Krintafel (tafenoquine succinate tablets)

FDA Advisory Committee Briefing Document

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ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
AP	All Primary studies in the radical cure program: 582 Part 1, 582 Part 2, 564
AST	Aspartate Aminotransferase
AUC	Area under the concentration time curve
CI	Confidence Interval
CQ	Chloroquine
CSR	Clinical Study Report
CYP	Cytochrome P450
DRM	Drug-related material
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
G6PD	Glucose-6-Phosphate Dehydrogenase
GI	Gastrointestinal
GSK	GlaxoSmithKline
Hb	Hemoglobin
ICH	International Council on Harmonization
ITT	Intent-to-Treat
IU	International Units
MATE1	Multidrug and toxic compound extrusion protein-1
MATE2-K	Multidrug and toxic compound extrusion protein-2K
mITT	Microbiologic Intent-to-Treat
OCT2	Organic cation transporter-2
PC	Placebo-controlled studies in the radical cure program: 582 Part 1, 582 Part 2
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PQ	Primaquine
P. falciparum	Plasmodium falciparum
P. vivax	Plasmodium vivax
QTc	Corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
QWBA	Quantitative whole-body autoradiography
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SD	Single dose
StdD	Standard Deviation
SOC	System Organ Class
TQ	Tafenoquine
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

1. EXECUTIVE SUMMARY

GlaxoSmithKline (GSK) is seeking Food and Drug Administration (FDA) approval for 300 mg single dose tafenoquine (TQ) and upon approval would make TQ available to treat patients with *Plasmodium vivax (P. vivax)* malaria in the US. Based on the small numbers of *P. vivax* patients in the US, TQ has Orphan Drug Designation. TQ was granted Breakthrough Therapy status in 2013 due to the potential substantial treatment benefit in a serious infectious disease.

GSK has been developing 300mg single dose TQ together with the not for profit organization Medicines for Malaria Venture (MMV) as part of GSK's Global Health program aimed at improving healthcare for underprivileged populations. In addition to providing a treatment option to US patients, FDA review and approval of the NDA would be informative to other regulatory agencies and subsequent World Health Organization (WHO) prequalification to support future TQ use in malaria-endemic countries where there is significant unmet medical need for effective therapies. Furthermore, GSK and MMV's global development of tafenoquine to treat P. vivax malaria aligns with USAID and US Government initiatives on the global fight to treat and eradicate this disease.

1.1. Disease and Therapeutic Background

1.1.1. *P. vivax* infection can be severe, and is associated with a significant global disease burden

The global disease burden of malaria due to *P. vivax* is significant and *P. vivax* has the largest geographic distribution of human malarias [Gething, 2012]. The WHO World Malaria Report estimated 8.5 million (uncertainty range 6.6 to 10.8 million) cases in 2015 [WHO, 2016].

The clinical features of *P. vivax* malaria include fever, chills, vomiting, malaise, headache and myalgia. *P. falciparum* is generally considered to be responsible for most malaria-associated deaths and severe disease; however, in endemic areas, *P. vivax* is a common cause of severe malaria: 16% of all cases of severe malaria in Papua are due to *P. vivax;* in Thailand and Indonesia, almost 30% of patients hospitalized for malaria have *P. vivax* infection [Price, 2007]. In another review, the risk of a fatal outcome in patients with severe malaria was indistinguishable between those with *P. falciparum* versus *P. vivax* malaria [Barcus, 2007].

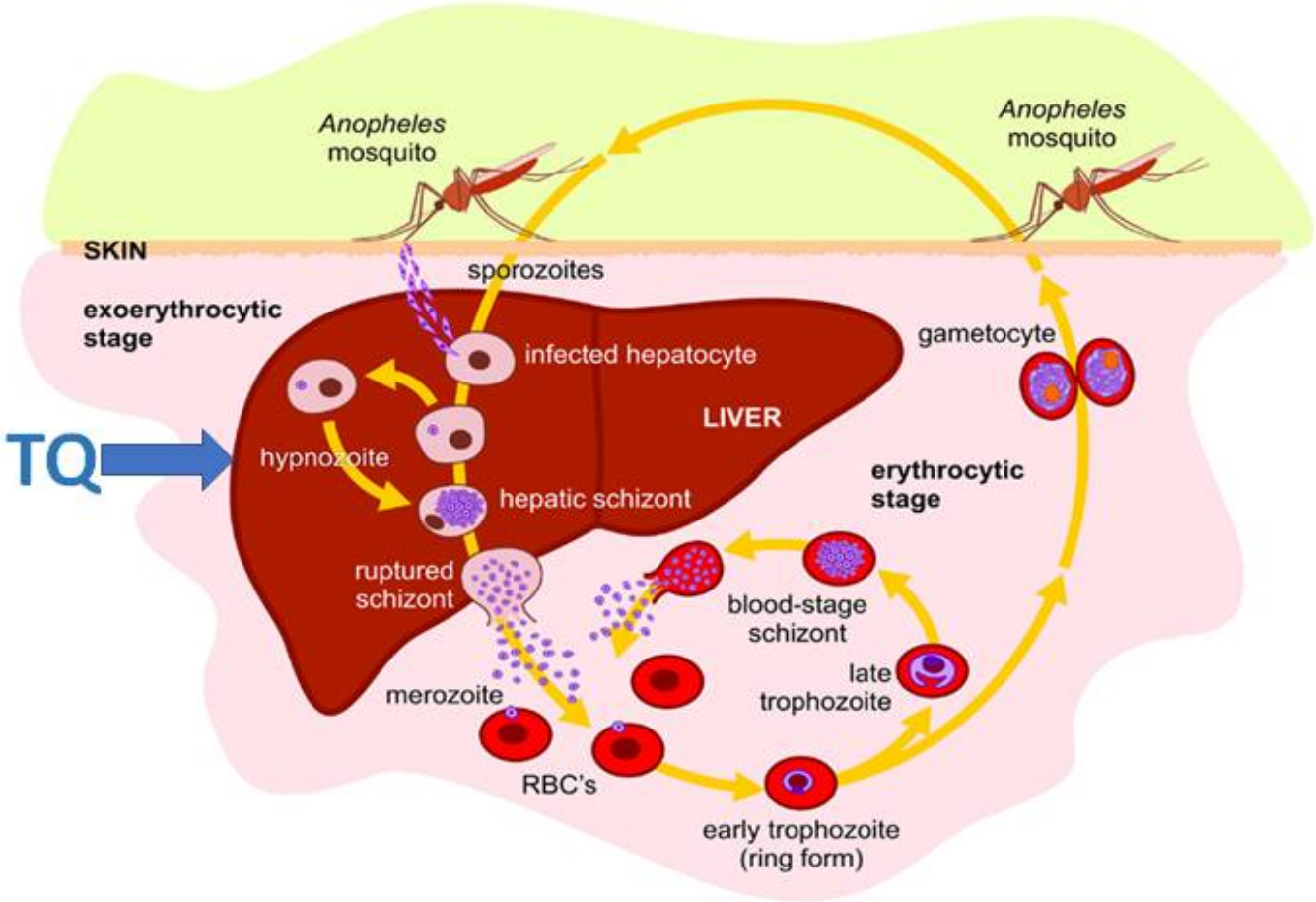
In countries that have eliminated malaria, the majority of cases reported are in returning travelers [Mace, 2017; Queensland Health, 2015]. In 2014, there were 230 cases of imported *P. vivax* reported to the US CDC. Of these, India, Pakistan and Ethiopia contributed the largest number of cases [Mace, 2017]. A review of >12,000 cases of *P. vivax* in returning US travelers found that 0.09% of cases resulted in death and 1.3% were classified as severe, including cerebral malaria, acute respiratory distress syndrome and/or renal failure (29.4%) [Hwang, 2014].

The persistence of mosquito vectors capable of transmitting malaria can make countries that have previously eradicated malaria susceptible to outbreaks of imported malaria (which could be due to relapse in a traveler who arrived some months previously, see below) [Filler, 2006; European Centre, 2017; Queensland Health, 2015; Wells, 2010].

1.1.2. Parasite life cycle

P. vivax infection in humans consists of both blood (erythrocytic) and liver (exo-erythrocytic) stages. Treatment of the blood stage infection (with medicines such as quinine, chloroquine or artemisinin-based combination therapies [ACTs]) does not clear the latent liver stage (hypnozoites). Activation of the hypnozoite can subsequently cause a relapse of malaria weeks, months or years later, without another infected mosquito bite. Patients may suffer from several relapses, and relapsing malaria can be a substantial proportion of the clinical cases in an area.

Figure 1 *P. vivax* Parasite Life Cycle in Humans



a. [Lima, 2016]

1.1.3. Current Therapies

Effective therapy requires not only treatment of the symptom-causing blood stage infection, but also of the hypnozoite burden in the liver, which will otherwise remain a source of recurrent infection. Of the many available antimalarial drugs, chloroquine is currently the most widely used for the treatment of the acute *P. vivax* blood stage infection. Liver hypnozoites are much less susceptible to treatment than the blood stage parasite, and currently, only the 8-aminoquinoline class of drugs, of which primaquine (PQ) is the only FDA approved 8-aminoquinoline, have shown efficacy. Using a drug to target the hypnozoite, in combination with standard anti-malarial drugs (such as chloroquine or ACTs) is called 'radical cure', since both the blood and liver stages of *P. vivax* are eliminated. Whilst a current focus of research, *in vitro* and *in vivo* models of *P. vivax* relapse are poorly developed and thus currently the precise mechanism of action for PQ and TQ anti-hypnozoite activity is unknown.

1.1.3.1. PQ is current standard of care for radical cure, but compliance is often poor

PQ was approved in the US in 1952 for the treatment of malaria, and remains the only FDA-approved drug that can eliminate all liver stages of *P. vivax* [Wells, 2010]. Without radical cure, relapses do occur in US patients and can lead to death. According to 2015 data collected by the Centers of Disease Control and Prevention (CDC) approximately 40% of US patients received primaquine treatment for P. vivax infection. [Mace, 2018].

PQ is administered as a once daily oral dose for 14 days, but in real world use this regimen is associated with poor compliance, resulting in lower efficacy than that reported by carefully-conducted clinical trials. Although data in the US are lacking, it has been estimated that the observed PQ efficacy in a population is reduced 3- to 4- fold when used in an unsupervised or semi-supervised manner [Abreha, 2017, Takeuchi, 2010; Douglas, 2017]. This can occur when as few as 3 doses out of 14 are omitted [Abreha, 2017].

In fact, compliance with unsupervised PQ treatment is reported to be as low as 30% in some settings [Abreha, 2017, Khantikul, 2009]. Fever and other malaria symptoms disappear when the blood stage infection is cleared. However, patients are required to continue taking PQ for several more days, in the absence of symptoms, to appropriately treat the liver hypnozoites. In one study patients with *P. vivax* were randomized to receive PQ by directly observed therapy (DOT) or self-administered therapy (SAT). DOT patients were approximately 6 times less likely than SAT patients to have *P. vivax* reappearance within the 90-day follow-up period. One of the factors related to the reappearance of vivax malaria was inadequate total PQ dosage [Takeuchi, 2010].

PQ DOT improves effectiveness, but requires a corresponding increase in health resource utilization [Takeuchi, 2010]. Current guidelines do not mandate DOT [WHO, 2015].

There are no International Council on Harmonisation (ICH) regions for which systematically collected data on real-world PQ compliance are available; however, it is known that compliance with short-course anti-infectives can be poor. An Australian

study of antibiotic compliance in a general practice showed that 27% of patients failed to complete at least 80% of a prescribed antibiotic course [Cockburn, 1987]. Data from one US center showed that 49% of patients failed to complete a short course of antibiotics following discharge from the Emergency Department [Suffoletto, 2012]. It is therefore reasonable to expect that a similar situation for PQ compliance could exist in the ICH regions as well.

There is thus evidence of poor compliance to PQ in the real world, which is associated with poor efficacy. This limits the benefit derived by the patients, which has important global public health consequences. In many countries, malaria elimination efforts are challenged by the capacity of *P. vivax* to relapse, and new tools are urgently needed.

1.1.3.2. TQ to address the unmet medical need

Given the reported poor compliance to PQ treatment and reduced effectiveness of the current 14-day standard of care regimen of PQ, there is a clear unmet medical need for a well-tolerated and effective therapy that targets the liver hypnozoite, and that can be administered as a shorter treatment duration.

TQ, administered as a single dose in conjunction with the standard 3-day treatment with chloroquine (CQ), is a simple dosing regimen that is anticipated to provide high treatment compliance even in the real-world setting, resulting in improved individual and public health outcomes.

1.1.3.3. Indication for 300 mg single dose Tafenoquine for *P. vivax* malaria

The proposed therapeutic indication for 300 mg single dose TQ is for the radical cure (prevention of relapse) of *P. vivax* malaria in patients 16 years and older.

Radical cure requires the elimination of the dormant (hypnozoite) liver stage of the parasite. Radical cure cannot be achieved by drugs used to treat the acute blood stage infection, such as chloroquine or ACTs, but requires in addition an 8-aminoquinoline, such as primaquine (PQ) or TQ, a derivative of PQ.

TQ is to be coadministered with CQ on the first or second day of CQ treatment.

1.1.3.4. 8-aminoquinolines and G6PD deficiency

PQ and TQ, as 8-aminoquinolines, can cause hemolysis in individuals with a deficiency in glucose-6-phosphate dehydrogenase (G6PD) enzyme activity, a hereditary X-linked condition [Cappellini, 2008]. The key factors determining the severity of drug-induced hemolysis are dose and the degree of G6PD enzyme activity.

Males, having one copy of the G6PD gene (one X-chromosome), have either normal or deficient enzyme activity. Females carry two copies of the gene, and can therefore be heterozygous for G6PD deficiency, and may have intermediate enzyme activity levels.

To manage this hemolysis risk, patients must be tested, and G6PD-deficient patients then excluded from treatment with TQ or PQ. The prescribing information for PQ contains a contraindication for patients with G6PD deficiency, and G6PD testing is performed routinely in the US before prescribing PQ. In the TQ Phase 2b/3 clinical program all subjects were tested for G6PD deficiency. Including only patients with levels that were ≥70% of the site median proved effective in avoiding any cases of clinically significant hemolysis.

Access to G6PD testing remains a barrier to effective treatment of *P. vivax* malaria in many endemic countries. GSK and MMV are collaborating with PATH on the parallel development of a robust, portable, quantitative G6PD diagnostic suitable for use in resource-poor settings. This may also prove to be an important innovation in addressing the global disease burden of *P. vivax* malaria.

1.2. Clinical Development Program

The clinical development program for TQ in the radical cure of *P. vivax* was designed in consultation with regulatory authorities in the US and Australia and in consultation with the World Health Organization (WHO) Global Malaria Program.

Three primary studies (Table 1) have established that 300 mg TQ is an effective single-dose treatment for the radical cure of *P. vivax*:

- 300 mg was selected as the lowest efficacious dose from a placebo-controlled dose-ranging study: 582 Part 1 (Phase 2b)
- Efficacy of the selected 300 mg dose was confirmed, showing a 70% reduction in the risk of recurrence vs. CQ alone, in a pivotal placebo-controlled study: 582 Part 2 (Phase 3)
- An acceptable safety profile has been demonstrated for the selected 300 mg dose, when given together with CQ, throughout the 6-month follow-up: 582 Parts 1& 2, 564 (Phase 3)
- Efficacy and safety were observed to be similar to that of PQ, given together with CQ, the current standard of care: Studies 582 Parts 1& 2, Study 564.

The primary studies enrolled patients ≥16 years of age with a diagnosis of acute *P. vivax* malaria (parasite count 100-100,000 parasites/μL), and with G6PD enzyme activity ≥70% of normal. While the phase 2b/3 studies were conducted in malaria-endemic countries, i.e. at sites outside the US (See Appendix Sections 9.1, 9.2, 9.4), there is no reason to expect differing responses to treatment between US patients who acquired *P. vivax* due to travel, and patients in endemic regions with *P. vivax* disease.

Safety data from across the whole TQ development program include 33 studies in healthy volunteers and patients, which were used to inform the type and frequency of uncommon and rare events observed with TQ. Across the TQ development program, more than 4000 subjects have been exposed to TQ, including >800 subjects exposed to a 300 mg total dose, of which >700 received a single dose (Table 28).

In addition to the safety data from the primary studies, specific safety results from 2 key individual studies in healthy volunteers, the study assessing ophthalmic safety (TAF201807) and the definitive study of cardiac safety (TAF114582), provide clinically important safety observations.

Table 1 Overview of Key Studies Contributing Efficacy and Safety Data for 300 mg Single Dose TQ

	Primary Studies in *P. vivax*-infected Subjects			Specific Safety in Healthy Volunteers	
	Placebo-controlled Studies		Study TAF116564	Ophthalmic	QTc
	Study TAF112582 Part 1	Study TAF112582 Part 2		Study 201807	Study TAF114582
Study design	Randomized, double-blind, placebo- and active-controlled, double-dummy, parallel-group	Randomized, double-blind, placebo and active-controlled, double-dummy, parallel-group	Randomized, double-blind, active-controlled, double-dummy, parallel-group	Randomized, single-blind, placebo-controlled, parallel-group	Randomized, single-blind, placebo-controlled, parallel-group
Phase	Phase 2b	Phase 3	Phase 3	Phase 1	Phase 1
Study population	Subjects ≥16 yrs; confirmed *P. vivax* infection; ≥70% normal G6PD levels[b] stratified by baseline parasite count (≤7500/μL, >7500/μL)	Subjects ≥16 yrs[a]; confirmed *P. vivax* infection; ≥70% normal G6PD levels[b]	Subjects ≥16 yrs[a], confirmed *P. vivax* infection; males with ≥70% normal G6PD levels[b] and females with ≥40% normal G6PD levels[b]	Healthy subjects; 18 to 45 yrs (inclusive)	Healthy subjects; 18 to 65 yrs (inclusive)
Treatment groups (n)	CQ for 3 days plus: TQ 50 mg SD (n=55) TQ 100 mg SD (n=57) TQ 300 mg SD (n=57) TQ 600 mg SD (n=56) PQ 15 mg once daily for 14 days (n=50) Placebo (i.e., CQ alone) (n=54)	CQ for 3 days plus: TQ 300 mg SD (n=260) PQ 15 mg once daily for 14 days: (n=129) Placebo (i.e., CQ alone) (n=133)	CQ for 3 days plus: TQ 300 mg SD (n=166) PQ 15 mg once daily for 14 days (n=85)	TQ 300 mg (n=332) Placebo (n=168)	TQ 300 mg (n=52) TQ 600 mg (n=52) TQ 1200 mg (n=52) Moxifloxacin (n=52) Placebo (n=52)
Primary objective	Efficacy	Efficacy	Occurrence of clinically relevant hemolysis	Retinal effects (CFB)	QTcF effects (CFB)

Abbreviations: CFB=change from baseline; CSR=clinical study report; QTc=corrected QT interval; SD=single dose

a. In Ethiopia, ≥18 years

b. ≥70% of site median of G6PD normal males

1.3. Efficacy

1.3.1. Primary Endpoint

The primary endpoint for efficacy was the recurrence of *P. vivax* malaria over a 6-month duration of follow up, and the primary objective was to compare the efficacy of TQ +CQ

versus CQ alone. Studies were conducted in malaria-endemic areas, and therefore there was a continuous risk of re-infection throughout the follow-up period. For *P. vivax* recurrences, it is not possible to completely distinguish true relapses from new infections, even using parasite genotyping.

The observed efficacy in the Phase 2b/3 studies thus demonstrates the overall benefit of TQ in preventing recurrence, even in the presence of likely re-infection over the 6-month period of follow-up.

All three Phase 2b/3 studies included a PQ+CQ treatment arm as a benchmark treatment, but were not designed to have sufficient power to make formal comparisons of efficacy (e.g., non-inferiority) of single dose TQ to PQ for 14 days when co-administered with standard doses of CQ. Treatment comparisons were made to the CQ alone group in the placebo-controlled studies. Efficacy for 300 mg single dose TQ was similar to that observed for compliant treatment with PQ for 14 days.

- 300mg single dose TQ, when given with CQ, resulted in a clinically and statistically significant reduction in the risk of recurrence over 6 months by 70.1% (95% confidence interval [CI]: 59.6%, 77.8%; p<0.001) compared with CQ alone, based on a Cox proportional hazards model (Study 582 Part 2) (Table 2). The Kaplan Meier estimates of recurrence-free efficacy at 6 months were 27.7% (95% CI: 19.6%,36.3%) in the CQ alone group and 62.4% (95% CI: 54.9%, 69.0%) in the TQ+CQ group.
- Treatment with PQ+CQ resulted in a reduction in the risk of recurrence at any time over 6 months by 73.8% (95% CI: 61.3%, 82.2%; p<0.001) compared with CQ alone. The estimate of recurrence-free efficacy at 6 months was 69.6% (95% CI: 60.2%,77.1%) in the PQ+CQ group.

Table 2 6-Month Recurrence-free Efficacy by Cox Proportional Hazards Analysis in 582 Part 2 (mITT Population)

	CQ alone N=133	TQ+CQ N=260	PQ+CQ N=129
Recurrences over 6 months, n (%)	88 (66)	85 (33)	36 (28)
Hazard Ratio vs CQ alone (95% CI)	--	0.299 (0.222,0.404)	0.262 (0.178,0.387)
p-value	--	<0.001	<0.001

An alternative logistic regression analysis (where subjects who were not confirmed recurrence-free at 6 months were assumed treatment failures) was consistent with the survival analyses (Table 3). There was a 75.9% reduction in the odds of recurrence (95% CI: 61.8%, 84.8%; p<0.001) in TQ+CQ treatment compared with CQ alone.

Table 3 Logistic Regression Analysis of 6-Month Recurrence-free Efficacy in 582 Part 2 (mITT Population)

	CQ alone N=133	TQ+CQ N=260	PQ+CQ N=129
Missing, n (%)	10 (8)	20 (8)	10 (8)
Recurrences over 6 months, n (%)	98 (74)	105 (40)	46 (36)
Odds Ratio for Recurrence vs CQ alone (95% CI)	--	0.241 (0.152,0.382)	0.198 (0.117,0.335)
p-value	--	<0.001	<0.001

The two other primary studies (582 Part 1 and 564) provided consistent and supportive evidence of efficacy for the 300 mg single dose TQ+CQ treatment:

- The dose range finding study, 582 Part 1 (Table 49), showed a statistically significant difference in efficacy between TQ+CQ compared to CQ alone. The estimates of recurrence-free efficacy at 6 months were 37.5% (95% CI: 23%, 52%) in the CQ alone group, 89.2% (95% CI: 77%, 95%) in the 300 mg TQ+CQ group, and 77.3% (95% CI: 63%,87%) in the PQ+CQ group.
- In Study 564 (Table 60) the estimates of recurrence-free efficacy at 6 months were 72.7% (95% CI: 64.8%, 79.2 %) in the TQ+CQ group, and 75.1% (95% CI: 64.2%, 83.2%) in the PQ+CQ group.

The results of all pre-specified sensitivity analyses of the primary endpoint were consistent with the primary analyses for the Phase 3 studies.

In the pivotal and supportive efficacy studies, demographic characteristics were well-balanced across the treatment groups and the baseline disease characteristics were similar across treatment groups. In all 3 efficacy studies, the study completion rate was ≥94% in all treatment groups and there were no adverse events (AEs) leading to withdrawal from the studies.

In the Phase 3 studies, study sites were able to achieve very high (≥96%) compliance with all study medications based on reinforced, targeted efforts; hence almost all of the PQ+CQ group received the full 14-day treatment course of PQ. However, outpatient compliance with PQ in TAF112582 Part 1, was lower in comparison with the other studies.

1.3.2. Secondary Endpoints

It was anticipated that the majority of relapses would occur within the first 4 months of follow up (as shown in the Kaplan-Meier analysis of the time to recurrence in the CQ only arm), and that there would be a background risk of re-infection throughout the duration of the study. Hence efficacy was also evaluated at the 4-month time period, in order to attempt to minimize the confounding effect of re-infection (which cannot be

assessed by any genotypic evaluation, as discussed above), and this is a key secondary endpoint. This endpoint was derived using the follow up data up to 4 months.

