
- FDA: Bonferroni adjustment for the 4 TQ vs placebo comparisons (type I error was 0.05/4=0.0125.
- Confidence level: 98.75%.

Study 045: Baseline Characteristics

	Placebo	TQ 200 mg	MQ
Randomized	96	94	48
Safety	94	93	46
Males, n(%)	62 (66.0)	61 (65.6)	32 (69.6)
Mean age for males	39	40	36
Mean age for females	53	54	53

Study 045: Efficacy Results, Week 12

	Placebo (N=94)	TQ 200 mg (N=93)	MQ (N=46)
Parasitemia, n(%)	88 (93.6)	25 (26.9)	8 (17.4)
Actual	86	12	6
Missing (discontinued)	2 (2.1)	13 (14.0)	2 (4.3)
AE	1	8 (8.6)*	0
Non-compliance	1	5 (5.4)	2 (4.3)
PE (%)		**71.3**	81.4
98.75% CI for PE (%)		**55.8**, 81.4	58.4, 91.7

*3 Hb reduced, 5 ALT increased.

Study 045: Efficacy Results

- The majority of the subjects with observed parasitemia (98% or 183/187) were infected with *P. falciparum*.
- *P. malariae* parasites were only detected in 4 subjects in the placebo group (1 in Week 3 and 3 in Week 5).

Study 045: Subgroup Results

Parasitemia, n/N(%)	Placebo	TQ 200 mg	MQ
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)

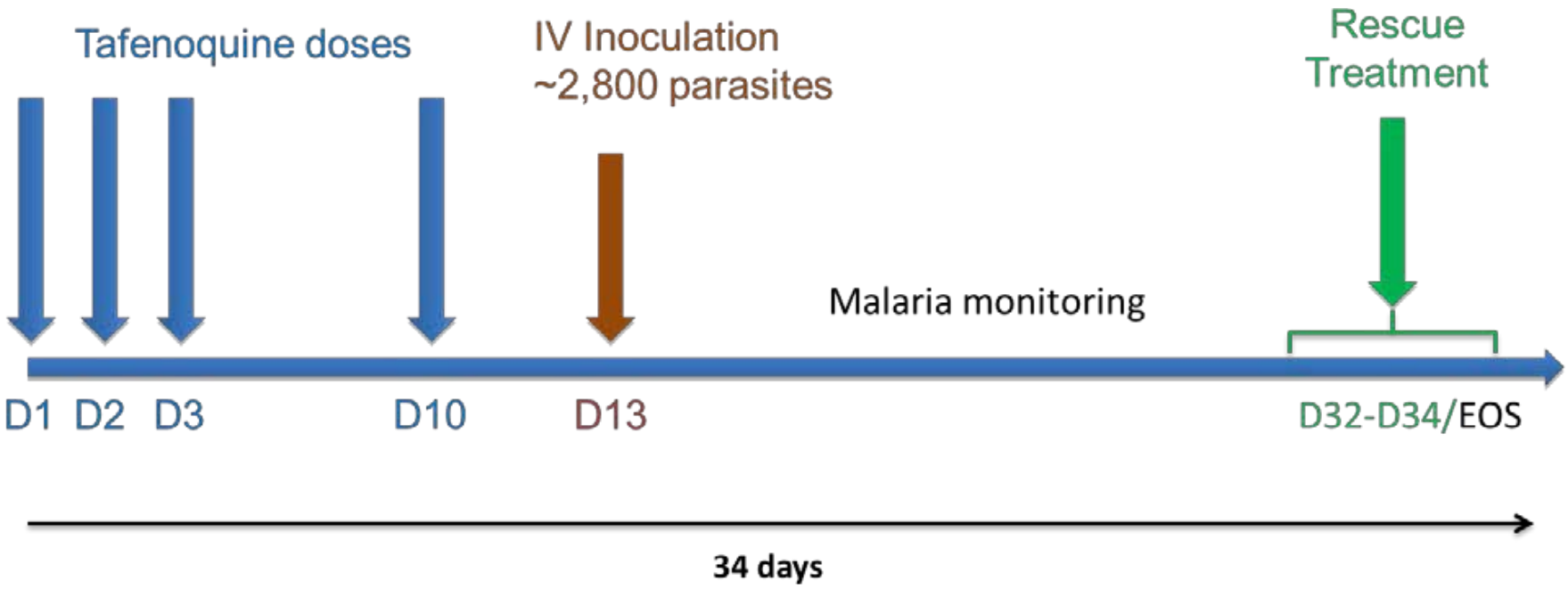
Study 045: Results by Site

Parasitemia, n/N(%)	Placebo (N=94)	TQ 200 mg (N=93)	MQ (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)

Study TQ-2016-02: Challenge Study

- Phase 1b, placebo-controlled study conducted in Australia in healthy, non-immune adults to determine the efficacy of TQ after blood stage *P. falciparum* challenge.

Study TQ-2016-02: Study Design



Source: NDA submission, study report

Study TQ-2016-02: Study Design

- 16 subjects were randomized (3:1) to one of the 2 groups (TQ or placebo).
- The efficacy endpoint was malaria by the end of study (Day 32-34) based on parasitemia and clinical symptoms.

Study TQ-2016-02: Analysis

- **ITT population**: all randomized participants. No subjects were removed from any analysis.
- **Analysis**: Proportion of malaria by the end of study was compared using Fisher's exact test.

Study TQ-2016-02: Demographic factors

	Placebo (N=4)	TQ (N=12)
Males, n(%)	2 (50)	4 (33.3)
Mean age (yrs)	34.3	25
Race white, n(%)	3 (75)	12 (100)

Study TQ-2016-02: Results

- All 4 placebo subjects developed malaria, starting from Days 20 or 21.
- All TQ subjects were PCR negative.

	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**

All placebo subjects received rescue treatment after developing malaria.
All TQ subjects, close to the end of the study.

Study 033: Study Design

- Phase III, active-controlled, double-dummy study.
- For prevention of *P. falciparum* and *P. vivax* malaria in East Timor in non-immune Australian soldiers.

Study 033: Study Design

- Subjects were randomized 3:1 to

	Prophylactic Phase (26 weeks)	Relapse follow-up Phase (24 Weeks)
TQ	Loading + maintenance doses	Placebo
MQ	Loading + maintenance doses	PQ (15 mg twice daily for 14 days)

MQ: mefloquine. PQ: primaquine.

Study 033: Study Design

- Inclusion Criteria: Healthy male or female subjects between the ages of 18 and 55 years.
- Exclusion Criteria:
  - Demonstrated glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - History of allergy or intolerance to MQ, PQ or any other 8-aminoquinolines.
  - Clinically significant abnormalities

Study 033: Primary Endpoint

- **Prophylactic success** during the prophylactic phase: no clinical malaria. Clinical malaria defined as single positive smear with concurrent clinical signs and symptoms consistent with malaria infection.

Study 033: Analysis Populations

- FDA: **ITT population**: All randomized subjects who took at least one dose of prophylactic study medication during the prophylaxis treatment period.
- Applicant: **Per-Protocol (PP) population**

Study 033: Statistical Methods

- Difference in prophylactic failure rates with a 95% CI.
- Attempted to establish noninferiority of TQ to MQ.

Study 033: Demographic/baseline

	TQ (N=492)	MQ (N=162)
Age (yrs): mean (SD)	25.4 (5.2)	26.0 (6.5)
Male	478 (97.2)	154 (95.1)
Weight (kg): Mean (SD)	80.95 (11.9)	81.34 (12.2)
Race: White, n(%)	484 (98.4)	160 (98.8)
History of malaria, n(%)	15 (3.0)	4 (2.5)
Malaria attacks in last 6 months, n(%)	9 (1.8)	1 (0.6)
At least one medical condition, n(%)	95 (19.3)	41 (25.3)

Study 033: Results

Prophylactic outcome (26 weeks)

	TQ (N=492)	MQ (N=162)
Success	473 (96.1%)	157 (96.9%)
Missing	19 (3.9%)	5 (3.1%)
Difference in success proportion (TQ-MQ) [Exact 95% CI]	-0.78% [**-3.71%,** 3.57%]	

Study 033: Results

Prophylactic outcome during the study (50 weeks)

	TQ (N=492)	MQ (N=162)
Success	468 (95.1%)	156 (96.3%)
Failure (*P. vivax*)	4 (0.8%)	1 (0.6%)
Missing	20 (4.1%)	5 (3.1%)
Difference in success proportion (TQ-MQ) [95%CI]	-1.2% [-4.7%, 2.3%]	

Missing subjects had no smear and malaria symptom data during the relapse follow-up phase

Study 033: Noninferiority

- Difficult to estimate a placebo attack rate for subjects in the study.
- Evidence that malaria was present in the region.
- Cannot to extrapolate how much soldiers were exposed to malaria pathogen.
- Did lack of malaria seen during prophylaxis phase point to high efficacy or limited exposure.
- Study provides important reassuring evidence in non-immune subjects.

Study 030: Study Design

- Placebo- and active-controlled
- Semi-immune population, Western Kenya
- Subjects received 3-day of halofantrine to clear any existing parasitemia.
- Malaria-free subjects were randomized to one of the groups: placebo, TQ, and MQ
- Efficacy assessment of prophylactic failure at week 25

Study 030: Study Results
Original Slide Reading (Week 25)

	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: Study 030 Re-analysis Report

Did not show any effect, even for MQ

Study 030: Study Results
Unplanned, Blinded Slide Re-reading

Initial Reading	NAMRU-2 Re-read			
	Positive	**Negative**	**Missing**	**Total**
Positive	**31**	220	0	251
Negative	5	507	0	512
Missing	0	3	0	3
Total	36	730	0	766

Source: Study Report 030, Table 33.

The lack of an effect of TQ seen in Study 030 does not appear to be a cause of concern.

NDA 210607: Summary

Study	Population	Treatment	Parasitemia	PE [Adjusted CI]/ Difference in failure
043	ITT	Placebo	57/62 (91.9%)	
		TQ	15/61 (24.6%)	PE: 73.3% [54.0%, 84.5%]
045	mITT	Placebo	88/94 (93.6%)	
		TQ	25/93 (26.9%)	PE: 71.3% [55.8%, 81.4%]
TQ-2016-02	ITT	Placebo	4/4 (100%)	
		TQ	0/12 (0%)	Diff: 100%, significant
033	ITT	MQ	5/162 (3.1%)	
		TQ	10/492 (3.9%)	Diff: 0.78%[-3.57%, 3.71%]

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Tafenoquine: Nonclinical Pharmacology and Toxicology

Owen McMaster, PhD

Pharmacology/Toxicology Reviewer, DAIP

Nonclinical Pharmacology Toxicology Program

- Synthetic analogue of primaquine (8-aminoquinoline)
- Cationic amphiphilic compound
- Pharmacology
- Pharmacokinetics
- Toxicology
  - Single and repeat dosing
  - Genotoxicity
  - Reproductive Toxicology
  - Juvenile Toxicology
  - Carcinogenicity

Pharmacology

- Cardiovascular/pulmonary
- Cardiovascular (hERG, Purkinje fibers)
- Neurobehavioral assessment

Evaluation of Neurotoxic Potential

- Single oral dose, neurobehavioral assessment in adult rats
- Multiple dose, oral, juvenile toxicity study in rats

Single Oral Dose Neurobehavioral Assessment

- Rats (6/sex/group) single oral gavage dose of tafenoquine (TQ)
- Doses 125, 250 or 500 mg/kg
- Neurofunctional assessments
  - Functional Observational Battery (FOB)
  - Motor activity

Single Oral Dose Neurobehavioral Assessment

Timepoint	Observations
Day prior to dosing	FOB + Locomotor activity
30 mins. postdose	FOB
3 hours postdose	FOB
6 hours postdose	Locomotor activity
24 hours postdose	Locomotor activity
48 hours postdose	Locomotor activity

