**FDA Briefing Document**

**Tafenoquine Tablet, 150 mg**
**Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)**

**July 12, 2018**

*The committee will discuss new drug application (NDA) 210795 for tafenoquine tablet, 150 mg, sponsored by GlaxoSmithKline, for the proposed indication of the radical cure (prevention of relapse) of Plasmodium vivax malaria in patients 16 years of age and older.*

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 has brought tafenoquine tablet 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 describes the safety and efficacy data for tafenoquine (TQ), 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 radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients in patients 16 years of age and older.

# 2 Background

TQ is an 8-aminoquinoline antimalarial. TQ possesses activity against all stages of the *P. vivax* lifecycle, including the dormant liver hypnozoite. TQ has slow clearance of blood stage; therefore, co-administration with another faster acting blood schizonticide, chloroquine (CQ) for 3 days, is required for treatment of *P. vivax* malaria as this combination (TQ+CQ) targets both blood and liver hypnozoite stages of infection. The proposed indication is the radical cure, of *P. vivax* malaria in patients 16 years of age and older. The proposed regimen is 300 mg as a single dose, i.e. two 150 mg tablets, administered on Day 1 or Day 2 of CQ therapy.

# 3 Product Information

TQ is a novel 8-aminoquinoline antimalarial drug, a synthetic analog of primaquine (PQ), for oral administration. Each immediate release TQ tablet contains 150 mg of tafenoquine (equivalent to 188.2 mg tafenoquine succinate).

# 4 Regulatory History

TQ was granted orphan drug designation and breakthrough therapy designation for the radical cure of *P. vivax* malaria.

# 5 Clinical Pharmacology

Maximum plasma concentrations of TQ were generally observed 12 to 15 hours following oral administration. Compared to the fasted state, plasma TQ AUC and Cmax increased by 41% and 31% respectively, when TQ was administered as a capsule formulation with a high-fat meal. Protein binding of TQ is >99.5%. The average terminal half-life is approximately 15 days. Slow and negligible metabolism was observed in vitro in human liver microsomes and hepatocytes. The excretion pathway of TQ in humans is unknown.

*Specific Populations*
Pharmacokinetics (PK) of TQ were not significantly impacted by age, sex, ethnicity, and body weight. The effect of renal or hepatic impairment on PK of TQ is unknown.

*Drug-Drug Interactions*
No clinically significant effects on PK of TQ were seen following co-administration with CQ, dihydroartemisinin-piperaquine, or artemether-lumefantrine. No clinically significant effects on the PK of dihydroartemisinin, piperaquine, artemether, lumefantrine, or substrates of cytochrome P450 isoenzymes were seen following co-administration with TQ.

The effect of co-administration of TQ 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 which may increase the risk of toxicity of these drugs. Co-administration with OCT2 and MATE substrates (e.g., dofetilide, metformin) should be avoided.

*Dose/Exposure-Response for Efficacy*
Dose/exposure-response analyses based on the efficacy and PK data for TQ 50, 100, 300, and 600 mg single dose in combination with CQ (TAF112582 Part 1 study) showed that the recurrence-free rate at 6 months reached a plateau with a dose of 300 mg or higher.

# 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 cell shrinkage[5].

*Activity against P. vivax*

[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. Cell Physiol Biochem 39: 2464-2476.

TQ is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *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 via increased glycolytic ATP synthesis[1,6]. Studies with *P. falciparum* strains/isolates suggest a potential for cross-resistance with PQ, an 8-aminoquinoline. The clinical relevance of such findings is not known.

# 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.

[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.

**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

Relevant clinical trials for NDA 210795 are included in Table 1. Three clinical trials, TAF112582 Part 1 (Study 582 part 1), TAF112582 Part 2 (Study 582 part 2) and TAF116564 (Study 564), are multicenter, double-blind, double-dummy, randomized, controlled trials to support efficacy and safety of TQ. Study 582 part 1 and part 2 were conducted and assessed independently and are considered as separate trials.

**Table 1. NDA 210795: Clinical Trials Supporting Safety and Efficacy**

| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|
| 582<br>Part 1 | Multicenter, double-blind, double-dummy, randomized, placebo- and active-controlled | TQ 50 mg,<br>TQ 100 mg,<br>TQ 300 mg,<br>TQ 600 mg,<br>PQ,<br>CQ alone.<br>All groups with CQ (Day 1-3)<br>Oral route. | Recurrence-free efficacy at 6 months | 15 days/6 months | Randomized<br>55<br>57<br>57<br>56<br>50<br>54 | Positive Giemsa smear for *P. vivax*<br><br>Parasite density >100/μL and <100,000/μL | 7 centers<br>4 countries |
| 582<br>Part 2 | Multicenter, double-blind, double-dummy, randomized, placebo- and active-controlled | CQ (Day 1 to 3) + 300 mg TQ single dose (Day 1 or 2)<br><br>CQ (Day 1 to 3) + 15 mg PQ once daily from Day 2 for 14 days<br><br>CQ alone regimen (Day 1 to 3)<br>Oral route. | Recurrence-free efficacy at 6 months | 15 days/6 months | Randomized<br>260<br>129<br>133 | Positive malarial smear for *P. vivax*.<br><br>Parasite density of >100 and <100,000/μL. | 8 centers<br>6 countries |
| 564 | Multicenter, double-blind, double-dummy, randomized, active-controlled | CQ (Day 1 to 3) + 300 mg TQ single dose (Day 1 or 2)<br><br>CQ (Day 1 to 3) + 15 mg PQ once daily from Day 1 or 2 for 14 days<br>Oral route. | Recurrence-free efficacy at 6 months | 15 days/6 months | 166<br>85 | | 7 centers<br>5 countries |

# 9 Phase 3 Clinical Trials in Radical Cure of *P. vivax* malaria

## 9.1 Study Design

### 9.1.1 Study 582 Part 1

Study 582 was a multi-center, double-blind, double-dummy, parallel-group, randomized, active-controlled trial conducted in two parts. Part 1 was a dose ranging trial, and the optimal TQ dose level from Part 1 was investigated further in Part 2. Each part represented a distinct and independent study.

In Study 582, part 1, stratified randomization was performed by baseline parasite count (≤7500/µL and >7500/µL). Eligible subjects were randomized to one of the following 6 treatment groups:

1. CQ + 50 mg TQ single dose (Days 1 or 2)
2. CQ + 100 mg TQ single dose (Days 1 or 2)
3. CQ + 300 mg TQ single dose (Days 1 or 2)
4. CQ + 600 mg TQ single dose (Days 1 or 2)
5. CQ +15 mg PQ once daily for 14 days (Days 2 to 15)
6. CQ only group

All subjects were treated with CQ on Days 1 to 3 (600, 600, and 300 mg) to treat the blood-stage malaria infection. Each subject received the same number of tablets/capsules (either active or placebo) for 15 days, such that all arms were blinded. Following randomization, subjects were treated for 15 days. Study visits included Day 1 (Screening), Days 2, 3, 5, 8, 11, 15, 22, 29, 60, 90, 120, and 180.

CQ monotherapy was chosen for the control group as it does not have any activity in preventing the relapse of hypnozoites once blood levels have declined sufficiently. Therefore, it allowed a test of superiority to confirm and quantify anti-relapse efficacy. A PQ comparator arm was included to provide a concurrent benchmark against a treatment that has activity against liver-stage hypnozoites and was expected to have comparable efficacy to TQ.

The primary efficacy endpoint was relapse-free efficacy 6 months post-dosing. Treatment success was defined as initial clearance of parasitemia (parasite numbers below the limit of detection in thick blood smear and remaining undetectable in the second smear collected 6 to 12 hours later) with no presence of *P. vivax* asexual stage parasites within 6 months.

**Key Inclusion and Exclusion Criteria**

***Inclusion criteria***

1. Positive Giemsa smear for *P. vivax*
2. Parasite density >100 and <100,000/µL
3. Age ≥16 years

***Exclusion criteria***

1. Mixed malaria infections (e.g., identified by Giemsa-stained smear or rapid diagnostic test)
2. Severe *P. vivax* malaria as defined by World Health Organization (WHO) criteria
3. Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, assessed by a quantitative spectrophotometric phenotype assay:
    a. Males: Any subject with an enzyme level <70% of the site median value for G6PD normals
    b. Females: (i) screening Hemoglobin (Hb) ≥10 g/dL if their enzyme level was <70% of the site median value for G6PD normals (ii) Hb ≥7 but <10 g/dL if an enzyme level was not >90% of the site median value for G6PD normals

### 9.1.2 Study 582 Part 2

Part 2 was a Phase 3, randomized, double-blind, double-dummy, active-controlled trial. Eligible subjects were randomized 2:1:1 at each center to one of the three treatment arms:

1. CQ (Days 1 to 3) + 300 mg TQ single dose (Days 1 or 2) (CQ+TQ)
2. CQ (Days 1 to 3) + 15 mg PQ once daily for 14 days (Days 2 to 15) (CQ+PQ)
3. CQ (Days 1 to 3) (CQ alone)

All subjects received the same number of tablets/capsules for 15 days for blinding purposes. Subjects stayed in the clinic and received directly observed therapy from Days 1 to 3 or until parasite clearance was confirmed. All patients received a 3-day course of CQ. The CQ+PQ arm was included to provide a concurrent benchmark.

The primary efficacy endpoint was recurrence-free efficacy at 6 months. A subject was considered to be recurrence-free at 6 months if all of the following criteria were true:

- A non-zero *P. vivax* asexual parasite count at baseline.
- Initial clearance of *P. vivax* parasitemia: two negative asexual *P. vivax* parasite counts, with at least 6 hours between counts.
- No positive asexual *P. vivax* parasite count at any assessment prior to or on Day 201 following initial parasite clearance.
- No concomitant medications with antimalarial activity at any point between Day 1 and the last parasite assessment.
- Parasite-free at 6 months: negative asexual *P. vivax* parasite count at the first parasite assessment performed on or after Day 166.

Secondary efficacy endpoints included early treatment failure by Day 32, time to *P. vivax* recurrence, time to parasite clearance, time to fever clearance, gametocyte clerance time, recrudescence, and incidence of *P. falciparum* malaria.

**Key Inclusion and Exclusion Criteria**

***Inclusion criteria***

1. Positive Giemsa smear for *P. vivax*
2. Parasite density >100 and <100,000/µL
3. Age: ≥16 years (≥18 years in Ethiopia)

***Exclusion criteria***

1. Mixed malaria infections (e.g., identified by Giemsa-stained smear or rapid diagnostic test)
2. Severe *P. vivax* malaria as defined by World Health Organization (WHO) criteria

### 9.1.3 Study 564

This was a prospective, double-blind, double-dummy, multi-center, comparative trial. A total of 300 subjects were planned to be randomized 2:1 to receive CQ+TQ or the active comparator, CQ+PQ. All subjects received CQ on Days 1 to 3 to treat the blood stage of the infection followed by TQ (one dose of 300 mg) or PQ on Day 1 or 2. PQ was administered 15 mg once daily for 14 days. Matching placebos were given to blind the trial.

The primary endpoints for this study were safety endpoints. No primary efficacy endpoint was defined. Our review focused on the recurrence-free efficacy 6 months post-dosing. A subject would be considered to have demonstrated relapse-free efficacy at 6 months for the purposes of the analysis if *P. vivax* asexual parasites at baseline were cleared and remained absent by 6 months.

**Key Inclusion and Exclusion Criteria**

***Inclusion criteria***

1. Positive malarial smear for *P. vivax.*
2. Parasite density of >100 and <100,000/μL.
3. Male or female subject aged 16 years or older (18 years or older in Ethiopia) at the time of signing the informed consent.
4. The subject has a G6PD value (measured by a quantitative spectrophotometric phenotype assay) as follows:
   - Females: enzyme level ≥40% of the site median value for G6PD normal males.
   - Males: enzyme level ≥70% of the site median value for G6PD normal males.
5. A screening Hb value as follows:
   - Any subject with a G6PD value ≥70% of the site median value must have a screening Hb value ≥70 g/L.
   - Female subjects with a G6PD value is ≥40% - <70% of the site median value must have a screening Hb value ≥80 g/L.

***Exclusion criteria***

1. A mixed malaria infection (identified by a malarial smear or rapid diagnostic test).
2. Severe *P. vivax* malaria as defined by WHO criteria.
3. A history of allergy to CQ, MQ, TQ, PQ, or to any other 4- or 8-aminoquinoline.

## 9.2 Statistical Methodologies

### 9.2.1 Study 582 Part 1

**Analysis Populations**

The following analysis populations were defined:

**Intent to Treat (ITT) Population**: all randomized subjects. This population was the primary population for all efficacy analyses.

**Modified ITT (mITT) population**: all subjects in the ITT population who were not from regions excluded from the analysis due to inadequate CQ-only relapse rates in the patient population. This population was used for the purposes of sensitivity analysis of the primary endpoint. The Reporting and Analysis Plan states that on unblinding of the study, if any geographical region demonstrates a level of relapse in the CQ alone arm which is inadequate for demonstrating a potential treatment effect, additional analyses would be performed on the mITT population. This is the definition used by the Applicant.

**Per Protocol (PP) Population**: all subjects in the ITT population for whom there were no major protocol violations. This population was used by the Applicant for sensitivity/supporting analyses of efficacy data only.

**Safety Population**: all randomized subjects who received at least one dose of study medication. If subjects received a treatment different to their randomized treatment, they were analyzed according to the treatment actually received. This was the primary population for all safety analyses and data presentations.

**Analysis Methods**
The proportion of subjects with recurrence-free efficacy at 6 months was summarized by treatment group for the ITT (primary analysis) and PP populations. For the primary analysis, recurrence-free efficacy at 6 months was analyzed using Kaplan-Meier method. Subjects who did not relapse would be censored at the time of last available smear. The planned Kaplan-Meier analysis assumed non-informative censoring, which assumes that the censoring was unrelated to study treatment. The FDA conducted an additional analysis that treated early censored subjects as treatment failures as a sensitivity analysis.

Treatment efficacy at 6 months was compared between a TQ group and the CQ alone group using a log-rank test with a two-sided 5% significance level. To control the possible inflation of the type I error due to multiple treatment arms, a closed testing approach was adopted, i.e., no adjustment for each hypothesis test was considered, but hypotheses were tested in order. Each of the four TQ groups against the CQ alone group was tested in a step-down approach, starting with the highest dose. As soon as a dose was not found to be statistically significantly better than CQ alone, testing stopped.

Secondary analysis of the categorized primary endpoint included Fisher's exact test for treatment differences in relapse-free proportions using the ITT and PP populations and assuming that subjects who were lost to follow up were treatment failures.

### 9.2.2 Study 582 Part 2

**Analysis Populations**
The following analysis populations were defined.

**Microbiologic intent-to-treat population (micro-ITT):** All randomized subjects who received at least 1 dose of study medication and who had a positive parasite smear for *P.*

*vivax* at baseline. Subjects were analyzed according to their randomized treatment. This population was the primary population for all efficacy analyses in Part 2 of the study.

**Per Protocol (PP) population:** All subjects in the micro-ITT population for whom there were no major protocol violations. This population was used by the Applicant for sensitivity/supporting analyses of efficacy data only.

**Safety population:** All randomized subjects who received at least 1 dose of study medication.

**Analysis Methods**
The proportion of subjects with recurrence-free efficacy at 6 months was summarized by treatment group for both the micro-ITT and the PP populations. For the primary analysis, recurrence-free efficacy at 6 months was analyzed using Kaplan-Meier and Cox proportional hazards methodology to compare the CQ+TQ or CQ+PQ group with the CQ alone group. Statistical comparisons between CQ+TQ and CQ+PQ groups were not performed. The Cox proportional hazards model was fitted with region and treatment as covariates. In addition to the survival primary analysis, a logistic regression model was used to analyze recurrence-free efficacy at 6 months (including terms for treatment and region). In this analysis, subjects that did not demonstrate initial clearance, or took a concomitant medication with antimalarial activity, or did not have a 6-month parasite assessment were assumed to have had a recurrence (i.e., missing=failure analysis).

### 9.2.3 Study 564

**Analysis Populations**
The primary analysis population for all efficacy analyses was the micro-ITT population, defined as all randomized subjects who received at least one dose of blinded study medication and had microscopically-confirmed *P. vivax* parasitemia.

Per Protocol (PP) Population included all subjects in the micro-ITT population for whom there were no major protocol violations. This population was used for sensitivity/supporting analyses of efficacy data only.

**Analysis Methods**
The primary comparisons of interest between the 2 treatment arms were the proportion of all subjects with *P. vivax* experiencing clinically relevant hemolysis, and the proportions in the subgroup of females with *P. vivax* and moderate G6PD deficiency. For results of these analyses, please see safety section of this document.