1.3.2.1. Recurrence at 4 months

In Study 582 Part 2, TQ, when given with CQ, resulted in a reduction in the risk of recurrence at any time over 4 months by 72.9% (95% CI: 62.4%, 80.5%; p<0.001) compared with CQ alone. The estimates of recurrence-free efficacy at 4 months were 36.0% (95% CI 26.8%,45.4%) in the CQ alone group and 73.0% (95% CI: 66.0%,78.9%) in the TQ+CQ group.

Supportive efficacy studies showed similar results at 4 months:

- Study 582 Part 1 (Table 50) showed a statistically significant difference in efficacy between TQ+CQ compared to CQ alone. The estimates of the recurrence-free efficacy at 4 months were 46.5% (95% CI: 32%, 60%) in the CQ alone group and 89.4% (95% CI: 75%, 96%) in the 300 mg TQ+CQ group.
- In Study 564 (Table 62) the estimate of recurrence-free efficacy at 4 months was 82.3% (95% CI: 74.9%,87.7%) in the TQ+CQ group

1.3.2.2. Other secondary endpoints

Additional secondary endpoints evaluated the initial parasitological and symptomatic response of the presenting episode of *P. vivax* malaria. Endpoints included: number of patients who did not clear their initial infection by Day 33, time to fever clearance, time to parasite clearance, and the incidence of *P. falciparum* infection. Very few subjects failed to clear the initial infection, and there were very few secondary *P. falciparum* infections, and no differences were observed in these and other secondary endpoints between treatment groups across the studies.

1.4. Safety

The safety profile of TQ at the recommended 300 mg single dose supports its use for radical cure. In Phase 2b/3 studies the safety profile of TQ was similar to that of PQ 15 mg daily for 14 days.

Across the TQ development program with all dosing regimens, more than 4000 subjects have been exposed to TQ, including >800 subjects exposed to a 300 mg total dose. The Phase 2b/3 studies outlined above provide the primary evidence of an appropriate safety profile for the TQ 300 mg single dose in the radical cure of *P. vivax* malaria, when given with CQ, and are discussed in detail in this document. Altogether, a total of 483 subjects with P. vivax malaria have been exposed to TQ+CQ in the 3 primary studies. This dataset of 483 patients with acute *P. vivax* malaria who received TQ+CQ enables comparison both with patients who received CQ alone (TQ+CQ: N 317; CQ alone: N 187) across the placebo-controlled studies (PC grouping), and who received PQ+CQ (TQ+CQ: N 483; PQ+CQ: N 264) across the three Phase 2b/3 studies (all primary, AP grouping).

1.4.1. Adverse events

Overall, the AE profiles for treatment groups in the PC grouping were similar (Table 4).

Table 4 AEs at 5% or More in Any Treatment Group in the PC Grouping (Safety Population)

Preferred term	CQ alone N=187	TQ+CQ N=317	PQ+CQ N=179
Any event	**127 (68)**	**202 (64)**	**108 (60)**
Pruritus	27 (14)	42 (13)	17 (9)
Headache	39 (21)	37 (12)	24 (13)
Dizziness	16 (9)	30 (9)	14 (8)
Nausea	15 (8)	26 (8)	13 (7)
Vomiting	9 (5)	24 (8)	16 (9)
Viral upper respiratory tract infection	9 (5)	19 (6)	12 (7)
Diarrhoea	10 (5)	18 (6)	9 (5)
Myalgia	22 (12)	16 (5)	12 (7)
Abdominal pain upper	18 (10)	17 (5)	14 (8)
Pharyngitis	7 (4)	15 (5)	11 (6)
Back pain	4 (2)	17 (5)	5 (3)
Haemoglobin decreased	3 (2)	15 (5)	3 (2)
Pyrexia	23 (12)	14 (4)	16 (9)
Urinary tract infection	9 (5)	12 (4)	7 (4)
Blood creatine phosphokinase increased	10 (5)	11 (3)	7 (4)
Alanine aminotransferase increased	9 (5)	10 (3)	7 (4)
Abdominal pain	9 (5)	8 (3)	7 (4)
Chills	20 (11)	6 (2)	12 (7)

The incidence of relapse was higher in the CQ only group; this may account for the higher incidence of AEs that might be associated with a *P. vivax* malaria recurrence, and/or re-treatment with CQ and PQ. Therefore, in order to account for this confounding effect, AEs occurring within the first 29 days (prior to the first documented *P. vivax* recurrence on any study arm) were also analyzed (Table 5).

Within the first 29 days, pruritus was the most common AE in all 3 treatment groups in the PC grouping, which is consistent with the known effects of CQ. The majority of subjects with AEs had events that were mild or moderate in severity and few severe AEs (Grade ≥3) were reported.

Dizziness and hemoglobin decrease were more frequently reported in the TQ+CQ group compared with CQ alone. These findings are discussed under hematologic safety and CNS effects, below.

Table 5 AEs With Onset On Or Prior to Study Day 29 Reported in at Least 5% of Subjects in Any Treatment Group by Preferred Term (PC Safety Population)

Preferred Term	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)
Any event	**90 (48)**	**160 (50)**	**88 (49)**
Pruritus	24 (13)	37 (12)	17 (9)
Dizziness	6 (3)	25 (8)	10 (6)
Nausea	12 (6)	20 (6)	8 (4)
Hemoglobin decreased	3 (2)	15 (5)	3 (2)
Headache	12 (6)	15 (5)	9 (5)
Vomiting	7 (4)	17 (5)	10 (6)
Abdominal pain upper	14 (7)	13 (4)	12 (7)

1.4.2. Serious Adverse Events

There were no deaths in the 3 primary studies, 582 Part 1 and Part 2, and 564, or in the radical cure program studies.

Decreased hemoglobin was the most common serious AE (SAE), and the only SAE reported in >1 subject in the TQ+CQ group, based on the placebo-controlled studies (PC) grouping, and occurred in 4% of TQ+CQ patients, compared with 2% in the CQ alone, and 2% in the PQ+CQ groups.

As hematologic safety was of special interest (discussed further, below), decreased hemoglobin (Hb) was pre-defined as an SAE in the protocols (Hb decreases of ≥30% or >30 g/L from baseline; or, an overall drop in Hb below 60 g/L in the first 15 days of the study). Events in the studies that met these criteria, and hence were counted as SAEs, did not, in any instance, otherwise fulfill the criteria for 'serious', such as life-threatening or requiring hospitalization. In fact, none of these events required any specific intervention and no patient had a Hb below 60 g/L.

1.4.3. Laboratory evaluations

No clinically significant hepatobiliary or renal effects were observed.

Transient, sporadic increases in liver transaminases have been observed, but no clinically significant hepatobiliary effects were observed across the clinical program. All hepatobiliary AEs were mild or moderate in intensity and no subjects discontinued study treatment or withdrew from any of the 3 primary studies due to hepatobiliary AEs.

No renal toxicity signal was observed across the TQ development program. The proposed 300 mg single dose TQ was associated with small reversible increases in creatinine, which were consistent with the known renal transporter inhibition effect.

1.4.4. AEs of Special Interest

Given the known safety profile of TQ and that of other currently used anti-malarials, particular aspects of the safety profile for TQ were evaluated further (QT prolongation, ophthalmic safety, hematologic safety, CNS effects), either through the conduct of targeted studies, or through additional analyses. These potential safety issues are discussed below.

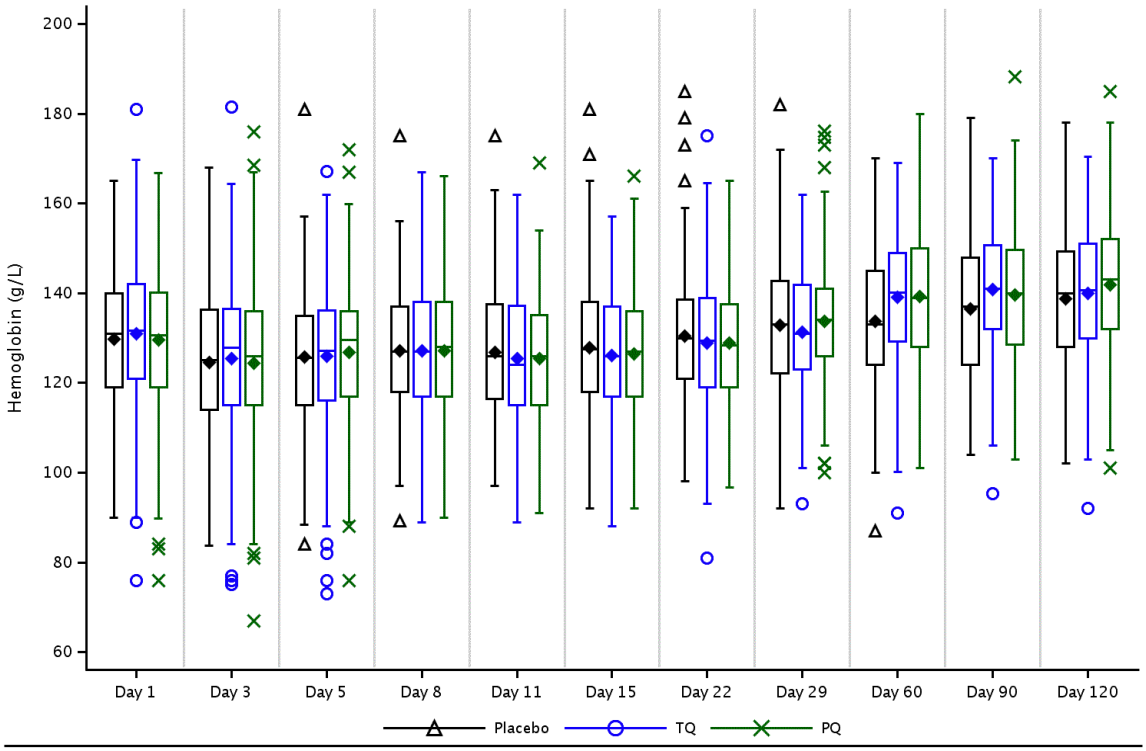
1.4.4.1. Hematologic safety

The hematologic safety profile for TQ 300mg single dose has been well-characterized, and the TQ development program has established that excluding patients with G6PD activity <70%, which was the cut-off in the clinical trials, is effective at preventing clinically significant drug-induced hemolysis in patients with *P. vivax* malaria.

The main safety concern for 8-aminoquinolines such as PQ and TQ, is drug-induced hemolysis in patients with G6PD enzyme deficiency. Patients with G6PD deficiency (<70% normal enzyme activity) were therefore excluded from the studies, and our proposed labeling for TQ currently under review by the FDA includes a contraindication in G6PD deficiency (G6PD enzyme levels <70% of normal). This contraindication would be consistent with labelling, and WHO guidelines, on the use of 8-aminoquinolines. In the US and other ICH regions, quantitative laboratory diagnostics are readily available for use prior to administration of 8-aminoquinolines [Trinity Biotech, 2012].

In G6PD normal patients, overall trends in Hb changes over time were similar across the treatment groups in the PC grouping (Figure 2), consistent with the hematologic effects of, and recovery from an acute episode of malaria. None of these changes were regarded as clinically significant.

Figure 2 Hb Values by Visit (PC Safety Population)



Subjects	Day 1	Day 3	Day 5	Day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120
Placebo	187	187	186	185	184	186	184	183	181	181	132
TQ	317	315	313	312	310	310	308	309	309	308	251
PQ	179	179	177	175	173	173	173	172	173	168	123

Placebo = CQ alone; TQ = TQ+CQ; PQ = PQ+CQ

1.4.4.2. Ophthalmic safety

Ophthalmic assessments in the Phase 3 studies, and in a healthy volunteer study (201807) which used more detailed and sensitive ophthalmic techniques, did not identify any signal for retinal toxicity with use of a 300 mg single dose TQ.

In common with other cationic amphiphilic drugs, TQ has the potential to cause phospholipid accumulation in the cornea, a benign and reversible keratopathy; this finding has been observed in studies where higher doses and longer durations of TQ treatment were used. CQ (in high cumulative doses) is associated with retinopathy; retinal toxicity has also been associated with use of quinine and quinidine. Ophthalmic safety was therefore of special interest in the TQ studies.

Ophthalmic evaluations were included for a subset of patients enrolled in the primary studies, according to capabilities at individual study sites. Across the primary studies there was no evidence of retinal toxicity or corneal changes associated with vision changes for the proposed 300 mg TQ single dose. AEs associated with ocular changes were infrequent and similar across the treatment groups in the PC and AP groupings, and

all events were mild or moderate in severity. No clinically significant changes to ophthalmic safety parameters were observed, based on visual acuity measurements, anterior segment examination with evaluation for vortex keratopathy, posterior segment examination including fundus photographs, color perception assessment, and Humphrey visual field perimetry.

Given the limited capacity for Phase 3 clinical trial sites to conduct detailed ophthalmic safety assessments, a specific placebo-controlled safety study, Study 201807, was conducted in healthy US volunteers using highly sensitive ophthalmic techniques (Spectral Domain Optical Coherence Tomography, and Fundus Autofluorescence) to establish whether there is a risk of retinopathy with the proposed 300 mg single dose of TQ. This study did not identify any signal for retinal toxicity with use of a single 300 mg dose of TQ.

1.4.4.3. Cardiac safety

In a definitive cardiac safety study at 2 US sites (Study TAF114582) there was no indication of a QT effect at clinically relevant doses of TQ (300 mg and 600 mg) compared with placebo. The maximum effect on QTcF at the supratherapeutic dose of 1200 mg compared to placebo was <10 msec and within the FDA E14 guidelines for lack of effect.

Data from other clinical studies did not show an additional effect of TQ 300mg single-dose on the corrected QT interval (QTcF) duration to that recognized for CQ or ACTs such as dihydroartemisinin/piperaquine (DHA/PQP).

1.4.4.4. Central Nervous System effects

CNS effects in P. vivax patients treated with 300 mg single dose TQ

No serious CNS AEs were reported in the PC and AP groupings from the phase 2b and 3 studies; all neurologic and psychiatric AEs were mild to moderate in severity, and self-limiting.

In the PC and AP groupings, headache and dizziness were the most commonly reported neurologic events (Table 35). A higher incidence of headache in the CQ only arm (likely to be associated with the higher incidence of *P. vivax* relapse) was observed. This prompted a review of CNS events occurring within the first 29 days, before any documented malaria recurrence (Table 6). This analysis of neurologic and psychiatric AEs showed that dizziness was more frequently reported in the TQ+CQ group, compared with CQ alone, which is consistent with what was reported in healthy volunteers treated with TQ, in the absence of malaria.

Insomnia and anxiety were the only psychiatric AEs reported at any time by patients receiving TQ+CQ across the entire 6-month follow-up, and were reported at similar rates in the PQ+CQ group.

Table 6 Central Nervous System AEs with Onset On or Prior to Day 29 by System Organ Class and Preferred Term (PC and AP Safety Populations)

	PC Grouping			AP Grouping	
System Organ Class Preferred Term	**CQ alone (N=187) n (%)**	**TQ+CQ (N=317) n (%)**	**PQ+CQ (N=179) n (%)**	**TQ+CQ (N=483) n (%)**	**PQ+CQ (N=264) n (%)**
Nervous System Disorders, any event	**19 (10)**	**36 (11)**	**18 (10)**	**75 (16)**	**35 (13)**
Dizziness	6 (3)	25 (8)	10 (6)	52 (11)	23 (9)
Headache	12 (6)	15 (5)	9 (5)	34 (7)	19 (7)
Syncope	0	2 (<1)	0	2 (<1)	0
Tremor	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Dysaesthesia	0	0	1 (<1)	0	1 (<1)
Migraine	1 (<1)	0	0	0	0
Somnolence	0	1 (<1)	0	1 (<1)	0
Psychiatric Disorders, any event	**5 (3)**	**12 (4)**	**8 (4)**	**14 (3)**	**9 (3)**
Insomnia	5 (3)	12 (4)	8 (4)	14 (3)	8 (3)
Anxiety	0	2 (<1)	0	2 (<1)	1 (<1)

CNS events in studies evaluating other TQ dosing regimens

Central nervous system (CNS) events i.e. nervous system and psychiatric disorders, are recognized for some anti-malarials, including CQ and quinine, and most noticeably with the 4-quinolinemethanol, mefloquine, but are typically reversible and rarely persist long term. In 2016 we first received spontaneous reports of possible long-term CNS effects from soldiers who had participated in studies conducted by GSK over 15 years ago with the Australian Defense force (discussed below). This prompted a thorough evaluation of all available clinical trial data and relevant literature.

Following this review, terms relating to mild or moderate, self-limiting CNS effects with 300 mg SD TQ have been included in proposed labeling subject to FDA review. Additionally, a conservative position is being taken with regard to patients with a history of serious psychiatric disorders, which to date have only been observed at doses higher than the proposed 300 mg single dose. Precautionary language has been added to the proposed label that is currently under FDA review (See Section 6.5, CNS Events).

A limited number of serious psychiatric events have been reported in individuals who have received a total dose of TQ ≥350 mg. These were mainly in individuals with a history of significant psychiatric disorders. Amongst the clinical trial database of > 4000 subjects who have been exposed to TQ, including all healthy volunteer and prophylaxis studies, a total of 9 individuals receiving TQ single or multiple doses reported severe or serious psychiatric disorders (n 7), or otherwise considered medically important for the purposes of this evaluation (n 2) (Table 36).

Four of the 9 were reported in patients and healthy volunteers who received a single dose of TQ. They received doses ranging from 350 mg to 600 mg: 2 reports (1 healthy volunteer, 1 *P. vivax*-infected subject) of depressed mood and 2 reports (both healthy

volunteers) of psychosis. One of the subjects with depressed mood had a history of depression. Both of the subjects with psychosis had a history of psychosis that was not disclosed at study entry. In the subject with no relevant past medical history, the depressed mood was mild, lasted for 3 days, and resolved without intervention, suggesting that patients without a history of serious psychiatric disorders may be at a lower risk. All of the serious events resolved fully during follow-up with treatment.

The remaining 5 were reported in individuals who received repeat doses of TQ (cumulative doses up to 5200 mg) in prophylaxis or other healthy volunteer studies. Two individuals, with no previous relevant history, developed mild depression/bipolar depression, of which one resolved without intervention, and one occurred 2 months after the last dose of TQ, but was subsequently lost to follow-up. One individual, with a history of closed head injury, developed moderate depression, and one individual with a relevant past history developed suicidal behavior in association with alcohol intoxication. One individual, with an undisclosed history of psychosis, reported an episode of psychosis.

While a causal role for TQ has not been established, a current or prior history of psychiatric disorder may be a risk factor for these events.

Reports from subjects in previous TQ studies

Starting in 2016, reports of psychiatric disorders have been received from a total of 18 subjects out of the >1500 individuals who received TQ in studies (mostly for prophylaxis) conducted with the Australian Defense Force (ADF) (Study SB252263/033, Study SB252263/046, and Study SB252263/049), which were conducted >15 years ago.

The self-reported medical histories contained in these more recent reports from former ADF study participants describe more CNS events than were reported at the time of the study, including anger outbursts, confusional state, and hallucinations. These reports provided only limited medical information, and were not medically confirmed. The majority of soldiers making reports were exposed to triggers for post-traumatic stress syndrome, the symptoms of which are similar to those included in the reports. These aspects taken together make evaluation more challenging and mean that a firm conclusion cannot be drawn although a role for tafenoquine cannot be excluded.

While there may be reasons why symptoms were under-reported at the time, the rate for CNS effects was nonetheless higher in the ADF study SB252263/033 compared to study SB252263/057, which studied the same TQ dosing regimen (200mg x 3 loading dose, then 200mg weekly for 6 months) but in healthy volunteers including non-deployed military personnel. The absence of an untreated control group in Study SB252263/033 poses difficulties in interpretation of this data compared to background rates of CNS events in a military population. Literature suggest that there is a substantial background rate of depression (~12%, Brignone, 2017; Fanning, 2013; Ilgen, 2010 O'Toole, 2015; Ramsawh, 2014) and anxiety disorders (~10%, Brignone, 2017; Fanning, 2013; Ilgen, 2010; McFarlane, 2011; O'Toole, 2015) in military populations.

To date, due to limitations in the data available and the inability to perform an accurate and non-confounded retrospective analysis, e.g. recruitment/selection and recall bias, it has not been possible to make a connection between mild to moderate side effects reported during Study SB252263/033, and any permanent serious long- term effects with onset after completion of the study. It is therefore possible that the deployed ADF soldiers represented a higher risk population.

Preclinical evaluation of CNS Effects

Tafenoquine does not induce neurotoxicity in single and repeat dose toxicology studies in mice, rats and dogs, or specific neurobehavioral studies in rats at exposures that are comparable to or in excess of those seen at the recommended treatment dose for patients (Section 3).

CNS Safety Conclusion

In the >800 subjects who have received a total dose of 300mg TQ, no serious CNS events have been reported and the observed events have been mild to moderate and self-limiting. Therefore, the single 300 mg TQ dose + CQ for radical cure of *P. vivax* malaria is anticipated to have a low risk of significant CNS effects in patients without an active or past history of serious psychiatric disorders.

Adopting a conservative approach and given the totality of both clinical data and the scientific literature, the proposed labeling for 300 mg single dose TQ currently under review by the FDA indicates that caution is advised when administering TQ to patients with a current or past history of serious psychiatric disorder. The intention is for the safety of tafenoquine to be monitored carefully post-registration (see Benefit:Risk Section 7)

1.5. Benefit : Risk

P. vivax malaria is responsible globally for a very significant burden of illness, despite being rare in the US. Relapse from the dormant liver stages, which has been reported in US patients [Mace, 2017; Mace, 2018], undoubtedly contributes to this burden of disease in the individual patient, and also to the onward transmission of the infection. Patient compliance with a full (14 day) course of PQ, as the current standard of care, is typically incomplete, and this is associated with significantly diminished effectiveness, and hence persistent infection. There is a clear unmet need for a simple regimen that provides radical cure and offers US prescribers a viable alternative to PQ.

The Phase 2b/3 program has demonstrated high efficacy for TQ, even in the face of likely re-infections during the 6-month follow-up. These studies demonstrated an appropriate safety profile throughout the 6-month follow-up, that supports use in this indication, and the risks of hemolysis in G6PD deficiency can be safely managed by testing prior to treatment. Identified potential risks are described in proposed labeling subject to FDA review, and methods for active surveillance (enhanced pharmacovigilance) for the US and in endemic countries, are currently being developed, under consultation with the FDA and the WHO ‘Smart Safety Surveillance’ initiative.

Based on the data from studies of 300 mg single dose TQ, the benefit:risk for the radical cure of *P. vivax* malaria in adults and adolescents ≥16 years of age with G6PD levels ≥70% of normal is favorable.

1.6. Conclusion

TQ would provide a new treatment option for the radical cure of *P. vivax* malaria. The safety profile of TQ 300 mg single dose is acceptable and broadly similar to that of PQ 15 mg for 14 days. Coupled with high efficacy, and a very simple and convenient dosing regimen, TQ would be an important and significant new tool in the treatment of *P. vivax* malaria for US patients, as well as addressing the high global burden of this disease.

2. INTRODUCTION AND BACKGROUND

2.1. Current Therapies for Treatment of *P. vivax* malaria

Historically, a variety of drugs of diverse structures and mechanisms of action have been utilized in the treatment of malaria species (Table 7), including treatments for both active infection and prophylaxis.

Table 7 Chemical Classification of Antimalarial Drugs

Class	Drugs
4-Aminoquinolines	Chloroquine, amodiaquine, hydroxychloroquine
8-Aminoquinoline	Primaquine, tafenoquine, pamaquine, pentaquine
Quinoline-containing cinchona alkaloids	Quinine, quinidine
4-quinolinemethanols	Mefloquine
Phenanthrene methanol	Halofantrine, lumefantrine
Biguanides	Proguanil, chlorproguanil
Diaminopyrimidines	Pyrimethamine
Sulfonamides	Sulfalene, sulfadoxine, dapsone
Antibiotics	Tetracycline, doxycycline, arithromycin
Hydroxynaphthoquinones	Atovaquone
Artemisinin derivatives	Artemisin, artesunate, artemether, arteether

Source: [Bitta, 2017; Nqoro, 2017; Staines, 2012]

Any effective *P. vivax* treatment regimen needs to not only treat the blood stage infection causing symptoms, but also to remove the hypnozoite burden in the liver. Currently, only the 8-aminoquinolines, like PQ and TQ, can accomplish this (Figure 3). Using these drugs in combination with standard anti-malarial drugs (such as CQ or ACT) is called 'radical cure', since both the blood and liver stages of *P. vivax* are then eliminated.