Functional Observational Battery

grip strength	landing foot splay	tremors
posture	piloerection	gait
eyelid closure	chromodacryorrhea	pupil response
vocalization	convulsions	ease of locomotion
air righting	salivation	exophthalmia
ease of removal	response to visual approach	reactivity to handling
arousal	auditory assessments	stereotypy
pinna reflex	proprioception	pain perception
fasciculation	body temperature	condition of coat
unformed feces	number of fecal pellets	number of pools of urine

Motor Activity

- 60 minute session (12 x 5 minutes)
- Total horizontal and vertical recorded
- No drug-related adverse findings.
- Lowest dose estimated at 13-fold human dose based on C_{max} comparisons

Oral Juvenile Toxicity Study in Rats

- Juvenile rats (dosed postnatal day (PND) 7-62)
- Tafenoquine doses
  - 0 (vehicle), 5, 15 or 25 mg/kg orally every five days
  - PND 27 increased to 0, 10, 20 or 50 mg/kg every five days
  - Two-weeks drug-free
  - Motor activity
  - Pre-pulse inhibition of auditory startle response and
  - Learning and memory ability (Morris water maze)
- No drug-related effects on neurobehavioral function
- Lowest dose estimated at 7-fold human dose based on C_{max} comparisons

Toxicology

- Single- and Repeat-dose studies (6 months rat, 1 year in dogs)
- Reproductive performance (rats)
- Embryofetal development (rats, rabbits)
- Pre- and post-natal development (rats)
- Carcinogenicity (2 years in rats and mice)
- *In vitro* and *in vivo* genotoxicity studies

Adverse Events of Special Interest

- Blood
  - Methemoglobinemia / Mild anemia/ Reticulocytosis
- Kidney
  - Nephrosis (may reflect protein (hemoglobin) reabsorption consistent with oxidative stress driven red blood cell damage)
  - Increased renal tumors (male rat)
- Lung
  - Increased numbers of foamy macrophages, eosinophilic material in alveoli, phospholipidosis
  - Increased lung weight
- Liver
  - Increased weight, subacute inflammation, apoptosis, small increases in plasma enzyme markers
  - Cytoplasmic vacuoles and hemosiderin deposition (partially reversible)
- Reproductive
  - Abortions (rabbit)

Carcinogenicity

- ICH S1A: The need for carcinogenicity studies of pharmaceuticals
- Rats and mice, dosed daily (lifetime)
- Renal tumors in male rats

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1A/Step4/S1A_Guideline.pdf

Renal Tumors in Rat Carcinogenicity Study

Tumor	Tafenoquine dose (mg/kg)					
	0 Control	0 Control	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

Carcinogenicity

- Renal tumors in male rats
- No tumors in mice or female rats
- Non-genotoxic
- Unclear if this finding indicates a risk to humans taking TQ for prophylaxis

Reproductive Toxicology

- Pregnant rabbits dosed with TQ during organogenesis
- High dose: Abortions in the presence of maternal toxicity (decreased food consumption and body weight, 16 mg/kg)
- Mid dose: Abortion in the absence of maternal toxicity (7 mg/kg, about half the clinical dose based on body surface area comparisons)

Adequacy of Nonclinical Neurotoxicity Assessment

- Published data indicate that some 8-aminoquinolines are associated with neurotoxicity
- Monkeys, rats, and dogs are sensitive to the neurotoxicity of the 8-aminoquinoline, plasmocid
- Evidence of adverse neurologic symptoms and histological changes (Richter 1949; Schmidt 1949)

Plasmocid Neurobehavioral Effects

- Schmidt IG, (1949)
- Monkeys - Hyperesthesia, nystagmus, loss of pupillary reflexes, loss of equilibrium, incoordination, difficulty walking.

- Dogs - Paralysis of the nictitating membrane, abdominal cramping and repeated attempts to evacuate bowels, intestinal intussusceptions, bradycardia, slowed respiration (plus tremors, increasing muscle weakness, ataxia, and loss of deep reflexes per Richter et al. 1949)

- Rats - Paralysis of the lower jaw and tongue
- Mice - Ataxia, paralysis of the hind limbs/tongue/ lower jaw

Histopathology Findings - Plasmocid

- Monkeys - severe degenerative lesions in the spinal cord, brain stem and cerebellum

- Dogs - severe lesions limited to in the dorsal motor nucleus of the vagus and moderate lesions in the dorsal root ganglion, cortex and basal ganglion

- Rats - moderate/severe lesions the mesencephalic V nucleus

Neurotoxicity Conclusions

- Lethal doses of plasmocid produce a variety of effects which vary across species and across studies.
- Since
  - Neurobehavioral effects vary across species and across studies
  - Rats and dogs are sensitive to the neurotoxicity of plasmocid.
  - Brain lesions do not always predict neurobehavioral effects
  - Neurobehavioral effects do not always predict brain lesions
- Additional nonclinical studies would be difficult to interpret and are not warranted
- TQ was appropriately evaluated and was not associated with similar neurobehavioral or histological effects in rats or mice or dogs at clinically relevant doses

Conclusion

- The principal nonclinical toxicology findings were hematological, pulmonary, hepatic, renal and reproductive. Reversible or not adverse.

- TQ not associated with neurobehavioral or histopathology findings.

U.S. FOOD & DRUG ADMINISTRATION

NDA 210607
Tafenoquine

Presentation of Clinical Safety

Sheral Patel, MD
Medical Officer, DAIP

Pharmacokinetic (PK) Highlights

Absorption	Distribution
Tafenoquine (TQ) 2 x 100 mg tablet (Fed) • **Median T_{max} : 14 hours (range 6.1 – 72 hours)** • **Mean C_{max}:** 147 ng/mL (%CV 20.7%) • **Mean AUC_{inf}** : 70.1 hr*µg/mL (%CV 24.6%) TQ accumulation ratio upon multiple dose: 4.4	• Highly protein bound (>99.5%) • Mean Vd/F in healthy adult subjects: 2470 L (Inter-Individual Variability 24.1 %)
Metabolism	**Excretion**
• Slow and negligible in vitro CYP450 metabolism in human liver microsomes and hepatocytes • Following administration of TQ 400 mg once daily for 3 days to humans, unchanged TQ was the only notable drug related component in plasma at approximately 3.3 days following the first dose of TQ	• **Mean $T_{1/2}$: 16.5 days (range 10.8 – 27.3 days)** • Full excretion pathway of TQ in humans is unknown
Drug Interactions	
• **No significant effect of TQ on the PK of substrates of CYP2D6, 3A4, 2C9, and 1A2** • **No significant transporter interactions**	

Overview

1. Safety Review Approach
2. Exposure
3. Adverse Event Summary
4. Discontinuations/ Study Withdrawal
5. Serious Adverse Events
6. Treatment Emergent Adverse Events
7. Submission Specific Safety Issues (6)

1. Safety Review Approach

- More than 20 clinical trials included by the Applicant
  - Most conducted 1992 – 2006
- Pooled analyses
  - Conducted to detect potential low-frequency events
  - All subjects receiving the tafenoquine anticipated clinical regimen (TQ ACR), regardless of exposure duration, were included (Extended Dosing Safety Set)
  - Acknowledge inherent weaknesses in combining data from heterogeneous studies
  - Avoided drawing safety conclusions across treatment groups from the pooled analyses
- Submission-specific safety issues
  - Individual study data, as well as pooled data from select studies, were reviewed
- Several Agency disciplines contributed to safety review
  - Center for Drug Evaluation and Research
    - Division of Anti-Infective Products
    - Division of Cardiovascular and Renal Products
    - Division of Neurology Products
    - Division of Psychiatry Products
    - Division of Transplant and Ophthalmology Products
  - Center for Devices and Radiological Health
    - Ear, Nose and Throat Devices Branch

1. Safety Review Approach

Key Studies – Extended Dosing Safety Set

- **Study 033** *(Australian Defence Force)*
  - Phase 3, conducted 2000 –2001
  - Randomized, double-blinded, active comparator
  - Non-immune subjects, deployed military personnel
  - TQ ACR (n=492) vs. MQ (n=162)
  - Most number of subjects with planned TQ dosing for >23 weeks

- **Study 057** *(Healthy volunteer)*
  - Phase 1, conducted 2003 – 2006
  - Randomized, double blinded, placebo-controlled
  - Healthy volunteers, evaluate renal and ocular safety
  - TQ ACR (n=81) vs. placebo (n=39)
  - Planned TQ dosing for >23 weeks

- **Study 030, 043, and 045** *(Semi-immune)*
  - Phase 2/3 studies; Study **030**: 2000; **043**: 1997; **045**: 1998
  - All were randomized, double blinded, placebo-controlled
  - Study 030 and 045 also had active comparator
  - Semi-immune subjects in Kenya and Ghana
  - TQ ACR (n=252) versus comparators including other TQ doses, MQ (n=147) and/or placebo (n=256)
  - Planned TQ dosing 12 to 15 weeks

TQ= tafenoquine, MQ=mefloquine, ACR=anticipated clinical regimen (TQ 200 mg daily for 3 days, then 200 mg weekly.)

2. Exposure

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

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

2. Exposure

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

Extended Dosing Safety Set

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

3. Adverse Event Summary

Extended Dosing Safety Set

	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR)[1] (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[2]	0	0	0
At least one SAE[3]	47 (5.7%)	10 (3.4%)	11 (3.6%)
SAE[2] leading to study withdrawal	11 (1.3%)	1 (0.3%)	2 (0.6%)
At least one TEAE[4]	692 (83.9%)	189 (64.1%)	249 (80.6%)
TEAE[3] leading to study withdrawal	34 (4.1%)	10 (3.4%)	5 (1.6%)

[1]Anticipated Clinical Regimen (ACR): TQ 200 mg daily for 3 days, then 200 mg weekly.
[2]One subject received TQ 50 mg weekly and died due to suspected hepatocellular carcinoma.
[3]SAE=serious adverse event.
[4]TEAE=treatment emergent adverse event.

4. Discontinuations/ Study Withdrawal

- Most **common TEAEs** leading to study discontinuation in **TQ ACR**[1] group
  - increased ALT (n=6, 0.7%)
  - decreased hemoglobin (n=3, 0.4%)
  - decreased GFR (n=2, 0.2%)

- **SAEs** leading to study discontinuation
  - **TQ ACR** (selected)
    - visual field defect (n=1, 0.1%)
    - hemolytic anemia (n=1, 0.1%)
    - suicide attempt (n=1, 0.1%)
    - glomerular filtration rate decreased (n=2, 0.2%)
  - **Placebo**
    - metamorphopsia (n=1, 0.3%)
  - **MQ**
    - anxiety (n=1, 0.3%) and rash (n=1, 0.3%)

[1]**Anticipated Clinical Regimen (ACR):** TQ 200 mg daily for 3 days, then 200 mg weekly.
[2]**Metamorphopsia**: visual distortion in which straight lines appear curved.

5. Selected Serious Adverse Events

Extended Dosing Safety Set

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)
Number of subjects (%) with at least one SAE	**47 (5.7%)**	**10 (3.4%)**	**11 (3.6%)**
Keratopathy	5 (0.6%)	0	0
Glomerular filtration rate decreased	5 (0.6%)*	2 (0.7%)	0
Gastroenteritis	3 (0.4%)	0	0
Retinal disorder	2 (0.2%)	0	1 (0.3%)
Hemolytic anemia	1 (0.1%)*	0	0
Visual field defect	1 (0.1%)*	0	0
Suicide attempt	1 (0.1%)*	0	0
Anxiety	0	0	1 (0.3%)

**Includes subjects in TQ ACR group who discontinued from study due to SAE.*

6. Selected TEAEs ≥ 2%

Extended Dosing Safety Set

System Organ Class/ Dictionary Derived Term	TQ 200 mg daily x3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=295)	MQ 250 mg daily x3 days, then 250 mg weekly (n=309)
Ear and labyrinth disorders			
Vertigo, vertigo positional, motion sickness	3%	0%	3%
Gastrointestinal disorders			
Abdominal pain	8%	15%	13%
Diarrhea	13%	3%	11%
Nausea	6%	2%	6%
Vomiting	4%	2%	4%
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain, back pain, neck pain	21%	18%	24%
Arthralgia	7%	5%	10%
Myalgia	3%	9%	5%
Nervous system disorders			
Headache	22%	32%	30%
Dizziness	3%	3%	6%
Lethargy	3%	0%	4%

7. Submission Specific Safety Issues

1. Ophthalmic
2. Cardiac
3. Hematologic
4. Neurologic
5. Psychiatric
6. Hepatobiliary and Gastrointestinal

7. Submission Specific Safety Issues

Approach

- Describe known safety issues in labels for quinoline drugs approved for malaria prophylaxis or treatment.
- Discuss submission specific analyses.