Other comparisons included clinical and parasitological efficacy, safety and tolerability of TQ+CQ compared to CQ+PQ. Estimates for the recurrence-free efficacy rate at 6 months and time to recurrence were determined for each treatment group using the Kaplan-Meier method.

A Cox proportional hazards model with region and treatment as covariates was used. Subjects who did not have a positive *P. vivax* asexual count at baseline, cleared the

original infection, took a concomitant medication with anti-malarial activity, or could not be confirmed parasite-free at 6 months were censored.

A second analysis used a logistic regression model where subjects were classified as a treatment failure if they had a recurrence, did not have a 6-month result, did not clear the initial infection, or took any drug with activity against *P. vivax*. In another logistic regression model, subjects who were censored prior to 6 months were excluded from the analysis.

## 9.3 Patient Disposition

### 9.3.1 Study 582 Part 1

A total of 329 subjects were randomized. All were included in the ITT population, 319 (97%) completed the study, and 10 subjects were withdrawn due to loss to follow-up. All except for 3 subjects, who met QTc withdrawal criteria, completed study medication. See Table 2. Following unblinding, India was considered to have an inadequate background relapse rate of 10% in the CQ group and, therefore, 57 subjects from India were excluded from the mITT population.

**Table 2. Study 582 Part 1: Patient Disposition**

| | **CQ (N=54)** | **CQ+TQ 50 mg (N=55)** | **CQ+TQ 100 mg (N=57)** | **CQ+TQ 300 mg (N=57)** | **CQ+TQ 600 mg (N=56)** | **CQ+PQ (N=50)** |
|---|---|---|---|---|---|---|
| **Completed study, n(%)** | | | | | | |
| Yes | 54 (100) | 54 (98) | 54 (95) | 56 (98) | 54 (96) | 47 (94) |
| Withdrawn (lost to follow-up) | 0 | 1 (2) | 3 (5) | 1 (2) | 2 (4) | 3 (6) |
| **Completed study medication, n(%)** | | | | | | |
| Yes | 53 (98) | 54 (98) | 57 (100) | 57 (100) | 56 (100) | 49 (98) |
| No. Withdrawn (subject met QTc withdrawal criteria (protocol-defined stopping criterion)) | 1 (2) | 1 (2) | 0 | 0 | 0 | 1 (2) |
| **Analysis population** | | | | | | |
| Safety | 54 | 55 | 57 | 57 | 56 | 50 |
| Intent-to-Treat (ITT) | 54 | 55 | 57 | 57 | 56 | 50 |
| Modified ITT (mITT) | 44 | 44 | 46 | 48 | 46 | 44 |
| Per Protocol (PP) | 35 | 40 | 40 | 43 | 36 | 37 |
| Reasons for excluding subjects in mITT from PP[a] | | | | | | |
| *Assessment procedures* | 1 | 1 | 2 | 1 | 2 | 2 |
| *Biological specimen sample procedures* | 1 | 0 | 0 | 0 | 0 | 0 |
| *Eligibility criteria* | 1 | 0 | 0 | 0 | 0 | 0 |
| *Prohibited medication or device* | 1 | 0 | 0 | 0 | 1 | 0 |
| *Supply procedures* | 0 | 0 | 0 | 0 | 0 | 1 |
| *Visit schedule* | 5 | 3 | 4 | 5 | 8 | 5 |
| *Withdrawal criteria* | 1 | 1 | 0 | 0 | 0 | 0 |

[a] Results from data set. Subjects could be excluded for more than one reason.

**Demographic Characteristics**

Table 3 shows the demographic characteristics in the ITT population. The majority of subjects were male, younger than 65 years old, and were from Peru or Thailand. The mean age was 35.4 years. The demographic factors were well-balanced between the groups.

**Table 3. Study 582 Part 1: Demographic characteristics (ITT population)**

| | Control Group CQ alone (N=54) | Treatment Group (N=275) | | | | | Total (N=329) |
|---|---|---|---|---|---|---|---|
| | | CQ+TQ 50 mg (N=55) | CQ+TQ 100 mg (N=57) | CQ+TQ 300 mg (N=57) | CQ+TQ 600 mg (N=56) | CQ+PQ (N=50) | |
| **Sex, n(%)** | | | | | | | |
| Male | 39 (72) | 37 (67) | 44 (77) | 43 (75) | 45 (80) | 35 (70) | 243 (74) |
| Female | 15 (28) | 18 (33) | 13 (23) | 14 (25) | 11 (20) | 15 (30) | 86 (26) |
| **Age in years** | | | | | | | |
| Mean | 33.6 | 36.3 | 34.6 | 36.2 | 35.7 | 36.0 | 35.4 |
| SD | 14.16 | 13.28 | 14.09 | 13.49 | 15.06 | 13.91 | 13.94 |
| Median | 28.0 | 36.0 | 34.0 | 36.0 | 35.0 | 34.0 | 34.0 |
| Minimum | 16 | 17 | 16 | 16 | 17 | 16 | 16 |
| Maximum | 68 | 68 | 74 | 64 | 68 | 72 | 74 |
| **Age group** | | | | | | | |
| < 65 years | 53 | 54 | 55 | 57 | 53 | 48 | 320 |
| ≥ 65 years | 1 | 1 | 2 | 0 | 3 | 2 | 9 |
| **Race, n(%)** | | | | | | | |
| American Indian or Alaska Native | 27 (50) | 27 (49) | 28 (49) | 29 (51) | 29 (52) | 25 (50) | 165 (50) |
| Asian – Central/ Southeast Asian Heritage | 10 (19) | 11 (20) | 11 (19) | 9 (16) | 10 (18) | 6 (12) | 57 (17) |
| Asian – South East Asian Heritage | 16 (30) | 16 (29) | 16 (28) | 19 (33) | 16 (29) | 16 (32) | 99 (30) |
| Mixed Race | 1 (2) | 1 (2) | 2 (4) | 0 | 1 (2) | 3 (6) | 8 (2) |
| **Ethnicity, n(%)** | | | | | | | |
| Hispanic or Latino | 28 (52) | 28 (51) | 30 (53) | 29 (51) | 30 (54) | 28 (56) | 173 (53) |
| Not Hispanic or Latino | 26 (48) | 27 (49) | 27 (47) | 28 (49) | 26 (46) | 22 (44) | 156 (47) |
| **Body weight (kg)** | | | | | | | |
| Mean | 59.3 | 59.9 | 59.4 | 59.4 | 62.2 | 60.0 | 60.0 |
| SD | 13.79 | 11.17 | 10.55 | 9.78 | 13.58 | 12.61 | 11.93 |
| Median | 57.4 | 59.0 | 57.0 | 59.0 | 60.0 | 59.4 | 59.0 |
| Minimum | 34 | 37 | 44 | 43 | 42 | 40 | 34 |
| Maximum | 101 | 91 | 95 | 84 | 106 | 99 | 106 |
| **Country** | | | | | | | |
| Brazil | 6 (11.1) | 6 (10.9) | 6 (10.5) | 6 (10.5) | 7 (12.5) | 6 (12.0) | 37 (11.2) |
| India | 10 (18.5) | 11 (20.0) | 11 (19.3) | 9 (15.8) | 10 (17.9) | 6 (12.0) | 57 (17.3) |
| Peru | 22 (40.7) | 22 (40.0) | 24 (42.1) | 23 (40.4) | 23 (41.1) | 22 (44.0) | 136 (41.3) |
| Thailand | 16 (29.6) | 16 (29.1) | 16 (28.1) | 19 (33.3) | 16 (28.6) | 16 (32.0) | 99 (30.1) |

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

Table 4 shows other baseline characteristics, including G6PD enzyme activity, splenomegaly, previous malarial episode, and *P. vivax* parasite counts. Baseline characteristics and malarial signs and symptoms (data not shown) were well-balanced between treatment groups.

**Table 4. Study 582 Part 1: Other baseline characteristics (ITT population)**

| | Control Group CQ alone (N=54) | Treatment Group (N=275) | | | | | Total (N=329) |
|---|---|---|---|---|---|---|---|
| | | CQ+TQ 50 mg (N=55) | CQ+TQ 100 mg (N=57) | CQ+TQ 300 mg (N=57) | CQ+TQ 600 mg (N=56) | CQ+PQ (N=50) | |
| **G6PD enzyme activity (IUg/Hb)** | | | | | | | |
| Mean | 9.2 | 9.9 | 9.4 | 9.2 | 9.4 | 9.5 | 9.4 |
| SD | 2.49 | 2.98 | 2.89 | 2.36 | 2.65 | 2.55 | 2.65 |
| Median | 8.7 | 9.1 | 8.9 | 8.6 | 8.8 | 9.0 | 8.8 |
| Range | 5, 17 | 6, 18 | 6, 19 | 4, 15 | 5, 18 | 5, 16 | 4, 19 |
| **Splenomegaly, n(%)** | | | | | | | |
| Yes | 1 (2) | 2 (4) | 3 (5) | 4 (7) | 5 (9) | 2 (4) | 17 (5) |
| No | 53 (98) | 53 (96) | 54 (95) | 53 (93) | 51 (91) | 48 (96) | 312 (95) |
| **Previous malarial episode, n (%)** | | | | | | | |
| Yes | 33 (61) | 35 (64) | 36 (63) | 28 (49) | 31 (55) | 31 (62) | 194 (59) |
| No | 21 (39) | 20 (36) | 20 (35) | 27 (47) | 25 (45) | 18 (36) | 131 (40) |
| Unknown | 0 | 0 | 1 (2) | 2 (4) | 0 | 1 (2) | 4 (1) |
| ***P. vivax* - asexual parasite count, n (%)** | | | | | | | |
| ≤7500/µL | 37 (69) | 38 (69) | 41 (72) | 37 (65) | 35 (63) | 36 (72) | 224 (68) |
| >7500/µL | 17 (31) | 17 (31) | 16 (28) | 20 (35) | 21 (38) | 14 (28) | 105 (32) |
| **Subjects with gametocytes, n(%)** | | | | | | | |
| Yes | 41 (76) | 41 (75) | 44 (77) | 47 (82) | 44 (79) | 36 (72) | 253 (77) |
| ***P. vivax* - gametocyte parasite count per µL** | | | | | | | |
| Mean (SD) | 41 (76) | 41 (75) | 44 (77) | 47 (82) | 44 (79) | 36 (72) | 253 (77) |
| Median | 149 | 160 | 77.0 | 138 | 141 | 106 | 111 |
| Range | 0, 3000 | 0, 3500 | 0, 7275 | 0, 4378 | 0, 8175 | 0, 9046 | 0, 9046 |

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Table 5 shows treatment compliance, which was high and comparable for all groups.

**Table 5. Study 582 Part 1: Treatment Compliance (ITT population)**

| | Control Group CQ alone (N=54) | Treatment Group (N=275) | | | | | Total (N=329) |
|---|---|---|---|---|---|---|---|
| | | CQ+TQ 50 mg (N=55) | CQ+TQ 100 mg (N=57) | CQ+TQ 300 mg (N=57) | CQ+TQ 600 mg (N=56) | CQ+PQ (N=50) | |
| **Number of compliant doses of CQ, n (%)** | | | | | | | |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0 | 1 (2) | 0 | 0 | 0 | 1 (2) | 2 (<1) |
| 3 | 54 (100) | 54 (98) | 57 (100) | 57 (100) | 56 (100) | 49 (98) | 327 (>99) |
| **Compliant with TQ/TQ placebo dosing, n (%)** | | | | | | | |
| Yes | 54 (100) | 55 (100) | 57 (100) | 55 (96) | 56 (100) | 50 (100) | 327 (>99) |
| No | 0 | 0 | 0 | 2 (4) | 0 | 0 | 2 (<1) |
| **Compliance with PQ/PQ placebo dosing on Day 2, n (%)** | | | | | | | |

| | Control Group CQ alone (N=54) | Treatment Group (N=275) | | | | | Total (N=329) |
|---|---|---|---|---|---|---|---|
| | | CQ+TQ 50 mg (N=55) | CQ+TQ 100 mg (N=57) | CQ+TQ 300 mg (N=57) | CQ+TQ 600 mg (N=56) | CQ+PQ (N=50) | |
| Yes | 54 (100) | 55 (100) | 57 (100) | 57 (100) | 56 (100) | 49 (98) | 328 (>99) |
| No | 0 | 0 | 0 | 0 | 0 | 1 (2) | 1 (<1) |
| **Compliance with PQ/PQ placebo dosing on Day 3, n (%)** | | | | | | | |
| Yes | 53 (98) | 54 (98) | 57 (100) | 57 (100) | 56 (100) | 49 (98) | 326 (>99) |
| No | 1 (2) | 1 (2) | 0 | 0 | 0 | 1 (2) | 3 (<1) |
| **Number of outpatient doses of PQ/placebo dosing taken[a], n (%)** | | | | | | | |
| 10 or fewer | 23 (43) | 19 (35) | 21 (37) | 20 (35) | 22 (39) | 16 (32) | 121 (37) |
| 11 to 13 | 10 (19) | 15 (27) | 12 (21) | 14 (25) | 13 (23) | 13 (26) | 77 (23) |
| 14 or more | 21 (39) | 21 (38) | 24 (42) | 23 (40) | 21 (38) | 21 (42) | 131 (40) |

[a] PQ was given as a 14-dose course for Days 2 to 15. The calculation of tablets was dependent on the number of tablets returned.

Only two subjects in the CQ alone group had prior medication use. Use of concomitant medications was similar between treatment groups and was unlikely to impact the interpretation of the study results. About 74% of subjects used acetaminophen for treating pain and fever.

### 9.3.2 Study 582 Part 2

This study was conducted between April 2014 and November 2016 in 8 centers in Brazil, Ethiopia, Cambodia, Peru, Philippines, and Thailand. Table 6 shows patient disposition. All randomized subjects were included in the micro-ITT population. The majority of subjects (96%) completed the study. Reasons for discontinuation were well-balanced. Table 7 shows demographic characteristics.

**Table 6. Study 582 Part 2: Patient disposition**

| | CQ alone (N=133) | CQ+TQ (N=260) | CQ+PQ (N=129) | Total (N=522) |
|---|---|---|---|---|
| **Completion status, n (%)** | | | | |
| Completed | 129 (97) | 250 (96) | 123 (95) | 502 (96) |
| Withdrawn | 4 (3) | 10 (4) | 6 (5) | 20 (4) |
| **Primary reason for withdrawal from study, n (%)** | | | | |
| Adverse event | 0 | 0 | 0 | 0 |
| Protocol deviation | 0 | 0 | 0 | 0 |
| Subject reached protocol-defined stopping criteria | 0 | 0 | 0 | 0 |
| Study closed/terminated | 0 | 0 | 0 | 0 |
| Lost to follow-up[a] | 2 (2) | 4 (2) | 2 (2) | 8 (2) |
| Physician decision[a] | 1 (<1) | 1 (<1) | 0 | 2 (<1)[a] |
| Withdrawal by subject | 1 (<1) | 5 (2) | (3) | 10 (2)[a] |
| **Per Protocol population** | 106 (80) | 192 (74) | 108 (84) | 406 (78) |

[a] Reasons for withdrawal due to physician decision or withdrawal by subject were primarily related to logistical issues or personal decisions. None of the withdrawals were due to AEs.

**Table 7. Study 582 Part 2: Demographic characteristics**

| | Control Group CQ alone (N=133) | Treatment Group (N=389) | | Total (N=522) |
|---|---|---|---|---|
| | | CQ+TQ (N=260) | CQ+PQ (N=129) | |
| **Sex, n(%)** | | | | |
| Male | 97 (73) | 196 (75) | 99 (77) | 392 (75) |
| Female | 36 (27) | 64 (25) | 30 (23) | 130 (25) |
| **Age in years** | | | | |
| Mean (SD) | 35.3 (14.2) | 35.0 (14.4) | 34.7 (14.3) | 35.0 (14.3) |
| Median | 31.0 | 31.5 | 33.0 | 32.0 |
| Min, max | 17.0, 71.0 | 15.0, 79.0 | 15.0, 66.0 | 15.0, 79.0 |
| **Age group, n(%)** | | | | |
| < 65 years | 131 (98.5) | 253 (97.3) | 126 (97.7) | 510 (97.7) |
| ≥ 65 years | 2 (1.5) | 7 (2.7) | 3 (2.3) | 12 (2.3) |
| **Race, n(%)** | | | | |
| American Indian or Alaska native | 43 (32) | 81 (31) | 41 (32) | 165 (32) |
| Asian - Southeast Asian heritage | 26 (20) | 50 (19) | 26 (20) | 102 (20) |
| Black or African American | 14 (11) | 28 (11) | 13 (10) | 55 (11) |
| Multiple | 47 (35) | 97 (37) | 47 (36) | 191 (37) |
| White | 3 (2) | 4 (2) | 2 (2) | 9 (2) |
| **Ethnicity, n(%)** | | | | |
| Hispanic or Latino | 93 (69.9) | 182 (70.0) | 89 (69.0) | 364 (69.7) |
| Not Hispanic or Latino | 40 (30.1) | 78 (30.0) | 40 (31.0) | 158 (30.3) |
| **Country, n(%)** | | | | |
| Brazil | 53 (39.8) | 105 (40.4) | 52 (40.3) | 210 (40.2) |
| Ethiopia | 14 (10.5) | 28 (10.8) | 13 (10.1) | 55 (10.5) |
| Cambodia | 10 (7.5) | 19 (7.3) | 9 (7.0) | 38 (7.3) |
| Peru | 40 (30.1) | 77 (29.6) | 38 (29.5) | 155 (29.7) |
| Philippines | 1 (0.8) | 3 (1.2) | 2 (1.6) | 6 (1.1) |
| Thailand | 15 (11.3) | 28 (10.8) | 15 (11.6) | 58 (11.1) |

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

Other baseline characteristics, such as G6PD enzyme activity, malarial signs and symptoms (not shown), splenomegaly, previous malarial episode, and *P. vivax* parasite counts, were well balanced in the three treatment groups. See Table 8.