Figure 3 P. vivax Malaria Treatment Options Adapted from CDC

Option	Blood Stage Treatment	Liver Stage Treatment
1st	**Chloroquine (x 3 days)**	**Primaquine phosphate (x 14 days)**
2nd	Atovaquone-proguanil **or** artemether-lumefantrine	
3rd	Quinine sulfate combinations (+ doxycycline, tetracycline, or clindamycin)	
4th	Mefloquine	

TQ and PQ are both 8-aminoquinolines with a potential to cause drug-induced hemolysis in patients with a deficiency in G6PD enzyme activity, a condition which is sex-linked. Patients with G6PD deficiency must therefore be excluded from taking TQ or PQ. The estimated prevalence of G6PD deficiency in the US population is 4-7% [Nkhoma, 2009]. The prevalence of G6PD deficiency is higher in many malaria endemic areas, because this genetic defect appears to offer some protection against malaria infection [Howes, 2013]. The co-incidence of malaria and this enzyme deficiency is therefore common and highly relevant clinically.

The distribution of G6PD enzyme activity in males is bimodal and individuals are either normal or deficient, since they carry only one copy of the G6PD gene. Females carry two copies of the gene, and can therefore be heterozygous for G6PD deficiency.

There are more than >180 known G6PD gene alleles [Luzzatto, 2016], and as a consequence genetic testing to identify G6PD-deficient subjects is at present not routinely performed. Instead, males hemizygous for G6PD deficiency and females homozygous for G6PD deficiency are readily identified by qualitative enzymatic tests such as the fluorescent spot test, and therefore readily excluded from treatment with drugs that cause hemolysis.

Females who are heterozygous for G6PD deficiency have varying levels of X-chromosome inactivation, resulting in a spectrum of G6PD enzyme activity ranging from fully deficient to, intermediate levels of deficiency through to normal levels of enzyme activity. The difference in G6PD activity is at a cellular level, with individual cells being either deficient or normal [Shah, 2012]. Qualitative tests such as the fluorescent spot test are unable to reliably identify heterozygous females with intermediate levels of G6PD deficiency [Baird, 2015]. In the US high quality quantitative laboratory testing for G6PD deficiency is readily available.

The long half-life of TQ (about 15 days compared with 4 9 hours for PQ) means that treatment once administered cannot be withdrawn, making it imperative that patients with G6PD deficiency are not prescribed TQ [Rajapakse, 2015]. However, the shorter half-life of PQ does not improve the benefit-risk calculation as much as one might assume,

because with drug-induced hemolysis secondary to PQ, Hb continues to decline for 3 to 4 days after withdrawal of PQ [Hodgkinson, 1961; George, 1967; Charoenlarp, 1972].

2.2. Clinical Development Program and Key Studies Contributing Efficacy and Safety Data

The primary studies were based on ex-US sites for recruitment and observation of relapse because there is no endemic malaria in the US, and the generally shorter time to relapse in tropical regions. However, there is no reason to expect *P. vivax* disease in endemic region patients to differ from US patients who contract malaria due to travel or occupational exposure. More than 400 healthy volunteers have been dosed with TQ in clinical pharmacology studies at study sites in the US and no clinically relevant differences in systemic exposure (AUC) have been observed for TQ in US subjects compared to those enrolled in the Phase 2b/3 program.

GSK and FDA agreed a subset of 13 studies that directly supported the *P. vivax* radical cure program (Table 8). Overall, 33 clinical studies of TQ have been completed. Clinical studies include Phase 1, 2, and 3 studies, single and multiple oral dose studies, studies in fasted and non-fasted subjects, bioavailability studies for different TQ formulations, drug-drug interaction studies, malaria challenge studies, malaria prophylaxis studies, and *P. vivax* malaria treatment studies (i.e., for radical cure, defined as prevention of relapse) (Appendix Section 9.7).

Table 8 Studies Directly Supporting TQ in the *P. vivax* Radical Cure Program

Study	Description of Study
TAF112582 Part 1	Phase IIb dose finding study in patients with *P. vivax* malaria
TAF112582 Part 2	Pivotal Phase III efficacy study in patients with *P. vivax* malaria
TAF116564	Phase III safety study in patients with *P. vivax* malaria
SB252263/022	Phase I Food effect study in healthy volunteers
TAF114582	Phase I Thorough QT study in healthy volunteers
201807	Phase I Ophthalmic safety study in healthy volunteers
SB252263/015	Phase I Drug-drug interaction study with desipramine in healthy volunteers
SB252263/040	Phase I Drug-drug interaction study with midazolam, flubiprofen and caffeine in healthy volunteers
TAF106491	Phase I Drug-drug interaction study with chloroquine in healthy volunteers
200951	Phase I Drug-drug interaction study with artemether-lumefantrine, and dihydroartemisinin-piperaquine tetraphosphate in healthy volunteers
TAF110027	Phase I dose escalation study in healthy volunteers and G6PD deficient healthy volunteers
201780	Phase I study in healthy volunteers to determine the effects of tablet aging (dissolution profiles) on the PK of TQ
TAF115226	Non-interventional study in healthy volunteers to establish site level normal ranges for G6PD enzyme activity

The primary evidence for the clinical efficacy and safety of 300 mg single dose TQ for radical cure of *P. vivax* malaria is provided by 3 randomized, double-blind studies (hereafter referred to as the primary studies) (Table 1): 582 Part 1 (Phase 2b), 582 Part 2 (pivotal Phase 3), and 564 (Phase 3). In all 3 primary studies, 300 mg single dose TQ was co-administered with CQ (Days 1 to 3) (TQ+CQ) and subjects treated with PQ 15 mg once daily for 14 days also received CQ (Days 1 to 3) (PQ+CQ). Altogether, a total of 483 subjects with *P. vivax* malaria have been exposed to TQ+CQ in the 3 primary studies.

In addition to the safety data from the primary studies, specific safety results from 2 individual studies in healthy volunteers, the study assessing ophthalmic safety and the definitive study of cardiac safety, provide clinically important safety observations to the regulatory submission under review:

- **Study 201807:** Ophthalmic safety data were collected across several studies prior to the launch of the primary studies in *P. vivax* subjects (SB252263/033, SB252263/057, SB252263/058 and TAF106491), as well as in the Phase 2b and Phase 3 studies. Study 201807 was a definitive ophthalmic safety study based on regulatory agency guidance.
- **Study TAF114582:** Similarly, while electrocardiogram (ECG) data were evaluated across multiple studies, including the primary studies, Study TAF114582 is considered the definitive study of cardiac safety. The primary endpoint was QT duration corrected for heart rate by Fridericia's formula (QTcF).

Safety data from the 3 primary studies of TQ for the radical cure of *P. vivax* malaria were pooled, as agreed with US FDA, to address the primary objectives (Table 9). The principal pooled data for assessing TQ+CQ compared with CQ alone includes Parts 1 and 2 of TAF112582 (PC grouping). The grouping that includes all 3 primary studies provides further evidence for TQ+CQ in *P. vivax* malaria compared with the current standard of care, PQ+CQ (AP grouping). In addition, a comprehensive evaluation of safety across the diverse TQ development program is supported by pooled safety data from different dosing regimens and populations, including an All Studies grouping with an All TQ group.

Table 9 Pooled Groupings for Analysis of Safety Data

Grouping label	Studies included	Subjects
All Studies	26 completed studies with available safety datasets[a]	All treated
All Primary Studies (AP)	582 Part 2, 582 Part 1 (CQ alone, 300 mg TQ), 564	*P. vivax*-infected
Placebo-controlled Studies (PC)	582 Part 2, 582 Part 1 (CQ alone, 300 mg TQ)	*P. vivax*-infected

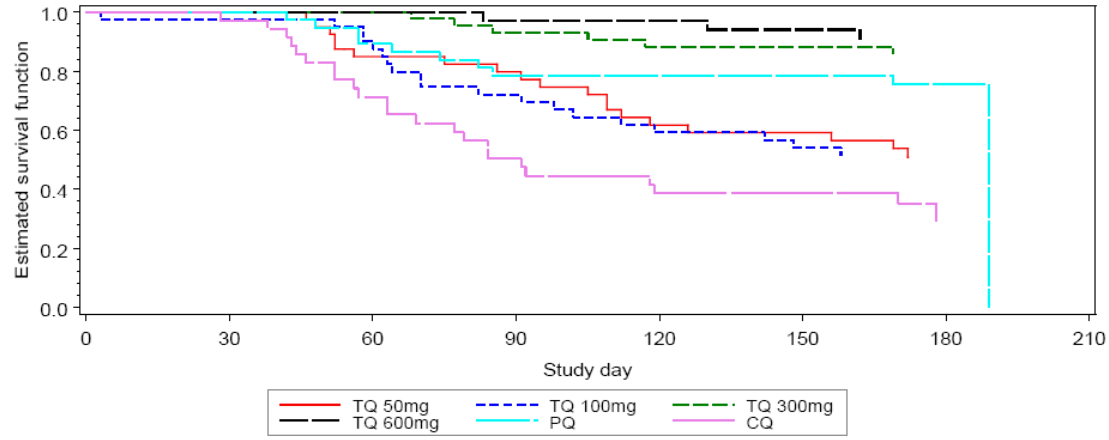
a. Data from studies SB252263/003, 036, 050, 051, 052, 053 and 054 have been excluded from the pooled groupings; Interim data from Study 201807 included.

2.3. Rationale for 300 mg Single Dose TQ Treatment

TQ 300 mg is an effective single-dose treatment for the radical cure of *P. vivax*. The simple dosing regimen is anticipated to provide high treatment compliance, even in the real-world setting, resulting in improved individual and public health outcomes.

Study 582 Part 1 was a Phase 2b dose-ranging study used to define the optimal dose for Phase 3. Doses ranging from 50 mg to 600 mg were chosen for Study 582 Part 1 in order to minimize risk to G6PD-deficient individuals with moderate deficiency, while optimizing the chance of identifying an efficacious dose. Of the 4 TQ doses studied in Part 1, 300 mg and 600 mg TQ+CQ met the efficacy criteria for selection to Part 2 (statistically significant difference compared to CQ alone ($p \leq 0.05$).

Figure 4 Survival Curves for Time to P. vivax Relapse in TAF112582 Part 1 (ITT Population)



Number of subjects at risk during the interval

TQ 50mg	40	33	31	24	22	6
TQ 100mg	39	36	28	23	21	5
TQ 300mg	43	43	40	37	37	15
TQ 600mg	36	36	33	32	30	9
PQ	37	33	28	28	28	10
CQ	34	24	17	13	13	5

A categorical and regression tree (CART) analysis identified TQ exposure (AUC) of 56.4 µg.hr/mL as a breakpoint exposure threshold that was a significant predictor of relapse outcome. The initial population PK model predicted that 93% of subjects were predicted to have an AUC value exceeding the CART-derived breakpoint of 56.4 µg.h/mL with the 300 mg TQ dose (Section 4.5.3).

Criteria for an acceptable safety profile were applied considering all safety data. No new safety concerns were identified at any of the TQ dose levels in Study 582 Part 1. However, based on the lack of evidence of any increase in efficacy between 300 mg and 600 mg TQ, the 300 mg dose was selected for evaluation in the Phase 3 studies.

In addition, the TQ development program has established that excluding patients with G6PD activity <70% is effective at preventing clinically significant drug-induced

hemolysis, and the safety of TQ dosing is supported by a well-defined G6PD enzyme activity cut-off. In ICH regions, existing quantitative laboratory diagnostics already have this capability [Trinity Biotech, 2012].

3. SUMMARY OF NON-CLINICAL STUDIES

Mechanism of Action

TQ is being developed for radical cure of *P. vivax* malaria infections, however, the exact antimalarial mechanism of action of TQ has not been identified. Several possible mechanisms of action have been postulated for TQ and other related 8-aminoquinolines in relation to their activity against the parasite liver stage hypnozoite. The 4-amino-1-methylbutyl side chain has been shown to generate superoxides, which may contribute to the activity of this drug class against exoerythrocytic parasites. TQ has been reported to inhibit hematin polymerization, which may contribute to its schizonticidal activity, although this effect has not been demonstrated for PQ. Sporogony of *P. berghei* was shown to be interrupted by TQ with inhibition of oocyst production and development, and decreased sporozoite release and invasion of mosquito salivary glands. Finally, treatment with the 8-aminoquinolines may result in mitochondrial dysfunction and alteration of intracellular membrane structures in both erythrocytic and exoerythrocytic stages of this parasite [Crockett, 2007]. To date, no molecular target has been identified as responsible for TQ activity. Co-administration with another blood schizonticide (initially CQ) will be required for treatment of *P. vivax* malaria since the combination targets with high efficacy both blood and liver stages of infection.

Resistance

The probability of pre-existing resistance to TQ is low. Multi-drug resistant strains of *P. falciparum* were susceptible to TQ in vitro. TQ exhibited equivalent activity to primaquine against CQ-susceptible strains; however, CQ-resistant and other multi-drug (mefloquine, pyrimethamine) resistant strains were more susceptible to TQ. In primate models, blood stages of CQ-resistant *P. vivax* were successfully treated with TQ [Vennerstrom, 1999].

There is no indication of *in vitro* or *in vivo* resistance of *Plasmodium* liver stages to TQ. However, some observations have been reported in the literature with respect to resistance development to TQ by human malaria parasite blood stages [Kaewpruk, 2016; Manzano, 2011; Peters, 2003]. However, as variations in measured IC50s were <2-fold and because acquisition of resistance can largely be suppressed by combination of CQ, any clinical resistance is unlikely to occur.

However, *in vitro* and *in vivo* models of *P. vivax* relapse are poorly developed, limiting the definition of mechanism of action and study of hypnozoite resistance.

Safety Pharmacology

There were no findings in safety pharmacology studies on respiratory, cardiovascular or neurobehavioral function (including motor activity) that would indicate an unacceptable risk for single dose oral administration of TQ.

Toxicology

Repeat Exposure

TQ has been evaluated in repeat dose toxicity studies of up to 13, 26 and 52-week in duration in mice, rats and dogs and a 4-day PK study in monkeys. Principal findings, following repeat dosing, were mortality and morbidity, hematological (e.g., decreased Hb, increased methemoglobin), pulmonary (e.g., increased numbers of foamy macrophages and the presence of eosinophilic material in alveoli), hepatic (e.g., increased liver weight, subacute inflammation), and renal toxicity (e.g., renal tubular lesions). The majority of the hematologic, hepatic, pulmonary and renal affects were both dose- and duration-dependent, and reversible upon cessation of treatment.

Nervous System

A series of studies to assess the potential CNS effects of TQ in nonclinical species have been conducted including; histopathological assessments in numerous single and repeat dose studies (mice, rats and dogs), investigation of the tissue/organ distribution of TQ in rats, and detailed assessments of both neurobehavioral function and neurohistopathology in both single and repeat dose studies in rats.

There was no evidence that TQ administration was associated with changes in brain weight, gross macroscopic abnormalities of the brain or abnormal microscopic histopathological changes in the brain in the repeat dose toxicology studies conducted with mice, rats and dogs of up to 13, 26, and 52 weeks in duration, respectively, and no evidence of any abnormal non-neoplastic microscopic histopathological changes in the brain in the carcinogenicity studies in mice and rats.

The distribution of TQ was investigated in male rats in studies following a single oral dose of [^{14}C]-TQ up to 25 mg/kg, and in male and female rats as part of a quantitative whole-body autoradiography (QWBA) study following a single oral dose of [^{14}C]-TQ at 0.5 mg/kg.

Although TQ drug-related material (DRM) penetrates the blood-brain barrier in rats, brain concentrations of radiolabelled DRM were low, both in term of absolute levels (<1% dose), and levels relative to concentrations in other body tissues/organs. In rat tissue, plasma concentration ratio for TQ levels in the brain was amongst the lowest among all body tissues assessed with QWBA.

In a rat, single dose neurobehavioral and CNS-pathology study no test article related CNS-pathological effects were observed. There was no effect on functional observation battery, the only observation was a test article related attenuation in spontaneous locomotor activity. Following consultation with the FDA, neurobehavioral evaluations were included in the repeat dose juvenile rat toxicology study. In this repeat dose study,

no test article related neurobehavioral or CNS-pathological effects were observed in juvenile rats.

Neurobehavioral alterations and /or CNS-pathology with certain quinoline anti-malarials have been variously observed in mice, rats, dogs and/or rhesus monkeys [Dow 2006, Lee 1981, Korte 1979, Korte 1982, Schmidt 1948, Schmidt 1949, Schmidt 1950, Schmidt 1951]. TQ has been tested in species (mice, rats and dogs) that have been shown to be sensitive for these changes; the effect of TQ on the CNS of the monkey has not been examined in a toxicology study.

In summary, TQ does not induce neurotoxicity in single and repeat dose toxicology studies in mice, rats and dogs, or specific neurobehavioral studies in rats at exposures that are comparable to or in excess of those seen at the recommended treatment dose for patients.

Carcinogenicity
TQ was not genotoxic in a standard battery of vitro or in vivo assays. TQ was not carcinogenic in mice but was carcinogenic in rats (following exposure for 2 years) inducing an increase in the incidence of renal cell tumors and hyperplasia in males.

Teratogenicity
In a rat fertility study in the presence of toxicity, there was reduced fertility in female rats. No developmental toxicity was seen in rats or rabbits. In a pre- and postnatal development study in rats, in the presence of toxicity, decreased offspring body weight gain (not observed at maturity) was associated with a delay in eye opening and decrease in motor activity.

4. OVERVIEW OF CLINICAL PHARMACOLOGY

4.1. Clinical Pharmacology Summary

Overall, the PK, PD, PK/PD relationships in patient populations, and drug interaction profiles support 300 mg single dose TQ therapy for the radical cure of *P. vivax*.

4.1.1. Pharmacokinetics

- TQ is slowly absorbed following oral administration to humans with maximum concentrations reached approximately 12-15 h post dose.
- TQ should be administered with food in order to improve systemic absorption and minimize GI side effects.
- PK is linear with dose proportional increase in systemic exposures up to 1200 mg.
- TQ exhibits a biphasic concentration-time profile with high volume of distribution and long elimination half-life of 15 days on average.
- Whole blood TQ levels are higher than plasma concentrations reflecting the preferential partitioning of drug in erythrocytes.

- No dose adjustment needed based on age or race.
- Dose adjustments in patients with hepatic or renal impairment are unlikely to be required based on the available nonclinical and clinical data, and as TQ is administered as a single dose.

4.1.2. Drug-Drug Interactions

- TQ does not have any clinically relevant impact on cytochrome P450 (CYP) 2D6, CYP3A4, CYP2C8, CYP2C9, CYP1A2 substrates.
- TQ can be administered without dose adjustment with other commonly prescribed anti-malarial drugs such as CQ and ACTs, namely dihydroartemisinin/piperaquine (DHA/PQP) or artemether/lumefantrine (AL).
- TQ inhibited the *in vitro* transport of [^{14}C]-metformin via human organic cation transporter (OCT)2, multidrug and toxic compound extrusion protein (MATE)1 and MATE2-K. There may be a small risk of lactic acidosis in patients due to increased metformin exposure secondary to blockade of these transporters. Therefore, TQ should be used with caution with metformin.
- Drugs with small therapeutic index that are substrates of the renal transporters OCT2 and MATEs should not be co-administered regardless of renal function.

4.1.3. Pharmacodynamics

- TQ has no clinically significant effect on QT at clinically relevant doses of 300 and 600 mg compared to placebo. The maximum effect on QTcF prolongation with the supratherapeutic dose of TQ 1200 mg compared to placebo was within the safety margin of 10 msec set out in the regulatory guidelines.
- TQ demonstrates dose-dependent Hb declines in heterozygous G6PD deficient subjects with increasing doses of TQ. The highest median Hb declines observed in G6PD heterozygous females with intermediate levels of deficiency (G6PD activity >40% <70%) at the TQ 300mg dose was comparable to PQ (15mg daily for 14 days).
- No clinically significant Hb declines have been reported in subjects with G6PD ≥70% normal.

4.1.4. PK/PD Relationships

The exposure-response analysis identified a systemic exposure threshold AUC (56.4 μg.h/mL) above which the recurrence-free rate at the end of 6 months was 89% as compared to when AUC <56.4 μg.h/mL with a recurrence-free rate of 48%.

The 300 mg dose is expected to achieve systemic exposures higher than this threshold in the majority of the patients.

4.2. Absorption, Distribution, Metabolism, and Excretion

4.2.1. Absorption and Distribution

TQ is slowly absorbed in humans following oral administration with median t_{max} of 12-15 hours. The slow absorption is consistent with nonclinical data where t_{max} was generally >6 hours after single or repeat oral dosing in rat, dog and monkey. Systemic exposure generally increased proportionately with dose and substantial accumulation of TQ is observed (up to 10x) on repeat dosing consistent with its long half-life.

Dosing TQ with food leads to increased exposure with average increases of 41% and 31% in AUC and Cmax respectively. Administering with food leads to better tolerability and fewer incidences of GI disturbances. TQ is recommended to be taken with food to increase systemic absorption and minimize GI side effects consistent with the approach employed in all patient studies. TQ exhibits linear PK with approximate dose proportional increases in exposure between 36 mg to 1200 mg oral doses.

TQ exhibits very high plasma protein binding in nonclinical species and humans (>99.5%) with higher blood concentrations as compared to plasma levels. This reflects preferential partitioning of the drug in the erythrocytes. TQ has moderate absorptive membrane permeability *in vitro* and is widely distributed in both nonclinical species and human with a large apparent oral volume of distribution (>1500 L) as identified from the population PK analysis.

Following dosing of [^{14}C]-TQ to rats, concentrations of radioactivity peaked between 12 and 24 h with the highest concentrations observed in the GI tract, adrenal cortex, pituitary, ovary, liver, lungs, Harderian gland, spleen and small intestine mucosa. In contrast, the lowest levels of radioactivity were associated with the central nervous system (including brain), white fat and blood. Tissue levels of radioactivity declined slowly and at 240 h after dosing, most tissues still contained quantifiable levels of radioactivity.

4.2.2. Metabolism

Negligible metabolism of TQ was evident in multiple *in vitro* incubations performed (nonclinical and /or human hepatocytes, microsomes or recombinant drug metabolizing enzymes [CYPs and monoamine oxidases (MAOs)]. All drug-related components observed were detected in sample and control incubations, and definitive investigations highlighted that the DRM present, other than TQ, was generated via visible light instability and not directly formed via metabolism. In humans (including both G6PD normal and G6PD deficient females), following administration of 300 mg single oral doses of TQ, DRM identified in blood and plasma was almost exclusively in the form of unchanged TQ. All other circulating components observed were minor, the most notable being a carboxylic acid metabolite, which represented ≤6% of the parent concentration. Drug-related components were excreted very slowly in human urine, primarily as products of O-demethylation, oxidation, O-dearylation and glucuronide conjugation all of which had been previously seen in both rat and dog. It was noted that within in vivo

studies it was not possible to determine whether several of the observed drug-related components were formed by ex vivo degradation and/or in vivo metabolism.

4.2.3. Excretion

Definitive elimination data in humans has not been generated. The slow absorption and long elimination half-life makes an ADME study infeasible in clinic. Therefore, no clinical ADME study has been conducted with [^{14}C]-TQ. Nonetheless, some data has been obtained showing very slow excretion via the urine (as determined over a 6-day collection period) and renal elimination of unchanged TQ in humans was a very minor route. Overall, TQ is slowly eliminated with an average terminal half-life of approximately 15 days. The population PK analysis also identified a low apparent oral clearance of approximately 3 L/hr.