Quinoline anti-malarials		
Drug	**Class**	**Initial Approval**
TQ	8-aminoquinoline	Under review for prophylaxis
PQ	8-aminquinoline	1952
CQ/h-CQ	4-aminoquinoline	1949
MQ	4-quinolinemethanol	1989

TQ=tafenoquine (not approved); PQ=primaquine; CQ=chloroquine; h-CQ=hydroxychloroquine; MQ=mefloquine

7.1 **Ophthalmic**

Quinoline anti-malarial labeling		
Drug	**Label Section (selected)**	**Issues (selected)**
PQ	None	-
CQ/h-CQ	Contraindications, Warnings	Ciliary body, cornea, retina, visual field defects; Irreversible retinal damage with long term use or high dosages
MQ	Warnings	Optic neuropathy, retinal disorders

7.1 **Ophthalmic**

Overview - Extended Dosing Safety Set

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)
Ophthalmic TEAEs leading to discontinuation			
Night blindness	1 (0.1%)	-	-
Visual acuity reduced	1 (0.1%)	-	-
Metamorphopsia	-	1 (0.3%)	-
Ophthalmic SAEs			
Keratopathy	5 (0.6%)[1]	-	-
Retinal disorder	2 (0.2%)	-	1 (0.3%)
Metamorphopsia	-	1 (0.3%)[2]	-
Ophthalmic TEAEs occurring ≥1% study subjects			
Conjunctivitis	24 (2.9%)	18 (6.1%)	13 (4.2%)

[1]All subjects in Study 033; [2]SAE led to discontinuation.

Metamorphopsia: visual distortion in which straight lines appear curved.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 33.

7.1 **Ophthalmic**

Overview - Extended Dosing Safety Set

Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)
Ophthalmic TEAEs leading to discontinuation	
Night blindness	1 (0.1%)
Visual acuity reduced	1 (0.1%)
Metamorphopsia	-
Ophthalmic SAEs	
Keratopathy	5 (0.6%) [1]
Retinal disorder	2 (0.2%)
Metamorphopsia	-
Ophthalmic TEAEs occurring ≥1% study subjects	
Conjunctivitis	24 (2.9%)

[1]All subjects in Study 033; [2]SAE led to discontinuation.

Keratopathy

Vortex keratopathy

- Drugs with cationinc amphilic structures can cause corneal epithelial deposits.
- No effect on visual acuity and few ocular symptoms.
- Deposits usually resolve with cessation of therapy.

All subjects with keratopathy enrolled in Study 033, which was one of 3 studies conducting ophthalmic assessments.

Metamorphopsia: visual distortion in which straight lines appear curved.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 33.

7.1 **Ophthalmic**

- Detailed ophthalmic assessments conducted in 3 studies
  - Cornea: **TQ is associated with reversible keratopathy.**
  - Retina: Potential problem with quality of fundoscopic examinations and/or their interpretation
- Ongoing healthy volunteer study (60PH04)
  - Characterize TQ ophthalmic effects over 1 year (TQ vs. placebo; 300 subjects/arm)

Keratopathy observed in studies conducting detailed ophthalmic assessments		
Study	**Tafenoquine**	**Comparator**
033	**TQ ACR:** 69/74 (93.2%) at 6 months Resolved in 42/69 at 3 months post-treatment, all resolved by 1 year.	**MQ**: 0/21 (0%)
057	**TQ ACR:** 15/70 (21.4%) during treatment Resolved in 14 subjects by 14 weeks of onset, and by 48 weeks in 1 subject.	**Placebo:** 4/32 (12.5%) All resolved by 6 weeks of onset
058	**TQ 400 mg/day for 3 days** (*P. vivax* treatment): 12/46 (26.1%) at Day 28 By Day 90, resolved in 6 subjects; ongoing in 4 subjects, and 2 subjects lost to follow-up	**Primaquine/Chloroquine:** 0/24 (0%) at Day 28

7.2 **Cardiac**

Quinoline anti-malarial labeling		
Drug	**Label Section (selected)**	**Issues (selected)**
PQ	Precautions	Potential QT prolongation
CQ/h-CQ	Adverse Reactions, Overdosage	Cardiac arrhythmias; cardiomyopathy
MQ	Warnings, Precautions	QTc Interval Prolongation; other cardiac effects

7.2 **Cardiac**

- No thorough QT study data submitted

- ECG data from Study 014
  - 58 healthy subjects received one of three TQ 200 mg formulations
  - Dose: 400 mg each day for 3 days
  - No significant relationship between TQ concentration and QTc interval changes
  - **No large mean increase (i.e. >20 ms) in the QTc interval for TQ 400 mg**

- Preclinical studies did not reveal QT liability

7.3 **Hematologic**

Quinoline anti-malarial labeling		
Drug	**Label Section (selected)**	**Issues (selected)**
PQ	Warnings, Precautions	Hemolytic anemia and G6PD deficiency; Anemia, methemoglobinemia, and leukopenia
CQ/h-CQ	Precautions, Adverse Reactions	Hemolytic anemia and G6PD deficiency; Pancytopenia, aplastic anemia, reversible agranulocytosis, thrombocytopenia and neutropenia
MQ	Precautions	Agranulocytosis and aplastic anemia

7.3 **Hematologic**

Overview – Extended Dosing Safety Set

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)
Hematologic TEAEs leading to discontinuation			
Hb decreased	3 (0.4%)	1 (0.3%)	-
Hemolytic anemia	2 (0.2%)	-	-
Platelet decreased	-	1 (0.3%)	-
Hematologic SAEs			
Hemolytic anemia	1 (0.1%)	-	-
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%)

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 29.

7.3 **Hematologic**

Overview – Extended Dosing Safety Set

Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)
Hematologic TEAEs leading to discontinuation	
Hb decreased	3 (0.4%)
Hemolytic anemia	2 (0.2%)
Platelet decreased	-
Hematologic SAEs	
Hemolytic anemia	1 (0.1%)
Hematologic TEAEs occurring ≥1% study subjects	
Anemia	10 (1.2%)
Leukocytosis	8 (1.0%)
Thrombocytopenia	10 (1.2%)

Hb decreased

All 3 subjects in Study 045, where study criteria had subjects discontinue for minor changes in laboratory parameters.

For all three cases, no treatment was required and TEAE resolved in 28 to 50 days.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 29.

7.3 **Hematologic**

Overview – Extended Dosing Safety Set

Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)
Hematologic TEAEs leading to discontinuation	
Hb decreased	3 (0.4%)
Hemolytic anemia	2 (0.2%)
Platelet decreased	-
Hematologic SAEs	
Hemolytic anemia	1 (0.1%)
Hematologic TEAEs occurring ≥1% study subjects	
Anemia	10 (1.2%)
Leukocytosis	8 (1.0%)
Thrombocytopenia	10 (1.2%)

Hemolytic anemia

- Both subjects G6PD negative.
- Hemoglobin drop
  - 14.4 g/dL to 9 g/dL at Day 3
  - 13.1 g/dL to 10.9 g/dL at Day 23
- One subject treated with multivitamins and ferrous sulfate, while the other received no treatment.
- Anemia resolved in both subjects.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 29.

7.3 **Hematologic**

Hemoglobin Decrease - Extended Dosing Safety Set

- TQ associated with decreases in hemoglobin levels.

Hemoglobin Change Decrease from Baseline – Interval Categories	**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)
≥1 to < 2g/dL decrease	293 (36%)	58 (20%)	80 (26%)
≥2 to <3 g/dL decrease	64 (8%)	11 (4%)	13 (4%)
≥3 g/dL decrease	19 (2%)	3 (1%)	5 (2%)

7.3 **Hematologic**

Methemoglobin Increase - Study 033 and 043

- TQ associated with increases in methemoglobin levels.
- No subject had a methemoglobin level ≥10% (where cyanosis may appear)

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

7.4 **Neurologic**

Quinoline anti-malarial labeling		
Drug	**Label Section (selected)**	**Issues (selected)**
PQ	Adverse Reactions	Dizziness
CQ/h-CQ	Precautions, Adverse Reactions	Muscular weakness or skeletal muscle myopathy; Auditory effects; Headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia, polyneuritis
MQ	Boxed Warning; Contraindications; Warnings; Precautions; Adverse Reactions	Dizziness or vertigo, tinnitus, and loss of balance; May increase risk of convulsions in patients with epilepsy; Headache, somnolence; Reports of sensory and motor neuropathies (including paresthesia, tremor and ataxia), hearing loss

7.4 Neurologic

Overview - Extended Dosing Safety Set

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)
Neurologic TEAEs leading to discontinuation			
Hyperesthesia	1 (0.1%)	-	-
Visual field defect	1 (0.1%)		
Headache	-	1 (0.3%)	-
Neurologic SAEs			
Headache	1 (0.1%)	-	-
Visual field defect	1 (0.1%)[1]	-	-
Loss of consciousness	-	1 (0.3%)	-
Neurologic TEAEs occurring ≥1% 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%)	-	11 (3.6%)

[1]SAE led to discontinuation.

Limitations for TQ studies:

- Systematic monitoring for neurologic symptoms not performed; may underestimate true incidence.
- Neurologic TEAEs after TQ discontinuation difficult to assess.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 35.

7.4 Neurologic

Overview - Extended Dosing Safety Set

Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)
Neurologic TEAEs leading to discontinuation	
Hyperesthesia	1 (0.1%)
Visual field defect	1 (0.1%)
Headache	-
Neurologic SAEs	
Headache	1 (0.1%)
Visual field defect	1 (0.1%)[1]
Loss of consciousness	-
Neurologic TEAEs occurring ≥1% study subjects	
Headache	178 (21.6%)
Dizziness	22 (2.7%)
Lethargy	24 (2.9%)

[1]SAE led to discontinuation.

Hyperesthesia

- Study 033
- 26-year-old White male, hepatitis B carrier positive, reported moderate hyperesthesia on Study Day 12.
- Prior to the TEAE, study personnel documented at least 1 episode of heavy alcohol use in the subject, together with alcohol-associated malaise while on study.
- Hyperesthesia was treated using unspecified non-medicinal modalities and resolved after 130 days.

Limitations for TQ studies:

- Systematic monitoring for neurologic symptoms not performed; may underestimate true incidence.
- Neurologic TEAEs after TQ discontinuation difficult to assess.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 35.

7.4 Neurologic

Overview - Extended Dosing Safety Set

Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)
Neurologic TEAEs leading to discontinuation	
Hyperesthesia	1 (0.1%)
Visual field defect	1 (0.1%)
Headache	-
Neurologic SAEs	
Headache	1 (0.1%)
Visual field defect	1 (0.1%)[1]
Loss of consciousness	-
Neurologic TEAEs occurring ≥1% study subjects	
Headache	178 (21.6%)
Dizziness	22 (2.7%)
Lethargy	24 (2.9%)

[1]SAE led to discontinuation.

Visual field defect

- Study 057
- 45-year-old female developed mild reduction in visual field approximately three weeks after starting treatment.
- Confirmed in both eyes by a visual field analyzer.
- No retinopathy observed.
- The subject received no treatment and the event resolved approximately six weeks after onset.