**Table 8. Study 582 Part 2: Other baseline characteristics (micro-ITT population)**

| | Control Group CQ alone (N=133) | Treatment Group (N=389) | | Total (N=522) |
|---|---|---|---|---|
| | | CQ+TQ (N=260) | CQ+PQ (N=129) | |
| **G6PD enzyme activity (IUg/Hb)** | | | | |
| Mean (SD) | 8.4 (1.3) | 8.5 (1.5) | 8.6 (1.2) | 8.5 (1.4) |
| Median | 8.2 | 8.3 | 8.5 | 8.3 |
| Min, max | 5.8, 12.0 | 5.6, 15.5 | 5.4, 12.5 | 5.4, 15.5 |
| **Splenomegaly, n (%)** | | | | |
| Yes | 4 (3) | 13 (5) | 4 (3) | 21 (4) |
| No | 129 (97) | 247 (95) | 125 (97) | 501 (96) |
| **Previous malarial episode, n (%)** | | | | |

| | Control Group CQ alone (N=133) | Treatment Group (N=389) | | Total (N=522) |
|---|---|---|---|---|
| | | CQ+TQ (N=260) | CQ+PQ (N=129) | |
| Yes | 106 (80) | 219 (84) | 109 (84) | 434 (83) |
| No | 26 (20) | 41 (16) | 18 (14) | 85 (16) |
| Unknown | 1 (<1) | 0 | 2 (2) | 3 (<1) |
| ***P. vivax* - asexual parasite count/µL** | | | | |
| Median | 5615.0 | 5313.5 | 4380.0 | 5220.0 |
| Minimum | 101 | 112 | 125 | 101 |
| Maximum | 66010 | 99604 | 87380 | 99604 |
| ***P. vivax* - gametocyte parasite count/µL** | | | | |
| Median | 55.0 | 53.5 | 31.0 | 47.0 |
| Minimum | 0 | 0 | 0 | 0 |
| Maximum | 1110 | 7201 | 4949 | 7201 |

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Treatment compliance was comparable among the three groups. All subjects received the scheduled in-clinic dose of TQ or TQ placebo. The majority of the subjects completed the additionally assigned doses. As expected, only the subjects in the CQ+PQ group had detectable PQ concentrations. See Table 9.

**Table 9. Study 582 Part 2: Treatment compliance (micro-ITT population)**

| | Control Group CQ alone (N=133) n (%) | Treatment Group (N=389) | | Total (N=522) n (%) |
|---|---|---|---|---|
| | | CQ+TQ (N=260) n (%) | CQ+PQ (N=129) n (%) | |
| **Number of compliant doses of CQ** | | | | |
| 1 | 0 | 1 (<1) | 0 | 1 (<1) |
| 2 | 3 (2) | 6 (2) | 1 (<1) | 10 (2) |
| 3 | 130 (98) | 253 (97) | 128 (>99) | 511 (98) |
| **Total number of PQ doses[a]** | | | | |
| <12 | 7 (5) | 12 (5) | 1 (<1) | 20 (4) |
| ≥12 | 125 (94) | 239 (92) | 124 (96) | 488 (93) |
| Missing | 1 (<1) | 9 (3) | 4 (3) | 14 (3) |
| **Subjects with detectable PQ concentrations at Day 8 or Day 15** | | | | |
| n[b] | NA | NA | 125 | NA |
| Subjects who met criteria | NA | NA | 122 (98) | NA |
| **Subjects with PQ count ≥12 and detectable PQ concentrations at Day 8 or Day 15** | | | | |
| n[c] | NA | NA | 124 | NA |
| Subjects who met criteria | NA | NA | 120 (97) | NA |

a. 14 tablets taken was perfect adherence. The calculation of tablets was dependent on the number of tablets returned, not administration that was directly observed.
b. Number of subjects with a PQ PK assessment on Day 8 or Day 15.
c. Number of subjects with a PQ pill count AND a PQ PK assessment on Day 8 or Day 15.

### 9.3.3 Study 564

The study was conducted between April 2015 and November 2016 in 7 sites in 5 countries (Brazil, Colombia, Peru, Thailand, and Vietnam). A total of 251 subjects out of 369 screened for eligibility were randomized. The majority of randomized subjects (97%) completed the study. Only 4% of subjects stopped treatment prematurely in both groups. All randomized subjects were included in the micro-ITT population and safety population. About 88% of the subjects in the micro-ITT population were included in the PP population. See Table 10.

**Table 10. Study 564: Patient disposition**

| | **CQ+TQ (N=166) n (%)** | **CQ+PQ (N=85) n (%)** | **Total (N=251) n (%)** |
|---|---|---|---|
| **Micro-ITT population/safety population** | 166 | 85 | 251 |
| **Per protocol population** | 135 (81) | 75 (88) | 210 (84) |
| **Study completion status** | | | |
| Completed | 160 (96) | 83 (98) | 243 (97) |
| Withdrawn | 6 (4) | 2 (2) | 8 (3) |
| **Primary reason for withdrawal** | | | |
| Loss to follow-up | 4 (2) | 2 (2) | 6 (2) |
| Withdrawal by subject | 2 (1) | 0 | 2 (<1) |
| **Study treatment stopped permanently before the scheduled end of the treatment period?** | | | |
| No | 160 (96) | 82 (96) | 242 (96) |
| Yes | 6 (4) | 3 (4) | 9 (4) |
| **Reason for discontinuation from study medication** | | | |
| Adverse event | 1 (<1) | 1 (1) | 2 (<1) |
| Subject reached protocol-defined Hb stopping criteria | 2 (1)[a] | 1 (1) | 4 (2)[a] |
| Lost to follow-up | 1 (<1) | 1 (1) | 2 (<1) |
| Physician decision | 1 (<1) | 0 | 1 (<1) |
| Other | 1 (<1) | 0 | 1(<1) |

[a] Including one subject not properly recorded in the eCRF and the data set.

**Demographic Characteristics**

Demographic characteristics (age, sex, race, geographic location, and body mass index) are presented in Table 11. The two groups were comparable. The mean age was 38 years old. The majority of subjects were American Indian males from Brazil and Peru.

**Table 11. Study 564: Demographic characteristics (micro-ITT population)**

| | **CQ+TQ (N=166)** | **CQ+PQ (N=85)** | **Total (N=251)** |
|---|---|---|---|
| **Age in years** | | | |
| Mean(SD) | 37.5 (14.28) | 37.7 (14.69) | 37.6 (14.39) |
| Range | 16, 75 | 15, 74 | 15, 75 |
| **Sex, n(%)** | | | |
| Male | 114 (69) | 53 (62) | 167 (67) |
| Female | 52 (31) | 32 (38) | 84 (33) |
| **Race, n(%)** | | | |
| American Indian or Alaska Native* | 87 (52) | 43 (51) | 130 (52) |
| Asian (Southeast Asian Heritage) | 41 (25) | 23 (27) | 64 (25) |

| | CQ+TQ (N=166) | CQ+PQ (N=85) | Total (N=251) |
|---|---|---|---|
| Black or African American | 2 (1) | 0 | 2 (<1) |
| Multiple† | 36 (22) | 19 (22) | 55 (22) |
| **Body mass index (kg/m2)** | | | |
| Mean | 25.6 | 25.5 | 25.6 |
| Median | 24.79 | 25.24 | 24.91 |
| Min, Max | (16.7, 48.9) | (17.4, 40.4) | (16.7, 48.9) |
| **Country, n(%)** | | | |
| Brazil | 45 (27.1) | 23 (27.1) | 68 (27.1) |
| Colombia | 13 (7.8) | 6 (7.1) | 19 (7.6) |
| Peru | 67 (40.4) | 33 (38.8) | 100 (39.8) |
| Thailand | 12 (7.2) | 8 (9.4) | 20 (8.0) |
| Vietnam | 29 (17.5) | 15 (17.7) | 44 (17.5) |

*All were from Brazil, Colombia, and Peru. †From Brazil

## Other Baseline Characteristics

Malaria signs and symptoms at baseline were similar between the two groups (not shown). Table 12 shows a summary of splenomegaly, previous malarial episodes, and *P. vivax* parasite counts at baseline. The two groups had similar distributions with these baseline characteristics.

**Table 12. Study 564: Splenomegaly, previous malarial episodes, and *P. vivax* parasite counts at baseline (micro-ITT population)**

| | CQ+TQ (N=166) | CQ+PQ (N=85) | Total (N=251) |
|---|---|---|---|
| **Splenomegaly, n(%)** | | | |
| Yes | 0 | 1 (1) | 1 (<1) |
| No | 166 (100) | 84 (99) | 250 (>99) |
| **Previous malaria episode, n(%)** | | | |
| Yes | 132 (80) | 63 (74) | 195 (78) |
| No | 32 (19) | 22 (26) | 54 (22) |
| Unknown | 2 (1) | 0 | 2 (<1) |
| ***P. vivax*-asexual parasite count ($10^3$/mL)** | | | |
| Median | 3617.5 | 5128.0 | 3990.0 |
| Range | 102, 45410 | 104, 82650 | 102, 82650 |
| ***P. vivax*-gametocyte parasite count ($10^3$/mL)** | | | |
| Median | 44.5 | 60 | 49.0 |
| Range | 0, 2015 | 0, 5340 | 0, 5340 |

## Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Table 13 presents a summary of treatment compliance. Compliance was high (≥96%) and the two groups were comparable.

**Table 13. Study 564: Exposure and treatment compliance (micro-ITT population)**

| | CQ+TQ (N=166) n/N (%) | CQ+PQ (N=85) n/N (%) | Total (N=251) n/N (%) |
|---|---|---|---|
| **Number of compliant doses of CQ** | | | |
| 2 | 1 (<1) | 1 (1) | 2 (<1) |
| 3 | 165 (>99) | 84 (99) | 249 (>99) |
| **Was subject compliant with TQ?** | | | |
| Yes | 165 (>99) | 84 (99) | 249 (>99) |
| No | 1 (<1) | 1 (1) | 2 (<1) |
| **Total number of PQ doses taken** | | | |
| <12 | 6 (4) | 1 (1) | 7 (3) |
| at least 12 | 160 (96) | 83 (98) | 243 (97) |
| Missing | 0 | 1 (1) | 1 (<1) |

The most frequently used concomitant medications started on or after Day 1 were PQ (25% of subjects) and CQ (25% of subjects), primarily for the treatment of recurrence. Use of these concomitant medications was similar between treatment groups.

## 9.4 Efficacy Results

### 9.4.1 Study 582 Part 1

A summary of Applicant's results is included below. Among the 4 CQ+TQ groups, the 300-mg TQ group achieved the highest relapse-free efficacy at 6 months. The 300- and 600- mg TQ groups and PQ group had a statistically significant higher relapse-free proportion compared with the control group. FDA's analysis assuming censoring prior to 6 months as failure yields similar results. Table 14 contains the results based on the survival analysis of time to relapse.

**Table 14. Study 582 Part 1: Relapse-free efficacy at 6 months (ITT population)**

| | Control Group CQ alone (N=54) | Treatment Group (N=275) | | | | |
|---|---|---|---|---|---|---|
| | | CQ+TQ 50 mg (N=55) | CQ+TQ 100 mg (N=57) | CQ+TQ 300 mg (N=57) | CQ+TQ 600 mg (N=56) | CQ+PQ (N=50) |
| **Number of Subjects, n(%)** | | | | | | |
| Relapse-free efficacy at 6 months | 21 (39) | 29 (53) | 29 (51) | 48 (84) | 43 (77) | 34 (68) |
| Relapse | 31 (57) | 22 (40) | 25 (44) | 6 (11) | 4 (7) | 12 (24) |
| Censored [a] | 2 (4) | 4 (7) | 3 (5) | 3 (5) | 9 (16) | 4 (8) |
| *Taking antimalarial in first 6 months (and not parasitemic)* | 1 | 3 | 1 | 1 | 4 | 2 |
| *No asexual P. vivax parasites at baseline* | 0 | 0 | 1 | 0 | 0 | 0 |
| *No assessment at 6 months* | 1 | 1 | 1 | 2 | 5 | 2 |
| **Relapse-free efficacy rate at 6 months, %** | | | | | | |
| Estimate | 37.5 | 57.7 | 54.1 | 89.2 | 91.9 | 77.3 |
| 95% CI | 23,52 | 43,70 | 40,66 | 77,95 | 80,97 | 63,87 |
| **Difference from CQ at 6 months, %** | | | | | | |
| Estimated difference | | 20.3 | 16.6 | 51.7 | 54.5 | 39.9 |

| | Control Group CQ alone (N=54) | Treatment Group (N=275) | | | | |
|---|---|---|---|---|---|---|
| | | CQ+TQ 50 mg (N=55) | CQ+TQ 100 mg (N=57) | CQ+TQ 300 mg (N=57) | CQ+TQ 600 mg (N=56) | CQ+PQ (N=50) |
| 95% CI | | 0,40 | -3,36 | 35,69 | 38,71 | 21,59 |
| Log rank test p-value[b] | | 0.048[c] | 0.158 | <0.0001 | <0.0001 | 0.0004 |

a. Subjects were censored by definition if they did not have *P. vivax* at baseline, or failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 6 month assessment. No subjects were censored due to failure to demonstrate initial parasite clearance.
b. A two-sided log rank test was performed over 6 months using a 5% significance level.
c. Not significant due to step-down procedure to adjust for multiple comparisons.

Table 15 contains the results of a categorical efficacy endpoint at 6 months that does not take the amount of time to clear the parasite into account. This analysis considers subjects who are not confirmed to be relapse free as failures. The first row is the same as that in the previous table. This table provides the reasons for failures. As in the previous analysis, the 300- and 600-mg TQ groups and PQ group had a statistically significant higher relapse-free proportion compared with the control group using Fisher's exact test.

**Table 15. Study 582 Part 1: Efficacy results (categorical) at 6 months (ITT population)**

| | Control Group CQ alone (N=54) | Treatment Group (N=275) | | | | |
|---|---|---|---|---|---|---|
| | | CQ+TQ 50 mg (N=55) | CQ+TQ 100 mg (N=57) | CQ+TQ 300 mg (N=57) | CQ+TQ 600 mg (N=56) | CQ+PQ (N=50) |
| **Categorical efficacy results** | | | | | | |
| Relapse-free efficacy at 6 months (primary analysis), n (%) | 21 (39) | 29 (53) | 29 (51) | 48 (84) | 43 (77) | 34 (68) |
| No asexual *P. vivax* parasites at baseline | 0 | 0 | 1 (2) | 0 | 0 | 0 |
| Recurrence of parasitemia in 6 months after initial clearance | 31 (57) | 22 (40) | 25 (44) | 6 (11) | 4 (7) | 12 (24) |
| Taking antimalarial in first 6 months (and were not parasitemic) | 1 (2) | 3 (5) | 1 (2) | 1 (2) | 4 (9) | 2 (4) |
| Missing parasite assessment at 6 months | 1(4) | 1 (2) | 1(2) | 2 (4) | 5 (9) | 2 (4) |
| **Difference in relapse-free efficacy from CQ, %** | | | | | | |
| Estimated Difference | | 13.8 | 12.0 | 45.3 | 37.9 | 29.1 |
| 95% CI | | -5,32 | -6,30 | 29,61 | 21,55 | 11,47 |
| p-value from Fisher's exact test | | 0.180 | 0.253 | <0.0001 | <0.0001 | 0.003 |

The results in the mITT and PP populations also demonstrated that the 300- and 600-mg TQ groups achieved significantly higher relapse-free efficacy results compared with the control group. A more traditional micro-ITT analysis in which subjects without baseline

pathogen are excluded would likely produce similar results given that only one subject did not have *P. vivax* at baseline.