In nonclinical species following administration of [^{14}C] TQ to rats, dogs and monkeys, feces was the predominant route of elimination accounting for between 35% and 67% of the administered dose, consisting primarily of unabsorbed TQ. Biliary secretion in the rat and dog was low and accounted for approximately 5% and 20% of the administered oral dose, respectively (absorbed drug being eliminated as metabolites and unchanged TQ). Urinary excretion was responsible for the elimination of up to 21% of the administered radiolabelled dose in non-cannulated rats, dogs and monkeys and was largely in the form of drug-related components (in vivo metabolites and/or ex vivo degradants). Slow protracted excretion of radioactivity was noted beyond 10-days post dose in these studies (in tissues/carcass where measured).

4.3. PK Analysis of TQ Exposure

4.3.1. Summary of TQ PK parameters

The PK of TQ can be characterized adequately based on dense serial PK sampling in clinical studies with healthy subjects (Table 10).

Table 10 PK Parameters from Healthy Volunteer Studies

Population	Dose	Formulation	Data Source	Cmax (ng/mL)	$AUC_{0\text{-}inf}$ (ug.hr/mL)	Mean $T_{1/2}$ (days)
Healthy	200 mg (fasted)	Capsule	SB252263/022	113	46.5	15.4
	200 mg (fed)	Capsule	SB252263/022	152	66.5	15.5
	300 mg (fed)	Tablet	200951	200	97.2	15.8
	300 mg (fed)	Tablet	201780	224	97.1	15.1

Note: TQ administered alone as a single dose regimen
AUC and Cmax – geometric means; 201780 - geometric LS means
All studies were conducted in the US or EU.

The single dose radical cure for *P. vivax* clinical studies employed sparse PK sampling (Table 11). The exposure in these patient populations was primarily characterized with a

population PK analysis. The PK data show similar PK profiles for healthy volunteers, including subjects from the US, and *P. vivax*-infected subjects from endemic regions.

Table 11 PK Parameters in the Patient Population from Population PK Analysis

Population	Dose	Study/Data Source	Formulation	Cmax (ng/mL)	$AUC_{0\text{-}60days}$ (ug.hr/mL)
Patients with *P vivax* malaria infection	300 mg	TAF112582 Part 1	Capsule	335 (188 – 549)	93.6 (62.3 – 152)
	300 mg	TAF112582 Part 2	Tablet	330 (193 – 505)	104 (61.1 – 152)
	300 mg	TAF116564	Tablet	302 (179 – 428)	96 (62.3 – 135)

Note: Based on the final population PK model post hoc estimates; AUC and Cmax - Median (90% prediction intervals)

4.3.2. PK in Special Populations

The PK of TQ in subjects with G6PD deficiency was assessed in a safety study (TAF110027). The study characterized TQ exposure in 24 G6PD-normal and 27 G6PD-genetically heterozygous females administered single doses ranging from 100 to 300 mg. There was no difference in exposure across subjects with or without G6PD deficiency.

TQ has not been studied in patients with hepatic impairment. Dose adjustments in patients with hepatic impairment are unlikely to be required as TQ is administered as a single dose.

Similarly, TQ has not been studied in patients with renal impairment. Dose adjustments in patients with renal impairment are unlikely to be required as TQ is administered as a single dose.

4.3.3. Population PK

Population PK analysis was conducted using TQ exposure data pooled from multiple studies ranging from Phase 1 with healthy volunteers through Phase 3 with *P. vivax*-infected subjects. The analysis demonstrated a lack of clinically relevant impact of age, gender, ethnicity or disease status on TQ PK. No dose adjustment is deemed necessary based on any of these factors.

4.4. Drug-Drug Interaction

4.4.1. Effect of TQ on the PK of Other Agents

In vitro, in human liver microsomes, TQ inhibited CYP1A2, CYP2A6, CYP2C8, CYP2C9 and CYP3A4 enzymes with Ki values ranging from 2 to 10 μM, with no evidence of metabolism dependent inhibition. Nonetheless, subsequent clinical drug-drug interaction studies demonstrated no clinically relevant inhibition of these CYP enzymes. No clinically significant changes were observed in concentrations of desipramine (CYP2D6 substrate), midazolam (CYP3A4 substrate), or flurbiprofen

(CYP2C9 substrate) when these drugs were either co-administered with TQ or administered alone.

The *in vivo* data from studies evaluating the impact of TQ on co-administration with other anti-malarial pharmacotherapy such as CQ and ACTs, i.e. DHA/PQP or AL (Table 12) demonstrated that no dose adjustment is deemed necessary for CQ or ACTs, as TQ has no clinically relevant impact on their systemic exposure [Miller, 2013; Green, 2016].

TQ inhibited the *in vitro* transport of [14C]-metformin via human OCT2 and MATE. This may be potentially correlated to the mild and transient serum creatinine increases observed in clinical studies across a range of doses and regimens due to inhibition of tubular transport. Risk assessments based on systemic concentrations (unbound Cmax) of TQ at therapeutic doses, compared with the in vitro IC50 values indicated a potential, but low, drug interaction risk with OCT2 and MATE substrates.

There may be a small risk of lactic acidosis in patients due to increased metformin exposure secondary to blockade of these transporters. Therefore, language indicating TQ should be used with caution with metformin is included in proposed labeling subject to FDA review. Drugs with narrow therapeutic index that are substrates of the renal transporters OCT2 and MATEs should not be co-administered regardless of renal function (e.g. phenformin, buformin, dofetilide, procainamide and pilsicainide).

The risk of clinically relevant drug interactions with other drug transporter substrates is considered limited based on the single dose regimen of TQ. Inhibition of PgP, BCRP, and OATP has not been studied.

Table 12 Effect of TQ on Concomitant Medications

Concomitant Drug	Concom Drug Dose (mg)[a]	TQ Dose (mg)	N[d]	Geometric Mean Ratio (90% CI) Co-ad drug+TQ/co-ad drug alone		Study	Conclusion
				AUC[c]	Cmax		
Desipramine	100	400 (x 3 day)	34	0.94 (0.89, 1.00[e])	1.04 (0.98, 1.10)	SB252263/015	No dose adjustment for CYP2D6 substrates
Midazolam	5	400	N_{Cmax} =25 N_{AUC} = 22	0.88 (0.83, 0.94)	0.97 (0.83, 1.13)	SB252263/040	No dose adjustment for CYP3A4 substrates
Flurbiprofen	50	400	24	1.13 (1.09, 1.16)	0.98 (0.91, 1.04)	SB252263/040	No dose adjustment for CYP2C9 substrates
Caffeine	200	400	24	1.01 (0.98, 1.05)	0.95 (0.89, 1.01)	SB252263/040	No dose adjustment for CYP1A2 substrates
Chloroquine[b]	1500	900	18	1.00 (0.84, 1.18)	Day2 – 0.89 (0.74, 1.08) Day3 – 1.04 (0.86, 1.25)	TAF106491	No CQ dose adjustment
Dihydroartemisinin (DHA)[b]	320/40 for 3 days	300	$N_{DHA/PQP}$=23 $N_{DHA/PQP+Taf}$=24	1.00 (0.82, 1.24)	0.95 (0.75, 1.20)	200951	No DHA/PQP dose adjustment
Piperaquine (PQP)[b]	320/40 for 3 days	300	N_{AL}=22 N_{AL+Taf}=24	0.94 (0.81, 1.08)	0.91 (0.76, 1.08)	200951	
Artemether (A)[b]	120/20 at 0,8,24,36,48 and 60 hrs	300	N_{AL}=22 N_{AL+Taf}=24	1.03 (0.52, 2.04)	1.03 (0.71, 1.49)	200951	No AL dose adjustment
Lumefantrine (L)[b]	120/20 at 0,8,24,36,48 and 60 hrs	300	22	1.13 (0.87, 1.45)	1.08 (0.86, 1.36)	200951	

a. Unit dose given for DHA-PQP and AL; total dose given for CQ.
b. refer to individual study reports for all study design details including dosing and PK sampling schedule
c. reflects AUC0-inf, AUC0-tau or AUC0-t as appropriate. Refer to individual study reports
d. all studies are parallel-design

4.4.2. Effect of Other Agents on the PK of TQ and Dose Recommendations

In vitro hepatocyte or microsomal studies demonstrated no metabolic turnover of TQ. Furthermore, the potential for TQ to be a victim of drug interactions is considered low due to its very slow *in vivo* metabolism, extended excretion and the single dose regimen.

Although the P-glycoprotein (Pgp) substrate status of TQ could not be reliably determined, if it were assumed TQ was a Pgp substrate, there exists some potential for an interaction at the level of the GI tract which could, potentially, increase TQ systemic exposure if co-administered with strong Pgp inhibitor(s). The OATP substrate status of TQ has not been studied, but based on the rat QWBA data and the principles outlined in Mikkaichi et al [Mikkaichi, 2015] TQ is not considered to be an OATP substrate. Nonetheless, TQ has been safely administered at doses of 600 mg single dose and 1200 mg (administered as 400 mg once daily for 3 days) which is 2-4 times higher than the currently recommended 300 mg single dose for *P. vivax* radical cure. Collectively, the risk of any clinically significant drug transporter mediated interaction is considered to be very low.

Further clinical drug interaction studies demonstrated a minor increase in TQ C_{max} when TQ was co-administered with CQ with no significant effect on the overall exposure. Similarly, there was an increase in TQ C_{max} on co-administration with the DHA/PQP (Table 13). These changes in TQ exposure are not considered to be clinically relevant. There was no change in TQ exposure on co-administration with AL. TQ can be co-administered with other anti-malarial drugs such as CQ or ACTs without any dose adjustment.

Table 13 Effect of Concomitant Medications on TQ and Dose Recommendations

Concomitant Drug	Concom Drug Dose (mg)[a]	TAF Dose (mg)	N[d]	Geometric Mean Ratio (90% CI) Co-ad drug+TAF/co-ad drug alone		Study	TQ Dose Recommendation
				AUC[c]	Cmax		
Chloroquine[b]	1500	900	N_{Taf}=20 $N_{DTaf+Chloroq}$=18	0.98 (0.84, 1.14)	Day2 – 1.38 (1.17, 1.64) Day3 – 1.13 (0.96, 1.34)	TAF106491	No dose adjustment
Dihydroartemisinin/Piperaquine (DHA/PQP)[b]	320/40 for 3 days	300	24	1.12 (1.01, 1.26)	1.38 (1.25, 1.52)	200951	No dose adjustment
Artemether/Lumefantrine(AL)[b]	120/20 at 0,8,24,36, 48 and 60 hrs	300	24	1.05 (0.93, 1.20)	1.04 (0.95, 1.15)	200951	No dose adjustment

a. Unit dose given for DHA-PQP and AL; total dose given for CQ.
b. refer to individual study reports for all study design details including dosing and PK sampling schedule
c. reflects AUC0-inf
d. all studies are parallel-design

4.5. PD, PK-PD and Dosing Recommendations

4.5.1. Effect on Cardiac Repolarization

In a randomized, single blind, placebo controlled parallel-group study (TAF114582), 260 subjects received oral administration of either placebo, 400 mg moxifloxacin (active control), 300 mg, 600 mg or supratherapeutic 1200 mg doses of TQ. All doses were administered as single doses except the supratherapeutic TQ dose of 1200 mg administered as 400 mg once daily for three days. The clinically relevant 300 mg and 600 mg TQ doses demonstrated a lack of effect on QTcF prolongation. The maximum effect on QTcF at the supratherapeutic dose of 1200 mg compared to placebo was <10 msec and within the FDA E14 guidelines for lack of effect. The largest effects in this 1200 mg dose group were observed at 36 hours post final dose (mean 6.39 msec, 90% CI: 2.86, 9.92) and at 72 hours post final dose (mean 6.39 msec, 90% CI; 2.85, 9.94).

Co-administration of TQ with other antimalarial drugs such as CQ or ACTs such as DHA/PQ or AL did not show an additional effect from TQ on the QTcF interval prolongation as evidenced in clinical studies TAF106491 and 200951.

4.5.2. Hemolytic potential in G6PD Deficiency

In an open label, single dose, dose-escalation study (TAF110027), TQ (100, 200 and 300 mg doses) was administered to female healthy volunteers genetically normal or heterozygous for a mutation conferring G6PD deficiency (40 60% G6PD activity). The study also evaluated PQ 15 mg once daily × 14 days as a positive control.

In contrast to the G6PD normal subjects, there was a dose dependent decline in Hb in heterozygous G6PD-deficient subjects with intermediate levels of G6PD activity with increasing doses of TQ, although the PK for the 2 groups was similar (Section 4.3.2). The highest median Hb declines were observed in G6PD deficient females in the TQ 300 mg and PQ group. No subjects reported any major clinical symptoms relating to their observed Hb decline.

Similar median Hb decreases were observed in subjects heterozygous for a G6PD gene mutation and with >60% G6PD activity, compared to control subjects without the mutation, leading to a recommended cut-off of ≥70% G6PD activity for 300 mg single dose TQ treatment [Rueangweerayut, 2017].

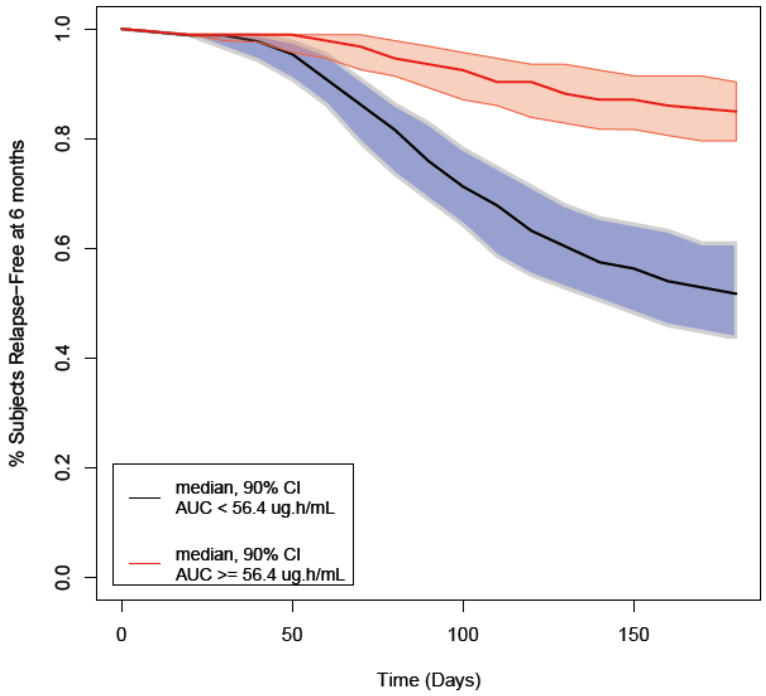
4.5.3. PK/PD relationship

TQ PK/PD relationship was conducted based on the TQ exposure (PK) and *P. vivax* malaria recurrence at the end of 6 months response (PD) data obtained from the dose ranging Phase 2b trial 582 Part 1. A categorical and regression tree (CART) analysis identified TQ exposure (AUC) of 56.4 µg.hr/mL as a breakpoint exposure threshold that was a significant predictor of relapse outcome. When AUC was ≥56.4 µg.h/mL, 89%

were recurrence-free at 6 months (72 success, 9 failure), whereas when AUC was <56.4 µg.h/mL, only 48% were recurrence-free at 6 months (40 success, 43 failure) (χ^2 test: p <0.001). Based on the time-to-relapse model simulations (Figure 5), the probability of being relapse-free at 6 months for subjects with an AUC above and below 56.4 µg.h/mL are:

- 85% (95% CI: 80% to 90%) in subjects with an AUC ≥56.4 µg.h/mL; and
- 52% (95% CI: 44% to 61%) in subjects with an AUC <56.4 µg.h/mL.

Figure 5 Probability of being Relapse-Free Below and Above the CART Analysis TQ Exposure Breakpoint



Dose based on PK/PD relationship

The initial population PK model predicted that 93% of subjects were predicted to have an AUC value exceeding the CART-derived breakpoint of 56.4 µg.h/mL with a 300 mg TQ dose, the dose which was evaluated in Phase 3 studies.

The 5th percentile of AUC across the two Phase 3 studies in the final population PK model is greater than the previously identified CART breakpoint exposure of 56.4 ug.hr/mL, providing most (>95%) subjects with exposures that have high likelihood of being relapse-free (Table 14). TQ efficacy has been clearly established in these Phase 3 studies. These data collectively support 300 mg single dose TQ for the radical cure of *P. vivax* malaria.

Table 14 Summary of TQ Exposures Obtained Using the Population PK Model

Dose	Study	Formulation	Cmax (ng/mL)	$AUC_{0\text{-}60days}$ (ug.hr/mL)
300mg	TAF112582 Part 2	Tablet	330 (193 – 505)	104 (61.1 – 152)
300mg	TAF116564	Tablet	302 (179 – 428)	96 (62.3 – 135)

Note: Based on the final population PK model post hoc estimates
AUC and Cmax - Median (90% prediction intervals)

5. OVERVIEW OF EFFICACY

The primary evidence for the clinical efficacy of TQ for the radical cure of *P. vivax* malaria is provided by one fully powered Phase 2b (582 Part 1) to confirm dose selection, and two Phase 3 studies (582 Part 2 and 564). The pivotal efficacy study was Study 582 Part 2 and supportive efficacy data came from Study 582 Part 1 and Study 564.

Based on the results from Study 582 Part 1, the 300 mg dose was selected for Phase 3. No clinically relevant additional benefit was seen with the 600 mg dose, and the hemolytic potential of the 300 mg dose was comparable to that of PQ 15 mg daily × 14 days + CQ treatment in G6PD-normal subjects.

Treatment with 300 mg single dose TQ, when co-administered with standard doses of CQ, resulted in a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 6 months relative to treatment with CQ alone in Study 582 Part 2. Similarly in the alternative logistic regression analysis, a larger proportion of subjects treated with TQ+CQ were recurrence-free during the first 6 months compared with CQ treatment alone and there was a clinically and statistically significant reduction in the odds of recurrence.

Analysis at 4 months follow-up, which reduced the complication of re-infections, also showed a higher recurrence-free rate for 300 mg single dose TQ+CQ compared to CQ alone.

Recurrence-free efficacy results at 6 months and at 4 months from Studies 582 Part 1 and 564 supported the results of the pivotal efficacy study.

Table 15 Recurrence-free Efficacy Results from the Primary Studies (mITT Population)

	582 Part 2			582 Part 1			TAF116564	
	CQ N=133	TQ+CQ N=260	PQ+CQ N=129	CQ N=54	TQ+CQ[e] N=57	PQ+CQ N=50	TQ+CQ N=166	PQ+CQ N=85
6 M Recurrence-free, n (%)	35 (26)	155 (60)	83 (64)	21 (39)	48 (84)	34 (68)	112 (67)	60 (71)
Estimate[c] at 6 M (95% CI)	27.7 (19.6,36.3)	62.4 (54.9,69.0)	69.6 (60.2,77.1)	37.5 (23,52)	89.2 (77,95)	77.3 (63,87)	72.7 (64.8,79.2)	75.1 (64.2,83.2)
6 M HR for recurrence (95% CI)	--	0.30 (0.22,0.40)	0.26 (0.18,0.39)	ND	ND	ND	0.98 (0.58,1.68)[b]	--
Missing=failure OR for 6 M recurrence (95% CI)	--	0.24 (0.15,0.38)[a]	0.20 (0.12,0.34)[a]	ND	ND	ND	1.14 (0.64,2.03[b]	--
4 M Recurrence-free[d], n (%)	47 (35)	177 (68)	90 (70)	24 (44)	51 (89)	34 (68)	127 (77)	63 (74)
Estimate[c] at 4 M (95% CI)	36.0 (26.8,45.4)	73.0 (66.0,78.9)	74.7 (65.7,81.6)	46.5 (32,60)	89.4 (75,96)	78.4 (64,88)	82.3 (74.9,87.7)	79.7 (68.9,87.1)

a. Compared to CQ alone
b. Compared to PQ+CQ
c. Kaplan-Meier estimate for recurrence-free efficacy rate
d. Based on 4 months FU
e. Results from the 300 mg TQ group

5.1. Study TAF112582 Part 2

5.1.1. Study Design for Study TAF112582 Part 2

The pivotal study in the TQ development program was Study 582 Part 2, a multi-center, double-blind, double-dummy, parallel-group, randomized, active- and placebo-controlled study with sites in Brazil, Peru, Ethiopia, Thailand, Cambodia and the Philippines.

In 582 Part 2, the null hypothesis for the primary endpoint was that the 6-month relapse-free efficacy rate was not different between the CQ+TQ and CQ alone treatment groups. A two-sided hypothesis test was performed at the 5% level.

Of note, it had initially been planned that TAF112582 Part 2 would comprise of two replicate and independently powered Phase 3 studies. After all the subjects were enrolled, centres were to be allocated to one of the two studies, based on the number of subjects. However, following the statistically significant TAF112582 Part 1 result, in consultation with the FDA, this plan was changed and all data in TAF112582 Part 2 was to be analysed together.

The primary comparison was made using a Cox's Proportional Hazards Model, adjusting for region, and utilized the microbiological intent-to-treat (mITT) population. The sample size assumptions for 582 Part 2 remained the same as in Part 1 (Section 5.2.1), resulting in >99% power for the primary comparison, based on a planned sample size of 300 subjects on TQ+CQ, and 150 on CQ. The larger sample size was required in order to ensure a sufficiently large safety database for the TQ *P. vivax* development program.

The PQ+CQ treatment arm was included as a benchmark, to help further interpret the TQ+CQ results. No formal comparison between the TQ+CQ and PQ+CQ treatment groups was planned.

Eligible subjects had a positive blood smear for *P. vivax* at entry with G6PD assay value of ≥70% of the site median. There was no stratification for baseline parasite count in Study 582 Part 2 (See Appendix Section 9.1). At least 600 subjects were planned to be randomized to 1 of 3 treatment groups, in a 1:2:1 ratio. Due to slow recruitment and in agreement with regulatory agencies, the target number of subjects recruited to the study was reduced from 600 subjects to 522 subjects, including 260 subjects in the TQ+CQ group.

All subjects were treated with CQ on Days 1 to 3 to treat the blood stage malaria infection, followed by their randomized treatment (300 mg single dose TQ, PQ for 14 days, or placebo [i.e., CQ only regimen]) (Table 16). All subjects received the same number of tablets/capsules for 15 days, according to the double-dummy study design.

Table 16 Treatment Groups in Study 582 Part 2

Treatment Groups		N
1	CQ only regimen (Days 1 to 3)	133
2	CQ (600 mg on Days 1 to 3) + TQ 300 mg single dose (Day 1 or 2)	260
3	CQ (600 mg on Days 1 to 3) + PQ 15 mg once daily for 14 days (Days 2 to 15)	129

It should be noted that although the endpoint measure was described as 'relapse' in the study protocols, it was in fact a composite of relapse (i.e., re-appearance of the parasite arising from untreated hypnozoite infection), and new infection. For *P. vivax* infections, it is not possible to distinguish relapses from new infections, even using genotyping; therefore, the term 'recurrence' was used throughout the Phase 3 clinical study reports (CSRs) to more accurately reflect the efficacy assessments reported in the studies.

The key efficacy studies were performed in regions endemic for *P. vivax* malaria. There was, therefore, a continuous risk of infection throughout the follow-up period of the studies and an expectation that re-infection would be similar in the treatment groups. Study sites were selected on the basis of historical evidence that time to relapse was short (approximately 3 to 6 weeks) [Battle, 2014]. Given the inability to distinguish relapse from new infection, a key secondary endpoint in Study 582 Part 2 and Study 564 was recurrence-free efficacy over 4-months post-dosing at which point there would have been

less opportunity for new infection to occur. The data up to and including the 4-month follow up visit were used in this analysis.

The primary objective of Study 582 Part 2 (pivotal Phase 3 efficacy study) was to determine the efficacy of TQ as a radical cure for *P. vivax* malaria, relative to a CQ-only control (a placebo-like arm, because CQ has no effect on radical cure). The primary comparison was the difference in recurrence-free efficacy between 300 mg TQ+CQ and CQ alone over 6 months using the mITT population. The 6-month primary endpoint was agreed between GSK and the US FDA at a Type C meeting in March 2010.