Limitations for TQ studies:

- Systematic monitoring for neurologic symptoms not performed; may underestimate true incidence.
- Neurologic TEAEs after TQ discontinuation difficult to assess.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 35.

7.4 **Neurologic**

Study 033 *(Australian Defence Force)*

- TQ ACR associated with neurologic TEAEs.
- Numerically lower or similar to MQ.

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

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

7.4 **Neurologic**

Study 057 (*Healthy volunteer)*

- TQ ACR associated with myalgia.

Adverse Event	**TQ ACR[1] N=81** n (%)	**Placebo N=39** n (%)
Headache[2]	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

[1]Anticipated Clinical Regimen (ACR): TQ 200 mg daily for 3 days, then 200 mg weekly.
[2]Includes headache and migraine.

7.4 **Neurologic**

Study 030, 043, and 045 *(12 to 15 week duration exposure, semi-immune)*

- TQ ACR associated with headache, myalgia, and dizziness.
- In general, TEAEs higher or similar to placebo, and lower than MQ.

Dictionary Derived Term	**TQ ACR[1] N=252** n (%)	**Placebo N=256** n (%)	**MQ N=147** n (%)[2]
Headache[3]	84 (33.3%)	78 (30.5%)	68 (46.3%)
Myalgia	24 (9.5%)	31 (12.1%)	14 (9.5%)
Dizziness, lightheadedness, fall	13 (5.2%)	8 (3.1%)	15 (10.2%)
Fatigue and lethargy	1 (0.4%)	1 (0.4%)	1 (0.7%)
Visual disturbance	1 (0.4%)	0	1 (0.7%)
Vertigo and tinnitus	0	0	2 (1.4%)

[1]Anticipated Clinical Regimen (ACR): TQ 200 mg daily for 3 days, then 200 mg weekly.
[2]Study 043 did not have a mefloquine arm
[3]Includes headache, migraine, sinus headache and tension headache.

7.5 **Psychiatric**

Quinoline anti-malarial labeling		
Drug	**Label Section (selected)**	**Issues (selected)**
PQ	None	-
CQ/h-CQ	Warnings, Adverse Reactions	Irritability, nervousness, emotional changes, nightmares, psychosis, suicidal behavior.
MQ	Boxed Warning; Contraindications; Warnings; Precautions; Adverse Reactions	Major psychiatric disorders, history of convulsions; Anxiety, paranoia, and depression to hallucinations and psychotic behavior; Sleep disorders (insomnia, abnormal dreams); Suicidal ideation and suicide

7.5 **Psychiatric**

Overview - Extended Dosing Safety Set - Most studies excluded patients with psychiatric history.

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)
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]
Psychiatric TEAEs occurring ≥1% study subjects			
Any within Psychiatric Disorders SOC[2]	32 (3.9%)	3 (1.0%)	10 (3.2%)
Any sleep symptom[3]	21 (2.5%)	3 (1.0%)	7 (2.3%)

[1]SAE led to discontinuation. [2]System Organ Class.
[3]Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.

Limitations for TQ studies:

- Systematic monitoring for psychiatric symptoms not performed; may underestimate true incidence.
- Psychiatric TEAEs after TQ discontinuation difficult to assess.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 36.

7.5 **Psychiatric**

Overview - Extended Dosing Safety Set

Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)	
Psychiatric TEAEs leading to discontinuation		
Depression	1 (0.1%)	
Suicide attempt	1 (0.1%)	
Anxiety	-	
Psychiatric SAEs		
Suicide attempt	1 (0.1%)[1]	
Anxiety	-	
Psychiatric TEAEs occurring ≥1% study subjects		
Any within Psychiatric Disorders SOC	32 (3.9%)	
Any sleep symptom[2]	21 (2.5%)	

[1]SAE led to discontinuation.
[2]Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somna

Depression

- Study 033
- A 28-year-old White male 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.
- His depression resolved after 87 days.

Limitations for TQ studies:

- Systematic monitoring for psychiatric symptoms not performed; may
- Psychiatric TEAEs after TQ discontinuation difficult to assess.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 36.

7.5 **Psychiatric**

Overview - Extended Dosing Safety Set

Dictionary Derived Term	TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) (n=825)
Psychiatric TEAEs leading to discontinuation	
Depression	1 (0.1%)
Suicide attempt	1 (0.1%)
Anxiety	-
Psychiatric SAEs	
Suicide attempt	1 (0.1%)[1]
Anxiety	-
Psychiatric TEAEs occurring ≥1% study subjects	
Any within Psychiatric Disorders SOC	32 (3.9%)
Any sleep symptom[2]	21 (2.5%)

[1]SAE led to discontinuation.

[2]Includes abnormal dreams, insomnia, nightmares, sleep disorder, and son

Suicide attempt

- Study 043
- A 24 year-old male was found to be acutely intoxicated with ethanol eight days after TQ exposure.
- The family reported that the subject had marital problems and had taken poison for suicide. He had ethanol on his breath, was combative and disoriented on presentation to the drug center.
- The subject was hospitalized and the event resolved 2 days later.

Limitations for TQ studies:

- Systematic monitoring for psychiatric symptoms not performed; may
- Psychiatric TEAEs after TQ discontinuation difficult to assess.

Note: Adapted from NDA 210607 Module 2.7.4 Summary of Clinical Safety, Table 36.

7.5 **Psychiatric**

Study 033 *(Australian Defence Force)*

- Psychiatric TEAEs numerically higher in TQ versus MQ group.
- Sleep symptoms similar in TQ and MQ groups.

Dictionary Derived Term	**TQ 200 mg daily for 3 days, then 200 mg weekly (ACR) N=492** n (%)	**MQ 250 mg daily for 3 days, then 250 mg weekly N=162** n (%)
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%)
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.

7.5 **Psychiatric**

Study 057 (*Healthy volunteer)*

- Any psychiatric adverse event similar in TQ and placebo groups.
- TQ associated with depression.

Adverse Event	**TQ ACR[1] N=81** n (%)	**Placebo N=39** n (%)
Any Psychiatric Adverse Event	**4 (4.9%)**	**2 (5.1%)**
Insomnia	2 (2.5%)	2 (5.1%)
Depression[1]	2 (2.5%)	0 (0%)

[1]Anticipated Clinical Regimen (ACR): TQ 200 mg daily for 3 days, then 200 mg weekly.
[2]Includes depression and depressed mood. One patient with depression also had an adverse event of bipolar disorder the same day, which is not enumerated separately.

7.5 **Psychiatric**

Study 030, 043, and 045 *(12 to 15 week duration exposure, semi-immune)*

- Any Psychiatric TEAE in TQ group numerically lower than MQ group, higher than placebo.
- Suicide attempt noted in TQ group.

Dictionary Derived Term	**TQ ACR[1] N=252** n (%)	**Placebo N=256** n (%)	**MQ N=147** n (%)[1]
Any Psychiatric TEAE	**3 (1.2%)**	**1 (0.4%)**	**3 (2.0%)**
Any Sleep Symptom[2]	1 (0.4%)	1 (0.4%)	0
Suicide attempt	1 (0.4%)	0	0
Anxiety[3]	1 (0.4%)	0	2 (1.4%)
Insomnia	0	1 (0.4%)	0
Loss of libido	0	0	1 (0.7%)

[1]Anticipated Clinical Regimen (ACR): TQ 200 mg daily for 3 days, then 200 mg weekly.
[2]Study 043 did not have a mefloquine arm. [3]Includes insomnia and sleep disorder. [4]Includes anxiety and neurosis.

7.5 **Psychiatric**

TEAEs in subjects with underlying psychiatric illness exposed to TQ

- Did not receive TQ ACR[1]
- However, time of onset of TEAE relative to TQ $t_{1/2}$ (~16.5 days) notable

Subject Age (years) /Sex	**Study**	**Dose**	**TEAE**	**Time of event**	**Underlying illness undisclosed at enrollment**
23/ Male	014	TQ 400 mg/day x 3 d	Paranoid ideation and hallucinations	25 d	Psychosis
22/ Male	050	TQ 350 mg single dose	Psychosis	3 wks	Two psychiatric hospitalizations
30/ Male	050	TQ 500 mg single dose	Psychosis	1 wk	Schizophrenia
44/ Female	001	TQ 8 mg single dose	Nervousness	3 wks	Self-medicating with diazepam, promethazine and tramadol

[1]**Anticipated Clinical Regimen (ACR):** TQ 200 mg daily for 3 days, then 200 mg weekly.

7.6 **Gastrointestinal and Hepatobiliary**

Quinoline anti-malarial labeling		
Drug	**Label Section (selected)**	**Issues (selected)**
PQ	Adverse Reactions	Nausea, vomiting, epigastric distress, abdominal cramps
CQ/h-CQ	Precautions; Adverse Reactions	Caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs; Hepatitis increased liver enzymes, anorexia, nausea, vomiting, diarrhea, abdominal cramps
MQ	Precautions; Adverse Reactions	Periodic evaluation of hepatic function with long term use; Drug-related hepatic disorders from asymptomatic transient transaminase elevations to hepatic failure; Nausea, vomiting, loose stools or diarrhea, abdominal pain

7.6 Gastrointestinal and Hepatobiliary

No major gastrointestinal or hepatobiliary toxicity observed with TQ ACR.

Extended Dosing Safety Set				
Withdrawal	2 subjects (0.2%): **Abdominal pain upper, Irritable bowel syndrome** (both SAEs) 6 subjects (0.7%): **Increased ALT** (all enrolled in Study 045)			
SAE	3 subjects (0.4%), 4 events: Abdominal pain, Abdominal pain upper, Irritable bowel syndrome, Diarrhea **No subjects met Hy's Law criteria**			
TEAE ≥1%	**Extended Dosing Safety Set**	Diarrhea	TQ 13%	placebo 3% MQ 11%
		Nausea	TQ 6%	placebo 2% MQ 6%
		Vomiting	TQ 4%	placebo 2% MQ 4%
		Abdominal pain	TQ 8%	placebo 11% MQ 14%
	Study 033	Diarrhea	TQ 18%	MQ 20%
		Nausea	TQ 7%	MQ 9%
		Vomiting	TQ 5%	MQ 6%
		Abdominal pain	TQ 5%	MQ 7%
Limitations	Difficult to assess TQ ACR safety when administered without food.			

Conclusions

	Issue	Key Safety Findings Associated with TQ ACR[1]
1	Ophthalmic	Reversible vortex keratopathy. Ongoing study may help clarify effects on vision and retina.
2	Cardiac	No large mean increase in QTc interval anticipated at TQ 400 mg, a dose higher than ACR.
3	Hematologic	Decrease in hemoglobin, hemolytic anemia, and methemoglobinemia.
4	Neurologic	Headache, lethargy, dizziness, vertigo/tinnitus, and myalgia.
5	Psychiatric	Psychiatric adverse reactions, particularly sleep disturbances. Adverse reactions leading to study discontinuation included suicide attempt and depression.
6	Gastrointestinal and Hepatobiliary	No major gastrointestinal or hepatobiliary toxicity observed with TQ ACR. Diarrhea, nausea, vomiting common TEAEs.

[1]Anticipated Clinical Regimen (ACR) - TQ 200 mg daily for 3 days, then 200 mg weekly.

Acknowledgements

Entire FDA Review Team


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FDA Briefing Document

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

July 26, 2018

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

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

Table of Contents

1 Introduction

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

2 Background

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

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

3 Product Information

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

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

4 Regulatory History

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

5 Clinical Pharmacology

Pharmacokinetics

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

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

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

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

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

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

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

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

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

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

6 Microbiology

Mechanism of Action

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

Activity against Plasmodium species

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

Resistance

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

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

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[1] Vennerstrom JL, Nuzum EO, Miller RE, Dorn A, Gerena L, Dande PA, Ellis WY, Ridley RG, and Milhous WK, 1999, 8-aminoquinolines active against blood stage *Plasmodium falciparum i*n vitro inhibit hematin polymerization. AAC 43 (3): 598-602.