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

**Gender, Race, Age, Weight, Country, and Baseline Parasite Count Stratum**
Table 16 shows results of the subgroup analyses, most of which show results similar to the overall study results. It is difficult to make conclusions for age, as the numbers of subjects who were 65 years or older were too small. The treatment effects were similar in male and females. It is important to consider race along with geographic region since all Asians were from India and Thailand and, as noted previously, the CQ-alone rate in India was high, reducing the treatment effect of TQ. It appeared that the treatment effect varied by body weight, but this could also have been related to geographic region and race.

**Table 16. Study 582 Part 1: Relapse-free efficacy at 6 months (ITT population) by age, sex, and weight**

| n/N (%) | Control Group CQ alone (N=54) | Treatment Group (N=275) | | | | |
|---|---|---|---|---|---|---|
| | | CQ+TQ 50 mg (N=55) | CQ+TQ 100 mg (N=57) | CQ+TQ 300 mg (N=57) | CQ+TQ 600 mg (N=56) | CQ+PQ (N=50) |
| **Age (yrs)** | | | | | | |
| <65 | 20/53 (37.7) | 28/54 (51.9) | 29/55 (52.7) | 48/57(84.2) | 41/53(77.4) | 33/48(68.8) |
| ≥65 | 1/1 (100) | 1/1 (100.0) | 0/2 | 0 | 2/3 (66.7) | 1/2 (50) |
| **Sex** | | | | | | |
| Male | 17/39 (43.6) | 18/37 (48.7) | 21/44 (47.7) | 37/43 (86.1) | 34/45 (75.6) | 25/35 (71.4) |
| Female | 4/15 (26.7) | 11/18 (61.1) | 8/13 (61.5) | 11/14 (78.6) | 9/11 (81.8) | 9/15 (60.0) |
| **Race** | | | | | | |
| American Indian or Alaska Native* | 4/27 (14.8) | 10/27 (37.0) | 10/28 (35.7) | 21/29 (72.4) | 19/29 (65.5) | 14/25 (56.0) |
| Asian | 17/26 (65.4) | 19/27 (70.4) | 18/27 (66.7) | 27/28 (96.4) | 23/26 (88.5) | 19/22 (86.4) |
| Multiple | 0/1 | 0/1 | 1/2 (50) | 0 | 1/1(100) | 1/3(33.3) |
| **Weight (kg)** | | | | | | |
| <60 | 14/30 (46.7) | 16/33 (48.5) | 18/35 (51.4) | 26/30 (86.7) | 19/27 (70.4) | 18/26 (69.2) |
| ≥60 | 7/24 (29.2) | 13/22 (59.1) | 11/22 (50.0) | 22/27 (81.5) | 24/29 (82.8) | 16/24 (66.7) |
| **Country** | | | | | | |
| Brazil | 1/6(16.7) | 1/6(16.7) | 2/6(33.3) | 5/6(83.3) | 6/7(85.7) | 4/6(66.7) |
| India | 9/10(90.0) | 10/11(90.9) | 8/11(72.7) | 9/9(100.0) | 10/10(100) | 6/6(100.0) |
| Peru | 3/22(13.6) | 9/22(40.9) | 9/24(37.5) | 16/23(69.6) | 14/23(60.9) | 11/22(50.0) |
| Thailand | 8/16(50.0) | 9/16(56.3) | 10/16(62.5) | 18/19(94.7) | 13/16(81.3) | 13/16(81.3) |
| **Baseline parasite count (/µL)** | | | | | | |
| ≤7500 | 14/37(37.8) | 21/40(52.5) | 19/39(48.7) | 32/39(82.1) | 32/38(84.2) | 26/36(72.2) |
| >7500 | 7/17(41.2) | 8/15(53.3) | 10/18(55.6) | 16/18(88.9) | 11/18(61.1) | 8/14(57.1) |

*Subjects from Brazil and Peru were classified as this race in the data set.

**Conclusions**
Although the first part of the study was designed to find the optimal dose to evaluate in Part 2, the selected 300-mg TQ single dose given with CQ did demonstrate significantly improved efficacy compared with CQ alone.

### 9.4.2 Study 582 Part 2

**Recurrence-Free Efficacy**

The estimated recurrence-free efficacy proportions over 6 months from the Kaplan-Meier analysis were 62.4% and 27.7% in the CQ+TQ and CQ alone group, respectively. Time-to-event analysis indicated that the risk of recurrence was reduced by 70.1% (95% CI: 59.6%, 77.8%) with CQ+TQ treatment as compared with CQ alone (HR=0.299, 95% CI [0.222, 0.404], p<0.001). The risk of recurrence was also significantly reduced in the CQ+PQ group compared with the CQ alone group. The proportions of subjects who were censored in the primary analysis were similar across the three groups, as shown in Table 19. Results of the FDA's analysis matched those of the Applicant. The FDA also conducted a sensitivity analysis by assuming that subjects who were censored early were treatment failures. The results were similar, although the treatment effect was slightly reduced. Additionally, an analysis assuming early censoring=success in the CQ alone and early censoring=failure for the CQ+TQ group (a worst-case scenario) continued to show statistical significance of CQ+TQ over CQ alone (data not shown). This extreme method of handling censoring resulted in statistically significant results, indicating that missing data did not impact our ability to make conclusions from this trial.

The analysis of recurrence-free efficacy at 6 months from a logistic regression in the micro-ITT population as a sensitivity analysis (missing/censoring=failure) is also shown in Table 17 (the last 3 rows). The odds of recurrence at 6 months in the CQ+TQ group were statistically significantly reduced compared with the CQ alone group. Similarly, the CQ+PQ group had a statistically significantly reduced risk of recurrence. Analysis with missing/censoring=success in the CQ alone and missing/censoring=failure for the CQ+TQ group also yielded statistically significant results (data not shown). Additionally, the analysis in the PP population showed comparable results to the micro-ITT population (data not shown).

**Table 17. Study 582 Part 2: Recurrence-free efficacy over 6 months (micro-ITT population)**

| | **Control Group CQ alone (N=133)** | **Treatment Group (N=389)** | | **Total (N=522)** |
|---|---|---|---|---|
| | | **CQ+TQ (N=260)** | **CQ+PQ (N=129)** | |
| **Number of subjects, n(%)** | | | | |
| Recurrence-free at 6 months | 35 (26) | 155 (60) | 83 (64) | 273 (52) |
| Recurrence prior to or at 6 months | 88 (66) | 85 (33) | 36 (28) | 209 (40) |
| Censored, prior to 6 month assessment | 10 (8) | 20 (8) | 10 (8) | 40 (8) |
| *No demonstration of initial clearance of P. vivax parasitemia* | 1 (<1) | 2 (<1) | 0 | 3 (<1) |
| *Taking antimalarial in first 6 months (and not parasitemic)* | 5 (4%) | 11 (4%) | 4 (3%) | 20 (4%) |
| *Missing 6 month assessment* | 4 (3%) | 7 (3%) | 6 (5%) | 17 (3%) |
| **Recurrence-free efficacy rate at 6 months[a]** | | | | |
| Estimate (95% CI) | 27.7 (19.6,36.3) | 62.4 (54.9,69.0) | 69.6 (60.2,77.1) | |
| **Hazard ratio of risk of recurrence vs CQ alone[b]** | | | | |

| | | | | |
|---|---|---|---|---|
| Estimate (95% CI) | | 0.30 (0.22,0.40) | 0.26 (0.18,0.39) | |
| p-value | | <0.001 | <0.001 | |
| **Hazard ratio of risk of recurrence vs CQ alone[b] (Censoring=failure)** | | | | |
| Estimate (95% CI) | | 0.35 (0.26, 0.46) | 0.31 (0.22, 0.44) | |
| p-value | | <0.001 | <0.001 | |
| **Odds ratio of risk of recurrence vs CQ alone[b] (missing=failure)** | | | | |
| Estimate (95% CI) | | 0.24 (0.15,0.38) | 0.20 (0.12,0.34) | |
| p-value | | <0.001 | <0.001 | |

[a] Kaplan-Meier methodology

[b] A hazard ratio or odds ratio <1 indicates a lower chance of recurrence compared with CQ alone.

**Early Treatment Failure and Recrudescence by Day 32**

Early failures were defined as subjects who did not demonstrate initial clearance of *P. vivax* parasitemia or demonstrated initial clearance and had a subsequent non-zero asexual *P. vivax* parasite count on or before Day 32. Only 3 subjects in the CQ+TQ (1.2%) and 2 subjects in the CQ alone group (1.5%) experienced early treatment failures. Three of these 5 subjects (1 CQ alone and 2 CQ+TQ) withdrew from the study prior to Day 5, and were not available for assessment of initial clearance of parasitemia. These three subjects were censored for not demonstrating initial clearance of *P. vivax* parasitemia in the Applicant's analysis. For the remaining 2 subjects, one subject, who was in the CQ alone group (0.8%), experienced recrudescence prior to Day 33 and the other subject in the TQ+CQ group experienced failure. These two subjects were considered to have recurrence of parasitemia in 6 months after initial clearance in the Applicant's analysis.

**Incidence of *P. falciparum* Malaria**

The incidence of *P. falciparum* malaria (i.e. the proportion of positive *P. falciparum* asexual parasite count) post-baseline and during the study was low in the three groups (CQ alone: 3 (2%), CQ+TQ: 7 (3%), and CQ+PQ: 1 (<1%)).

**Early Response to Treatment**

Early responses to treatment included time to parasite clearance, to fever clearance, and to gametocyte clearance. Table 18 shows the numbers of subjects with clearance and time to clearance. All subjects received a therapeutic dose of CQ and the clearance proportion was high (≥97%). The clearance proportions and median time to clearance for the three events were similar across all three treatment groups. Therefore, TQ and PQ appeared to have a minimal effect on these early responses.

**Table 18. Study 582 Part 2: Analysis of early response to treatment (micro-ITT population)**

| | **Control Group CQ alone (N=133)** | **Treatment Group (N=389)** | |
|---|---|---|---|
| | | **CQ+TQ (N=260)** | **CQ+PQ (N=129)** |
| **Number of subjects, n(%)** | | | |
| Parasite clearance achieved | 129 (97) | 254 (98) | 127 (98) |
| Censored, parasite clearance not achieved | 4 (3) | 6 (2) | 2 (2) |
| **Time to parasite clearance (hours)** | | | |

| | Control Group CQ alone (N=133) | Treatment Group (N=389) | |
|---|---|---|---|
| | | CQ+TQ (N=260) | CQ+PQ (N=129) |
| Median (95% CI) | 43 (41,48) | 45 (42,47) | 42 (39,45) |
| **Number of subjects, n(%)** | | | |
| Fever clearance achieved | 48 (36) | 102 (39) | 47 (36) |
| Censored, at baseline | 85 (64) | 158 (61) | 82 (64) |
| **Time to fever clearance (hours)** | | | |
| Median (95% CI) | 7 (5,14) | 7 (5,12) | 8 (6,18) |
| **Number of subjects, n(%)** | | | |
| Gametocyte clearance achieved | 85 (64) | 168 (65) | 79 (61) |
| Censored, at Baseline | 47 (35) | 92 (35) | 49 (38) |
| Censored, gametocyte clearance not achieved | 1 (<1) | 0 (0) | 1 (<1) |
| **Time to gametocyte clearance (hours)** | | | |
| Median (95% CI) | 38 (32,40) | 39 (37,41) | 36 (24,41) |

Source: Table 20, Study Report.

**Subgroup Analyses by Gender, Race, Age, Country, and Body Weight**

Recurrence-free efficacy at 6 months by gender, race, age, geographic location (country) and body weight is presented in Table 19. No concerning signals were seen in these analyses.

**Table 19. Study 582 Part 2: Recurrence-free efficacy at 6 month by gender, race, age, and body weight, and country (micro-ITT population)**

| n/N (%) | Control Group CQ alone (N=133) | Treatment Group (N=389) | |
|---|---|---|---|
| | | CQ+TQ (N=260) | CQ+PQ (N=129) |
| **Gender** | | | |
| Male | 23/97(24) | 108/196(55) | 67/99 (65) |
| Female | 12/36(33) | 47/64 (73) | 19/30(63) |
| **Race** | | | |
| American Indian or Alaska native | 13/43 (30) | 53/81 (65) | 24/41 (59) |
| Asian - Southeast Asian heritage | 8/26 (31) | 28/50 (56) | 21/26 (81) |
| Black or African American | 3/14 (21) | 16/28 (57) | 10/13 (77) |
| Multiple | 11/47 (23) | 56/97 (58) | 28/47 (60) |
| White | 0/3 (0) | 2/4 (50) | 0/2 (0) |
| **Age in years** | | | |
| <65 | 34/131 (26) | 150/253 (59) | 81/126 (64) |
| ≥65 | 1/2 (50) | 5/7 (71) | 2/3 (67) |
| **Body weight (kg)** | | | |
| <60 | 11/46 (24) | 75/115 (65) | 38/54 (70) |
| ≥60 | 24/87 (28) | 80/145 (55) | 45/75 (60) |
| **Country** | | | |
| Brazil | 12/53 (23) | 61/105 (58) | 30/52 (58) |
| Ethiopia | 3/14 (21) | 16/28 (57) | 10/13 (77) |
| Cambodia | 1/10 (10) | 6/19 (32) | 6/9 (67) |
| Peru | 12/40 (30) | 50/77 (65) | 22/38 (58) |
| Philippines | 0/1 (0) | 3/3 (100) | 2/2 (100) |
| Thailand | 7/15 (47) | 19/28 (68) | 13/15 (87) |

**Conclusions**
The Applicant concluded that there was a clinically and statistically significant reduction in the risk of recurrence at 6 months in the CQ+TQ arm compared with CQ treatment alone. Our review confirmed the Applicant's results.

### 9.4.3 Study 564

Table 20 presents the results of recurrence-free efficacy at 6 months from a survival analysis. The recurrence-free efficacy proportion was comparable between the two groups. The results from the Cox proportional hazards model did not indicate a significant difference.

**Table 20. Study 564: Recurrence-free efficacy over 6 months (micro-ITT population)**

| | **CQ+TQ (N=166)** | **CQ+PQ (N=85)** |
|---|---|---|
| **Number of subjects, n(%)** | | |
| Subjects observed to recurrence prior to or at 6 months | 42 (25) | 20 (24) |
| Censored, prior to 6-month assessment | 12 (7) | 5 (6) |
| *Taking antimalarial in first 6 months (and were not parasitemic)* | 6 (4) | 2 (2) |
| *Missing 6 month assessment* | 6 (4) | 3 (4) |
| Recurrence-free at 6 months | 112 (67) | 60 (71) |
| **Recurrence-free efficacy rate at 6 months, %** | | |
| Estimate (95% CI) | 72.7 (64.8,79.2) | 75.1 (64.2,83.2) |
| **Hazard ratio of risk of recurrence vs CQ+PQ** | | |
| Estimate (95% CI) | 0.984 (0.577,1.678) | 1 |

Table 21 presents the results of recurrence-free efficacy at 6 months (missing=failure) using a logistic regression. The confidence interval for the odds ratio (relative to CQ+PQ) included 1, which was consistent with the results from the Cox proportional hazards model. The analysis excluding subjects with missing values reached a similar conclusion.

**Table 21. Study 564: Analysis of recurrence-free efficacy at 6 months (logistic regression, missing=failure, micro-ITT population)**

| | | | | **Comparison with CQ+PQ** | |
|---|---|---|---|---|---|
| **Treatment** | **N** | **Subjects Recurrence-Free (%)** | **Subjects with a Recurrence (%)** | **Odds Ratio of Recurrence** | **95% CI** |
| CQ+TQ | 166 | 112 (67) | 54 (33) | 1.141 | 0.643, 2.027 |
| CQ+PQ | 85 | 60 (71) | 25 (29) | | |

According to an FDA analysis, the difference in recurrence-free efficacy proportions was -3.4% with a 95% CI [-16.0%, 9.8%], indicating that CQ+TQ could be as much as 16% worse than CQ+PQ. If the 5 censored subjects in the PQ group were considered as successes and 12 TQ censored subjects were considered as failures (the most conservative approach), then the difference was -9.0% with a 95% CI [-21.4%, 3.4%]. These analyses indicated that CQ+TQ could meet a 16% to 22% noninferiority margin, which is smaller than the conservative treatment effect of CQ+PQ compared to CQ alone as estimated from the previous studies (26%). This noninferiority margin was derived

based on FDA meta-analysis (random effect model) using the data from TAF112582 Part 1 & 2 which showed that the treatment effect of CQ+PQ compared to CQ alone (CQ+PQ minus CQ) was 35.2%, with a 95% CI [26.1%, 45.2%]. Based on this analysis we can conclude that the study provides supportive evidence for efficacy.

There were no concerning differences seen between the two groups in time to parasite clearance, to fever clearance, and to gametocyte clearance.