The primary survival analysis and alternative logistic regression analysis were performed on this endpoint and the conclusions from both analyses of the data were consistent:

- **Survival analysis** (Kaplan-Meier and Cox proportional hazards) using time to recurrence as defined in the WHO Protocol on Assessment and Monitoring of Antimalarial Drug Efficacy [WHO, 2003]. This was defined as the primary analysis in the Reporting and Analysis Plan (RAP).
- **Categorical analysis** using proportions (logistic regression) after imputation of treatment failure for those who were not confirmed recurrence-free at the end of the 6-month follow up or who took an anti-malarial medication other than study medication. This analysis was implemented for Study 582 Part 2 following discussion with the US FDA at the End of Phase 2 meeting in 2013, and is not available for Study 582 Part 1.

Safety assessments included monitoring of AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. Additional ophthalmic assessments were performed at selected sites. Key safety endpoints of interest were as follows:

- Clinically relevant hemolysis leading to decreases in Hb/hematocrit or complications thereof (required transfusions, acute renal failure)
- Changes in methemoglobin
- GI tolerability - incidence of abdominal pain, heartburn, diarrhea, constipation, nausea, and vomiting
- Ophthalmic safety - incidence of corneal deposits and retinal and visual field abnormalities.

5.1.2. Study Population Results in 582 Part 2

Although *P. vivax*-infected US subjects were not included in the studies, US patients would be most likely to acquire the infections from travel to, or occupational exposure in, endemic areas, and the disease would be expected to have similar characteristics in those patients.

5.1.2.1. Demographic Characteristics

In the pivotal efficacy study, demographic characteristics were well-balanced across the treatment groups. A higher percentage of males than females were enrolled, which represents the epidemiology of the disease.

Table 17 Demographic Characteristics in Study 582 Part 2 (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Age (years)				
Mean	35.3	35.0	34.7	35.0
Standard deviation	14.23	14.39	14.26	14.29
Sex, n (%)				
Male	97 (73)	196 (75)	99 (77)	392 (75)
Female	36 (27)	64 (25)	30 (23)	130 (25)
Race[a], n (%)				
Multiple	47 (35)	97 (37)	47 (36)	191 (37)
American Indian or Alaska native	43 (32)	81 (31)	41 (32)	165 (32)
Asian - Southeast Asian heritage	26 (20)	50 (19)	26 (20)	102 (20)
Black or African American	14 (11)	28 (11)	13 (10)	55 (11)
White	3 (2)	4 (2)	2 (2)	9 (2)
Ethnicity, n (%)				
Hispanic or Latino	93 (70)	182 (70)	89 (69)	364 (70)
Not Hispanic or Latino	40 (30)	78 (30)	40 (31)	158 (30)
Body mass index (kg/m²)				
n	133	260	128	521
Median	23.70	23.35	23.80	23.50
Minimum	14.9	15.9	15.7	14.9
Maximum	39.8	47.0	38.8	47.0
G6PD enzyme activity (IU/g Hb)				
Median	8.24	8.26	8.48	8.35
Minimum	5.8	5.6	5.4	5.4
Maximum	12.0	15.5	12.5	15.5
G6PD enzyme activity (as % of site median)				
Median	99.67	100.38	103.54	101.50
Minimum	72.6	70.2	70.4	70.2
Maximum	155.3	188.9	153.9	188.9

a. Subjects were categorized based on standard racial groupings, even though all subjects were ex-US.

5.1.2.2. Baseline Disease Characteristics

In the pivotal efficacy study, the baseline disease characteristics were similar across treatment groups (Table 18). The most common symptoms were headache, chills and rigors, and dizziness, consistent with a diagnosis of malaria. The majority of subjects reported a previous episode of malaria and there were no clinically meaningful

differences between treatment groups at baseline in *P. vivax* asexual parasite or gametocyte counts (Table 19).

Table 18 Malarial Signs and Symptoms in Study 582 Part 2 (mITT Population)

Symptom Severity	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Chills and rigors, n (%)				
Absent	8 (6)	18 (7)	8 (6)	34 (7)
Mild	47 (35)	88 (34)	35 (27)	170 (33)
Moderate	37 (28)	66 (25)	38 (29)	141 (27)
Severe	41 (31)	88 (34)	48 (37)	177 (34)
Headache, n (%)				
Absent	6 (5)	7 (3)	4 (3)	17 (3)
Mild	36 (27)	79 (30)	39 (30)	154 (30)
Moderate	29 (22)	74 (28)	37 (29)	140 (27)
Severe	62 (47)	100 (38)	48 (37)	210 (40)
Unknown	0	0	1 (<1)	1 (<1)
Dizziness, n (%)				
Absent	50 (38)	92 (35)	47 (36)	189 (36)
Mild	60 (45)	125 (48)	61 (47)	246 (47)
Moderate	19 (14)	38 (15)	16 (12)	73 (14)
Severe	4 (3)	5 (2)	5 (4)	14 (3)
Abdominal pain, n (%)				
Absent	94 (71)	158 (61)	88 (68)	340 (65)
Mild	32 (24)	85 (33)	36 (28)	153 (29)
Moderate	7 (5)	16 (6)	5 (4)	28 (5)
Severe	0	1 (<1)	0	1 (<1)
Anorexia, n (%)				
Absent	61 (46)	114 (44)	60 (47)	235 (45)
Mild	54 (41)	105 (40)	48 (37)	207 (40)
Moderate	18 (14)	36 (14)	16 (12)	70 (13)
Severe	0	5 (2)	5 (4)	10 (2)
Nausea, n (%)				
Absent	55 (41)	120 (46)	60 (47)	235 (45)
Mild	53 (40)	85 (33)	45 (35)	183 (35)
Moderate	24 (18)	51 (20)	24 (19)	99 (19)
Severe	1 (<1)	4 (2)	0	5 (<1)
Vomiting, n (%)				
Absent	93 (70)	190 (73)	93 (72)	376 (72)
Mild	32 (24)	51 (20)	28 (22)	111 (21)
Moderate	8 (6)	19 (7)	8 (6)	35 (7)
Severe	0	0	0	0
Diarrhea, n (%)				
Absent	127 (95)	241 (93)	120 (93)	488 (93)
Mild	4 (3)	17 (7)	7 (5)	28 (5)
Moderate	2 (2)	2 (<1)	1 (<1)	5 (<1)

Symptom Severity	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Severe	0	0	1 (<1)	1 (<1)
Pruritus/itching, n (%)				
Absent	118 (89)	214 (82)	111 (86)	443 (85)
Mild	12 (9)	29 (11)	11 (9)	52 (10)
Moderate	2 (2)	17 (7)	7 (5)	26 (5)
Severe	1 (<1)	0	0	1 (<1)
Coughing, n (%)				
Absent	109 (82)	221 (85)	103 (80)	433 (83)
Mild	22 (17)	39 (15)	22 (17)	83 (16)
Moderate	2 (2)	0	4 (3)	6 (1)
Severe	0	0	0	0

Note: Additional signs and symptoms were reported for some symptoms as 'Other'.

Table 19 Previous Malarial Episodes in Study 582 Part 2 (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Previous malarial episode, n (%)				
Yes	106 (80)	219 (84)	109 (84)	434 (83)
No	26 (20)	41 (16)	18 (14)	85 (16)
Unknown	1 (<1)	0	2 (2)	3 (<1)

a. Day 1 Assessment 1 values were used as Baseline.

5.1.2.3. Subject disposition and compliance

In the pivotal efficacy study, the completion rate was high (≥95%) across all treatment groups (Table 20). The most common reasons for withdrawal from the study overall were lost to follow-up (2%) or withdrawal by the subject (2%). There were no AEs that resulted in withdrawal from the study.

Table 20 Subject Disposition in Study 582 Part 2 (mITT population)

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

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

In the pivotal efficacy study, all subjects received their scheduled in-clinic dose of TQ/TQ placebo, according to randomization. Compliance with CQ study medication was ≥97% in all treatment groups. Compliance with PQ study medication in the PQ+CQ group was high (97%; assessed by returned tablet counts), which was confirmed in the applicable subjects using PK analysis of PQ and carboxy-PQ plasma concentrations at Day 8 and Day 15 (defined as PQ detectable concentration at either time point).

Table 21 Study Medication Compliance and Exposure in 582 Part 2 (Safety Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)	Total (N=522)
Number of compliant doses of CQ, n (%)				
1	0	1 (<1)	0	1 (<1)
2	3 (2)	6 (2)	1 (<1)	10 (2)
3	130 (98)	253 (97)	128 (>99)	511 (98)
Subject compliance with TQ/TQ-PBO treatment, n (%)				
Yes	133 (100)	260 (100)	129 (100)	522 (100)
Total number of PQ/PQ-PBO doses[a], n (%)				
<12	7 (5)	12 (5)	1 (<1)	20 (4)
≥12	125 (94)	239 (92)	124 (96)	488 (93)
Missing	1 (<1)	9 (3)	4 (3)	14 (3)
Subjects with detectable PQ concentrations at Day 8 or Day 15, n (%)				
n[b]	NA	NA	125	NA
Subjects who met criteria	NA	NA	122 (98)	NA
Subjects with PQ count ≥12 AND detectable PQ concentrations at Day 8 or Day 15, n (%)				
n[c]	NA	NA	124	NA
Subject who met criteria	NA	NA	120 (97)	NA

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

5.1.3. Efficacy Results for Study 582 Part 2

Treatment with 300 mg single dose TQ, when co-administered with standard doses of CQ, resulted in a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 6 months relative to treatment with CQ alone in the primary efficacy study.

There was also a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 4 months relative to treatment with CQ alone in Study 582 Part 2.

5.1.3.1. 6 Month Recurrence-free Efficacy

5.1.3.1.1. *Survival analysis*

In Study 582 Part 2, treatment with TQ+CQ resulted in a clinically and statistically significant reduction in the risk of recurrence over 6 months by 70.1% (95% CI: 59.6%, 77.8%; p<0.001) compared with CQ alone based on a Cox proportional hazards model. The Kaplan Meier estimates of recurrence-free efficacy at 6 months were 27.7% (95%

CI: 19.6%,36.3%) in the CQ alone group and 62.4% (95% CI: 54.9%, 69.0%) in the TQ+CQ group. (Table 22; Figure 6).

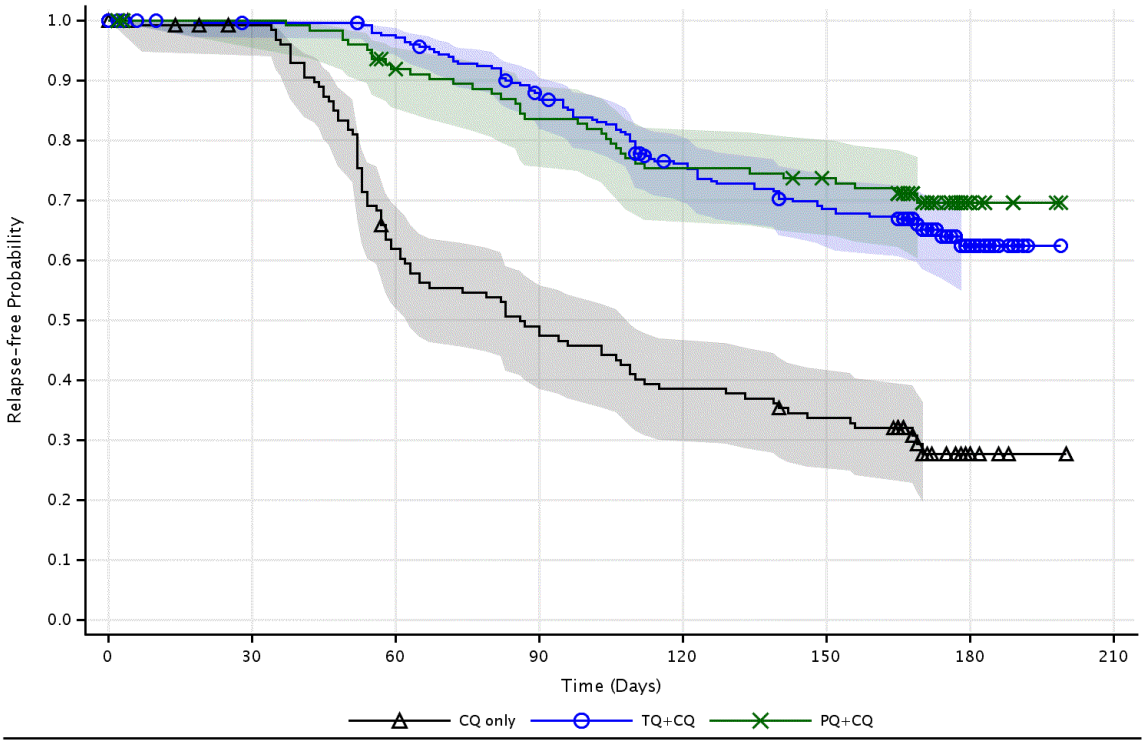
Supervised treatment with 15 mg PQ for 14 days, when co-administered with standard doses of CQ, also resulted in a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 6 months relative to treatment with CQ alone in the pivotal efficacy study (Table 22).

Table 22 Recurrence-Free Efficacy over 6 Months in 582 Part 2 (Kaplan Meier Analysis) (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)
Number of subjects, n (%)			
Recurrence-free at 6 months	35 (26)	155 (60)	83 (64)
Recurrence prior to or at 6 months	88 (66)	85 (33)	36 (28)
Censored, prior to 6 month assessment	10 (8)	20 (8)	10 (8)
Recurrence-free efficacy rate at 6 months			
Estimate (95% CI)	27.7 (19.6,36.3)	62.4 (54.9,69.0)	69.6 (60.2,77.1)
Number Needed to Treat (95%CI)[a]	--	2.9 (2.2,4.2)	2.4 (1.9,3.3)
Hazard Ratio of risk of recurrence vs CQ alone[b]			
Estimate (95% CI)		0.299 (0.222,0.404)	0.262 (0.178,0.387)
p-value		<0.001	<0.001

a. Number needed to treat to prevent one recurrence over 6 months compared to CQ alone.
b. A hazard ratio <1 indicates a lower chance of recurrence compared with CQ alone.

Figure 6 Survival Curves for Recurrence-Free Efficacy over 6 months in 582 Part 2 (mITT Population)



Subjects at Risk:								
CQ only	133	125	77	61	48	41	7	0
TQ+CQ	260	251	244	217	183	163	27	0
PQ+CQ	129	124	112	101	91	87	10	0

5.1.3.1.2. *Alternative logistic regression analysis*

In the Missing Failure logistic regression analysis for Study 582 Part 2, a larger proportion of subjects treated with TQ+CQ were recurrence-free during the first 6 months compared with CQ treatment alone and a clinically and statistically significant reduction in the odds of recurrence (75.9%, 95% CI: 61.8%, 84.8%; p<0.001) was observed for TQ+CQ treatment compared with CQ alone (Table 23).

The results for highly compliant PQ+CQ treatment were similar to those for TQ+CQ. A larger proportion of subjects treated with PQ+CQ were recurrence-free during the first 6 months compared with CQ treatment alone and a clinically and statistically significant reduction in the odds of recurrence (80.2%, 95% CI: 66.5%, 88.3%; p<0.001) was observed for PQ+CQ treatment compared with CQ alone.

Table 23 Recurrence-Free Efficacy at 6 Months in 582 Part 2 with Missing=Failure (Logistic Regression) (mITT Population)

Logistic regression analysis at 6 months[a]			
	CQ alone	TQ+CQ	PQ+CQ
Recurrence-free, n (%)	35 (26)	155 (60)	83 (64)
Subjects with a recurrence, n (%)	98 (74)	105 (40)	46 (36)
Odds ratio of recurrence (95% CI)[b]		0.241 (0.152,0.382)	0.198 (0.117,0.335)
p-value		<0.001	<0.001

a. Subjects with missing data were analyzed as failures.
b. Odds ratios <1 indicate a smaller chance of recurrence compared with CQ alone.

5.1.3.2. Sensitivity analyses

The results of all pre-specified sensitivity analyses of the primary endpoint were consistent with the primary analyses for Study 582 Part 2. Sensitivity analyses included using the Per Protocol Population, censoring homologous and heterologous relapses, and analyzing by CQ supply date. Together, these analyses show the robustness of the efficacy results.

5.1.3.3. Secondary Endpoint Results

5.1.3.3.1. *Recurrence-free efficacy at 4 months*

The key efficacy studies were performed in regions endemic for *P. vivax* malaria, and therefore there was a continuous risk of re-infection throughout the follow-up period of the study. Sites were selected on the basis of historical evidence that time to relapse was short [Battle, 2014]. Given the inability to distinguish relapse from new infection, recurrence-free efficacy over 4 months post-dosing was included as a secondary endpoint in Study 582 Part 2 and Study 564 because at that point there would have been less opportunity for new infection to occur. The analyses of the 4-month endpoint were based on the follow-up to the end of a 4-month window.

Survival analysis

In Study 582 Part 2, the reduction in the risk of recurrence at any time over 4 months was 72.9% (95% CI: 62.4%, 80.5%; p<0.001) compared with CQ treatment alone corresponding to a HR of 0.271 (0.195,0.376) (Table 24). The recurrence-free efficacy rate in the TQ+CQ group was approximately 10% higher at 4 months (73.0%) compared with results at 6 months (62.4%), and similar results were seen in the CQ alone group (36.0% at 4 months vs. 27.7% at 6 months) as would be expected with increases in new infections over time.

In the placebo arm (the CQ-only arm), the majority of recurrences occurred early in follow-up (Figure 6). The Kaplan-Meier curves are roughly parallel after the 4-month

mark, which is consistent with the expectation that the re-infection rate should be similar across all arms. This is consistent with the hypothesis that the majority of the events that occurred late in the follow-up period are in fact re-infections and not relapses, as none of the treatment regimens administered would have been expected to prevent these late re-infections.

The reduction in the risk of recurrence in the PQ+CQ group compared with the CQ alone group was consistent with the primary endpoint results at 6 months based on a Cox proportional hazards model. Treatment with PQ+CQ resulted in a clinically and statistically significant reduction in the risk of recurrence by 74.5% (95% CI: 61.0%, 83.3%; p<0.001) compared with CQ alone.

Table 24 Recurrence-Free Efficacy at 4 Months in 582 Part 2 (Kaplan Meier Analysis) (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)
Number of subjects, n (%)			
Recurrence-free at 4 months	47 (35)	177 (68)	90 (70)
Recurrence prior to or at 4 months	78 (59)	67 (26)	30 (23)
Censored, prior to 4 month assessment	8 (6)	16 (6)	9 (7)
Recurrence-free efficacy rate at 4 months			
Estimate (95% CI)	36.0 (26.8,45.4)	73.0 (66.0,78.9)	74.7 (65.7,81.6)
Hazard ratio of risk of recurrence vs CQ alone[a]			
Estimate (95% CI)		0.271 (0.195,0.376)	0.255 (0.167,0.390)
p-value		<0.001	<0.001

a. A hazard ratio <1 indicates a lower chance of recurrence compared with CQ alone.

Alternative logistic regression analysis (sensitivity analysis)

In the Missing Failure logistic regression analysis for Study 582 Part 2, a clinically meaningful and statistically significant reduction in the odds of recurrence (74.4%, 95% CI: 60.2%, 83.5%; p<0.001) was shown for TQ+CQ treatment compared with CQ alone (OR 0.256, 95% CI:0.165,0.398) (Table 25). Similar results were obtained for PQ+CQ treatment compared with CQ alone (OR 0.237, 95% CI:0.141,0.397; p<0.001).

Table 25 Recurrence-Free Efficacy at 4 Months in 582 Part 2 with Missing = Failure (Logistic Regression) (mITT Population)

				Comparison with CQ Alone		
Treatment	**N**	**Recurrence-Free, n (%)**	**Subjects with Recurrence, n (%)**	**Odds Ratio of Recurrence[a]**	**95% CI**	**P-Value**
CQ alone	133	47 (35)	86 (65)			
TQ+CQ	260	177 (68)	83 (32)	0.256	(0.165,0.398)	<0.001
PQ+CQ	129	90 (70)	39 (30)	0.237	(0.141,0.397)	<0.001

a. Odds ratios <1 suggest a smaller chance of recurrence compared with CQ alone.

The odds of recurrence at 4 months in the TQ+CQ group were similar to those in the PQ+CQ group (Table 25). As for the 6-month analysis, subjects who took an anti-malarial or not confirmed recurrence-free at 4 months were as assumed to be recurrences. The odds ratio was close to 1, suggesting that the odds of recurrence in the TQ+CQ and PQ+CQ groups are similar. These results are consistent with the survival analysis of recurrence-free efficacy over 4 months, and both analyses at 4-months were consistent with the analyses at 6-months.

5.1.3.3.2. *Early response to treatment*

Parasite clearance times were similar across treatment groups as expected due to CQ treatment (Table 26). Median parasite counts were rapidly reduced to zero by Day 3 in all 3 treatment groups. Gametocyte clearance times were also similar across treatment groups (Table 26). Median gametocyte counts were reduced to zero by Day 2 Assessment 2 in all treatment groups.

Fever clearance times were similar across treatment groups (Table 26). Of note, the use of paracetamol in the study was high (87%) and well-balanced across all 3 treatment groups.

Table 26 Analysis of Time to Parasite, Fever, and Gametocyte Clearance in 582 Part 2 (mITT Population)

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)
Parasite Clearance, n (%)			
Parasite clearance achieved	129 (97)	254 (98)	127 (98)
Censored, parasite clearance not achieved	4 (3)	6 (2)	2 (2)
Time to parasite clearance (hours)			
Median (95% CI)	43 (41,48)	45 (42,47)	42 (39,45)
Fever Clearance, n (%)			
Fever clearance achieved	48 (36)	102 (39)	47 (36)
Censored, at Baseline	85 (64)	158 (61)	82 (64)
Censored, fever clearance not achieved	0 (0)	0 (0)	0 (0)
Time to fever clearance (hours)			
Median (95% CI)	7 (5,14)	7 (5,12)	8 (6,18)
Gametocyte Clearance, n (%)			
Gametocyte clearance achieved	85 (64)	168 (65)	79 (61)
Censored, at Baseline	47 (35)	92 (35)	49 (38)
Censored, gametocyte clearance not achieved	1 (<1)	0 (0)	1 (<1)
Time to gametocyte clearance (hours)			
Median (95% CI)	38 (32,40)	39 (37,41)	36 (24,41)

5.1.3.3.3. *Early Failures and Recrudescence*

Early failures were defined as subjects who did not demonstrate initial clearance of *P. vivax* parasitemia OR demonstrated initial clearance and had a subsequent non-zero genetically homologous *P. vivax* parasite count on or before Day 32 (recrudescence). Three subjects in the TQ+CQ group (1.2%) and 2 subjects in the CQ alone group (1.5%) were considered early failures. Three of these 5 subjects (2 TQ+CQ and 1 CQ) withdrew from the study prior to Day 5; therefore, data were not available to demonstrate initial clearance of parasitemia and the subjects were classified as early failures based on the above definition.

Only 1 subject, who was in the CQ alone group (0.8%), had recrudescence prior to Day 33. One additional subject in the TQ+CQ treatment group had a heterologous infection, which did not meet the criteria for recrudescence.

5.2. Study 582 Part 1

5.2.1. Study Design for Study 582 Part 1

Part 1 of Study 582 was a Phase 2b, multi-center, double-blind, double-dummy, parallel group, randomized, active- and placebo-controlled, dose-selection study with sites in

Brazil, Peru, Thailand, and India. The purpose of the study was to select an optimal Phase 3 dose based on efficacy, safety, and PK data [Llanos-Cuentas, 2014].

In TAF112582 Part 1, the null hypothesis for the primary endpoint was that the 6-month relapse-free efficacy rate was not different between the CQ+TQ and CQ treatment groups. A two-sided hypothesis test was to be performed at the 5% level.

The primary comparison was made using a log rank test for the difference in relapse-free survival rates over 6 months, and utilized the intent-to-treat (ITT) population. The sample size calculations assumed a 60% relapse-free efficacy rate for the CQ treatment group, and a 90% rate for the TQ+CQ rate (30% difference). Assuming a 10% attrition rate, 54 subjects per treatment group provided >90% power.