[2] Lanners NH, 1991, Effect of the 8-aminoquinoline primaquine on culture-derived gametocytes of the malaria parasite *Plasmodium falciparum.* Parasitol Res 77: 478-481.

[3] Carvalho L, Luque-Ortega JR, Manzano JI, Castanys S, Rivas L, and Gamarro F, 2010, Tafenoquine, an antiplasmodial 8-aminoquinoline, targets *Leishmania* respiratory complex III and induces apoptosis. AAC 54 (12): 5344-5351.

[4] Carvalho L, Martínez-García M, Pérez-Victoria I, Manzano JI, Yardley V, Gamarro F, and Pérez-Victoria JM, 2015, The oral antimalarial drug tafenoquine shows activity against *Trypanosoma brucei.* AAC 59 (10): 6151-6160.

[5] Bhuyan AAM, Bissinger R, Stockinger K, and Lang F, 2016, Stimulation of suicidal erythrocyte death by tafenoquine. Cellular Physiology and Biochemistry 39: 2464-2476.

[6] Manzano JI, Carvalho L, Perez-Victoria JM, Castanys S, and Gamarro F, 2011, Increased glycolytic ATP synthesis is associated with tafenoquine resistance in *Leishmania major*. AAC 55 (3): 1045-1052.

7 Pharmacology/Toxicology (Nonclinical Neurobehavioral Assessment)

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

Tafenoquine Succinate: Neurobehavioral Assessment when Administered Orally in Rats

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

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

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

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

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

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

8 Overview of Clinical Development Program for the Prevention of Malaria

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

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

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

Table 2. Clinical Trials Relevant to Efficacy Assessment

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

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

8.1 Study 033

8.1.1 Study Design

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

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

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

Table 3. Study 033: Treatment Groups and Study Phases

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

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

Primary Efficacy Endpoint

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

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

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

Key Inclusion Criteria and Exclusion Criteria

Inclusion Criteria

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

Exclusion Criteria

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

8.1.2 Statistical Methodologies

Analysis Populations

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

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

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

Statistical Methods

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

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

8.1.3 Patient Disposition

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

Table 4. Study 033: Patient Disposition and Study Populations

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

AE=Adverse Event

Demographic Characteristics

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

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

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

Other Baseline Characteristics

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

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

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

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

8.1.4 Efficacy Results

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

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

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

Efficacy Results – Secondary and Other Relevant Endpoints

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

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

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

Evidence of Malaria Prevalence

Cross-sectional survey

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

UN/WHO Malaria Report and Published Data

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

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

Applicant's Justification of the Noninferiority Margin

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

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

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

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

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

Conclusions

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

8.2 Study 043

8.2.1 Study Design

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

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

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

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

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

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

Key Inclusion and Exclusion Criteria

Inclusion Criteria

The following inclusion criteria were used:

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

Exclusion Criteria

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

8.2.2 Statistical Methodologies

Analysis Populations

The following analysis populations are defined:

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

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

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

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

Statistical Methods

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

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

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

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

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

8.2.3 Patient Disposition

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

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

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

Table 9. Study 043: Patient Disposition

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

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

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

Demographic Characteristics

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

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

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

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

8.2.4 Efficacy Results

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

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

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

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

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

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

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

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

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

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

Conclusion

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

8.3 Study 045

8.3.1 Study Design

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

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

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

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

Inclusion and Exclusion Criteria

Inclusion Criteria

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

Exclusion Criteria

Exclusion criteria included, but were not limited to:

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

8.3.2 Statistical Methodologies

Analysis Populations

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

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

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

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

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

Analysis Methods

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

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

8.3.3 Patient Disposition

Table 13. Study 045: Patient disposition

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

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

Demographic Characteristics

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

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

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

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

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

8.3.4 Efficacy Results

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

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

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

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

Efficacy Results – Secondary and Other Relevant Endpoints

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

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

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

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

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

	Placebo (N=94)	TQ				MQ 250 mg (N=46)
		25 mg (N=93)	50 mg (N=93)	100 mg (N=94)	200 mg (N=93)	
Parasitemia	86	58	13	11	12	6
≤3 weeks	9(9.6%)	4(4.3%)	4(4.4%)	0	0	1(2.2%)
3-6 weeks	63(67.0%)	30(32.3%)	4(4.4%)	4(4.3%)	6(6.6%)	4(8.7%)
6-9 weeks	11(11.7%)	18(19.4%)	2(2.2%)	6(6.4%)	3(3.3%)	0
9-12 weeks	3(3.2%)	4(4.3%)	1(1.1%)	1(1.1%)	2(2.2%)	1(2.2%)
>12 weeks	0	2(2.2%)	2(2.2%)	0	1(1.1%)	0
Missing time	2	4	12	8	13	2

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

Gender, Race, Age, Weight

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

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

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

Geographic Location (Site)

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

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

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

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

Conclusion

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

8.4 Study 030

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

8.4.1 Study Design

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

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

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

Inclusion and Exclusion Criteria

Inclusion Criteria

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

Exclusion Criteria

Exclusion criteria included, but were not limited to:

- positive parasitemia following halofantrine treatment for radical cure.

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

8.4.2 Statistical Methodologies

Analysis Populations
The following analysis populations were defined:

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

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

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

8.4.3 Patient Disposition

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

Table 20. Study 030: Patient Disposition

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

Source: Tables 5 and 6, Study Report

Demographic Characteristics

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

characteristics were well-balanced across the three treatment groups.

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

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

Source: Table 7, Summary of Clinical Efficacy

8.4.4 Efficacy Results

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

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

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

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

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

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

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

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

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

Calculated by FDA reviewer.

Conclusion

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

8.5 Study TQ-2016-02

8.5.1 Study Design

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

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

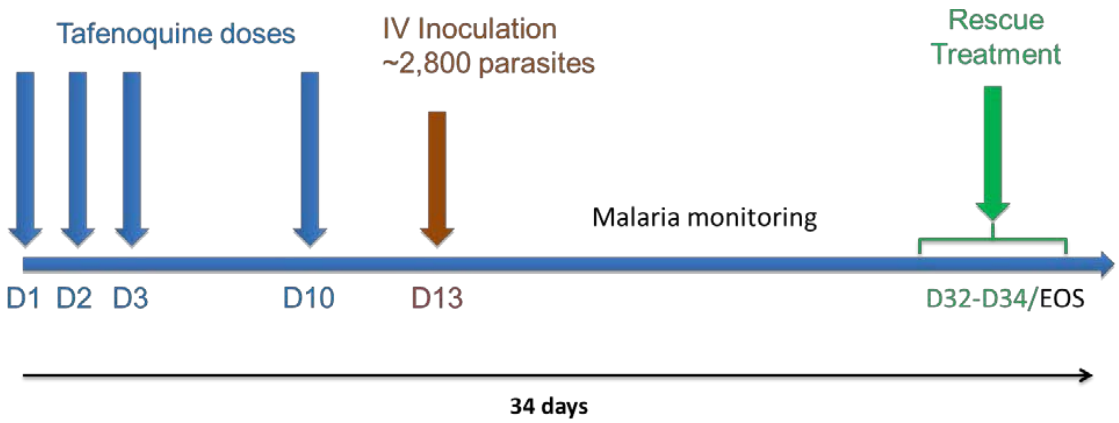

Figure 1. Study Scheme
While the primary endpoint was safety, the primary efficacy endpoints (exploratory) were malaria assessment by qPCR after challenge (qPCR parasitemia of >5,000 asexual blood stage estimated parasites/mL accompanied by a clinical symptom score of >6, or parasitemia of >5,000 asexual blood stage estimated parasites/mL and 2-fold increase within 48 hours), appearance of gametocytemia (pfs25 mRNA), and malaria clinical score.

Key Inclusion and Exclusion Criteria

Inclusion Criteria
Inclusion criteria included, but were not limited to:

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

Exclusion Criteria
Exclusion criteria included, but were not limited to:

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

8.5.2 Statistical Methodologies

Analysis Population
The following analysis populations were defined:

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

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

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

Analysis Methods

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

8.5.3 Patient Disposition

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

Table 25. Study TQ 2016-02: Patient Disposition

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

Demographic Characteristics

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

Table 26. Study TQ 2016-02: Demographic Characteristics

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

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

Exploratory Primary Efficacy Analysis

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

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

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

Source: Table 7, Study Report

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

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

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

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

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

Individual Trial

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

Conclusion

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

9 Overall Efficacy Summary

9.1 Assessment of Efficacy Across Trials

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

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

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

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

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

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

Subpopulations

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

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

9.2 Summary and Conclusions of Efficacy

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

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

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

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

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

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

10 Evaluation of Safety

10.1 Safety Summary

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

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

Key safety findings identified during the review include:

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

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

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

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

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

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

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

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

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

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

10.2 Methods

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

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

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

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

Table 30. Key Studies used to Evaluate Clinical Safety

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

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

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

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

10.3 Adverse Event Analysis

Summary of Adverse Events

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

Table 31. Summary of Adverse Events

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

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

Deaths

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

Serious Adverse Events

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

Adverse Events Leading to Study Discontinuation

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

Treatment Emergent Adverse Events

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

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

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

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

10.4 Adverse Reactions of Special Interest and Submission Specific Safety Issues

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

10.4.1 Ophthalmic

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

Corneal Disorders

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

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

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

Retinal Disorders

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

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

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

10.4.2 Cardiac

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

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

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

10.4.3 Hematologic

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

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

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

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

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

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

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

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

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

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

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

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

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

10.4.4 Renal

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

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

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

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

10.4.5 Neurologic

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10.4.6 Psychiatric

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

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

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

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

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

- *(Study 033):* A 28-year-old White ADF soldier with a history of intracranial head injury, reported moderate depression beginning on Study Day 24. He was withdrawn from the study and treated with paroxetine, and his depression resolved after 87 days. The subject's depression was considered suspected related to TQ.

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

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

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

TQ

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

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

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

Placebo

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

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

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

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

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

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

10.4.7 Hepatobiliary

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

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

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

10.4.8 Gastrointestinal

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

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

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

11 Draft Points for Advisory Committee Discussion

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

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARAKODA™ safely and effectively. See full prescribing information for ARAKODA™.

ARAKODA™ (tafenoquine) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
ARAKODA is an antimalarial indicated for the prophylaxis of malaria in patients aged 18 years and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA. (2.1)
- Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with ARAKODA. (2.1)

Regimen Name	Timing	Dosage
Loading regimen	For each of the 3 days before travel to a malarious area	200 mg (2 of the 100 mg tablets) once daily for 3 days
Maintenance regimen	While in the malarious area	200 mg (2 of the 100 mg tablets) once weekly – start 7 days after the last loading regimen dose
Terminal prophylaxis regimen	In the week following exit from the malarious area	200 mg (2 of the 100 mg tablets) one-time 7 days after the last maintenance dose

- Administer ARAKODA with food. (2.2)
- See full prescribing information for instructions on how to replace missed doses. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 100 mg of tafenoquine (3)

----------CONTRAINDICATIONS----------
- G6PD deficiency or unknown G6PD status (4)
- Breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if G6PD status is unknown (4, 8.2)
- Patients with a history of psychotic disorders or current psychotic symptoms (4. 5.4)
- Known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of ARAKODA. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hemolytic Anemia: G6PD testing must be performed before prescribing ARAKODA due to the risk of hemolytic anemia. Monitor patients for signs or symptoms of hemolysis. (5.1)
- G6PD Deficiency in Pregnancy or Lactation: ARAKODA may cause fetal harm when administered to a pregnant woman with a G6PD-deficient fetus. ARAKODA is not recommended during pregnancy. A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Check infant's G6PD status before breastfeeding begins. (5.2, 8.1, 8.2)
- Methemoglobinemia: Asymptomatic elevations in blood methemoglobin have been observed. Initiate appropriate therapy if signs or symptoms of methemoglobinemia occur. (5. 3)
- Psychiatric Effects: Serious psychotic adverse reactions have been observed in patients with a history of psychosis or schizophrenia, at doses different from the approved dose. If psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior) occur, consider discontinuation of ARAKODA therapy and, evaluation by a mental health professional as soon as possible. (5.4)
- Hypersensitivity Reactions: Serious hypersensitivity reactions have been observed with administration of ARAKODA. If hypersensitivity reactions occur, institute appropriate therapy. (5.5)
- Delayed Adverse Reactions: Due to the long half-life of ARAKODA (approximately 17 days), psychiatric effects, hemolytic anemia, methemoglobinemia, and hypersensitivity reactions may be delayed in onset and/or duration. (5.6, 12.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥1%) were: headache, dizziness, back pain, diarrhea, nausea, vomiting, , increased alanine aminotransferase (ALT), motion sickness, insomnia, depression, abnormal dreams, anxiety. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact 60 Degrees Pharmaceuticals at 1-888-834-0225 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Avoid co-administration with drugs that are substrates of organic cation transporter-2 (OCT2) or multidrug and toxin extrusion (MATE) transporters (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise women not to breastfeed a G6PD-deficient infant or infant with unknown G6PD status during treatment and for 3 months after the last dose of ARAKODA. (5.2, 8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARAKODA is indicated for the prophylaxis of malaria in patients aged 18 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 Tests to be Performed Prior to ARAKODA Dose Initiation

All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA *[see Contraindications (4), Warnings and Precautions (5.1)]*.

Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with ARAKODA *[see Use in Specific Populations (8.1 and 8.3)]*.

2.2 Recommended Dosage and Administration Instructions

The recommended dosage of ARAKODA is described in Table 1 below. ARAKODA can be administered for up to 6 months of continuous dosing.

Table 1: Recommended Dosage of ARAKODA in Patients (18 Years of Age and Older)

Regimen Name	**Timing**	**Dosage**
Loading regimen	For each of the 3 days before travel to a malarious area	200 mg (2 of the 100 mg tablets) once daily for 3 days
Maintenance regimen	While in the malarious area	200 mg (2 of the 100 mg tablets) once weekly – start 7 days after the last loading regimen dose
Terminal prophylaxis regimen	In the week following exit from the malarious area	200 mg (2 of the 100 mg tablets) taken one time, 7 days after the last maintenance dose

- Administer ARAKODA with food. *[see Clinical Pharmacology (12.3)]*.
- Swallow the tablet whole. Do not break, crush or chew the tablets.
- Complete the full course of ARAKODA including the loading dose and the terminal dose.

Table 2: How to Replace Missed Doses of ARAKODA

Dose(s) Missed	**How to Replace Missed Dose(s):**
1 Loading dose	1 dose of 200 mg (2 of the 100 mg tablets) so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
2 Loading doses	2 doses of 200 mg (2 of the 100 mg tablets) on 2 consecutive days so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
1 Maintenance (weekly) dose	1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose.
2 Maintenance (weekly) doses	1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose.
3 or more Maintenance (weekly) doses	2 doses of 200 mg (2 of the 100 mg tablets), taken as 200 mg (2 of the 100 mg tablets) once daily for 2 days up to the time of the next weekly dose.
Terminal prophylaxis dose	1 dose of 200 mg (2 of the 100 mg tablets) as soon as remembered.

3 DOSAGE FORMS AND STRENGTHS

ARAKODA tablets are dark pink, film-coated, capsule-shaped tablets debossed with ‘TQ100’ on one side containing 100 mg of tafenoquine.

4 CONTRAINDICATIONS

ARAKODA is contraindicated in:

- patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia *[see Warnings and Precautions (5.2)]*.
- breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown *[see Warnings and Precautions (5.3), Use in Specific Populations (8.2)]*.
- patients with a history of psychotic disorders or current psychotic symptoms (i.e., hallucinations, delusions, and/or grossly disorganized behavior) *[see Warnings and Precautions (5.4)]*
- patients with known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of ARAKODA *[see Warnings and Precautions* (*5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1. Hemolytic Anemia

Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA *[see Contraindications (4)]*. Due to the limitations with G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Treatment with ARAKODA is contraindicated in patients with G6PD deficiency or unknown G6PD status *[see Contraindications (4)]*. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients *[see Adverse Reactions (6.1)]*. Monitor patients for clinical signs or symptoms of hemolysis *[see Warnings and Precautions (5.6)]*. Advise patients to discontinue ARAKODA and seek medical attention if signs of hemolysis occur.

5.2 G6PD Deficiency in Pregnancy and Lactation

Potential Harm to the Fetus
The use of ARAKODA during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of ARAKODA. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy *[see Use in Specific Populations (8.1 and 8.3)]*.

Potential Harm to the Breastfeeding Infant
A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown *[see Contraindications (4)]*. Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with ARAKODA and for 3 months after the final dose *[see Use in Specific Populations (8.2)]*.

5.3 Methemoglobinemia

Asymptomatic elevations in methemoglobin have been observed in the clinical trials of ARAKODA *[see Adverse Reactions (6.1)]*. Institute appropriate therapy if signs or symptoms of methemoglobinemia occur *[see Warnings and Precautions (5.6)]*. Carefully monitor individuals with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency. Advise patients to discontinue ARAKODA and seek medical attention if signs of methemoglobinemia occur.

5.4 Psychiatric Effects

In patients receiving ARAKODA in clinical trials, psychiatric adverse reactions included sleep disturbances (2.5%), depression/depressed mood (0.3%), and anxiety (0.2%) *[see Adverse*

Reactions (6.1)]. ARAKODA was discontinued in a subject with an adverse reaction of suicide attempt (0.1%). Subjects with a history of psychiatric disorders were excluded from three of five ARAKODA trials in which mefloquine was included as a comparator.

Psychosis was reported in three patients with a history of psychosis or schizophrenia who received tafenoquine doses (350 mg to 500 mg single dose, or 400 mg daily for 3 days) different from the approved ARAKODA regimen. Safety and effectiveness of ARAKODA have not been established at doses or regimens other than the approved regimen; use of ARAKODA at doses or regimens other than a 200-mg weekly dose is not approved by FDA.

ARAKODA is contraindicated in patients with a history of psychotic disorders or current psychotic symptoms *[see Contraindication (4)]*. If psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior) occur, consider discontinuation of ARAKODA and prompt evaluation by a mental health professional as soon as possible. Other psychiatric symptoms, such as changes in mood, anxiety, insomnia, and nightmares, should be promptly evaluated by a medical professional if they are moderate and last more than three days or are severe *[see Warnings and Precautions (5.6)]*.

5.5 Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., angioedema and urticaria) have been observed with administration of tafenoquine. Hypersensitivity reactions have been reported in clinical trials of ARAKODA *[see Adverse Reactions (6.1)]*. Discontinue prophylaxis with ARAKODA and institute appropriate therapy if hypersensitivity reactions occur *[see Warnings and Precautions (5.6)]*. ARAKODA is contraindicated in patients who develop hypersensitivity to tafenoquine or any component of ARAKODA or other 8-aminoquinolines *[see Contraindications (4)]*.

5.6 Delayed Adverse Reactions, Including Hemolytic Anemia, Methemoglobinemia, Psychiatric Effects, and Hypersensitivity Reactions

Adverse reactions including hemolytic anemia, methemoglobinemia, psychiatric effects, and hypersensitivity reactions were reported with the use of ARAKODA or tafenoquine in clinical trials *[see Warnings and Precautions (5.1, 5.3, 5.4, 5.5)]*. Due to the long half-life of ARAKODA (approximately 17 days), psychiatric effects, hemolytic anemia, methemoglobinemia, and signs or symptoms of hypersensitivity reactions that may occur could be delayed in onset and/or duration. Advise patients to seek medical attention if signs of hypersensitivity occur *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions observed with ARAKODA are discussed in detail in the Warnings and Precautions section:

- Hemolytic Anemia *[see Warnings and Precautions (5.2)]*
- Methemoglobinemia *[see Warnings and Precautions (5.3)]*
- Psychiatric Effects *[see Warnings and Precautions (5.4)]*

- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of tafenoquine was studied in clinical trials at various doses and regimens in 3,184 subjects. The recommended ARAKODA regimen was evaluated in 825 subjects in 5 controlled clinical trials (Trials 1, Trial 2, Trial 3, Trial 4 and Trial 5). The mean duration of exposure to ARAKODA in these five clinical trials was 21 weeks (range 10-29 weeks). Trial 1, 2 and 4 were conducted in healthy semi-immune volunteers in Ghana or Kenya and were placebo-controlled; a mefloquine arm was included in Trials 2 and 4 as a benchmark. Trial 3, an active comparator (mefloquine) controlled trial was conducted in healthy soldiers deployed in East Timor (Timor Leste). A placebo-controlled Trial 5 was conducted in healthy volunteers in the United States and United Kingdom. The mean age of the subjects included in the five trials was 29 years (range 17 to 69 years); 84% were male.

Adverse Reactions Reported with ARAKODA in Trial 3 and Pooled Trials 1, 2, 4, and 5

Adverse reactions occurring in ≥1% of subjects in the ARAKODA group in the placebo-controlled pooled Trials 1, 2, 3, and 4 are presented in Table 3.

Table 3: Selected Adverse Reactions Occurring in ≥1% of Subjects Receiving ARAKODA in Pooled Trials 1, 2, 4, and 5 (Non-Deployed Subjects))

Adverse Reaction	ARAKODA[2] (n=333) %	Placebo (n=295) %	Mefloquine[3] (n=147) %
Nervous system Disorders	35	34	47
Headache[4]	32	32	44
Dizziness[5]	5	3	10
Musculoskeletal and connective tissue disorders	27	26	37
Back pain	14	9	11
Gastrointestinal disorders	31	33	46
Diarrhea	5	3	1
Nausea	5	2	2
Vomiting	2	2	1
Investigations	8	7	11
Alanine Aminotransferase (ALT) increased/abnormal	4	2	3
Psychiatric disorders	2	1	2
Any sleep symptom[6]	1	1	0
Insomnia	1	1	0
Depression/depressed mood	1	0	0

[1] Trials 2 and 4 included mefloquine arm in addition to placebo
[2] ARAKODA was administered as 200 mg daily for 3 days, then 200 mg weekly
[3] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly
[4] Includes headache, sinus headache, migraine and tension headache.
[5] Includes dizziness and dizziness postural
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.

Adverse reactions occurring in ≥1% of subjects in the ARAKODA group in the active-control Trial 3 conducted in military personnel deployed to malaria endemic areas are presented in Table 4.

Table 4: Selected Adverse Reactions Occurring in ≥1% of Subjects Receiving ARAKODA in Trial 3 (Deployed Subjects)

Adverse Reaction	ARAKODA[1] (n=492) %	Mefloquine[2] (n=162) %
Nervous system Disorders	22	27
Headache[3]	15	19
Dizziness[4]	1	1
Ear and labyrinth Disorders	7	11
Motion sicknesss[5]	5	6
Musculoskeletal and connective tissue disorders	29	30
Back pain	14	15
Gastrointestinal disorders	36	41
Diarrhea	18	20
Nausea	7	9
Vomiting	5	6
Psychiatric disorders	5	4
Any sleep symptom[6]	4	4
Insomnia	2	1
Abnormal dreams[7]	2	2
Anxiety[8]	1	0

[1] ARAKODA was administered as 200 mg daily for 3 days, then 200 mg weekly
[2] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly
[3] Includes headache, sinus headache, migraine and tension headache.
[4] Includes dizziness and dizziness postural
[5] Includes motion sickness, vertigo and vertigo positional.
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.
[7] Includes abnormal dreams, nightmares
[8] Includes anxiety disorder, panic attack and stress.