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

**Gender, Race, Age, Weight, and Country**

The results of subgroup analysis are presented in the Table 22. Results were generally consistent with the overall results. Note that some sample sizes were too small to make any conclusions. It appeared that gender and body weight had no effect on efficacy. Due to the small number of subjects ≥65 years old, it is difficult to make a reliable conclusion on age effect using this cutoff.

**Table 22. Study 564: Analysis of recurrence-free efficacy at 6 months by gender, race, age, weight, and country (micro-ITT population)**

| | CQ+TQ (N=166) | CQ+PQ (N=85) |
|---|---|---|
| **Sex, n(%)** | | |
| Male | 78/114 (68.4) | 38/53 (71.7) |
| Female | 34/52 (65.4) | 22/32 (68.8) |
| **Age (yrs)** | | |
| <65 | 108/159 (67.9) | 59/84 (70.2) |
| ≥65 | 4/7 (57.1) | 1/1 (100.0) |
| **Race, n(%)** | | |
| American Indian or Alaska Native | 55/87 (63.2) | 27/43 (62.8) |
| Asian | 30/41 (73.2) | 21/23 (91.3) |
| Black or African American | 1/2 (50.0) | 0 |
| Multiple | 26/36 (72.2) | 12/19 (63.2) |
| **Country, n(%)** | | |
| Brazil | 31/45 (68.9) | 15/23 (65.2) |
| Colombia | 8/13 (61.5) | 4/6 (66.7) |
| Peru | 43/67 (64.2) | 20/33 (60.6) |
| Thailand | 9/12 (75.0) | 8/8 (100.0) |
| Vietnam | 21/29 (72.4) | 13/15 (86.7) |
| **Weight (kg)** | | |
| <60 | 43/63 (68.3) | 25/31 (80.7) |
| ≥60 | 69/103 (67.0) | 35/54 (64.8) |

**Conclusions**

The Applicant concluded that TQ displayed comparable efficacy to PQ and the two treatments produced similar results in parasite clearance and clearance time. Our evaluation confirmed these findings. The recurrence-free efficacy endpoint could have made a 16% noninferiority margin considering all missing outcomes as treatment failures,

or a 22% noninferiority margin if considering all missing outcomes as failures in the CQ+TQ group and as successes in the CQ+PQ group (more conservative), which is smaller than the conservative treatment effect of CQ+PQ compared to CQ alone as estimated from the previous studies (26%). Based on this, we can state that the study provides supportive evidence of efficacy.

### 9.5 Overall Efficacy Summary

**Radical cure of *P. vivax* malaria**
The efficacy of TQ was evaluated in three clinical trials. All three trials were randomized, double-blind, double-dummy, controlled trials. Two of the trials included a placebo-equivalent i.e., CQ alone. CQ was used to clear the initial blood stage infection in all subjects in all three trials. Study 582 part 1 & 2, using CQ alone as a control group, demonstrated a statistically significant treatment effect for the proposed regimen for the radical cure (prevention of relapse) of *P. vivax*. Study 564, using CQ+PQ group as the control group, indicated that the two treatment groups produced similar efficacy results, supporting the efficacy of TQ.

## 10 Evaluation of Safety

### 10.1 Safety Summary

Safety information for the three clinical trials in patients with *P. vivax* malaria (Study 582 part 1 and 2, and Study 564) and three healthy volunteer studies (Study TAF110027, TAF114582 and 201807) is discussed. The healthy volunteer studies provided safety information for TQ alone without CQ.

**Healthy volunteer studies**
Three healthy volunteer studies evaluated TQ single dose alone compared to PQ or placebo. Gastrointestinal adverse reactions were relatively uncommon. TQ dosed with food was generally well tolerated. Nausea was the most common symptom and occurred in less than 10% of subjects. Dizziness was also reported. One subject without psychiatric medical history developed depression after treatment with TQ 600 mg which resolved spontaneously after three days. Hypersensitivity reactions manifested by symptoms such as angioedema, shortness of breath, and urticaria occurred in two healthy subjects approximately two weeks post treatment in one study but were not reported with TQ in the other single-dose clinical trials. Asymptomatic decreases in Hb of 1g/L to <3g/dL were associated with TQ use; no patient required blood transfusion. The decreases in Hb may be due to drug-induced lysis of red blood cells approaching the end of their lifespan as seen with the 8-aminoquinoline, PQ. Asymptomatic increases in methemoglobin (MetHb%) were observed in some patients. Transient mild elevations in hepatic transaminases were reported. The numbers of subjects in the healthy volunteer studies are relatively small; however, it appears that TQ has a safety profile similar to PQ, except for two case reports of hypersensitivity and one case of mild depression. TQ was reasonably safe and well tolerated in healthy individuals.

**Clinical trials of TQ plus CQ in *P. vivax* malaria**
The safety of TQ+CQ was compared to CQ (i.e., placebo equivalent) or to PQ+CQ in study 582 part 1 and part 2 and study 564. These three key trials evaluated the efficacy and safety of the proposed regimen of TQ 300 mg single-dose with CQ x 3 days for the treatment of *P. vivax* malaria. There were no deaths in the TQ development program and no patients were withdrawn from the trials for an adverse event (AE). Treatment emergent AEs associated with TQ+CQ and comparator drugs PQ+CQ and CQ are discussed:

**Gastrointestinal:** Gastrointestinal AEs were the most common treatment emergent adverse events (TEAEs) reported in the three clinical trials. As in the healthy volunteer studies, nausea was the most common AE associated with TQ+CQ.

**Cardiac:** In study 582 part 1 &2, differences in QTcF between treatment groups were not considered to be clinically significant. No subjects in the TQ+CQ treatment group met protocol-specified stopping rules for study medication discontinuation due to QTc prolongation. No additional effect on the QT interval was observed when TQ was added to CQ. No significant QTc prolongation effect of TQ was detected in the TQT study, TAF114582.

**Immunologic:** There was one case of anaphylaxis in a patient who was administered a single dose of CQ 600 mg. No other cases of hypersensitivity were reported. Pruritus, a known adverse reaction with CQ, was reported across all treatment groups. Pruritus was not associated with other allergic symptoms.

**Ophthalmic:** In study 582 part 2, one case of unilateral vortex keratopathy, not associated with changes in vision, was detected at Day 90 in the TQ 300 mg+CQ group. There were no reports of vortex keratopathy or other ophthalmic AEs in 582 part 2 in patients who received TQ 50 mg to 600 mg but it is not clear if all appropriate ophthalmic testing was performed. There were no reports of vortex keratopathy or retinal abnormalities following a single-dose TQ300 mg in ~300 healthy individuals in the dedicated ophthalmologic safety study 201807, which included all appropriate ophthalmologic tests. Reversible vortex keratopathy without visual abnormalities has been reported in malaria prophylaxis trials of TQ with up to 6 months of dosing.

**Neuropsychiatric:** Neuropsychiatric AEs were infrequent. Insomnia was the most common neurologic adverse reaction occurring in approximately 3% of subjects in the TQ+CQ, PQ+CQ, and CQ treatment groups. In the studies 582 part 1 & 2, more patients reported dizziness in the TQ 300 mg+CQ group i.e., 25 (7.9%) as compared to 6 (3.2%) in the CQ group. Anxiety was reported in 2 (< 1%) patients in the TQ 300 mg+CQ group within the first five days of treatment in study 582 part 2 and one patient was treated with diazepam. The anxiety resolved within 5 days. There were no cases of anxiety in the PQ+CQ and CQ groups. The close temporal relationship suggests an association between anxiety and TQ. Overall, anxiety was reported in 2 (0.4%) patients treated with TQ+CQ versus 3 (1.1%) patients treated with PQ+CQ in the three clinical trials. The patients fully recovered. Psychosis was reported in two subjects (one patient had history of two prior

psychotic episodes and one had recently diagnosed schizophrenia) who received single-dose TQ 350 mg and 600 mg during the clinical development program.

Neuropsychiatric AEs are associated with the 4-aminoquioline, mefloquine, and much less so with the 8-aminoquinoline, PQ. An association between TQ 300 mg and neuropsychiatric adverse reactions, i.e., dizziness, insomnia, and anxiety cannot be ruled out. The risk of developing a serious psychiatric AE is probably low with a single dose of TQ 300 mg; however, it would be appropriate to avoid TQ in patients with a documented history of psychiatric illness based on the cases described and the safety profile of mefloquine.

**Hepatic:** Some patients presented with elevated transaminases and bilirubin at baseline associated with *P. vivax* malaria. Patients were asymptomatic and ALT levels returned to normal values posttreatment. In study 582 part 1, there were no major differences between the treatment groups, TQ 50 mg to 600 mg administered with CQ, in the maximum changes from baseline in hepatic transaminases. In study 582 part 2, significant posttreatment elevations in ALT were associated with concurrent hepatitis B, hepatitis E, or relapse of *P. vivax* malaria. Two patients in the TQ+CQ group developed elevated transaminases (< 5x ULN) on treatment which resolved spontaneously. One patient had an SAE of hepatitis reported as a drug-induced liver injury which may have been related to ingestion of herbal medicines. The patient recovered. Elevations in total bilirubin (>2x ULN) at baseline in patients with malaria and at early time points during treatment were observed in all treatment groups and bilirubin levels returned to within normal limits for most subjects in the first week post-treatment.

**Laboratory Abnormalities**

Decrease in Hb levels: Similar to PQ, TQ+CQ was associated with decrease in Hb in some patients with G6PD deficiency. Decreases from baseline in Hb levels was also observed in the TQ 300 mg + CQ regimen in some G6PD-normal patients (defined as a G6PD activity > 70% in the trials) in the three clinical trials. For example, in Study 582 part 2, Hb decrease of >3.0g/dL occurred across the treatment groups: 5% of subjects on TQ 300 mg + CQ vs. 2% on PQ+CQ vs. 2% on CQ met a protocol defined SAE for hemolysis (Hb decreases of >3.0g/dL or ≥30% or an overall drop to below 6.0 g/dL from baseline). The maximum Hb decrease from baseline was in a subject who dropped Hb level by 5.3 g/dL from 19.2 g/dL at baseline. All patients were asymptomatic and mean Hb levels recovered to baseline levels spontaneously.

The pattern of Hb decline associated with mild increase in reticulocyte counts and subsequent recovery of Hb to baseline levels or higher is consistent with recovery from *P. vivax* malaria. It is difficult to distinguish drug-induced hemolysis from underlying hemolysis due to malaria; however, the frequency of Hb decreases was higher in the TQ 300 mg + CQ treated group as compared to PQ + CQ or CQ alone. TQ 300 mg may have contributed to the decline in Hb. Hydration in patients who were dehydrated at baseline may have also been a factor contributing to the observed declines in Hb. Approximately 40 to 50% of patients with *P. vivax* malaria had mild to moderate anorexia and nausea and approximately 30% reported vomiting at baseline. Elevations in blood urea nitrogen

(BUN) were present in 25 to 30% of patients at baseline in all treatment groups suggesting presence of dehydration. Therefore, it is difficult to discern the contribution of TQ to the decline in Hb.

G6PD deficiency: Patients with phenotypic G6PD deficiency were excluded from the placebo (CQ)-controlled trials based on a quantitative enzymatic assay. In study 582, part 1 the enzymatic assay failed to exclude three females who had G6PD genetic mutations; however, none of these patients experienced decreases in Hb > 2.5g/dL, a predefined Serious Adverse Event (SAE) in the study protocol.

The changes from baseline in other hematologic parameters such as white blood count, and platelet counts were generally not clinically significant. In general, platelet counts were high in all treatment groups at baseline and decreased over time to within the normal range. Eosinophilia was observed across all treatment groups and was associated with documented helminthic infections in 1 to 2% of subjects.

MetHb: Methemoglobinemia is a known adverse effect of PQ. Increases in MetHb% were observed in patients; however, there were no SAEs associated with methemoglobinemia. The largest mean increase in MetHb% was observed in the PQ+CQ treatment group. Maximum MetHb% levels were 13% (normal < 3%) in the trials; patients were asymptomatic except for complaints of fatigue.

Creatinine: Elevations in serum creatinine associated with study drugs was observed in the TQ+CQ treatment group. Elevations in creatinine from baseline were mild and transient.

Creatine phosphokinase (CPK): Elevations in CPK were observed in all treatment groups and were related to strenuous exercise and muscle injury in the majority of patients but remained unexplained in some. Elevations in CPK were not associated with renal injury or rhabdomyolysis.

**Conclusions**

TQ 300 mg single-dose was generally well-tolerated during the clinical development program. The safety profile of TQ was consistent with the known safety profile of the 8-aminoquinoline, PQ, except for the two cases of hypersensitivity that occurred in a healthy volunteer study. The overall safety profile of TQ 300 mg single dose was generally similar to PQ 15 mg daily for 14 days and to CQ alone for 3 days. There was no evidence that TQ exacerbates the adverse effects of CQ.

TQ 300 mg single-dose administered with a 3-day course of CQ was found to be reasonably safe for the treatment of *P. vivax* malaria in the subjects with G6PD enzyme activity > 70%. Patients must have G6PD testing done before starting TQ to avoid the risk of hemolytic anemia. Safety data are negligible for patients with G6PD enzyme activity in the 40 to 60% range, and TQ should not be prescribed to patients with G6PD enzymatic activity < 70% of normal.

Decrease in Hb levels of > 3g/dL was observed in G6PD-normal subjects (> 70% enzyme activity) who received TQ 300 mg + CQ at a higher frequency than in patients treated with CQ. The decrease in Hb levels was not in the anemic range in most patients. Patients were asymptomatic and Hb levels recovered without medical intervention. Monitoring of hematologic parameters in patients with vivax malaria who are treated with TQ 300 mg + CQ is warranted, especially in patients anemic at baseline. Although TQ's long elimination half-life ~ 15 days is the basis for a single-dose treatment (prevention of relapse) for *P. vivax* malaria, TQ-induced adverse reactions cannot be curtailed by stopping its administration as is the case with PQ which has a shorter half-life ($T_{1/2}$ ~ 8 hours).

TQ has not been studied in pregnant or lactating women. No animal or human studies have been conducted to determine if TQ or any of its metabolites are excreted in breast milk. Similar to PQ, TQ must not be used in pregnant or lactating women because of the risk of acute hemolytic anemia in the fetus or breastfed infant. TQ is contraindicated in pregnancy because the G6PD status of the fetus is not known even if the mother is G6PD normal.

## 10.2 Methods

The objective of the safety analysis was to evaluate the safety of TQ 300 mg single-dose in patients with *P. vivax* malaria. This safety review focuses primarily on a comparison of AEs associated with single-dose TQ 300 mg +CQ as compared to PQ+CQ and CQ only (placebo equivalent) in three randomized, double-blind, clinical trials, Study 582 part 1, Study 582 part 2, and Study 564. Safety results from two phase 1, placebo-controlled trials of TQ alone in healthy subjects: Study 201807, an ophthalmologic safety of single-dose TQ and Study TAF114582, a Thorough QT (TQT) study as well as a controlled healthy volunteer study, TAF110027, in G6PD deficient and G6PD normal subjects exposed to single-doses of TQ are also analyzed.

AEs of special interest such as hematologic, ophthalmologic, and neuropsychiatric AEs known to be associated with aminoquinoline antimalarial drugs were evaluated across trials.

## 10.3 Adverse Event Analysis

### 10.3.1 Healthy Volunteer Studies

**Study TAF110027**
Study TAF110027 (N=51) was a phase 1, open-label, dose-ranging study of TQ in which the hemolytic potential of TQ capsules (not the tablet used in phase 3 trials) was assessed in G6PD-deficient heterozygous female healthy subjects without the influence of disease-related confounding factors. G6PD-normal female healthy subjects were enrolled as controls. All the G6PD-deficient subjects (WHO class III variant) in the dose escalation cohorts were heterozygous adult females with 40 to 60% normal RBCs identified by enzyme activity assay. Additional subjects were recruited once the highest non-hemolytic dose of TQ had been defined and included adult female subjects with 61% to 80% G6PD

enzyme and 81%+ G6PD enzyme to evaluate hematological safety in heterozygous females with >60% G6PD activity.

Subjects in the TQ cohorts received a single dose of TQ 100 mg, 200 mg or 300 mg. PQ 15mg daily for 14 days was the comparator. Subjects with a screening and a Day 1 Hb <12 g/dL (or Hct <36%) were excluded. Dose limiting toxicity (DLT) was defined as a ≥2.5 g/dL decline in Hb (or Hct decline of 7.5%) from baseline or any clinically significant signs and symptoms of hemolysis (e.g., pallor, jaundice, hemoglobinuria, acute renal failure) as determined by the investigator(s). Dose escalation was stopped at TQ 300 mg, as per protocol, as three out of three subjects experienced a DLT.