To allow for multiple testing while preserving the overall Type I error rate at 5%, a step-down testing approach was employed, starting with the comparison of the highest TQ dose vs CQ

The PQ+CQ treatment arm was included as a benchmark, to help further interpret the TQ+CQ results. No formal comparison between the TQ+CQ and PQ+CQ treatment groups was planned.

Eligible subjects had a positive blood smear for *P. vivax* at entry (parasite density >100/μL and <100,000/μL). Subjects with G6PD deficiency were excluded, defined as G6PD values of <70% of the site median for males and <70% for females with a screening Hb ≥100 g/L; females with Hb concentration of ≥70 g/L and <100 g/L were excluded if their enzyme level was not >90% of the site median. Subjects were randomized to 1 of 6 treatment groups, stratified by baseline parasite count (≤7500/μL, >7500/μL). All subjects were treated with CQ on Days 1 to 3 to treat the blood stage malaria infection, followed by either a single dose of TQ (50 mg, 100 mg, 300 mg, or 600 mg), or PQ 15 mg for 14 days, or CQ alone (i.e., placebo) (Table 27). All subjects received the same number of tablets/capsules for 15 days to maintain the double-dummy study design.

Table 27 Randomized Treatment Groups in Study 582 Part 1

Treatment Groups		N
1	CQ (600 mg on Days 1 to 3) (i.e., CQ only regimen)	54
2	CQ (600 mg on Days 1 to 3) + TQ 50 mg single dose (Days 1 or 2)	55
3	CQ (600 mg on Days 1 to 3) + TQ 100 mg single dose (Days 1 or 2)	57
4	CQ (600 mg on Days 1 to 3) + TQ 300 mg single dose (Days 1 or 2)	57
5	CQ (600 mg on Days 1 to 3) + TQ 600 mg single dose (Days 1 or 2)	56
6	CQ (600 mg on Days 1 to 3) + PQ 15 mg once daily for 14 days (Days 2 to 15)	50

The primary objective was to determine the efficacy of TQ as a radical cure for *P. vivax* malaria, relative to a CQ control. Secondary objectives were safety, population PK, and potential PK/PD relationships of TQ in subjects with *P. vivax* malaria. Planned

enrolment for Part 1 was at least 324 subjects, randomized equally (54 subjects per group).

Safety assessments included monitoring of AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. Additional ophthalmic assessments were performed at selected sites. Key safety endpoints of interest were as follows:

- Clinically relevant hemolysis leading to decreases in Hb/hematocrit or complications thereof (required transfusions, acute renal failure)
- Changes in methemoglobin
- GI tolerability - incidence of abdominal pain, heartburn, diarrhea, constipation, nausea, and vomiting
- Ophthalmic safety - incidence of corneal deposits and retinal and visual field abnormalities.

The results of Study 582 Part 1 indicated that the 300 mg dose of TQ was optimal in terms of both safety and efficacy, as described in the clinical study report (Table 49).

5.2.2. Study Population Results for Study 582 Part 1

In Study 582 Part 1, the demographic characteristics were well-balanced across the treatment groups and a higher percentage of males than females were enrolled, similarly to Study 582 Part 2 (Table 45).

The baseline disease characteristics were also balanced across the treatment groups and were similar to Study 582 Part 2 (Table 46, Table 47). There were no clinically meaningful differences between treatment groups at baseline.

Similar to Study 582 Part 2, the study completion rate was ≥94% in all treatment groups and there were no AEs leading to withdrawal from the studies (Table 43).

In Study 582 Part 1, compliance with TQ and CQ was measured using pill counts (Table 48) whereas in Study 582 Part 2 it was measured using both pill count and TQ PK. In Study 582 Part 1, ≥96% of subjects in the 300 mg TQ, PQ+CQ and CQ treatment groups received their scheduled dose of TQ/TQ placebo, and compliance with CQ was 100% in these groups.

Outpatient compliance with PQ, based on a count of returned tablets, was lower with 26% of subjects in the PQ + CQ treatment group returning the number of tablets suggestive of taking all 12 (±1) doses and 42% taking 14 or more doses, while 32% took 10 or fewer doses.

5.2.3. Efficacy Results for Study 582 Part 1

5.2.3.1. 6-month recurrence-free efficacy

Recurrence-free efficacy at 6 months in the 300 mg TQ group in Study 582 Part 1 was consistent with that of Study 582 Part 2.

In Study 582 Part 1, there was a statistically significant difference in efficacy between TQ+CQ compared to CQ alone. The estimates of recurrence-free efficacy at 6 months were 37.5% (95% CI: 23%, 52%) in the CQ alone group and 89.2% (95% CI: 77%, 95%) in the 300 mg TQ+CQ group.

Similar Kaplan-Meier curves were obtained from the results for the TQ+CQ and PQ+CQ groups (Figure 4).

5.2.3.2. Secondary endpoint results

4-month recurrence-free efficacy

Recurrence-free efficacy at 4 months in the 300 mg TQ group in Study 582 Part 1 was consistent with the results of the pivotal efficacy study (Table 50).

In Study 582 Part 1, the recurrence-free efficacy for TQ+CQ and CQ alone were statistically significant ($p<0.0001$) from the two-sided log-rank test (Table 50). The estimates of the recurrence-free efficacy at 4 months were 46.5% (95% CI: 32%, 60%) in the CQ alone group and 89.4% (95% CI: 75%, 96%) in the 300mg TQ+CQ group which were slightly higher than at 6 months.

The recurrence-free efficacy at 4 months in the PQ+CQ group was comparable to that over 6 months.

Other secondary efficacy endpoints

The other secondary efficacy endpoints in Study 582 Part 1 were consistent with, and supported, the primary endpoint (Table 51, Table 52, Table 53). The results were similar to the secondary endpoints in the pivotal Study 582 Part 2.

5.3. Study 564

5.3.1. Design for Study 564

The design of Study 564 was similar to the pivotal Phase 3 study, 582 Part 2, but without the CQ alone control arm. This was a randomized, double-blind, active-controlled, double-dummy, parallel-group study with sites in Brazil, Peru, Colombia, Thailand, and Vietnam.

The primary objective in Study 564 was to compare the incidence of hemolysis from treatment by TQ+CQ vs. PQ+CQ. Study 564 also provided supportive efficacy data on recurrence-free efficacy.

Study 564 was primarily a supporting safety study. There was no hypothesis tested in the study. The planned sample size of 200 TQ+CQ subjects and 100 PQ+CQ subjects was based on the regulatory requirement to obtain an appropriate total safety database in subjects treated with TQ+CQ within the TQ *P. vivax* program, and was not based on statistical considerations. The total sample size of 300 subjects included a subgroup of 50 female subjects (randomized 2:1 to TQ+CQ:PQ+CQ) with moderate (40-70%) G6PD deficiency. As for the total sample size, this was not based on statistical considerations.

The primary endpoint was the occurrence of clinically relevant hemolysis in all subjects; defined as a decrease in Hb of ≥30% or >30g/L from baseline; or, an overall drop in Hb below 60 g/L. The proportion of subjects and 95% CIs within each treatment group, for all subjects, and for the subset of females with moderate G6PD deficiency, were to be derived, using the safety population. Assuming event rates of 50% in the subgroup of females with moderate G6PD deficiency, and 0% in the rest of the subjects, the total sample size of 300 provided 95% confidence intervals with precision of 4% for TQ+CQ and 5% for PQ+CQ.

Efficacy was assessed as secondary objective. There was no formal comparison of TQ vs PQ with respect to efficacy.

Eligible subjects had a positive blood smear for *P. vivax* at entry. The study planned to enroll subjects with a minimum G6PD assay value of ≥70% of the site median and only female subjects with G6PD values of ≥40% to <70% of the site median.

As described above, the study planned to enroll at least 50 female subjects who displayed moderate G6PD deficiency (≥40% to <70% of the site median G6PD value); however, only 1 female subject meeting this criterion was enrolled. With agreement from regulatory agencies, recruitment of subjects into the G6PD-deficient female cohort was halted after 6 additional months of recruitment, during which follow-up on the G6PD-normal subjects was being conducted. Consequently, the study recruited a total of 251 subjects (166 subjects in the TQ+CQ group and 85 subjects in the PQ+CQ group).

All subjects were treated with CQ on Days 1 to 3 to treat the blood stage malaria infection, followed by their randomized treatment (300 mg single dose TQ or 15 mg PQ once daily for 14 days) and matching placebo.

In addition to the assessment of hemolysis, safety assessments also included AEs, clinical laboratory tests, vital signs, ECGs, and physical examinations. Additional ophthalmic assessments were performed at a selected site.

5.3.2. Study Population Results for Study 564

In Study 564, the demographic characteristics were well-balanced across the treatment groups and a higher percentage of males than females were enrolled (Table 56), similar to Study 582 Part 2.

The baseline disease characteristics were also balanced across the treatment groups (Table 57, Table 58) and were similar to Study 582 Part 2. There were no clinically meaningful differences between treatment groups at baseline.

Similar to Study 582 Part 2, the completion rate was ≥94% in all treatment groups and there were no AEs leading to withdrawal from the study (Table 54).

In Study 564, compliance was ≥96% for all study medications in both treatment groups (Table 59). The high compliance observed in the PQ+CQ group based on tablet counts (98%) was confirmed by PK analysis of PQ and 7-carboxy-PQ plasma concentrations at Day 8 and Day 15.

5.3.3. Efficacy Results for Study 564

5.3.3.1. 6-month recurrence-free efficacy

In Study 564, the estimates of recurrence-free efficacy at 6 months were 72.7% (95% CI: 64.8%, 79.2 %) in the TQ+CQ group and 75.1% (95%CI: 64.2%,83.2%) in the PQ+CQ group using Kaplan-Meier methodology (Table 60).

The efficacy in the TQ+CQ and PQ+CQ groups appear similar over 6-months follow up, although the study was not powered to make formal comparisons of the treatment groups (Figure 9).

For the recurrence-free efficacy using missing failure analysis for Study 564, the odds of recurrence at 6 months in the TQ+CQ group were similar to those in the PQ+CQ group. The odds ratio was close to 1, suggesting that efficacy in the two groups were similar (Table 61). These results are consistent with the survival analysis of recurrence-free efficacy over 6 months.

5.3.3.2. Secondary endpoint results

4-month recurrence-free efficacy

Recurrence-free efficacy results at 4 months from Study 564 (Table 62) supported the results of the pivotal efficacy study for both the TQ+CQ and PQ+CQ treatments.

Results of analyses of recurrence-free efficacy over 4 months were similar to those over 6 months (Table 63), and to the 4-month results for Study 582 Part 2. The risk of recurrence over 4 months was comparable between treatment groups.

Other secondary efficacy endpoints

The other secondary efficacy endpoints in Study 564 were consistent with, and supported, the primary endpoint (Table 64). The results were similar to the secondary endpoints in the pivotal Study 582 Part 2.

5.4. Subgroup Analyses

The results of analyses of the major subgroups of age, race and gender are generally consistent with the overall results from the mITT and safety populations in Study 582 (Part 2) and Study 564 studies. For smaller subgroups, subject numbers do not allow for a meaningful comparison with the overall results from the mITT and Safety populations in the 582 (Part 2) and 564 studies.

In the major age subgroup of 18-64 years of age, the recurrence-free efficacy results were similar to the mITT Population results. The proportion of TQ subjects who were recurrence-free was much greater than in the placebo group, and the proportions in the TQ and PQ groups were similar.

In the gender subgroups, the recurrence-free efficacy results were generally similar to the mITT Population results, particularly for the CQ only and PQ treatment groups. The proportions of TQ subjects who were recurrence-free were much greater than in the placebo groups in both groups.

In the largest race subgroups of Multiple Races and American Indian/Alaska Native (predominantly Brazilian and Peruvian subjects, respectively), the recurrence-free efficacy results were similar to the mITT Population results. The proportion of TQ subjects who were recurrence-free was much greater than in the placebo group, and the proportions in the TQ and PQ groups were similar.

5.5. Efficacy Conclusions

The selection of the 300 mg single dose of TQ was based on both efficacy and safety considerations. No additional efficacy benefit was seen with the 600 mg dose in Study 582 Part 1, and the hemolytic potential of 300 mg single dose TQ was comparable to that of PQ 15 mg daily for 14 days in TAF110027.

In the pivotal efficacy study, Study 582 Part 2, treatment with 300 mg single-dose TQ, when co-administered with standard doses of CQ, resulted in a clinically and statistically significant reduction in the risk of recurrence of *P. vivax* malaria at 6 months by 70.1% compared with CQ alone ($p<0.001$). The alternative missing failure logistic regression analysis and all other sensitivity analyses supported the results of the primary analysis in the pivotal efficacy study. The number needed to treat was 2.8, i.e., over a six-month period, one malaria recurrence was prevented in one out of about every three patients treated with 300 mg single dose TQ compared to placebo.

The observed rates of recurrence were slightly higher in all arms (including the CQ alone/placebo arm) in Phase 3 compared to Phase 2b. The potential reasons for this are multiple. Firstly, it is not possible to distinguish between relapse and re-infection: the epidemiology of *P. vivax* varies from year to year, even at the same site; changes in the re-infection rate would therefore manifest as changes in the rate of recurrence year-on-year. A second reason for the higher rate of recurrence in Phase 3 may therefore be due to improvements in microscopy as sites became more experienced in the technique, resulting in a greater detection of low-level asymptomatic parasitemia. Despite this variability across studies, TQ efficacy was consistently demonstrated in all studies.

The PQ compliance (assessed by pill counts) seen in Study 582 Part 1 (Phase 2b) was only 68%, while that for TQ was 96% (recurrence-free efficacy [95%CI]: TQ 89.2 [77,95]; PQ 77.3 [63,87]). In Study 582 Part 2, the compliance rates were both TQ and PQ were high (TQ: 100%; PQ: 96%). This may explain some of the variation in results between Phase 2b and Phase 3. The apparent improvement in PQ compliance from Part 1 to Part 2 was due to a greater emphasis by sites on encouraging compliance through regular visits and pill counts during the treatment period. This high degree of compliance with PQ treatment is not seen in real world settings. The single dose regimen of TQ facilitates treatment compliance and ensures consistent real-world use.

In conclusion, 300 mg single dose TQ, co-administered with CQ, clinically and statistically significantly reduced the risk of *P. vivax* recurrence compared to CQ alone. The single dose regimen of TQ, if licensed, would facilitate treatment compliance and could ensure consistent real-world efficacy as seen as in our clinical studies.

6. OVERVIEW OF SAFETY

Safety data from across all clinical studies of TQ (includes 33 completed studies in healthy volunteers and patients) were used to inform the type and frequency of uncommon and rare events observed with TQ. These studies cover a range of TQ doses and durations, including higher doses and/or longer durations than the recommended 300 mg single dose regimen.

The primary evidence for the clinical safety of 300 mg single dose TQ for radical cure of *P. vivax* malaria is provided by 3 randomized, double-blind studies: TAF112582 Part 1 (Phase 2b), TAF112582 Part 2 (pivotal Phase 3), and TAF116564 (Phase 3) (Table 1). The overall safety profile of TQ at the recommended 300 mg single dose is appropriate to support use as radical cure, and similar to that of PQ 15 mg daily for 14 days.

In addition, safety results from 2 individual studies in healthy volunteers provide clinically important safety observations to this regulatory submission. Study 201807 specifically assessed ophthalmic safety, and the cardiac safety study, TAF114582, was a definitive QTc study.

The safety data from the phase 2b and phase 3 radical cure studies (Studies 582 part1, 582 part 2 and 564) were pooled in the placebo-controlled and/or all primary studies to

better characterize the safety of 300 mg single dose TQ in subjects with *P. vivax* malaria (Table 28). Additionally, the pooled groupings provided exposure and key safety information from multiple studies within the TQ development program, including those utilizing different dosing regimens, and in different indications and populations.

6.1. Extent of Exposure

Across the TQ development program, >4000 subjects have been exposed to TQ, including >800 subjects exposed to a 300 mg total dose (Table 67). A total of 483 *P. vivax*-infected subjects have been treated with 300 mg single dose TQ+CQ in the All Primary (AP) studies grouping (Table 28). As noted in the footnote to Table 67, an additional 220 healthy US volunteers have received the 300mg single dose in study 807; this data was not available for the data integration, but all safety data from these subjects has been reviewed, and is discussed where relevant.

Table 28 Exposure Across the TQ Development Program, by Grouping

Grouping	Subjects	Total TQ Dose	N
All Studies	**All treated**	**Any**	**4129**
		<300 mg	392
		300 mg	810[a,c]
		>300 mg	2927[b]
All Primary Studies (AP)	***P. vivax*-infected**	**300 mg**	**483**
Placebo-controlled Studies (PC)	*P. vivax*-infected	300 mg	317
Supportive Studies	***P. vivax*-infected**	**Any**	**303**
		<300 mg	112
		>300 mg	191
Clinical Pharmacology Studies	**Healthy volunteers**	**Any**	**720[c]**
		<300 mg	82
		300 mg	243[d]
		>300 mg	395
Malaria Prophylaxis Studies	**All Treated**	**Any**	**2703**
		<300 mg	198
		300 mg	83
		>300 mg	2422

Note: Data from studies SB252263/003, 036, 050, 051, 052, 053 and 054 have been excluded from the pooled groupings.

a. One subject in the Supportive Studies took 300 mg TQ instead of the planned >300 mg dose.
b. There were 81 subjects in Study SB252262/057 who received >300 mg TQ and were included in both the Malaria Prophylaxis Studies and in the Clinical Pharmacology Studies, but they were only counted once in the overall total.
c. Total includes >400 subjects enrolled at US sites.
d. The final data for the ophthalmic safety study 201807 include an additional 220 healthy volunteer subjects (all from US sites) in the 300 mg TQ group.

6.2. Analysis of AEs

Overall, the safety profiles for treatment groups in the PC and AP groupings were similar (Table 29).

Table 29 AE Overview (PC and AP Safety Populations)

	PC Grouping			AP Grouping	
	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)	TQ+CQ (N=483) n (%)	PQ+CQ (N=264) n (%)
Any AE	127 (68)	202 (64)	108 (60)	321 (66)	172 (65)
Any SAE	10 (5)	23 (7)	11 (6)	29 (6)	12 (5)
Any fatal AE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any AE leading to study withdrawal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any AE leading to discontinuation of study treatment	6 (3)	12 (4)	1 (<1)	13 (3)	2 (<1)
Any drug-related AE	29 (16)	31 (10)	26 (15)	45 (9)	37 (14)

6.2.1. Common AEs

Due to the AEs associated with recurrence and CQ/PQ retreatment, the summary of common AEs in this section focuses on events reported during the first 29 days of the study. Disease-related events of pyrexia, chills, rigor, and headache were to be reported separately from other AEs if the subject had a positive slide for *P. vivax* at the time of the event; however, this information was inconsistently reported by investigators, and the most common AEs were complicated by symptoms of malaria.

Within the first 29 days, pruritus was the most common AE in all 3 treatment groups in the PC grouping, which is consistent with the known effects of CQ (See Table 5, section 1.4.1) [Chloroquine US PI, 2013]. The AE profile in the TQ+CQ group based on the AP grouping was consistent with that observed in the TQ+CQ group for the PC grouping.

The majority of subjects with AEs had events that were mild or moderate in severity and few severe AEs (Grade ≥3) were reported.

6.2.2. SAEs and Deaths

There were no deaths in the 3 primary studies, or in the radical cure program studies.

Decreased Hb was the most common SAE, and the only SAE reported in >1 subject in the TQ+CQ group, based on the PC grouping (Table 30). Decreased Hb was a protocol-defined SAE (Hb decreases of ≥30% or >30 g/L from baseline; or, an overall drop in Hb below 60 g/L in the first 15 days of the study) and did not, in any instance, otherwise fulfill the criteria for 'serious'. The SAE profile observed for the TQ+CQ group based on the AP grouping was consistent with that observed in TQ+CQ group for the PC grouping.

Table 30 Non-Fatal SAEs by Preferred Term (PC Safety Population)

Preferred Term	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)
Any event	**10 (5)**	**23 (7)**	**11 (6)**
Haemoglobin decreased	3 (2)	14 (4)	3 (2)
ECG QT prolonged	5 (3)	1 (<1)	4 (2)
Abscess limb	0	1 (<1)	0
Hepatitis E	0	1 (<1)	0
Urinary tract infection	0	1 (<1)	0
Diarrhoea	0	1 (<1)	1 (<1)
Anaemia	0	1 (<1)	0
Drug-induced liver injury	0	1 (<1)	0
Abortion spontaneous	0	1 (<1)	0
Menorrhagia	0	1 (<1)	0
Alanine aminotransferase increased	1 (<1)	0	0
Gastroenteritis	1 (<1)	0	0
Nausea	0	0	1 (<1)
Vomiting	0	0	1 (<1)
Methaemoglobinaemia	0	0	1 (<1)
Hepatitis acute	0	0	1 (<1)
Dehydration	0	0	1 (<1)

6.2.3. AEs Leading to Withdrawal from the Study or Discontinuation of Study Treatment

No subject had an AE leading to withdrawal in the PC or AP groupings. The majority of AEs that led to the discontinuation of study treatment in the TQ+CQ group were protocol-defined SAEs of Hb decreased, which occurred in a higher proportion of subjects in the TQ+CQ group (3%) compared with the CQ alone (1%) or PQ+CQ groups (none) in the PC grouping (Table 31). The profile for AEs leading to discontinuation of study treatment in the TQ+CQ group based on the AP grouping was consistent with those observed in the TQ+CQ group for the PC grouping.

Table 31 AEs Leading to Discontinuation of Study Treatment by Preferred Term (PC Safety Population)

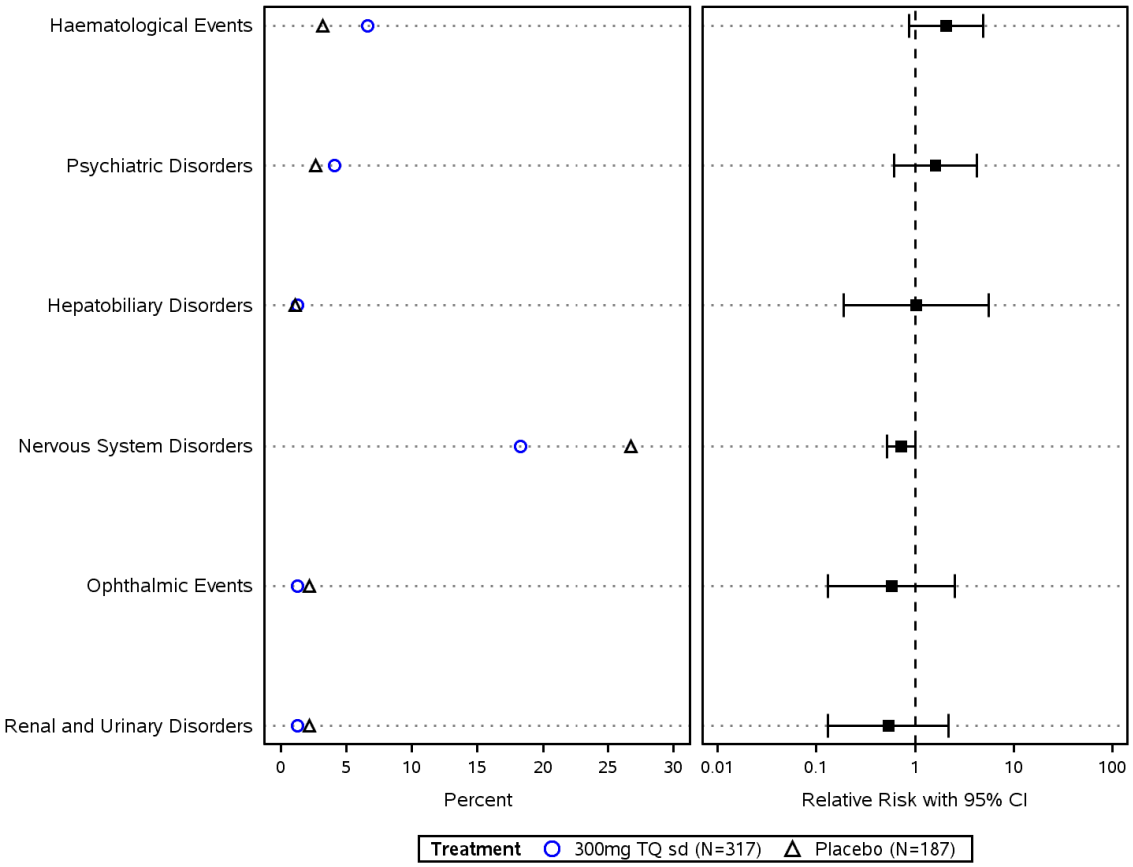
Preferred Term	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)
Any event	**6 (3)**	**12 (4)**	**1 (<1)**
Haemoglobin decreased	2 (1)	11 (3)	0
P. falciparum infection	0	1 (<1)	0
ECG QT prolonged	4 (2)	0	1 (<1)

6.2.4. AEs of Special Interest

The AEs of special interest (AESI) identified are considered risks or potential risks with TQ or treatments within the same class, including Hb-associated events, CNS events (i.e., nervous system disorders and psychiatric disorders), ophthalmic events, hepatobiliary disorders, and renal and urinary disorders.