Clinically Significant Adverse Reactions in Trials 1 to 5 (Overall Safety Population)

Clinically significant adverse reactions with ARAKODA (200 mg daily for 3 days, followed by 200 mg weekly) in Trials 1 to 5 (n= 825) are described below:

Ocular Adverse Reactions

Vortex keratopathy was reported in 21% to 93% of subjects receiving ARAKODA in the trials which included ophthalmic evaluations (Trials 3, 5, and Trial 6 (NCT # 01290601, an active-control trial in patients from Thailand with *P. vivax* malaria. The keratopathy did not result in any apparent functional visual changes and resolved within one year after drug cessation in all patients. Retinal abnormalities were noted in less than 1% of subjects receiving ARAKODA.

A total of 7 serious ocular adverse reactions (SARs) were reported in ARAKODA-treated subjects in the trials which included ophthalmic evaluations: 5 reports of keratopathy and two reports of retinal disorders.

Laboratory Abnormalities

Methemoglobinemia: Asymptomatic methemoglobin elevations were observed in 13% of subjects receiving ARAKODA.

Hemoglobin decrease: Hemoglobin decreases of ≥ 3 g/dL were observed in 2.3% of subjects receiving ARAKODA.

Adverse Reactions Reported in < 1% of Subjects Receiving ARAKODA in Trials 1 to 5

The following selected adverse reactions were reported in subjects receiving ARAKODA in Trials 1 to 5 at a rate of less than 1%.

Blood and lymphatic system disorders: hemolytic anemia, anemia, thrombocytopenia

Ear and labyrinth disorders: hyperacusis, Meniere's disease

Eye disorders: night blindness, photophobia, blurred vision, visual acuity reduced, visual impairment, vitreous floaters

Hepatobiliary disorders: hyperbilirubinemia, jaundice cholestatic

Immune system disorders: hypersensitivity

Investigations: blood bilirubin increased, blood creatinine increased, glomerular filtration rate decreased

Nervous system disorders: amnesia, coordination abnormal, hyperesthesia, hypoesthesia, somnolence, syncope, tremor, visual field defect

Psychiatric disorders: agitation, neurosis

Skin and subcutaneous tissue disorders: urticaria.

7 DRUG INTERACTIONS

7.1 Effect of ARAKODA on Organic Cation Transporter-2 (OCT2) and Multidrug and Toxin Extrusion (MATE) Substrates

The effect of coadministration of tafenoquine on the pharmacokinetics of OCT2 and MATE substrates in humans is unknown. However, in vitro observations suggest the potential for increased concentrations of these substrates *[see Clinical Pharmacology (12.3)]* which may increase the risk of toxicity of these drugs.

Avoid coadministration of ARAKODA with OCT2 and MATE substrates (e.g., dofetilide, metformin). If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction if needed based on approved product labeling of the coadministered drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The use of ARAKODA during pregnancy may cause hemolytic anemia in a fetus who is G6PD-deficient. Treatment with ARAKODA during pregnancy is not recommended. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy *[see Warnings and Precautions (5.2)]*. Available data with use of ARAKODA in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal studies, there were increased abortions, with and without maternal toxicity when tafenoquine was given orally to pregnant rabbits at and above doses equivalent to about 0.4 times the clinical exposure based on body surface area comparisons. No fetotoxicity was observed at doses about 1.5 times the clinical exposure (based on body surface area comparisons) in a similar study in rats.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk:

Malaria during pregnancy increases the risk for adverse pregnancy outcomes, including maternal anemia, prematurity, spontaneous abortion and stillbirth.

Data

Animal Data:

Tafenoquine resulted in dose-related abortions when given orally to pregnant rabbits during organogenesis (Gestation Days 6 to 18), at doses of 7 mg/kg (about 0.4 times the clinical exposure based on body surface area comparisons) and above. Doses higher than 7 mg/kg were also associated with maternal toxicity (mortality and reduced body weight gain). In a similar study in rats, doses of 3, 10, or 30 mg/kg/day resulted in maternal toxicity (enlarged spleen, reduced body weight and reduced food intake) but no fetotoxicity at the high dose (about 1.5 times the clinical exposure based on body surface area comparisons). There was no evidence of malformations in either species. In a pre- and postnatal development study in rats, tafenoquine administered throughout pregnancy and lactation produced maternal toxicity and a reversible decrease in offspring body weight gain and decrease in motor activity at 18 mg/kg/day, which is equivalent to about 0.6 times the clinical dose based on body surface area comparisons.

8.2 Lactation

Risk Summary

A breastfed infant with G6PD deficiency is at risk for hemolytic anemia from exposure to ARAKODA. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown *[see Contraindications (4) and Clinical Considerations]*.

There is no information regarding the presence of ARAKODA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAKODA and any potential effects on the breastfed infant from ARAKODA or from the underlying maternal condition.

Clinical Considerations

Check the infant's G6PD status before maternal breastfeeding commences. If an infant is G6PD-deficient, exposure to ARAKODA during breastfeeding may result in hemolytic anemia in the infant; therefore, advise the woman with an infant who has G6PD deficiency or whose G6PD status is unknown, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose of ARAKODA.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with ARAKODA. *[see Dosage and Administration (2.2), Warnings and Precautions, (5.2), and Use in Specific Populations (8.1)]*.

Contraception

ARAKODA may cause hemolytic anemia in a G6PD-deficient fetus *[see Warnings and Precautions (5.2), Use in Specific Populations (8.1)]*. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the final dose of ARAKODA.

8.4 Pediatric Use

Safety and effectiveness of ARAKODA in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials of ARAKODA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

The pharmacokinetics of ARAKODA have not been studied in patients with renal impairment. If ARAKODA is administered to such patients, monitoring for adverse reactions associated with ARAKODA is needed *[see Warnings and Precautions (5), Adverse Reactions (6)]*.

8.7 Hepatic Impairment

The pharmacokinetics of ARAKODA have not been studied in patients with hepatic impairment. If ARAKODA is administered to such patients, monitoring for adverse reactions associated with ARAKODA is needed *[see Warnings and Precautions (5), Adverse Reactions (6)]*.

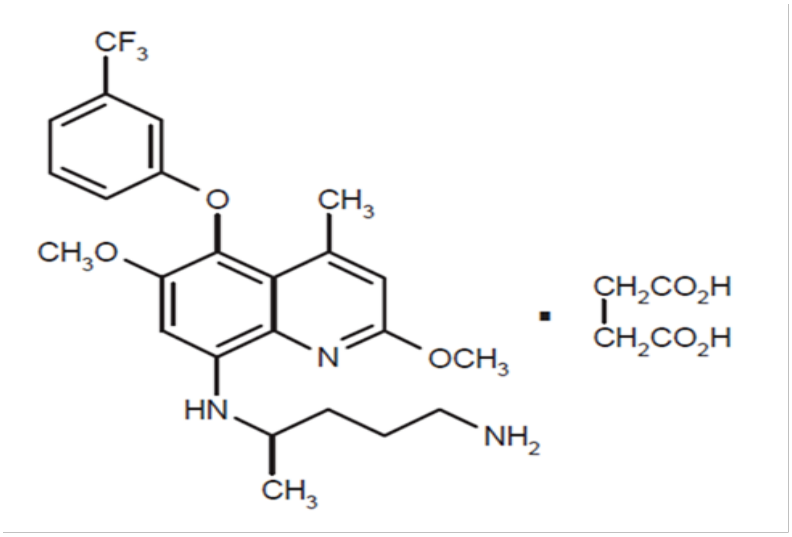
10 OVERDOSAGE

There were no reported cases of ARAKODA overdose. Hemoglobin decline and methemoglobinemia may be encountered in an overdose with ARAKODA. Treatment of overdosage consists of institution of appropriate symptomatic and/or supportive therapy.

11 DESCRIPTION

ARAKODA contains tafenoquine succinate, an antimalarial agent for oral administration. The structural formula of tafenoquine succinate is:

Figure 1: Tafenoquine Succinate Structure



The chemical name of tafenoquine succinate is (±)-8-[(4-amino-1-methylbutyl) amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl) phenoxy]quinoline succinate. The molecular formula of tafenoquine succinate is $C_{24}H_{28}F_3N_3O_3 \cdot C_4H_6O_4$ and its molecular weight is 581.6 as the succinate salt (463.49 as free base).

Each ARAKODA tablet contains 100 mg of tafenoquine (equivalent to 125.5 mg of tafenoquine succinate). Inactive ingredients include magnesium stearate, mannitol, and microcrystalline

cellulose. The tablet film coating inactive ingredients include: hypromellose, iron oxide red, macrogol/polyethylene glycol and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tafenoquine is an 8-aminoquinoline antimalarial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of tafenoquine on the QT interval was evaluated in a study of healthy adult subjects. In this study, subjects received once daily 400 mg (2 times the approved recommended dosage) doses of tafenoquine for 3 days. The results suggest that the mean increase in the QTcF interval for tafenoquine is less than 20 msec.

12.3 Pharmacokinetics

Absorption

A food effect study was not conducted with the 100 mg ARAKODA tablet. In majority of the clinical trials, tafenoquine was administered under fed conditions. Table 4 provides the pharmacokinetics of tafenoquine following single dose administration of 200 mg ARAKODA (two 100-mg ARAKODA tablets) in 65 healthy adult subjects under fed conditions. In this study, ARAKODA was administered with a high-calorie, high-fat meal (approximately 1000 calories with 19% protein, 31% carbohydrate, and 50% fat).

Table 4. Mean (%CV) Pharmacokinetic Parameters of Tafenoquine Following Single Oral Administration of Two 100-mg ARAKODA Tablets Under Fed Conditions in Healthy Adult Subjects (N=65)

Parameter	Value
C_{max}	147 ng/mL (20.7%)[a]
T_{max}	14 hr (6 – 72 hr)[b]
AUC_{inf}	70 hr*mcg/mL (24.6%)[a, c]

[a] Coefficient of Variance (CV)
[b] Median and (Range)
[c] Plasma tafenoquine AUC_{inf} increased by 41% when tafenoquine was administered as an investigational capsule formulation with a high-calorie, high-fat meal compared with the fasted state.

Following administration of a single dose of tafenoquine orally under fasted conditions in healthy adult subjects, AUC and C_{max} increased dose proportionally over the dose range from 100 mg to 400 mg. When healthy adult subjects received once-weekly administrations of 200 mg tafenoquine orally for ten weeks without a loading dose under fasting conditions, the mean plasma accumulation ratio of tafenoquine was approximately 4.4.

Distribution

Tafenoquine is greater than 99.5% bound to protein in humans. The apparent volume of distribution of tafenoquine in healthy adult subjects is 2470 L [Inter-Individual Variability (IIV): 24.1 %].

Elimination

The apparent oral clearance of tafenoquine is approximately 4.2 L/hr (IIV: 23.6 %) in healthy adult subjects. The mean terminal half-life following administration of ARAKODA is approximately 16.5 days (range: 10.8 days to 27.3 days) in healthy adult subjects.

Metabolism

Negligible metabolism of tafenoquine was observed in vitro in human liver microsomes and hepatocytes. Following administration of tafenoquine orally, once daily for three days to healthy adult subjects, unchanged tafenoquine represented the only notable drug-related component in plasma at approximately 3 days following the first dose of tafenoquine.

Excretion

The full excretion profile of tafenoquine in humans is unknown.

Specific Populations

The pharmacokinetics of tafenoquine were not significantly impacted by age, sex, ethnicity, and body weight. The effect of renal or hepatic impairment on tafenoquine pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

No clinically significant effects on the pharmacokinetics of substrates of cytochrome P450 isoenzymes (CYP)1A2 (caffeine), CYP2D6 (desipramine), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) were observed following coadministration with tafenoquine in healthy adult subjects.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

Tafenoquine inhibited metformin transport via human OCT2, MATE1 and MATE2-K transporters *[see Drug Interactions (7)]*.

Tafenoquine is not an inhibitor of human breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), Organic anion transporter 1/3 (OAT1 or OAT3), Organic anion transporting polypeptide 1B1/1B3 (OATP1B1 or OATP1B3) mediated transport at clinically relevant concentrations. Tafenoquine is also not a substrate of human OATP1B1 or OATP1B3 at clinically relevant concentrations. It is inconclusive as to whether tafenoquine is a substrate of P-gp and/or BCRP mediated transport.