**Treatment Emergent Adverse Events**
There were no deaths or SAEs reported in TAF110027. All AEs were mild in severity. No gastrointestinal AEs were reported. Decrease in Hb was the mostly frequently reported AE, reported in 4, 3, and 2 subjects in the TQ 100 mg, TQ 300 mg, and PQ 15 mg treatment groups, respectively. In the TQ groups, dizziness and headache were reported in two subjects. One subject had an elevated ALT (~1.5 x ULN). No significant effects of any dose of TQ or PQ on QT or QRS duration were reported.

**Decline in Hb Levels on Treatment**
TQ single-dose was associated with decline in Hb levels from baseline in G6PD-deficient heterozygous subjects and in G6PD-normal subjects.

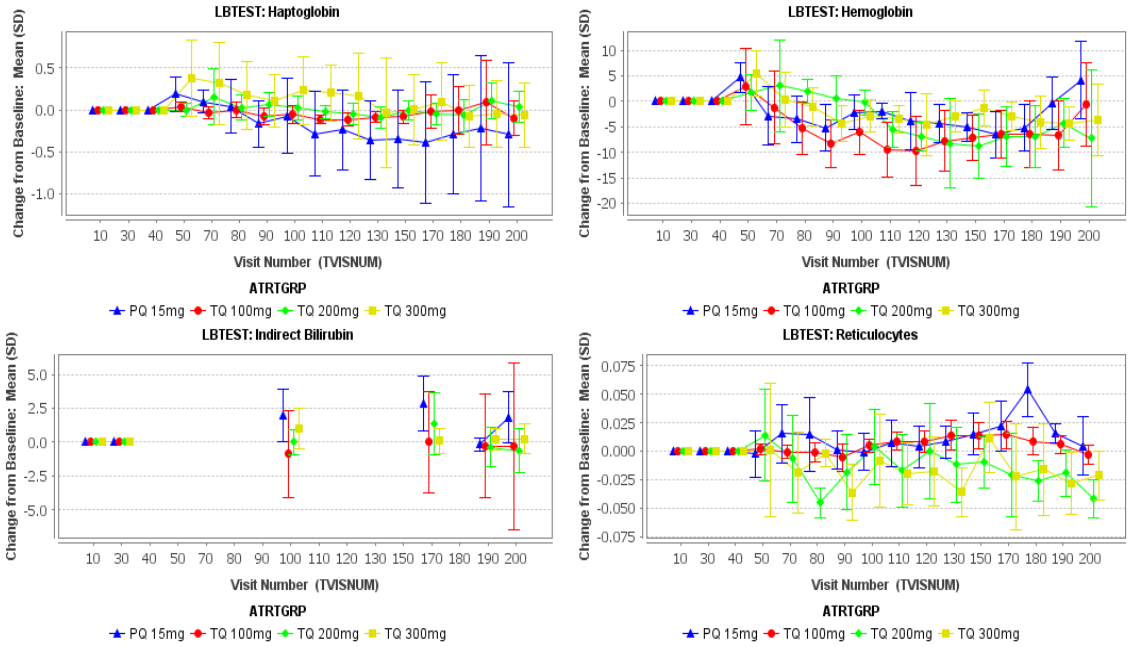
In G6PD-normal subjects, Hb decreases of ≥ 1g/dL were reported in > 60% of TQ-treated subjects. See Table 23. Hb nadirs occurred from Days 6 to 10 post treatment. The maximum Hb decline was 1.9g/dL.

**Table 23. TAF110027: Maximum Hemoglobin Decrease from Baseline – G6PD Normal Subjects, N=24**

| LABTEST | Hb Decrease (g/dL) | PQ 15mg N=6 | TQ 100mg N=6 | TQ 200mg N=6 | TQ 300 mg N=6 |
|---|---|---|---|---|---|
| Hemoglobin | < 1.0 | 3 (50.0%) | 1(16.6%) | 1(16.6%) | 4(66.7%) |
| | ≥ 1.0 | 3 (50.0%) | 5 (83.3%) | 5 (83.3%) | 2 (33.3%) |

Decreases in mean Hb from baseline were greater in the TQ 100 mg group than other dose groups. Mean reticulocyte count increases were higher in the PQ and TQ 100mg groups than in the other TQ groups. Mean haptoglobin levels declined in the PQ 15mg group but the declines were minimal in the TQ groups. Mean indirect bilirubin levels were elevated in PQ groups and the TQ 300 mg around study Day 7 (visit # 100). See Figure 1.

**Figure 1. TAF 110027: Changes in Mean (+/- SD) Hemoglobin, Reticulocytes and Bilirubin from Baseline by Study Visit – G6PD-normal subjects**




G6PD normal population
TQ:tafenoquine; PQ:Primaquine; CQ:Chloroquine

SD: standard deviation. Bilirubin levels were measured intermittently. Study Day/Visit #: Visit Screening:10 and 30, Day -1:30, Day 1: 40; Day 2: 50, Day4:70, Day 5:80, Day 6:90, Day 7:100, Day 8:110, Day 9:120, Day10:130, Day11:140; Day 12:150, Day13:160, Day 14:170, Day 21: 180, Day 28:190, Day 56:200.
Source: TAF110027: Laboratory dataset, JReview 12.0

In G6PD-deficient subjects, the greatest decline (3.1 g/dL) in Hb was observed in a subject with 40-60% G6PD enzyme activity who received TQ 200mg. A decrease in Hb of ≥ 2g/dL was observed in seven subjects in the TQ groups and two subjects in the PQ group. Two subjects in the PQ group and one subject in the TQ 200mg group had decrease in Hb ≥3g/dL. See Table 24.

**Table 24. TAF110027: Maximum Hemoglobin Decrease from Baseline in G6PD Deficient Subjects, N=27.**

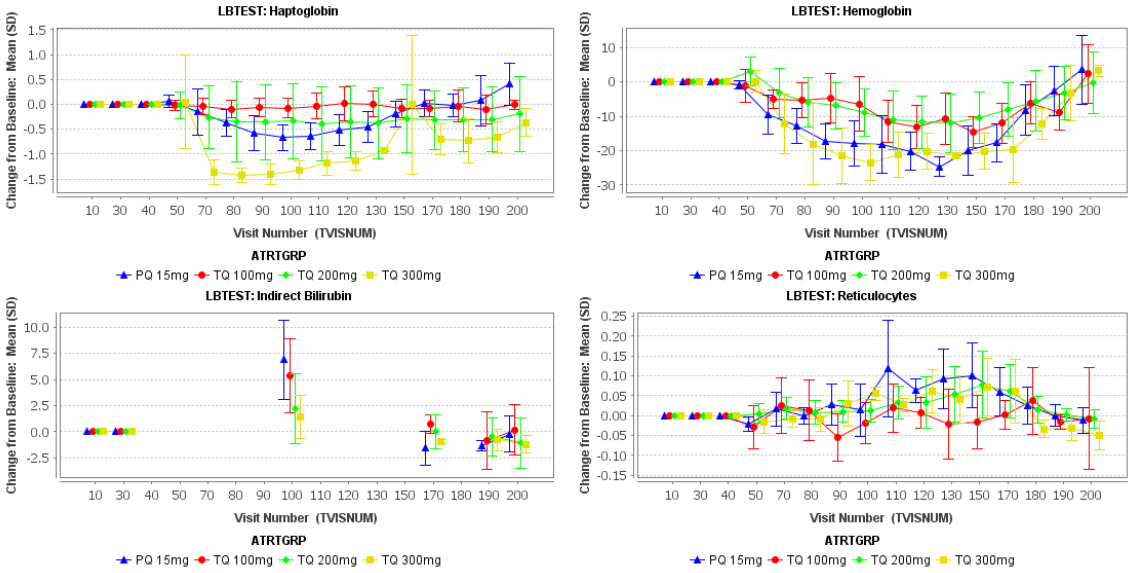
| LABTEST | Hb Decrease (g/dL) | PQ 15mg N=5 | TQ 100mg N=6 | TQ 200mg N=13[a] | TQ 300mg N=3 |
|---|---|---|---|---|---|
| Hemoglobin | < 1.0 | 0 | 1 (16.7%) | 0 | 0 |
| | ≥ 1.0 | 1 (20%) | 3 (50.0%) | 10 (76.9%) | 0 |
| | ≥ 2.0 | 2 (40%) | 2 (33.3%) | 2 (15.4%) | 3 (100.0%) |
| | ≥ 3.0 | 2 (40%) | 0 | 1 (7.7%) | 0 |

One subject (PQ 15 mg) withdrew consent for personal reasons on Day 6.
[a] Includes 7 patients with 61% to 80% G6PD enzyme (n=2) and 81%+ G6PD enzyme (n=5) to evaluate hematological safety in heterozygous females with >60%.

Mean Hb decreases were greater in TQ 300 mg and PQ groups than with lower TQ doses and all recovered without medical intervention. Mean reticulocyte count increases were higher in the TQ 300 mg group and PQ groups in the G6PD-deficient cohort than in the G6PD-normal cohort. Mean haptoglobin levels declined from baseline in the TQ 300 mg

and PQ groups. Mean indirect bilirubin levels were increased around Day 7 (visit # 100) and were more pronounced in the TQ 100 mg and PQ groups. Subjects recovered without medical intervention. See Figure 2.

**Figure 2. TAF 110027: Changes in Mean (+/- SD) Hemoglobin, Reticulocytes and Bilirubin from Baseline by Study Visit – G6PD-deficient subjects**




G6PD deficient population
TQ: Tafenoquine; PQ:Primaquine; CQ Chloroquine

Bilirubin levels were measured intermittently.
SD: standard deviation. Study Day/Visit #: Visit Screening:10 and 30, Day -1:30, Day 1: 40; Day 2: 50, Day 4:70, Day 5:80, Day 6:90, Day 7:100, Day 8:110, Day 9:120, Day10:130, Day11:140; Day 12:150, Day13:160, Day 14:170, Day 21: 180, Day 28:190, Day 56:200. Source: TAF110027: Laboratory dataset, JReview 12.0

Overall, there was a greater decline of Hb in the G6PD-deficient cohort who received TQ 300 mg as compared to the lower doses and to G6PD-normal controls but not to PQ; however, numbers of subjects were small and the study was not powered to conduct a formal comparison.

Other adverse reactions included dizziness which appeared to be related to TQ at all doses tested. All cases of dizziness were mild and of short duration. One case of elevated hepatic transaminases [ALT (59 IU/L) and AST (66 IU/L)] in a G6PD-deficient subject with normal baseline values who received TQ 200 mg was attributed to TQ. Three G6PD-deficient patients and one G6PD normal subject in the TQ-treated group had a MetHb% ≥ 3% (normal < 3%). However, PQ 15 mg daily was noted to cause larger increases in MetHb% (maximum 11.7%) than any dose of TQ in any G6PD cohort. No subject was reported to have clinical manifestations of methemoglobinemia. In this study, TQ had a similar safety profile (decline in Hb, increases in MetHb% and dizziness) to PQ.

**Study TAF114582**

Study TAF114582 (N=260) was a placebo-controlled Thorough QT study which enrolled 260 healthy volunteers who were G6PD normal. This study was designed to compare the effects of TQ monotherapy, as a single-dose (300 mg or 600 mg) or daily 400 mg dose

(1200 mg total) administered over three consecutive days, on the changes in QT interval to those observed in subjects dosed with moxifloxacin or placebo. This was a randomized, single-blind, placebo-controlled, parallel group study; moxifloxacin was used as a positive control.

**Treatment Emergent Adverse Events**
All AEs were mild or moderate in intensity, except for two cases of hypersensitivity and one severe AE of increase in serum CPK. TEAEs are summarized in Table 25.

AEs occurring in more than 3% of subjects in the TQ 300 mg group included nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, and upper respiratory tract infections (Table 25). Gastrointestinal AEs were the most common and were dose-related. Contact dermatitis and application site dermatitis were due to irritation caused by ECG electrodes.

Dizziness occurred in subjects in the moxifloxacin group and in the TQ groups. It appeared to be related to study drugs and all cases were mild, of short duration, and resolved spontaneously.

One male subject developed mild depression in the TQ 600 mg group at Day 4 post treatment in addition to abdominal pain, diarrhea and palpitations. He had no history of depression. The depression lasted for 3 days and resolved without medical intervention. The adverse reactions experienced by the subject were considered related to TQ.

**Table 25. TAF114582: Select Treatment Emergent Adverse Events (TEAE)**

| MedDRA preferred term | Placebo N=52 | Moxifloxacin N=52 | TQ 300mg N=52 | TQ 600mg N=52 | TQ 1200mg N=52 |
|---|---|---|---|---|---|
| Nausea | 2 (3.9%) | 0 | 5 (9.6%) | 8 (15.4%) | 17 (32.7%) |
| Dermatitis contact | 21 (40.4%) | 15 (28.9%) | 22 (42.3%) | 22 (42.3%) | 16 (30.8%) |
| Application site dermatitis | 4 (7.7%) | 4 (7.7%) | 5 (9.6%) | 2 (3.9%) | 6 (11.5%) |
| Diarrhea | 4 (7.7%) | 1 (1.9%) | 1 (1.9%) | 10 (19.2) | 5 (9.6%) |
| Headache | 4 (7.7%) | 2 (3.9%) | 7 (13.5%) | 6 (11.5%) | 5 (9.6%) |
| Back pain | 0 | 0 | 0 | 0 | 2 (3.9%) |
| Arthralgia | 0 | 0 | 0 | 0 | 2 (3.9%) |
| Dizziness | 0 | 3 (5.8%) | 2 (3.9%) | 2 (3.9%) | 2 (3.9%) |
| Musculoskeletal pain | 0 | 0 | 0 | 2 (3.9%) | 1 (1.9%) |
| Somnolence | 0 | 0 | 1 (1.9%) | 1 (1.9%) | 1 (1.9%) |
| Dyspepsia | 1 (1.9%) | 0 | 1 (1.9%) | 1 (1.9%) | 1 (1.9%) |
| Rash | 1 (1.9%) | 0 | 0 | 0 | 1 (1.9%) |
| Vomiting | 0 | 1 (1.9%) | 2 (3.9%) | 4 (7.7%) | 1 (1.9%) |
| Abdominal pain | 0 | 1 (1.9%) | 0 | 7 (13.5%) | 1 (1.9%) |
| Aspartate aminotransferase incr. | 0 | 0 | 0 | 2 (3.9%) | 0 |
| Urticaria | 1 (1.9%) | 0 | 1 (1.9%) | 0 | 0 |
| Palpitations | 1 (1.9%) | 0 | 0 | 1 (1.9%) | 0 |
| Blood creatine phosphokinase (CPK) incr. | 1 (1.9%) | 0 | 0 | 2 (3.9%) | 0 |
| Oropharyngeal pain | 0 | 1 (1.9%) | 1 (1.9%) | 2 (3.9%) | 0 |
| Myalgia | 0 | 2 (3.9%) | 0 | 0 | 0 |
| Pruritus | 0 | 2 (3.9%) | 1 (1.9%) | 0 | 0 |

**Serious Adverse Events**
There were no deaths. SAEs were reported in six subjects in the trial. Two cases of hypersensitivity were reported with an onset 13 to 15 days after TQ administration. Symptoms and signs reported included shortness of breath, angioedema, itchiness, and diffuse urticaria. The delay in onset of the events post treatment and the duration of symptoms were not consistent with anaphylaxis. The subjects recovered following with treatment with prednisone and diphenhydramine.

Decrease in Hb was reported for one subject in the TQ 600 mg group; his Hb was 13.3 g/dL on Day 6 (a drop of >2.5 g/dL from baseline of 16 g/dL). No other laboratory evidence of hemolysis was noted (no schistocytes, haptoglobin normal, total and indirect bilirubin normal, LDH normal, direct Coombs negative). Repeat Hb was 15.6g/dL on Day 12. There was no evidence of blood loss to explain the drop in Hb. TQ-related causality cannot be ruled out because of the temporal association to the adverse event. There were no reports of Hb decreases in the TQ 300 mg or TQ 1,200 mg groups.

The elevations in CPK levels observed in three patients and elevation in AST in one patient were associated with muscle injury due to strenuous physical exercise. SAEs are summarized in Table 26.

**Table 26. TAF114582: Serious Adverse Events**

| MedDRA Preferred Term | Placebo N = 52 | Moxifloxacin N=52 | TQ 300mg N= 52 | TQ 600mg N=52 | TQ 1200mg N=52 |
|---|---|---|---|---|---|
| Hypersensitivity | 0 | 0 | 0 | 1 (1.9%) | 0 |
| Blood CPK increased | 1 (1.9%) | 0 | 0 | 2 (3.9%) | 0 |
| Hemoglobin decreased | 0 | 0 | 0 | 1 (1.9%) | 0 |
| Urticaria | 0 | 0 | 1 (1.9%) | 0 | 0 |

**Disposition**
Table 27 presents subject disposition. Five subjects were lost follow up. Two subjects withdrew consent. One subject in the TQ 1,200 mg treatment group withdrew from the study because of nausea and vomiting after the first dose of TQ 400 mg, which resolved within 24 hours.