The analyses on the PC grouping showed no clinically significant differences between the TQ+CQ group compared with the CQ alone group in the relative risk of experiencing hematological, psychiatric, hepatobiliary, ophthalmic, or renal and urinary AEs (Figure 7). The risk of experiencing nervous system disorder AEs was estimated to be lower in the TQ+CQ group compared with CQ alone, which was likely driven by AEs of headache. The risk of a hematological events and psychiatric disorder AEs was estimated to be numerically higher in the TQ+CQ group compared with CQ alone. Of note, these event rates were based on 6-months follow-up.

Figure 7 AEs of Special Interest with Relative Risk and 95% CIs for the Comparison of TQ+CQ vs. CQ alone (PC Safety Population)



TQ+CQ = 300 mg TQ SD (N=317); CQ alone = Placebo (N=187)
Note: Estimated relative risk is adjusted for study and region using the Cochran-Mantel-Haenszel method.

6.3. Laboratory Evaluations

6.3.1. Hepatobiliary Laboratory Abnormalities

Mild asymptomatic elevations in transaminases have been reported for a number of quinolines such as CQ, quinine, and mefloquine, with rare reports of hepatitis [Mathur, 1990; Gotsman, 2000; Wielgo-Polanin, 2005]. Hepatobiliary events were identified as AESIs, based on observations of asymptomatic alanine aminotransferase (ALT) increases with TQ.

Transient, sporadic increases in liver transaminases have been observed in all clinical studies but no clinically significant hepatobiliary effects were observed in the primary studies or in the All Studies groupings. All hepatobiliary AEs were mild or moderate in intensity and no subjects discontinued study treatment or withdrew from any of the 3 primary studies due to hepatobiliary AEs.

Small increases in ALT were observed at Baseline and at early timepoints (Days 3 through 8) in all 3 treatment groups in the PC grouping. Increases in ALT that were considered potentially clinically significant occurred at a higher incidence in the CQ alone group compared with the TQ+CQ and PQ+CQ groups; these were likely disease-related. High bilirubin levels were observed at Baseline across treatment groups in the PC grouping and subsequently resolved with treatment in all 3 treatment groups, as would be expected for recovery from *P. vivax* malaria. Liver function parameters in the TQ+CQ group based on the AP grouping (N 483) showed a similar pattern to the TQ+CQ group based on the PC grouping.

Pooled data from the Clinical Pharmacology grouping show that healthy volunteers treated with TQ did not report hepatobiliary AEs. Transient, asymptomatic, dose-related elevations in liver transaminases (ALT and AST) have been observed in healthy volunteers who received single 300 mg, 600 mg and 1200 mg TQ doses in placebo-controlled Phase 1 studies. At the 300 mg dose, elevations were mild-to-moderate. None of the elevations were severe or considered to be clinically significant.

6.3.2. Renal Function and Parameters

No renal toxicity signal was observed in the AP or PC groupings or across the TQ development program. The proposed 300 mg single dose TQ treatment was associated with small reversible increases in creatinine, which were consistent with the known renal transporter inhibition effect.

There were no renal or urinary SAEs, and no events led to study withdrawal or discontinuation of study treatment.

6.4. Hemoglobin-associated Events and Assessments

In the primary studies in *P. vivax* malaria, the incidence of Hb declines observed in subjects treated with 300 mg single dose TQ was similar to that with PQ 15 mg for 14 days. At the recommended 300 mg single dose of TQ, none of the small Hb decreases were regarded as clinically significant or led to clinical sequelae.

PQ and TQ are both 8-aminoquiolines with a potential to cause drug-induced hemolysis in G6PD-deficient individuals. However, in a WHO review of 8-aminoquinoline safety, even in G6PD-normal individuals, PQ can cause small, non-clinically significant reductions in Hb (10-20 g/L) at standard therapeutic doses [Recht , 2014]. Recovery from malaria is itself associated with a small degree of hemolysis, as infected red blood cells are cleared from the circulation [Woodruff, 1979; Commons, 2017]. This was shown in the primary studies by reticulocytosis that accompanied malaria recovery, as described in the sections that follow. Therefore, it is challenging to detect small levels of drug-induced hemolysis within the context of ongoing disease. This is further confounded by the fact that many patients present with dehydration, as evidenced by high serum urea and hematocrit levels at Screening. Subsequent rehydration and hemodilution may therefore result in artefactual decreases in Hb concentration that are not clinically relevant. The 3 primary studies of TQ in *P. vivax* malaria focused on identifying clinically relevant Hb decreases instead of hemolysis *per se*.

Subjects with AEs that were potentially associated with Hb decreases were identified by clinical review prior to unblinding in all primary studies. In addition, decreased Hb laboratory values were required to be reported as SAEs if they met protocol-defined criteria. In the Phase 3 studies, the criterion was ≥30% or >30 g/L from Baseline or a decrease in absolute Hb below 60 g/L in the first 15 days of the studies. In the Phase 2b study, TAF112582 Part 1, smaller decreases met SAE criteria (≥25% or >25 g/L within the first 15 days).

Hb decreases were also evaluated across populations based on G6PD activity, as noted above and described in the sections that follow. In healthy volunteers (male or female) with normal G6PD enzyme activity (≥70% of site median by spectrophotometry), a 1200 mg TQ dose was associated with small Hb decreases and accompanying rises in total bilirubin that are consistent with drug-induced hemolysis.

Male subjects with G6PD deficiency and female subjects who are homozygous for G6PD deficiency are likely to experience larger decreases in Hb.

For female heterozygotes with G6PD activity ≥70%, the balance of risk versus benefit supports the use of 300 mg single dose TQ. For female heterozygotes with intermediate levels of G6PD deficiency <70%, for the same dose of TQ, subjects with lower G6PD enzyme activity are likely to have greater decreases in Hb than subjects with a higher G6PD activity.

6.4.1. Hemoglobin-related AEs

Hb-associated Events in the Primary Studies (PC and AP Groupings)

In the PC grouping, the incidence of Hb-associated AEs was higher in the TQ+CQ group compared with the CQ alone group, and in both the PC and AP groupings, the incidence was higher in the TQ+CQ groups compared with the PQ+CQ groups (Table 32). No Hb-associated AEs led to withdrawal from the primary studies. However, 3% of subjects in the TQ+CQ group in both groupings had events that lead to interruption or discontinuation of study treatment, compared with ≤1% in the other treatment groups. The majority of the events were mild or moderate in severity; 1 subject in the TQ+CQ group had a Grade 3 event (increased bilirubin).

The most common Hb-associated AE across all treatment groups were decreased Hb and the incidences aligned with the overall incidence of Hb-associated AEs (Table 32). All other Hb-associated AEs occurred in ≤1% of subjects across all treatment groups. There were a small number of subjects across treatment groups with protocol-defined SAEs of decreased Hb during the studies (≤5% in the TQ+CQ groups, ≤2% in the PQ+CQ and CQ alone groups). No subjects required transfusions during the studies.

Table 32 Hb-associated AEs of Special Interest (PC and AP Safety Population)

	PC Grouping			AP Grouping	
	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)	TQ+CQ (N=483) n (%)	PQ+CQ (N=264) n (%)
Overview of Hb-associated AEs					
Any AEs	6 (3)	21 (7)	5 (3)	29 (6)	8 (3)
SAEs	3 (2)	15 (5)	3 (2)	19 (4)	4 (2)
Severe AEs (Grade ≥3)	0	0	0	1 (<1)[a]	0
Drug-related AEs	3 (2)	1 (<1)	1 (<1)	2 (<1)	1 (<1)
AEs leading to withdrawal from study	0	0	0	0	0
AEs leading to interruption or discontinuation of study treatment	2 (1)	11 (3)	0	15 (3)	1 (<1)
Hb-associated AEs, by PT					
Haemoglobin decreased	3 (2)	15 (5)	3 (2)	19 (4)	4 (2)
Fatigue	2 (1)	2 (<1)	0	3 (<1)	0
Dyspnoea	0	2 (<1)	0	2 (<1)	0
Anaemia	0	1 (<1)	2 (1)	1 (<1)	3 (1)
Pallor	0	1 (<1)	0	1 (<1)	0
Hyperbilirubinaemia	1 (<1)	0	0	1 (<1)	1 (<1)
Blood bilirubin increased	0	0	0	1 (<1)	0
Tachypnoea	0	0	0	1 (<1)	0

a. Grade 3 increased bilirubin following *P. vivax* recurrence on Day 99

The adjusted relative risk of experiencing Hb-associated AEs was estimated to be 2.07 (95%CI:0.87,4.94) in the TQ+CQ group compared with CQ alone (Figure 7). The PQ+CQ group AE incidence was similar when compared to CQ alone. These analyses were completed based on event data over the full study periods.

Hb-associated AEs Across the TQ Development Program (All Studies Grouping)

Across the entire TQ development program, the most frequently reported Hb-associated AEs in the All TQ treatment group were consistent with those observed in the TQ+CQ groups in the PC and AP groupings. The only Hb-associated AE reported in ≥1% of subjects in the All TQ and All Placebo groups was fatigue.

6.4.2. Hemoglobin laboratory values and assessments

Hb changes over time were similar across the treatment groups in the PC grouping (Figure 2). In the first 15 days after treatment, there were few subjects (≤2%) with decreases in Hb that met the definition of potential clinical concern (Table 33), but none of the changes were considered clinically significant. Few subjects in the TQ+CQ group had Hb declines after the first 29 days of treatment. No subjects had Hb values less than 60 g/L at any point during the studies.

The profile for Hb changes from baseline for the TQ+CQ group based on the AP grouping (N 483) was consistent with that observed in the TQ+CQ group for the PC grouping.

Table 33 Subjects with Changes from Baseline in Hb of Potential Clinical Concern in the First 15 Days after Treatment (PC Safety Population)

Analysis visit	Category	CQ alone N=187 n (%)	TQ+CQ N=317 n (%)	PQ+CQ N=179 n (%)
Day 3	N	187	315	179
	Low	1 (<1)	4 (1)	0
Day 5	N	186	313	177
	Low	0	3 (<1)	0
Day 8	N	185	312	175
	Low	1 (<1)	4 (1)	0
Day 11	N	184	310	173
	Low	0	5 (2)	1 (<1)
Day 15	N	158	275	143
	Low	0	6 (2)	1 (<1)

In Study 564, the incidence of clinically relevant hemolysis was evaluated as a primary endpoint. The protocol defined clinically relevant hemolysis as a decrease in Hb of ≥30% or >30 g/L from Baseline or an overall decrease in Hb to below 60 g/L, the incidence was low in both treatment groups in G6PD-normal subjects. The majority of

Hb decreases in both treatment groups n Study 564 were low (<20 g/L) and of no clinical concern, and no subjects required a blood transfusion. Only 1 subject in the TQ+CQ treatment group experienced a Hb nadir <80 g/L, which was a Hb decrease of 20 g/L from Baseline to Day 3 that normalized without specific medical intervention. Although the primary endpoint was termed clinically relevant hemolysis, the events meeting these criteria were all based on Hb decreases. There was no evidence of hemolysis based on hemolytic markers of reticulocyte counts and urinalysis. Although it would be expected that the 1 G6PD-deficient female enrolled in the study, who was randomized to PQ+CQ, would have had some degree of hemolysis because of her G6PD heterozygous status, the subject's hematology profile was consistent with laboratory values typically observed in subjects recovering from malaria, including a transient decrease in Hb and transient rise in methemoglobin and reticulocyte counts.

In Study 582 Part 2, the incidence of subjects with Hb decreases >30 g/L or ≥30% from Baseline or >20 g/L to ≤30 g/L during the first 29 days of the study was low across the treatment groups (Table 34). The proportions of subjects with hemoglobin decreases were higher in the TQ+CQ group compared with those in the CQ alone group. These differences were not considered to be clinically significant because few subjects had Hb decreases that fell to below the lower limit of normal, and all subjects fully recovered without blood transfusion or other medical intervention.

Table 34 Hemoglobin Declines over First 29 Days (582 Part 2 Safety Population)

Maximum decline from Baseline	CQ alone (N=133) n (%)	TQ+CQ (N=260) n (%)	PQ+CQ (N=129) n (%)	Total (N=522) n (%)
All subjects				
n	133	259	129	521
≤20 g/L	120 (90)	214 (83)	114 (88)	448 (86)
>20 g/L to ≤30 g/L	11 (8)	31 (12)	12 (9)	54 (10)
>30 g/L or ≥30% of Baseline	2 (2)	14 (5)	3 (2)	19 (4)

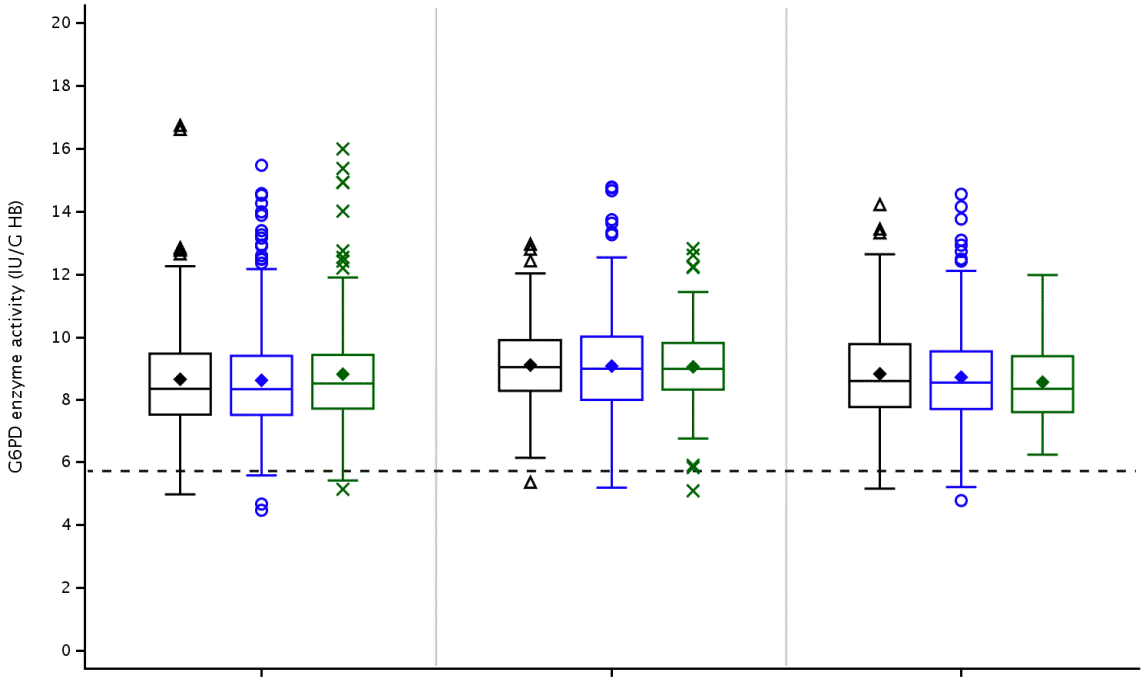
6.4.3. Subjects with G6PD deficiency

G6PD deficiency is known to be a risk factor for hemolysis in subjects treated with 8-aminoquinolines. An assay validation study in healthy G6PD-normal males at each site was used to determine G6PD eligibility requirements for the pivotal trials and found global median G6PD activity was 8.2 International units (IU)/g Hb, with 70% of median at 5.7 IU/g Hb (at 30ºC using Trinity assay). Regional G6PD values at 70% of median were similar across the studied regions: 5.8 for South America, 5.6 for SE Asia, 5.7 for Africa. In this trial, the minimum G6PD enzyme level of any subject was 5.4 IU/g Hb (TAF115226).

A spectrophotometric assay for G6PD enzyme activity was used during screening to exclude subjects with enzyme activity <70% of the site median from the Studies 582 Parts 1 and 2. In addition, all females randomized into the studies, as well as all males who had a protocol-defined SAE of decreased Hb, were genotyped for G6PD deficient alleles.

No clinically meaningful changes in G6PD activity over time were observed in the PC grouping. Values at each time point were consistent across treatment groups (Figure 8).

Figure 8 G6PD Enzyme Activity by Visit and Treatment Group (PC Safety Population)



Subjects			
Placebo	187	128	127
TQ	317	251	250
PQ	179	124	123

Placebo = CQ alone; TQ = TQ+CQ; PQ = PQ+CQ; Day 1 = Screening
Notes: Reference line denotes 5.71 IU/g Hb (70% of global median of 8.16 IU/gHB, obtained from Study TAF115226).
TAF112582 Part 1 data was only collected at Day 1 (i.e., Screening).

Male subjects with G6PD deficiency and female subjects who are homozygous for G6PD deficiency are likely to experience larger decreases in Hb; therefore, TQ must not be given to these individuals.

For female heterozygotes with G6PD activity ≥70%, 300 mg single dose TQ is associated with an acceptable safety profile. Any Hb declines seen were not clinically significant and resolved without specific medical intervention.

For female heterozygotes with intermediate levels of G6PD deficiency (<70%), for the same dose of TQ, subjects with lower G6PD enzyme activity are likely to have greater decreases in Hb than subjects with a higher G6PD activity.

Therefore, patients with G6PD activity <70% of normal must be excluded from treatment with 300 mg single dose TQ.

6.5. CNS Effects

Across the TQ development program, more than 800 subjects have received a cumulative 300 mg dose of TQ over ≤3 days. A comprehensive review of CNS AEs observed showed that all events were mild to moderate in severity and self-limiting.

A limited number of serious psychiatric events have been reported in older TQ studies at doses ≥350 mg, but mainly with multiple doses and in subjects with a prior history of significant psychiatric disorders. Consequently, CNS side effects have been analyzed in detail in the primary studies and across the entire TQ development program.

6.5.1. Results from the radical cure program (PC, AP groupings)

In the PC and AP groupings, no serious CNS AEs were reported, and no subjects withdrew from the studies or discontinued treatment due to CNS AEs. All CNS AEs were self-limiting and mild or moderate in intensity.

The incidence of CNS AEs over the full study period were similar in the TQ+CQ and PQ+CQ treatment groups and lower than in the CQ alone group (Table 35). This difference was driven primarily by AEs of headache, likely associated with malaria recurrence and CQ/PQ re-treatment.

Table 35 CNS AEs by System Organ Class and Preferred Term in the PC and AP Groupings (Safety Populations)

	PC Grouping			AP Grouping	
	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)	TQ+CQ (N=483) N (%)	PQ+CQ (N=264) N (%)
Nervous System Disorders, any event	**50 (27)**	**58 (18)**	**35 (20)**	**105 (22)**	**60 (23)**
Headache	39 (21)	37 (12)	24 (13)	64 (13)	40 (15)
Dizziness	16 (9)	30 (9)	14 (8)	59 (12)	30 (11)
Migraine	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
Syncope	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Tremor	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Somnolence	0	1 (<1)	0	1 (<1)	0
Burning sensation	0	0	1 (<1)	0	1 (<1)
Dysaesthesia	0	0	1 (<1)	0	1 (<1)
Balance disorder	0	0	0	1 (<1)	0
Hypoaesthesia	0	0	0	0	1 (<1)
Psychiatric Disorders, any event	**5 (3)**	**13 (4)**	**8 (4)**	**15 (3)**	**12 (5)**
Insomnia	5 (3)	13 (4)	8 (4)	15 (3)	8 (3)
Anxiety	0	2 (<1)	0	2 (<1)	3 (1)
Depression	0	0	0	0	1 (<1)

Given this confounding factor, CNS events with onset during the first 29 days of the study are considered a better reflection of the AE profile for the active arms (TQ+CQ and PQ+CQ) compared to placebo (CQ only group) (Table 6).

The overall incidence of dizziness was higher (≥3%) in both treatment groups in the AP grouping compared with the TQ+CQ and PQ+CQ groups in the PC grouping due to higher incidence in Study 564. However, the overall incidences of other CNS events were similar across the treatment groups in both pooled groupings (See Table 6, Section 1.4.4.4).

In the TQ+CQ group, the events of anxiety and somnolence were Grade 1 or Grade 2 in severity and transient. None of the events were considered to be related to study treatment by the investigator, however, due to the close temporal relationship to study treatment dosing, and given that these AEs are recognized effects of some quinoline antimalarial drugs and have been observed in prior studies of TQ, a causal role for TQ cannot be dismissed.

Pooled data from the Clinical Pharmacology grouping show that healthy volunteers treated with TQ experienced similar types of CNS events as those observed in *P. vivax*-infected subjects treated with TQ+CQ in the primary studies. The AEs followed the same general pattern as that observed in *P. vivax*-infected subjects, with increasing types of events and incidences at higher doses and longer durations of treatment.

6.5.2. All Studies grouping

Across all clinical studies with TQ across all indications/treatment regimes, there was a broader distribution of CNS AEs observed in the All TQ group compared with the All Placebo group, and the occurrence of various events and increased severity tended to increase with higher TQ doses and longer duration of treatment (Appendix Table 65). This pattern was more pronounced for the psychiatric AEs (Appendix Table 66).

Severe and serious psychiatric disorders reported across the program at any dose or duration

Over all the studies, a limited number of severe or serious psychiatric events (n 7) have been reported in older TQ studies at doses ≥350 mg, and most occurred after multiple doses (Table 36). In addition, there were 2 other medically important cases of mild depression/depressed mood that were included in this evaluation because they were considered medically important for the purposes of a comprehensive review, for a total of 9 subjects. The majority of subjects with these events had a history of significant psychiatric disorders or other confounding factors.

Table 36 Summary of Subjects with Severe or Serious Psychiatric Disorders, or Other Medically Important Events

Study ID	Dose	Event PT (Severity or Verbatim Terms)	Onset	Duration	Resolution	Relationship to Study Drug by the Investigator	Intervention/ Action Taken	Medical History
SB252262/033	1200 mg cumulative	Depression (moderate)	Day 24	87 days	Resolved	Related	Required corrective therapy (paroxetin)/ Withdrawn from study	Closed head injury 3 years prior to study
SB252262/043	750 mg cumulative	Suicidal behavior (associated with alcohol intoxication)[a]	Day 8	1 day after TQ discontinued	Resolved	Related (CQ co-suspect) [b]	Hospitalized and required corrective therapy (intervention unknown)/ Withdrawn due to unstable mental state	Family reported history of marital difficulties and previous suicide threat; no other relevant history or concomitant medications reported at Screening
TAF112582 Part 1	600 mg single dose	Depressed mood[c]	Day 6	Unknown	Resolved	Unrelated (CQ co-suspect)[b]	Hospitalized (on Day 88 for 2 days) with nausea, epigastric pain, diarrhea, and depression; treated with fluoxetine; consulted with psychiatric specialist (findings unknown)	History of depression but no suicidal tendencies; irregular psychiatric consults; frequent but irregular use of diazepam (10 mg)
SB252262/050[d] (Subject (b) (6))	350 mg single dose	Acute psychotic episode (severe)	Day 24	25 days	Recovered	Possibly related	Hospitalized following progressive emotional distress	Two previous episodes of psychosis (not disclosed at Screening)
SB252262/050[d](Subject (b) (6))	500 mg single dose	Psychotic episode (severe)	Day 8	9 days	Recovered	Remotely related	Hospitalized for a pre-scheduled psychiatric admission	Recent diagnosis of schizophrenia (not disclosed at Screening)
SB252262/057 (Subject (b) (6))	5200 mg[e] cumulative	Bipolar depression (mild); Depression (mild)	Day 223 (62 days since last dose)	Lost to follow-up	Unknown	Unlikely related	Bupropion and lithium started on Study Day 223 (ongoing)/Excluded due to a positive hepatitis/HIV screen	No relevant past history or concomitant medications.