12.4 Microbiology

Mechanism of Action
Tafenoquine, an 8-aminoquinoline antimalarial, is active against all the stages of *Plasmodium* species that include the hypnozoite (dormant stage) in the liver. Studies in vitro with the erythrocytic forms of *Plasmodium falciparum* suggest that tafenoquine may exert its effect by inhibiting hematin polymerization and inducing apoptotic like death of the parasite. In addition to its effect on the parasite, tafenoquine causes red blood cell shrinkage in vitro. The molecular target of tafenoquine is not known.

Antimicrobial activity
Tafenoquine is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species that include *P. falciparum* and *P. vivax.* The activity of tafenoquine against the pre-erythrocytic liver stages of the parasite, prevents the development of the erythrocytic forms of the parasite *[see Clinical Studies (14)]*.

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

Studies with the erythrocytic forms of *P. falciparum* strains/isolates suggest a potential for cross-resistance with primaquine, an 8-aminoquinoline. Clinical relevance of such findings is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Two-year oral carcinogenicity studies were conducted in rats and mice. Renal cell adenomas and carcinomas were increased in male rats at doses 1 mg/kg/day and above (0.5 times the clinical exposure based on AUC comparisons). Tafenoquine was not carcinogenic in mice. The relevance of these findings to a carcinogenic risk in humans is unclear.

Mutagenesis
Tafenoquine did not cause mutations or chromosomal damage in 2 definitive in vitro tests (bacterial mutation assay and mouse lymphoma L5178Y cell assay) or in an in vivo oral rat micronucleus test.

Impairment of Fertility
In a rat fertility study, tafenoquine was given orally at 1.5, 5, and 15 mg/kg/day (up to about 0.5 times the human dose based on body surface area comparisons) to males for at least 67 days, including 29 days prior to mating, and to females from 15 days prior to mating through early pregnancy. Tafenoquine resulted in reduced number of viable fetuses, implantation sites, and corpora lutea at 15 mg/kg in the presence of maternal toxicity (mortality, piloerection, rough coat, and reduced body weight).

14 CLINICAL STUDIES

Clinical Trials 1, 2, and 3

Three double-blind, randomized, controlled studies have been performed to evaluate the efficacy of ARAKODA.

Trial 1 (NCT #02491606) was a Phase IIb, placebo-controlled study conducted in Kenya, an area of holoendemic *P. falciparum* malaria. After taking a three-day presumptive course of halofantrine to eliminate any existing parasitemia, subjects were randomized into one of four groups (placebo and three different ARAKODA dosing groups; one group received 200 mg once daily for 3 days, then a maintenance regimen of weekly dose of 200 mg for 10-15 weeks). Sixty-one percent of subjects were male. The mean age was 32.4 years (range 17-55). Subjects were evaluated for parasitemia by weekly blood smears. Protective efficacy at 15 weeks was defined based on the reduced incidence of parasitemia during the prophylaxis phase relative to placebo. The results in the intention-to-treat population, which included all subjects who received three doses of halofantrine and were randomized, are shown in Table 5 below.

Table 5: Incidence of Parasitemia and Protective Efficacy of ARAKODA at 15 weeks for Trial 1

	Placebo	**ARAKODA[1]**
Number of subjects	62	61
Subjects free of parasitemia	5 (8.1%)	46 (75.4)
Subjects with parasitemia	54 (87.1%)	7 (11.5%)
Subjects with missing data	3 (4.8%)	8 (13.1%)
Protective efficacy [98.3% CI] [2]	–	73.3% [54.0%, 84.5%]

[1] 200 mg once daily for 3 days, then 200 mg weekly for 10-15 weeks
[2] Protective efficacy is reduced incidence of parasitemia relative to placebo (0: no protection; 1: full protection); CI: confidence interval. Bonferroni adjustment was used for multiple comparisons. Missing outcome was considered a failure due to parasitemia for this analysis.

Trial 2 (NCT #02488902) was a comparison of tafenoquine to placebo for prophylaxis in healthy semi-immune residents of a malarious region in Ghana. After treating existing parasitemia with quinine/doxycycline/primaquine, subjects were randomized into prophylactic groups including ARAKODA and placebo. Patients were administered a loading regimen of daily drug or placebo

for 3 days followed by a maintenance regimen of weekly drug or placebo for 12 weeks. For the ARAKODA and placebo groups, males were 65% of the total population. The mean age was 38.4 years and 53.5 years for males and females, respectively, as women in reproductive ages were excluded from the study. The mean weight was 55.4 kg and 47.5 kg for males and females, respectively. Subjects were evaluated for parasitemia by weekly blood smears. Parasitemia required a blood smear positive for asexual stage of *P. falciparum*. The incidence of parasitemia at week 12 for all randomized subjects who received at least one dose of ARAKODA or placebo is presented in Table 6 below.

Table 6: Incidence of Parasitemia and Protective Efficacy of ARAKODA at Week 12 for Trial 2

	Placebo	**ARAKODA**
Number of subjects	94	93
Subjects free of parasitemia	6 (6.4%)	68 (73.1%)
Subjects with parasitemia	86 (91.5%)	12 (12.9%)
Subjects with missing data	2 (2.1%)	13 (14.0%)
Protective efficacy [98.75% CI][2]	–	71.3% [55.8%, 81.4%]

[1] 200 mg once daily for 3 days, then 200 mg weekly for 12 weeks
[2] Protective efficacy is reduced incidence of parasitemia relative to placebo; CI: confidence interval. Bonferroni adjustment was used for multiple comparisons. Missing outcome was considered a failure due to parasitemia for this analysis.

Trial 3 compared ARAKODA with mefloquine for the prophylaxis of both *P. falciparum* and *P. vivax* malaria in healthy non-immune soldiers deployed to East Timor (now Timor-Leste). No subject developed malaria during the 26-week prophylactic phase. Subjects were exposed to *P. vivax* and there is a high likelihood that the study subjects were also exposed to *P. falciparum.* Since the precise degree of exposure to malaria in study subjects is unknown, this study provides only supportive evidence of efficacy.

Clinical Trial 7

In a randomized, double-blind, placebo-controlled trial (Trial 7) in healthy, non-immune volunteers, ARAKODA was shown to have prophylactic activity directed against blood-stage *P. falciparum* parasites. Twelve subjects received ARAKODA (200 mg once daily for 3 days, then 200 mg on 10 day) and 4 subjects received placebo. On Day 13, subjects were inoculated with erythrocytes containing viable *P. falciparum* parasites. Fifteen subjects (93.8%) were of white race. The mean age was 27.5 years (range 20-42). The mean body weight was 72.3 kg (range 56-97.7). The efficacy endpoint was parasitemia by Day 34; parasitemia was based on detection of *P. falciparum* 18S ribosomal DNA by real time polymerase chain reaction assay (PCR). There was a statistically significant difference in malaria incidence between the two groups; 4/4 (100%) subjects in the placebo group had detectable parasites from Day 17 compared to 0/12 (0%) subjects on ARAKODA were PCR negative at all visits ($p<0.0005$).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ARAKODA tablets contain 100 mg of tafenoquine (equivalent to 125.5 mg of tafenoquine succinate) and are dark pink, film-coated, capsule-shaped, and debossed with 'TQ100' on one side.

ARAKODA tablets are packed in polyamide aluminum and PVC formable laminate backed blisters with a peelable polyethylene terephthalate aluminum foil cover. Each blister card contains 8 tablets. Each carton contains 16 tablets (2 blister cards) (NDC 71475-257-01).

Storage

Store at 20°C to 25°C (68°F to 77°F). Temperature excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense only in the original carton.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

G6PD Testing and Hemolytic Anemia

Inform patients of the need for testing for G6PD deficiency before starting ARAKODA. Advise patients on the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their health care provider if they have darker lips or urine as these may be signs of hemolysis or methemoglobinemia *[see Warnings and Precautions (5.1)]*.

Important Administration Instructions

- Advise patients to take ARAKODA with food.
- Advise patients to swallow the tablet whole and not to break, crush or chew it.
- Advise patients to complete the full course of ARAKODA including the loading dose, maintenance dose and terminal dose.

Potential Harm to the Fetus

Advise females of reproductive potential of the potential risk of ARAKODA to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2) and Use in Specific Populations 8.1)]*.

Advise females of reproductive potential to avoid pregnancy or use effective contraception during treatment with ARAKODA and for 3 months after the final dose *[see Use in Specific Populations (8.3)]*.

Lactation
Advise women with a G6PD-deficient infant, or if they do not know the G6PD status of their infant, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose *[see Contraindication (4), Warnings and Precautions (5.2), Use in Specific Populations (8.2)]*.

Methemoglobinemia
Inform patients that methemoglobinemia has occurred with ARAKODA. Advise patients on the symptoms of methemoglobinemia and instruct them to seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.3)]*.

Psychiatric Symptoms
Advise patients who experience hallucinations, delusions, or confused thinking while taking ARAKODA to seek medical attention as soon as possible. Other psychiatric symptoms, such as changes in mood, anxiety, insomnia, and nightmares, should be promptly evaluated by a medical professional if they last more than three days or severe *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions have occurred with ARAKODA. Advise patients on the symptoms of hypersensitivity reactions and instruct them to seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.5)]*.

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Original article

Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis

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ABSTRACT

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

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

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

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

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

1. Introduction

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

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

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

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

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

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

2. Methods

2.1. Ethical approval and subject consent

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

2.2. Conduct of the studies

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

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

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

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

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

2.3. Conduct of the integrated safety analysis

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

3. Results

3.1. Demographics

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

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

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

3.2. Extent of exposure

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

3.3. Treatment discontinuations

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

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

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

3.4. Analyses of adverse events

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

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

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

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

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

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

Table 3
Overview of adverse events.

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

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

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

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

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

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

Table 4
Subjects with specific Categories of adverse events.

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

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

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

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

3.5. Common adverse events independent of extrinsic factors

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

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

3.6. Psychiatric adverse events

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

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

To potentially identify specific extrinsic factors in subjects who reported psychiatric AEs in the Deployed ADF subgroup versus the Resident Non-ADF subgroup, medical histories and non-psychiatric AEs were reviewed for subjects who reported insomnia or sleep disorder in these 2 subgroups (Table 7). Concurrent gastrointestinal illnesses, active pain, or upper respiratory illnesses affected 8 out of 10 subjects with insomnia or sleep disorders in the Deployed ADF subgroup and 2 of 3 subjects in the Resident Non-ADF subgroup. When these confounding illnesses and events were eliminated, comparable percentages (0.3%–0.4%) of the two subgroups experienced insomnia or sleep disorders. In terms of the Tafenoquine ACR Overall population, although insomnia or sleep disorder was reported in 1.6% of this population, only 3 of 825 subjects (0.4% of the Tafenoquine ACR Overall population) did not have an identifiable concurrent illness or injury that might have contributed to their inability to sleep (Table 7).

4. Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Notably, among the 25 Deployed ADF subjects who reported psychiatric disorders, the majority [18 (72%) of 25] developed problems related to sleep (insomnia, abnormal dreams, nightmares, sleep disorder). This underscores the potentially dramatic effect that deployment can have on sleep in military populations [23]. Sleep problems, particularly insomnia, are highly prevalent during military deployments [24,25] and insomnia is often reported not only during actual combat operations but also post-deployment after combat ends [26–28]. In a recent exhaustive study sponsored by the US Secretary of Defense, the RAND National Defense Research Institute (US) concluded that sleep problems—particularly insomnia, short sleep duration, and nightmares—are highly prevalent during combat operations [23]. These findings are relevant to the present analysis, as they support the conclusion that tafenoquine exposure was not the cause of an increased burden of sleep-related AEs in the Deployed ADF population.

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

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

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

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

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

Conflict of interest declaration

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

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Disclaimer

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

Appendix A. Supplementary data

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

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