**Table 27. TAF114582: Disposition**

| Reason for Discontinuation | Moxifloxacin | Placebo | TQ 300mg | TQ 600mg | TQ 1200mg |
|---|---|---|---|---|---|
| Lost to follow-up | 1 (1.9%) | 1 (1.9%) | 2 (3.9%) | 0 | 1 (1.9%) |
| Withdrew consent | 0 | 0 | 2 (3.9%) | 0 | 0 |
| Adverse event | 0 | 0 | 0 | 0 | 1 (1.9%) |
| Investigator discretion | 0 | 1 (1.9%) | 0 | 0 | 0 |
| Number Subjects | 52 (100%) | 52 (100%) | 52 (100%) | 52 (100%) | 52 (100%) |
| Number subjects completed | 51 (98%) | 50(96%) | 48 (92%) | 52(100%) | 50(96%) |

**Hematologic**: Small dose-related decreases in Hb (≤1g/dL) were observed on study; however, the number of patients experiencing Hb decrease from baseline in the TQ 300 mg group were similar to placebo. Dose-related increases in MetHb% were observed in subjects receiving single-doses of TQ 300 mg, 600 mg, and 1,200 mg. Increases in

MetHb% from baseline in TQ 300 mg single-dose group were < 5%. No subject was reported to have clinical signs or symptoms of methemoglobinemia.

**Cardiac:** There was no evidence of clinically significant changes in QT interval in healthy subjects who received TQ 300 mg, 600 mg, or 1,200 mg.

**Immune System**: Two cases of hypersensitivity manifesting as angioedema, shortness of breath, and urticaria occurred 13 and 15 days post treatment with TQ single-dose. No additional cases of hypersensitivity were reported in the single dose trials in patients with *P. vivax* malaria. There were no cases of anaphylaxis.

**Psychiatric**: One male patient in the TQ 600 mg group described in the TEAE section above developed mild depression at Day 4 post treatment.

**Laboratory Test Abnormalities:** TQ ≥ 600 mg was associated with transient elevations in hepatic transaminases observed in < 1% subjects. No increases in ALT > 3 x ULN were observed in the TQ 300 mg treatment group.

**Study 201807**
Study 201807 (N=498), a healthy volunteer ophthalmologic safety study, did not identify a clinically significant ocular risk associated with the use of TQ 300 mg single-dose treatment. There were no deaths or SAEs in the 330 subjects treated with a single-dose of TQ 300 mg and 168 subjects treated with placebo. Headache (23 subjects, 7%) and nausea (14 subjects, 4%), the most common AEs reported, were more frequent in the TQ 300 mg group as compared to placebo.

Nervous system AEs of dizziness, somnolence, and dysgeusia were reported in the TQ group (2 subjects, <1% each), but not the placebo group. There were no reports of decreases in Hb levels in the study.

In summary, TQ dosed for up to 3 days was reasonably safe and well tolerated in healthy individuals. Nausea and mild dizziness were associated with TQ use. Depression occurred in one subject who did not have a history of depression and he recovered without medical intervention. Two cases of hypersensitivity were reported and at least one of the cases was associated with TQ. Asymptomatic decreases in Hb levels associated with TQ may be due to lysis of red blood cells approaching the end of their lifespan. Asymptomatic increases in MetHb% were also observed. Transient mild elevations in hepatic transaminases were reported. The numbers of subjects in the healthy volunteer studies reviewed are relatively small; however, it appears that TQ has a safety profile similar to the 8-aminoquinoline, PQ, except for two case reports of hypersensitivity and one case of mild depression.

### 10.3.2 Malaria Treatment Trials

**Treatment Emergent Adverse Events in Patients with *P. vivax***
Common TEAEs occurring at ≥ 2.0% in three trials (pooled TQ 300 mg + CQ, PQ+CQ, and CQ treatment arms) up to Day 180 post treatment are summarized in Table 28.

Gastrointestinal, nervous system, skin and soft tissue disorders were the most frequently affected system organ classes in the TQ+CQ - treated patients. AEs occurring at ≥ 2 % in the TQ 300 mg + CQ group and at a rate greater than CQ included, nausea (10%), vomiting (8%), diarrhea (6%), dizziness (12%), viral upper respiratory tract infection (7%), pharyngitis (4%), Hb decreased (4%), insomnia (3%), and back pain (5%). Elevations in ALT (2%) and CPK (3%) were observed in patients treated with TQ 300 mg + CQ but at lower rates than in the CQ group. AEs of special interest such as decreases in Hb are discussed below.

**Table 28. Study 582 Part 1&2 and Study 564: Treatment Emergent Adverse Events occurring in ≥ 2% patients - Safety Population**

| Treatment Emergent Adverse Events | | TQ 300mg sd | | PQ 15mg od x14d | | CQ (Placebo) | |
|---|---|---|---|---|---|---|---|
| | | N=483 | | N=264 | | N=187 | |
| **Body System or Organ Class** | **Dictionary-Derived Term** | **Count** | **%** | **Count** | **%** | **Count** | **%** |
| Gastrointestinal disorders | Nausea | 47 | 9.7% | 20 | 7.6% | 15 | 8.0% |
| | Vomiting | 39 | 8.1% | 24 | 9.1% | 9 | 4.8% |
| | Abdominal pain upper | 27 | 5.6% | 15 | 5.7% | 18 | 9.6% |
| | Diarrhea | 30 | 6.2% | 12 | 4.5% | 10 | 5.3% |
| | Abdominal pain | 10 | 2.1% | 8 | 3.0% | 9 | 4.8% |
| Nervous system disorders | Headache | 64 | 13.3% | 40 | 15.2% | 39 | 20.9% |
| | Dizziness | 59 | 12.2% | 30 | 11.4% | 16 | 8.6% |
| Infections and infestations | Viral upper respiratory tract infection | 32 | 6.6% | 17 | 6.4% | 9 | 4.8% |
| | Urinary tract infection | 21 | 4.3% | 16 | 6.1% | 9 | 4.8% |
| | Pharyngitis | 20 | 4.1% | 17 | 6.4% | 7 | 3.7% |
| Skin and subcutaneous tissue disorders | Pruritus | 63 | 13.0% | 36 | 13.6% | 27 | 14.4% |
| Musculoskeletal and connective tissue disorders | Myalgia | 31 | 6.4% | 23 | 8.7% | 22 | 11.8% |
| | Back pain | 26 | 5.4% | 8 | 3.0% | 4 | 2.1% |
| General disorders and administration site conditions | Pyrexia | 21 | 4.3% | 22 | 8.3% | 23 | 12.3% |
| | Chills | 6 | 1.2% | 15 | 5.7% | 20 | 10.7% |
| Investigations | Blood creatine phosphokinase increased | 14 | 2.9% | 9 | 3.4% | 10 | 5.3% |
| | Alanine aminotransferase increased | 11 | 2.3% | 7 | 2.7% | 9 | 4.8% |
| | Hemoglobin decreased | 19 | 3.9% | 4 | 1.5% | 3 | 1.6% |
| Psychiatric disorders | Insomnia | 15 | 3.1% | 8 | 3.0% | 5 | 2.7% |
| Respiratory, thoracic and mediastinal disorders | Cough | 7 | 1.4% | 8 | 3.0% | 4 | 2.1% |

**Serious Adverse Events**

There were no deaths in the TQ clinical development program. SAEs occurred at similar rates across treatment arms and were < 5%. Decrease in Hb levels was the most common SAE observed in subjects treated with TQ 300 mg + CQ.

Decrease in Hb levels was the only SAE (protocol specified) reported in more than one subject in the TQ 300 mg + CQ treatment group. Decrease in Hb levels occurred at a higher incidence in subjects treated with TQ 300 mg + CQ (n=18, 3.7%) as compared to CQ only (n=3, 1.6%), or PQ + CQ (n= 4, 1.5%) suggesting a higher risk for Hb decrease in subjects who receive TQ 300 mg + CQ.

Asymptomatic prolongation of the QTc interval was the only SAE reported in more than one subject in the PQ+CQ (n=4, 1.5%) and the CQ (n=5, 2.7%) treatment groups. One possible case of drug-induced liver injury is discussed below. SAEs categorized by system organ class in the three trials are summarized in Table 29.

**Table 29. Study 582 Part 1&2 and Study 564: Serious Adverse Events**

| | | TQ 300mg sd | | PQ 15mg od x14d | | CQ (Placebo) | |
|---|---|---|---|---|---|---|---|
| | | N=483 | | N=264 | | N=187 | |
| **Body System or Organ Class** | **Dictionary-Derived Term** | **Count** | **%** | **Count** | **%** | **Count** | **%** |
| Investigations | Hemoglobin decreased | 18 | 3.7% | 4 | 1.5% | 3 | 1.6% |
| | Electrocardiogram QT prolonged | 1 | 0.2% | 4 | 1.5% | 5 | 2.7% |
| | Alanine aminotransferase increased | . | . | . | . | 1 | 0.5% |
| Infections and infestations | Abscess limb | 1 | 0.2% | . | . | . | . |
| | Gastroenteritis | . | . | . | . | 1 | 0.5% |
| | Hepatitis E | 1 | 0.2% | . | . | . | . |
| | Pneumonia | 1 | 0.2% | . | . | . | . |
| | Urinary tract infection | 1 | 0.2% | . | . | . | . |
| Gastrointestinal disorders | Diarrhea | 1 | 0.2% | 1 | 0.4% | . | . |
| | Nausea | . | . | 1 | 0.4% | . | . |
| | Vomiting | . | . | 1 | 0.4% | . | . |
| Blood and lymphatic system disorders | Anemia | 1 | 0.2% | . | . | . | . |
| | Methemoglobinemia | . | . | 1 | 0.4% | . | . |
| Hepatobiliary disorders | Drug-induced liver injury | 1 | 0.2% | . | . | . | . |
| | Hepatitis acute | . | . | 1 | 0.4% | . | . |
| General disorders and administration site conditions | Pyrexia | 1 | 0.2% | . | . | . | . |
| Metabolism and nutrition disorders | Dehydration | . | . | 1 | 0.4% | . | . |
| Pregnancy, puerperium and perinatal conditions | Abortion spontaneous | 1 | 0.2% | . | . | . | . |
| Reproductive system and breast disorders | Menorrhagia | 1 | 0.2% | . | . | . | . |

**Discontinuations due to Adverse Events**

No patients had AEs that resulted in withdrawal from the trials. Fifteen (3.1%) patients in the TQ 300 mg + CQ group and 2 (1.1%) patients in the CQ group who experienced SAE of Hb decrease post baseline were unblinded and discontinued from study drugs: see Table 30.

One patient in the TQ 300 mg + CQ group with mixed *P. falciparum* and *P. vivax* infection and splenomegaly at had a decrease in Hb of 3g/dL post baseline; TQ + CQ was stopped and the patient was treated with Coartem.

A higher proportion of subjects in the CQ group (4 subjects, 2%) had QTc prolongation on ECG leading to discontinuation of study drugs compared to the other treatment groups. No patient in the TQ 300 mg + CQ group experienced QTc prolongation on ECG.

**Table 30. Study 582 Part 1&2 and Study 564: Treatment emergent adverse events leading to withdrawal/ interruption of treatment**

| Treatment emergent adverse events | | TQ 300mg sd + CQ | | PQ 15mg od x14d + CQ | | CQ (Placebo) | |
|---|---|---|---|---|---|---|---|
| | | N=483 | | N=264 | | N=187 | |
| **Body System or Organ Class** | **Dictionary-Derived Term** | **Count** | **%** | **Count** | **%** | **Count** | **%** |
| Investigations | Hemoglobin decreased | 15 | 3.1% | 1 | 0.4% | 2 | 1.1% |
| | Electrocardiogram QT prolonged | . | . | 1 | 0.4% | 4 | 2.1% |
| Infections and infestations | *Plasmodium falciparum* infection | 1 | 0.2% | . | . | . | . |

Note: In Study 582, part 1, one patient in the TQ 50mg + CQ withdrew from study medication due to QTcF interval prolongation (asymptomatic) from baseline. No patient in the TQ 100mg + CQ or TQ 600 mg + CQ developed QTc prolongation.

**Adverse Reactions of Special Interest and Submission Specific Safety Issues**

TQ was evaluated for adverse reactions known to be associated with the 8-aminoquinoline antimalarial, primaquine phosphate, the 4-quinolinemethanol, mefloquine, and the 4-aminoquinoline, CQ.

Drug-induced hemolysis and methemoglobinemia are important safety concerns with PQ which is contraindicated in patients with severe G6PD deficiency and in patients taking potentially hemolytic drugs. Monitoring of Hb and hematocrit is recommended for G6PD-deficient and G6PD-normal patients during therapy with PQ.

Prolongation of the QT interval, dizziness, pruritus, and rash are also reported with PQ.

Neuropsychiatric adverse reactions are uncommon with PQ and were uncommon in the TQ trials. Neuropsychiatric adverse reactions are a safety concern with mefloquine. The mefloquine hydrochloride USPI has a boxed warning for neuropsychiatric events. Psychiatric symptoms ranging from anxiety, paranoia, depression, hallucinations, and psychotic behavior, and neurologic symptoms such as insomnia and vivid dreams, dizziness and vertigo have been reported with mefloquine.

**Hematologic Adverse Reactions**

In the three primary therapeutic trials, decrease in Hb levels was more frequent in the patients treated with TQ 300 mg + CQ (18 patients, 3.7%) than patients treated with PQ + CQ (4 patients, 1.5%) and CQ (3 patients, 1.6%). Study drugs were discontinued or interrupted for decrease in Hb >3g/dL in 15 (3%) and 2 (1%) patients in the TQ+CQ and CQ arms, respectively.

All other anemia-associated AEs such as fatigue, dyspnea, tachypnea, and pallor occurred at low rates (< 2%) across the three treatment arms. See Table 31. One patient (< 1%) each in the treatment groups experienced hyperbilirubinemia (grade 2 severity) at baseline; the levels returned to normal post treatment. Elevated bilirubin levels at baseline were probably related to *P. vivax* malaria; ALT levels were not significantly elevated.

**Table 31. Study 582 & Study 564: Hematologic Treatment Emergent Adverse Events**

| Dictionary Derived Term | TQ 300mg sd + CQ N = 483 | CQ (placebo) N = 187 | PQ x 14d + CQ N =264 |
|---|---|---|---|
| Anemia | 1 (0.2%) | 0 | 3 (1.1%) |
| Blood bilirubin increased | 1 (0.2%) | NR | 0 |
| Dyspnea | 2 (0.4%) | 0 | 0 |
| Fatigue | 3 (0.6%) | 2 (1.1%) | 0 |
| Hemoglobin decreased | 18 (3.7%) | 3 (1.6%) | 4 (1.5%) |
| Hyperbilirubinemia | 1 (0.2%) | 1 (0.5%) | 1 (0.4%) |
| Pallor | 1 (0.2%) | 0 | 0 |
| Tachypnea | 1 (0.2%) | 0 | 0 |
| Subjects | 28 (5.8%) | 6 (3.2%) | 8 (3.0%) |

**Decreases in hemoglobin from baseline**

In study 582 part 1 (n=329), the frequency of decrease in Hb of > 2.5g/dL was similar (2 to 4%) across treatment groups through Day 29 (visit # 100). See Table 32. The frequency of decrease in Hb >1.5 to ≤ 2.5g/dL from baseline were also similar, i.e. approximately 30% in the three treatment groups. Hb decrease of >2.5 g/dL (or ≥25% drop from baseline) was to be reported as an SAE if it occurred with first 15 days of treatment; six subjects were in this category. One subject did not fulfill the SAE criteria as the nadir of the Hb decline was observed at Day 22. Patients were asymptomatic and did not require medical intervention. Gene sequencing for G6PD mutations was negative in these six subjects.

**Table 32. Study 582, part 1: Hemoglobin decrease from baseline by treatment arm, Day 1 to Day 29 – Safety population**

| Hemoglobin decrease from baseline | CQ + TQ 50mg single dose N=55 | CQ + TQ 100mg single dose N=57 | CQ + TQ 300mg single dose N=57 | CQ + TQ 600mg single dose N=56 | CQ + PQ 15mg daily x 14 days N=50 | CQ (placebo) N=54 |
|---|---|---|---|---|---|---|
| ≤ 1.5 g/dL | 48 (87%) | 37(65%) | 38 (67%) | 33 (59%) | 34 (68%) | 38 (70%) |
| >1.5 and ≤ 2.5g/dL | 7(13%) | 19(33%) | 17(30%) | 22(39%) | 15(30%) | 15 (28%) |
| > 2.5g/dL or ≥25% of baseline | 0 | 1(2%) | 2(3%) | 1(2%) | 1(2%) | 1(2%) |

In study 582 part 2 (n=522), in the first 29 days of the trial, 14 (5%) patients treated with TQ 300 mg +CQ experienced a decrease in Hb > 3g/dL as compared to 3 (2%) patients in the PQ +CQ group and 2 (4%) patients in the CQ group. See Table 33. More than 80% of the patients in the three treatment groups experienced Hb decreases ≤ 2g/dL which were not considered clinically significant.

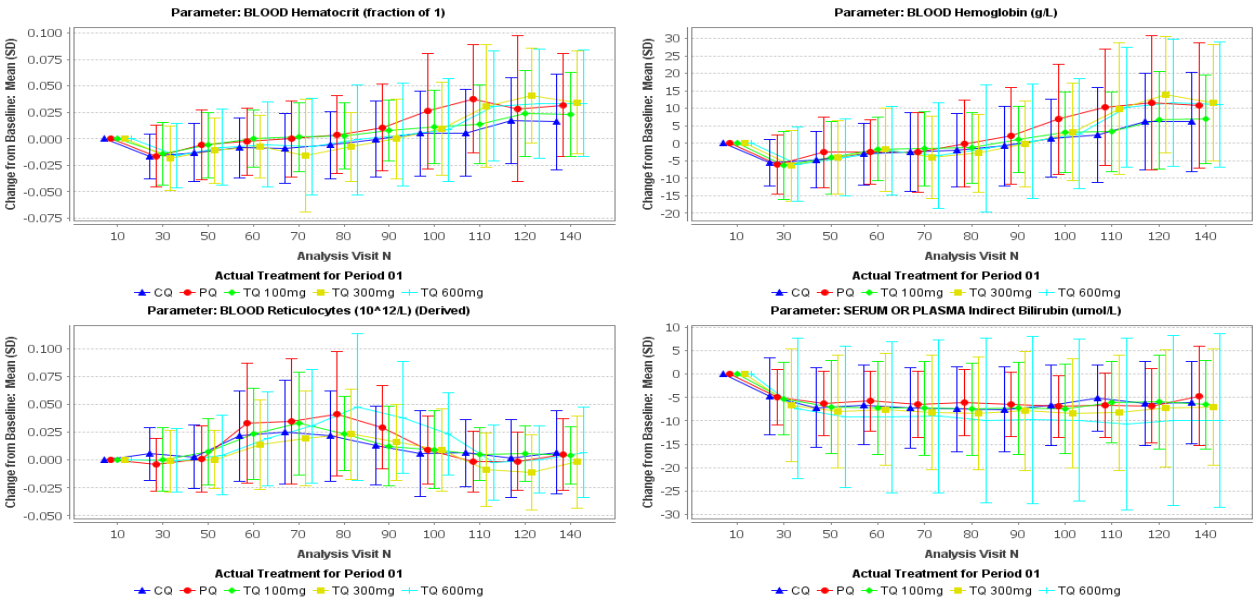
**Table 33. Study 582, part 2: Hemoglobin decrease from baseline by treatment arm, Day 1 to Day 29 – Safety population**

| Hemoglobin g/dL decrease from baseline | CQ+TQ 300mg N=260 | CQ+PQ 15mg N=129 | CQ (placebo) N=133 |
|---|---|---|---|
| ≤ 2g/dL | 214 (83%) | 114 (88%) | 120 (90%) |
| > 2g/dL and ≤ 3g/dL | 31 (12%) | 12 (9%) | 11 (8%) |
| > 3g/dL or ≥ 30% of baseline | 14 (5%) | 3 (2%) | 2 (2%) |

**Change in Hemoglobin levels from baseline by study visit**

In study TAF112582, part 1 (n=329), all treatment groups showed a post-baseline decline in Hb at around Day 3 (visit #30) with recovery to baseline or to higher between Day 22 (visit #90) and Day 29 (visit #100) post treatment. In study 582 part 1, an increase in reticulocyte count over time up to Day 15 was observed across all treatment groups. Some patients had elevated bilirubin levels at baseline probably associated with *P. vivax* malaria. See Figure 3.

**Figure 3. Study 582, Part 1: Changes in Mean (+/- SD) Hemoglobin, Reticulocytes, and Bilirubin by Study Visit - Safety Population**



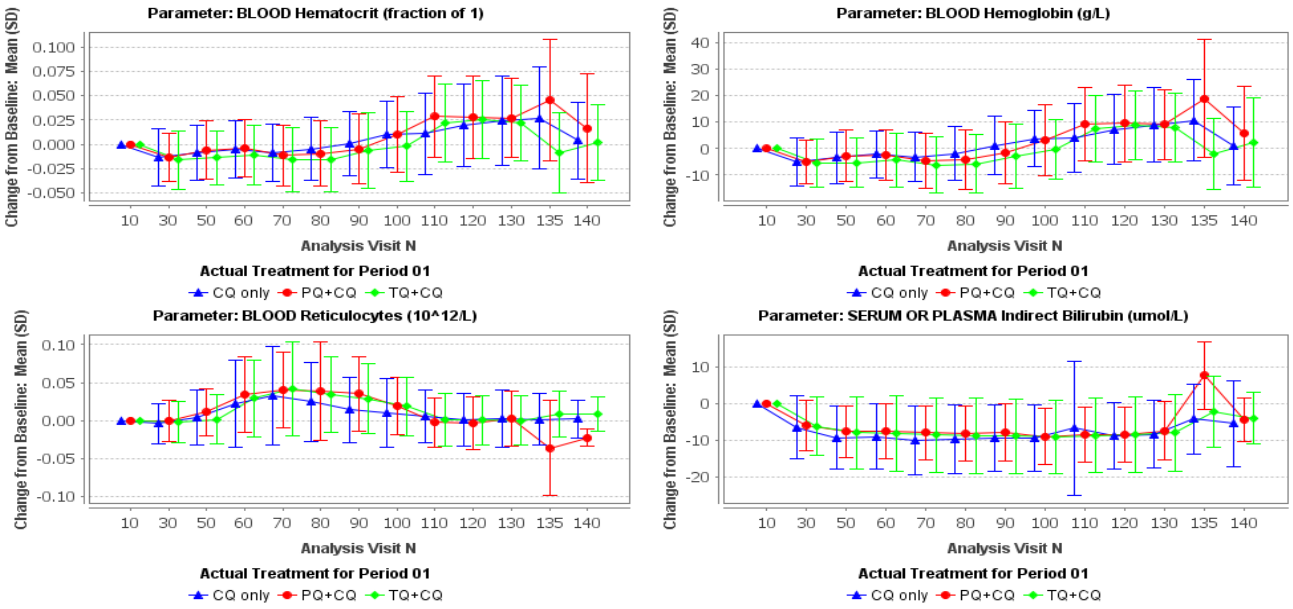

Study 582 part 1.
TQ:Tafenoquine; PQ: Primaquine: CQ:Chloroquine.

TQ 50mg+CQ is not shown.

SD: standard deviation. Visits N/Study day: Day of Visit 10: Day 1, Visit 30: Day 3, Visit 40: Day 4, Visit 50: Day 5, Visit 60: Day 8, Visit 70: Day 11, Visit 80: Day 15, Visit 90: Day 22, Visit 100: Day 29, Visit 110: Day 60, Visit 120: Day 90,Visit 130: Day 120,Visit 140: Day 180. Source: Study 582 part 1: Laboratory dataset, JReview 12.0

In TAF112582, part 2 (n=522), decreases in Hb levels over time were similar across treatment groups and showed recovery following treatment for *P. vivax* malaria. In the CQ+TQ 300 mg and PQ+CQ arms, mean Hb levels dropped from baseline on treatment and returned to baseline or higher after study Day 29 (visit # 100) compared to Day 22 on the CQ only arm. An increase in reticulocyte count occurred in all treatment groups from Day 8 to Day 22. The pattern of increase in reticulocyte counts paralleled the decrease in Hb levels and was consistent with recovery from *P. vivax* malaria. Baseline elevations in total and indirect bilirubin returned to normal limits for most subjects by Day 3. See Figure 4.

**Figure 4. Study 582, Part 2: Changes in Mean (+/- SD) Hemoglobin, Reticulocytes, and Bilirubin, by Study Visit - Safety Population.**




Study 582 part 2.
TQ:Tafenoquine; PQ:Primaquine; CQ:Chloroquine.

SD: standard deviation. Visits N/Study day: Day of Visit 10: Day 1, Visit 30: Day 3, Visit 50: Day 5, Visit 60: Day 8, Visit 70: Day 11, Visit 80: Day 15, Visit 90: Day 22, Visit 100: Day 29, Visit 110: Day 60, Visit 120: day 90, Visit 135: Day 150, Visit 140: Day 180. Source: Study 582 part 2: Laboratory dataset, JReview 12.0

It is challenging to distinguish hemolysis due to *P. vivax* malaria from drug-induced hemolysis in the three clinical trials. Decreases in Hb levels occurred on treatment with TQ + CQ and PQ + CQ; however, decreases in Hb levels occurred at a higher incidence in patients treated with TQ 300 mg + CQ (n=18, 3.9%) as compared to CQ alone (n=3, 1.6%), or PQ + CQ (n= 4, 1.5%) suggesting a higher risk for Hb decrease in subjects who receive TQ 300 mg + CQ. Dehydration due to fever from malaria followed by rehydration is a plausible contributing factor to the decline in Hb levels but it does not adequately explain the higher frequency of decreased Hb levels in the TQ + CQ versus CQ or PQ + CQ treatment groups.

**Methemoglobinemia**

Increases in MetHb% level were more frequent in the PQ+CQ group compared to the TQ+ CQ and CQ treatment groups in the three clinical trials. There were no SAEs related to methemoglobinemia in the TQ 300 mg + CQ group. The largest median increases in MetHb% in the TQ+CQ group were 1.85% in female subjects and 0.95% in male subjects. No subject had a MetHb >13% (normal < 3%). Patients were asymptomatic. In the PQ+CQ group, the largest median increase was 3.1% in female subjects and 2.2% in male subjects, and the maximum MetHb% value at any time point was 18.8%. A Grade 1 AE of methemoglobinemia was reported in one subject in the PQ+CQ group.

**QT Prolongation**
In Study 582 part 1, no differences were seen in QTcF interval changes between the CQ and TQ (50, 100, 300, 600 mg) treatment groups with all groups showing the same pattern of prolongation as CQ alone, in both the frequency and magnitude of changes. In Study 582 part 2, there was no evidence of a clinically significant additional effect of TQ on QTcF values patients treated with TQ 300 mg + CQ.

**Neurologic Adverse Events**
No subjects withdrew from a study due to a neurologic AE. Headache and dizziness were the most common neurologic AEs reported across the primary efficacy and safety trials. In the pooled trials, study 582 part 1&2, the incidence of headache was higher in the CQ group (21%) than in the TQ+CQ (11%) and PQ+CQ (13%) treatment groups. The overall incidence of dizziness in TQ+CQ (12.2%) and PQ+CQ (11.3%) groups was higher in the pooled primary efficacy and safety trials as compared to the pooled 582 trials, due to higher incidence of dizziness in Study 564. See Table 34.

**Table 34. Studies 582 & 564 (pooled TQ 300mg arms): Neurologic Treatment Emergent Adverse Events - Safety Population**

| | **Placebo(CQ) - controlled Trials: 582, Part 1 & 2, N=683** | | | **Primary Efficacy and Safety Trials: 582 part 1&2 and 564 N=747** | |
|---|---|---|---|---|---|
| **Dictionary Derived Term** | **TQ + CQ N = 317** | **CQ (placebo) N = 187** | **PQ + CQ N =179** | **TQ 300mg sd + CQ N = 483** | **PQ + CQ N = 264** |
| Balance disorder | - | - | - | 1 (0.3%) | 0 |
| Burning sensation | 0 | 0 | 1 (0.6%) | 0 | 1 (0.4%) |
| Dizziness | 30 (9.5%) | 16 (8.6%) | 14 (7.8%) | 59 (12.2%) | 30 (11.3%) |
| Dysesthesia | 0 | 0 | 1 (0.6%) | 0 | 1 (0.4%) |
| Headache | 37 (11.7%) | 39 (20.9%) | 24 (13.4%) | 64 (13.3%) | 40 (15.2%) |
| Hypoesthesia | - | - | - | 0 | 1 (0.4%) |
| Migraine | 3 (0.9%) | 1 (0.5%) | 0 | 3 (0.6%) | 1 (0.4%) |
| Somnolence | 1 (0.3%) | 0 | 0 | 1 (0.2%) | 0 |
| Syncope | 2 (0.6%) | 0 | 1 (0.6%) | 2 (0.4%) | 1 (0.4%) |
| Tremor | 1(0.3%) | 0 | 1(0.6%) | 1 (0.2%) | 1 (0.4%) |

Vertigo was reported in 3 (<1%) patients in the TQ + CQ group and zero patients in the CQ group. Vertigo and vestibular disorder were reported beyond 60 days post treatment with TQ+CQ and do not appear to be associated with study drugs. There were no auditory adverse effects reported in the TQ+CQ group. Auditory effects associated with CQ include nerve type deafness, tinnitus, and reduced hearing in patients with preexisting auditory damage after prolonged use. Such adverse effects would be unlikely following a three-day course of CQ. See Table 35.

**Table 35. Studies 582 & 564 (pooled TQ 300mg arms): Ear and Labyrinthine Treatment Emergent Adverse Events – Safety Population**

| | | Placebo - controlled Trials: 582, Part 1 & 2, N=683 | | | Primary Efficacy and Safety Trials: 582 part 1&2 and 564 N=747 | |
|---|---|---|---|---|---|---|
| **Body System or Organ Class** | **Dictionary Derived Term** | **TQ 300mg +CQ N=317** | **CQ (placebo) N=187** | **PQ +CQ N=179** | **TQ +CQ N=483** | **PQ+CQ N=264** |
| **Ear and labyrinth disorders** | Ear discomfort | 1 (0.3%) | 0 | 0 | 1(0.2%) | 0 |
| | Tinnitus | 0 | 0 | 1 (0.6%) | 0 | 1(0.4%) |
| | Vertigo | 2 0.6%) | 0 | 0 | 3 (0.6%) | 1(0.4%) |
| | Vestibular disorder | 0 | 0 | 0 | 1 (0.2%) | 0 |

**Psychiatric Adverse Events**

No subjects withdrew from the trials due to a psychiatric AE. Insomnia, anxiety, and depression were reported in a pooled analysis of psychiatric AEs in Study 582 and Study 564. Insomnia was the most common reported psychiatric AE with a similar incidence in the TQ+CQ and PQ+CQ treatment groups, 15 (3.1%) patients in the TQ 300 mg + CQ arm versus 8 (3.0%) patients in the PQ+CQ treatment arm. See Table 36.

Anxiety was reported in five patients, 2 (0.4%) in the TQ+CQ versus 3 (1.1%) in the PQ+CQ treatment groups. Anxiety was reported in two subjects within the first 5 days of treatment in Study 582 part 2; one subject was administered diazepam for anxiety and insomnia resulting in symptoms resolution within five days. The temporal association between onset of anxiety and TQ+CQ use suggests a possible association with the study drugs. Neuropsychiatric changes described in CQ product labeling include psychosis, delirium, anxiety, agitation, insomnia, confusion, hallucinations, personality changes and, depression.

There were no cases of depression reported in the TQ 300 mg + CQ treatment group. In study 582 part 1, depression occurred in one patient at a higher dose, TQ 600 mg + CQ. The patient had a history of depression and diazepam use prior to enrollment in the trial.

**Table 36. TAF112582 & TAF116564 (pooled TQ 300mg arms): Psychiatric Treatment Emergent Adverse Events**

| | Placebo - controlled Trials: TAF112582, Parts 1&2 N = 683 | | | Primary Efficacy and Safety Trials: TAF112582 parts 1&2 and TAF116564 N = 747 | |
|---|---|---|---|---|---|
| **Dictionary Derived Term** | **TQ 300mg + CQ N = 317** | **CQ N = 187** | **PQ + CQ N = 179** | **TQ 300mg sd + CQ N = 483** | **PQ 15mg od + CQ N = 264** |
| Anxiety | 2 (0.6%) | 0 | 0 | 2 (0.4%) | 3 (1.1%) |
| Depression | 0 | 0 | 0 | 0 | 1 (0.3%) |
| Insomnia | 13 (4.1%) | 5 (2.7%) | 8 (4.4%) | 15 (3.1%) | 8 (3.0%) |

# 11 Draft Points for Advisory Committee Discussion

- Evidence of the effectiveness of tafenoquine for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients 16 years of age and older.
- Evidence of the safety of tafenoquine for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients 16 years of age and older.