Study ID	Dose	Event PT (Severity or Verbatim Terms)	Onset	Duration	Resolution	Relationship to Study Drug by the Investigator	Intervention/ Action Taken	Medical History
SB252262/014	1200 mg cumulative	Paranoid hallucinotic psychosis (serious)	Day 27	3 days	Not resolved	Unrelated	Hospitalized and treated with olanzapine and lorazepam/None	History of "hallucinotic psychosis" 6 months earlier (not disclosed at Screening); no obvious signs of psychosis at Screening; negative drug screen
TAF114582	600 mg single dose	Depressed mood (mild)	Day 4	3 days	Resolved	Related	None	No relevant past medical history or concomitant medications were reported; at the time of the event, subject also reported abdominal pain, diarrhea, and palpitations
SB252262/057 (Subject (b) (6))	1600 mg cumulative	Depressed mood (mild)	Day 37	15 days	Resolved	Unlikely related	None/ No action taken	No relevant past history; treated for a UTI with sulfamethoxazole starting on Day 13 (co-suspect)

Note: UTI=urinary tract infection

a. Family reported that subject had taken "poison." The event was not assigned a body system and therefore does not appear in the pooled output for AEs in the psychiatric disorders SOC.
b. The sponsor considered CQ co-suspect.
c. The SAE was reported after dataset was frozen and, therefore, does not appear in the pooled groupings.
d. Cases from Study SB252262/050 (n=2) are not reported in pooled groupings.
e. Loading dose 200 mg/day for 3 days plus 200 mg weekly for 23 weeks.

Spontaneous Reports of Psychiatric Disorders from Subjects in Australian Defense Force Studies

Spontaneous reports of psychiatric disorders were recently received from 18 subjects who received TQ in prophylaxis studies conducted with the Australian Defense Force (ADF) (Study SB252262/033, Study SB252262/046, and Study SB252262/049).

Within these spontaneous reports from former ADF study participants, which were not medically confirmed, the self-reported medical histories describe more CNS events than were reported at the time and also report persisting long-term effects, many of which appear to overlap with symptoms of PTSD. These include anger outbursts, confusional state, and hallucinations.

Despite the potential underreporting at the time of the ADF clinical trials between 1999-2001, the rate for CNS effects was higher in the ADF study SB252262/033 compared with Study SB252262/57, in which TQ was administered at the same dosing regimen (weekly dosing for 6 months) but in healthy volunteers not serving in deployed armed services. This observation suggests that ADF study subjects may be at increased risk of experiencing CNS effects (see review of epidemiology below). The majority of soldiers were exposed to triggers for PTSD, the symptoms of which are similar to those included in the reports. Although a possible interaction with PTSD has been postulated [Nevin, 2014], due to these confounding factors, it is not possible to draw conclusions on the role of TQ in these cases although a role cannot be dismissed.

A literature review of epidemiology data was conducted to evaluate the background rate estimates of suicidality, depression, and anxiety in military populations. Rates ranged from ~0.1% for completed suicide (range 0.01% to 0.23%), ~6% for suicidal ideation or behavior (range 0.1% to 24%) to ~10% for severe depression and generalized anxiety disorders (ranges 5.1% to 14.5% and 7.3% to 14.5%, respectively) [Belik, 2010;Ilgen, 2010; Skegg, 2010; Waller, 2012; Kapur, 2009; Fanning, 2013; Ramsawh, 2014; Schoenbaum, 2014; O'Toole, 2015; Reger, 2015; Spiess, 2016; Brignone, 2017] High variations were observed depending on the reported study design, endpoints and populations, and higher rates were observed in veterans versus non-discharged military, and in deployed versus non-deployed military populations.

6.5.3. CNS Effects of Antimalarials

CNS side effects have been reported for some antimalarials, including non-quinoline and synthetic quinolines (most noticeably, the 4-quinolinemethanol, mefloquine [MQ], and including 4- and 8-aminoquinolines) [Schmidt, 1948; Schmidt, 1951; Phillips-Howard, 1995; Croft, 2002; Toovey, 2009; FDA, 2013; Ritchie, 2013; Nevin, 2014; McCarthy, 2015; Quinn, 2015; Nevin, 2016; Nevin, 2017; Eick-Cost, 2017]. Continued dosing following the emergence of mild CNS symptoms has been identified as a risk factor for development of more severe events [Mefloquine USPI, 2013], and a past history of mental disorders has been considered a risk factor for MQ-related CNS events. Less historical data appears to be available for 8-aminoquinolines compared with some other quinoline antimalarials [Schmidt, 1948; Loken, 1949; Lee, 1981; Saunders, 2014].

6.5.4. CNS Conclusions

In conclusion, a comprehensive review of CNS AEs showed that in the radical cure program, all CNS events were mild to moderate in severity and self-limiting. This includes the 483 patient in the primary studies and the 330 healthy US volunteers in Study 201807 who received a single TQ dose of 300 mg. While there were no reports of serious psychiatric disorders following 300 mg single dose TQ, cases of depression and psychosis have occurred in subjects following higher single doses of TQ (350 mg to 600 mg) or in multi-dose regimens (e.g. prophylaxis). Most of these events occurred in subjects with a previous history of psychiatric disorders. Serious psychiatric disorders, such as psychosis and depression, have also been associated with some quinoline antimalarials. Caution should be advised with TQ treatment in patients with a current or past history of serious psychiatric disorders. Our current proposed label for 300mg single dose TQ under review by the FDA includes related precautionary language.

The use of 300 mg single dose TQ with concomitant CQ for radical cure of *P. vivax* malaria, as used in the Phase 3 studies of TQ, showed that the risk of CNS effects is low in subjects without an active or past history of serious psychiatric disorders.

6.6. Ophthalmic Events and Assessment

6.6.1. Brief summary of historical data and concerns from the program and other indications

In common with other cationic amphiphilic drugs, TQ has the potential to cause phospholipidosis, a phospholipid storage disorder, leading to phospholipid accumulation in the cornea and reversible keratopathy [Halliwell, 1997; Hollander, 2004]. Photophobia and retinal toxicity have also been reported from quinine and quinidine treatment [Rheeder 1991].

Prior to the 3 primary studies evaluating 300 mg single dose TQ in the radical cure of *P. vivax* malaria, ophthalmic assessments had been conducted in more than 200 TQ-treated subjects across 4 studies (033, 057, 058, TAF106491). The majority of these subjects received supratherapeutic loading doses over 2 to 3 days (≥600 mg) and subsequent long-term maintenance therapy. The most significant ophthalmic finding in subjects from these studies was benign reversible vortex keratopathy, as confirmed by independent experts. There was no signal for retinal toxicity when 900 mg TQ was used in combination with CQ, which is 3 times the TQ dose used in the 3 primary studies.

6.6.2. Results from the radical cure program (PC, AP groupings)

Across the primary studies there was no evidence of retinal toxicity or corneal changes associated with vision changes for the proposed 300 mg single dose TQ. AEs associated with ocular changes were infrequent and similar across the treatment groups in the PC and AP groupings. All events were mild or moderate in severity. There were no ophthalmic SAEs. All of the events had onset within the first 29 days and all resolved. No clinically significant changes to ophthalmic safety parameters were observed, based

on visual acuity measurements, anterior segment examination with evaluation for vortex keratopathy, posterior segment examination including fundus photographs, color perception assessment, and Humphrey visual field perimetry.

6.6.3. Ophthalmic Safety Study 201807

Evaluation of the final data for the placebo-controlled Study 201807, conducted as per regulatory guidance, did not identify any signal for retinal toxicity with use of 300 mg single dose TQ. One subject in each treatment group met the primary endpoint, which was based on a composite of five parameters. Both subjects had an ellipsoid zone disruption (EZD) abnormality detected in 1 eye at Day 90. However, evaluation of the screening images from the subject in the TQ group showed a pre-existing EZD abnormality, and the subject should have been excluded from the study.

Study 201807 was a multi-center, randomized, single-blind, placebo-controlled, parallel-group study of a single, 300 mg oral dose of TQ in healthy adult subjects.

The primary objective of this study was to assess the PD effects of TQ on the retina via spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF). The secondary objective was to assess the overall ophthalmic safety of TQ compared with placebo (i.e., CQ alone).

Following initial screening assessments, eligible subjects underwent baseline ophthalmic examinations. Eligibility was confirmed by masked, independent central review of the baseline ophthalmological assessment data. Eligible subjects were randomized in a 2:1 ratio to 300 mg TQ or matched placebo within 7 days of the screening ophthalmic examinations. Subjects were followed for safety assessments and returned to the clinic for follow-up ophthalmic evaluations at approximately 90 days post-dose.

Ophthalmic assessments included key SD-OCT measurements of central retinal thickness and appearance of the retina on FAF at Screening and Day 90. Visual acuity was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) chart reading. Additional retinal morphology was assessed by SD-OCT and fundus photography captured at Screening and Day 90.

The primary endpoint was the proportion of subjects treated with TQ who developed significant protocol-defined retinal changes from Baseline to Day 90. A subject was considered to have a clinically significant retinal change if any of the following 5 parameters indicated a change from Baseline in either eye: SD-OCT central subfield thickness, SD-OCT total macular volume, SD-OCT central retinal lesion thickness, SD-OCT ellipsoid zone disruption (EZD), or abnormal autofluorescence patterns.

A sample size of 300 subjects was planned to be treated with TQ based on 95% probability of detecting an event when the underlying risk of clinically significant retinal findings at 90-day follow-up was 1%.

6.6.3.1. Primary endpoint – retinal assessments

In the final analysis, the primary endpoint was met by 1 subject in each treatment group, both of whom had EZD (Table 37).

No subject had a change from baseline for FAF.

The upper limit for the 95% one-sided CI for the proportion of subjects with retinal findings in either eye in the TQ group was 1.5%. The difference versus placebo was -0.3% (95% CI -3.1%, 1.3%) (Table 37).

No subjects in either treatment group had retinal findings in both eyes. The upper limit for the 95% one-sided CI for the proportion of subjects with retinal findings in both eyes in the TQ group was 0.9%. The difference versus placebo was 0.0% (95% CI -2.3%, 1.2%) (Table 38).

Table 37 Proportion of Subjects with Retinal Findings in Either Eye in 201807 (Ophthalmic Safety Population)

Endpoint	Retinal changes from baseline	Placebo N=161	TQ 300 mg N=306
Primary	Yes No Upper limit of 95% one-sided CI for proportion of subjects with retinal changes	1 (0.6) 160 (99.4)	1 (0.3) 305 (99.7) 1.5%
Secondary	Difference in proportion with retinal changes TQ vs. Placebo (95% CI)		-0.3% (-3.1%,1.3%)

Table 38 Proportion of Subjects with Retinal Findings in Both Eyes in 201807 (Ophthalmic Safety Population)

Endpoint	Retinal changes from baseline	Placebo N=161	TQ 300mg N=306
Primary	Yes No Upper limit of 95% one-sided CI for proportion of subjects with retinal changes	0 161 (100.0)	0 306 (100.0) 0.9%
Secondary	Difference in proportion with retinal changes TQ vs. Placebo (95% CI)		0.0% (-2.3%,1.2%)

Subject (b) (6) (EZD endpoint) (TQ group)

Subject (b) (6), had ellipsoid zone (EZD) disruption of >15% in width representing change from baseline in one (right) eye at the Day 90 follow up assessment. The contralateral (left) eye did not have a change from baseline. This subject was enrolled in error as there was an ellipsoid zone disruption at baseline and should have been excluded from the trial.

Additionally, there was a difference in the anatomical location of the Day 0 and Day 90 scans. The scan on Day 90 was taken from a superior location compared to the scan at Day 0 explaining the difference in EZD disruption. None of the other 4 parameters of the primary endpoint had changes from baseline. Of note this subject reported no visual AEs and best corrected visual acuity did not change from baseline. Fundus examination and photography were also unchanged from baseline.

Subject (b) (6) (EZD endpoint) (PBO group)

Subject (b) (6) had no EZD at baseline and an EZD of 128 μm at Day 90 follow-up, representing a change from baseline in one (right) eye. The contralateral (left) eye did not have a change from baseline. None of the other 4 parameters of the primary endpoint had changes from baseline.

6.6.3.2. Ophthalmological AEs

The ophthalmological AEs were generally balanced between the treatment groups (Table 39), with most occurring in only 1 subject in 1 or both treatment groups.

Table 39 Ophthalmological AEs Reported in Any Treatment Group (201807 Safety Population)

Preferred term	Placebo N=168	TQ 300mg N=330
Infections and infestations[a]		
Conjunctivitis	0	1 (<1)
Eye disorders		
Any event	7 (4)	9 (3)
Eye irritation	0	2 (<1)
Conjunctivitis allergic	1 (<1)	1 (<1)
Photophobia	1 (<1)	1 (<1)
Vision blurred	1 (<1)	1 (<1)
Corneal deposits	0	1 (<1)
Dry eye	0	1 (<1)
Eye disorder	0	1 (<1)[b]
Foreign body sensation in eyes	0	1 (<1)
Mydriasis	0	1 (<1)
Retinal exudates	0	1 (<1)
Astigmatism	1 (<1)	0
Blepharospasm	1 (<1)	0
Presbyopia	1 (<1)	0
Retinal haemorrhage	1 (<1)	0
Hepatobiliary disorders[a]		
Ocular icterus	0	1 (<1)[c]

a. Only ophthalmological-associated events from this SOC are included.
b. The verbatim text for Subject (b) (6) was 'peripheral pigment change of left eye'.
c. Subject (b) (6) also had ocular events of dry eye and foreign body sensation in eyes.

6.6.3.3. Vortex keratopathy

Vortex keratopathy was reported in 1 subject (TQ group) at the Day 90 assessment. This was not reported as an AE. Post-database freeze, Subject (b) (6) was described as having a Lasik scar with calcium deposits. Review of the source data confirmed this finding was present at baseline and unchanged at Day 90. The ophthalmologist indicated vortex keratopathy as 'absent' at Baseline and at Day 90. Therefore, the report of vortex keratopathy was due to a data entry error. There was no change in visual acuity for this subject from baseline and no ocular AEs were reported. No vortex keratopathy was actually present in this subject.

6.6.3.4. Best corrected visual acuity

The absolute and change from baseline BCVA (logMAR) results (Table 40) and the categorical changes from baseline (Table 41) did not indicate clinically meaningful changes from baseline in either group.

The small number of subjects with a definite change in vision was not considered a clinically significant difference between the treatment groups. The difference in occurrence of possible change in vision was not considered a meaningful difference between the treatment groups.

Table 40 BCVA (logMAR) Results from Assessment (201807 Safety Population)

Data	Treatment	Eye	N	Visit	n	Mean	StdD	Median	Min	Max
Absolute	Placebo	Right	168	Screening	168	-0.055	0.0866	-0.097	-0.20	0.20
			168	Day 90	162	-0.056	0.0959	-0.097	-0.30	0.40
		Left	168	Screening	168	-0.045	0.0924	0.000	-0.30	0.20
			168	Day 90	162	-0.044	0.0996	0.000	-0.30	0.40
	TQ 300mg	Right	330	Screening	330	-0.048	0.0936	0.000	-0.20	0.30
			330	Day 90	308	-0.043	0.0946	0.000	-0.30	0.30
		Left	330	Screening	330	-0.041	0.0948	0.000	-0.30	0.30
			330	Day 90	308	-0.029	0.0980	0.000	-0.30	0.40
Change	Placebo	Right	168	Day 90	162	-0.004	0.0888	0.000	-0.20	0.30
		Left	168	Day 90	162	0.001	0.0817	0.000	-0.20	0.20
	TQ 300mg	Right	330	Day 90	308	0.005	0.0877	0.000	-0.20	0.30
		Left	330	Day 90	308	0.011	0.0904	0.000	-0.30	0.40

StdD=standard deviation

Table 41 BCVA (logMAR) Change from Baseline by Category (201807 Safety Population)

	Placebo N=168				TQ 300 mg N=330			
Eye:	**Right**	**Left**	**Either**	**Both**	**Right**	**Left**	**Either**	**Both**
n	162	162	162	162	308	308	308	308
No	156 (96)	157 (97)	152 (94)	152 (94)	294 (95)	290 (94)	279 (91)	279 (91)
Possible[a]	5 (3)	5 (3)	9 (6)	1 (<1)	13 (4)	16 (5)	26 (8)[c]	2 (<1)
Definite[b]	1 (<1)	0	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)	0

a. A change from baseline ≥0.12 to <0.3 LogMAR
b. A change from baseline ≥0.3 logMAR
c. One TQ subject had a definite change in the right eye and possible change in the left eye and is summarised under Definite.

6.6.4. All Studies Grouping results

Across the TQ development program, ophthalmic AEs occurred in similar proportions of subjects in the All Placebo and All TQ groups, based on the All Studies grouping. Higher proportions of subjects in the All TQ group had corneal verticillata and keratopathy compared with the All Placebo treatment group. These events occurred only at supra-therapeutic and/or long-term doses of TQ. The incidences of retinopathy, retinal disorder, and retinal pigmentation changes were low (<1%) in the All TQ group, based on the All Studies grouping. All of these events were reported with supra-therapeutic and/or long-term doses of TQ and their clinical significance is uncertain.

Photophobia was reported in 6 subjects (<1%) in the All TQ group compared with no subjects in the All Placebo group. Based on sponsor evaluation, 2 events of photophobia showed a clear causal relationship with TQ. In both cases, the events started the day after dosing, were mild and resolved after ≤2 days.

6.7. Other Safety topics

6.7.1. Methemoglobin

Small increases in methemoglobin were observed in both the TQ+CQ and PQ+CQ treatment groups of the PC grouping. Increases in methemoglobin percentages were generally observed more frequently in the PQ+CQ group compared with the other treatment groups in the PC grouping.

6.7.2. Hypersensitivity

Two SAEs of hypersensitivity-related reactions were reported; both were in the healthy volunteer study, TAF114582. The first female received a 300 mg dose of TQ. On Day 17 after dosing, she had lip swelling, itching, and diffuse hives (SAE or urticaria). She also reported difficulty breathing that may have been related to an undisclosed part

history of asthma. The second female received 600 mg of TQ: on Day 18, she had difficulty swallowing, swelling of the throat, some swelling of the hands and feet, and hives (SAE of hypersensitivity). Both events resolved fully with diphenhydramine and corticosteroid treatment. The first case reported difficulty breathing that may have been related to an undisclosed past history of asthma. Both events were judged by the investigator to be possibly related to TQ.

6.7.3. ECGs and QTc Analysis in *P. vivax* Subjects Treated with CQ

There were no differences across the 3 treatment groups in the PC grouping in ECG assessments through 72-hours post-Baseline. There were no subjects with clinically significant abnormal ECG findings in the TQ+CQ group.

Observed changes in QTcF were consistent with the known effects of CQ on QT prolongation and there was no evidence of a clinically significant additional effect on QTcF values in the TQ+CQ group. Differences in QTcF between treatment groups were not considered to be clinically significant. Changes from baseline in QTcF resolved by Day 29 for most subjects across the 3 treatment groups.

Table 42 Summary of Maximum Post-Baseline QTcF Values (msec) Through 72 Hours by Category (PC Safety Population)

QTcF (msec)	CQ alone (N=187) n (%)	TQ+CQ (N=317) n (%)	PQ+CQ (N=179) n (%)
N	186	311	178
Increase <30	76 (41)	119 (38)	75 (42)
Increase ≥30 and <60	93 (50)	154 (50)	85 (48)
Increase ≥60 and QTcF ≤480	10 (5)	31 (10)	16 (9)
Increase ≥60 and QTcF >480	7 (4)	7 (2)	2 (1)

The QTcF prolongation observed in the TQ+CQ group based on the AP grouping was consistent with those observed in the PC grouping.

Cardiac Safety in Study TAF114582

Study TAF114582 was a thorough QT study conducted in accordance with the ICH E14 guidance to assess the effect of TQ on cardiac safety related to QT/QTc interval prolongation and the proarrhythmic potential [Green, 2014]. TQ doses of 300 mg single dose, 600 mg single dose and 1200 mg (400 mg once daily x 3 days), along with placebo and the positive control moxifloxacin, were studied in healthy volunteers.

The primary endpoint was change from Baseline in QTcF for a supratherapeutic dose of TQ compared with placebo.

In Study TAF114582, there was no indication of a QT effect at clinical doses of TQ (300 mg and 600 mg) compared with placebo. For the differences in mean changes from

time-matched baseline for QTcF, Bazett-corrected QT duration, and individually-corrected QT duration between TQ 300 mg and TQ 600 mg compared with placebo, the 90% confidence limits were less than 10 msec for all timepoints. The supra-therapeutic dose of TQ 1200 mg showed a maximum effect on QTcF prolongation, which was just within the safety margin of 10 msec to demonstrate lack of effect.

6.7.4. Pregnancy and lactation

There is very limited data on the safety of TQ in pregnancy from the TQ clinical program. Studies in animals have shown no adverse effects of TQ on embryofetal development at concentrations comparable to those achieved at the recommended human dose. However, TQ must not be used in pregnancy because of a risk of hemolysis in G6PD deficiency; and, even if a pregnant woman is not G6PD deficient, the fetus may be G6PD deficient.

It is not known whether TQ is excreted in human milk. TQ should not be used during breastfeeding when the infant has G6PD deficiency or the status is unknown as drug-induced hemolytic anemia may occur.

7. BENEFIT-RISK ASSESSMENT AND CONCLUSIONS

TQ offers high rates of relapse prevention with a simplified (single dose) regimen to aid compliance. It has the potential to play an important role in the elimination of *P. vivax* malaria, which is currently proving refractory. In keeping with the 8-aminoquinoline class, subjects with G6PD deficiency are at risk of hemolysis due to oxidative stress caused by TQ. Use in G6PD deficiency will therefore be contra-indicated and there will be pre-testing for G6PD deficiency. In conjunction with pre-testing for G6PD deficiency, the benefit: risk evaluation for TQ is considered favorable.

7.1. *P. vivax* Malaria is Responsible for Significant Morbidity and Mortality

P. vivax malaria is a global disease with a large geographic distribution, which includes South America, Asia and parts of Africa. Although it has been eradicated from many parts of the world (e.g., southern United States, southern Europe and northern Australia), many of these regions remain receptive to outbreaks of malaria imported by travelers.

In endemic areas, *P. vivax* malaria causes significant morbidity. It's ability to cause severe disease and mortality has previously been overlooked, but is now known to impose a significant clinical burden in many resource-poor settings [Price, 2007; Rahimi, 2014].

7.2. Relapse Prevention is Critical to Patient Management and Malaria Eradication

Unlike *P. falciparum, P. vivax* has a hypnozoite stage in its life cycle, which means the parasite may relapse days, weeks or months later following apparently effective treatment. While this is an important source of morbidity suffered by the patient, from a public health point of view, patients with relapsed disease may also serve as a focus for outbreaks, thus frustrating the malaria eradication efforts of national control programs. Compounds of the 8-aminoquinoline class, such as PQ and TQ, are currently the only ones able to target hypnozoites and thus prevent relapse.

PQ is the only 8-aminoquinoline currently available in most countries, but has some disadvantages. Compliance with PQ is poor in the real world, with many patients failing to complete the recommended 14-day course of treatment. Although there is no PQ compliance data from any ICH region, data on antibiotic compliance would predict that PQ compliance would be similarly poor.

Omission of just three doses of PQ results in a 3- to 4-fold reduction in efficacy [Abreha, 2017], which means that the full potential effectiveness of PQ is not seen, and both the patient and public health suffer as a consequence. The influence of PQ compliance on efficacy is suggested by the difference in relative efficacy between PQ and TQ seen in the two parts of TAF112582: In Part 1, PQ compliance was only 68% (efficacy 77.3%), while that for TQ 300 mg was 96% (efficacy 89.2%). In Part 2, the compliance rates were both TQ and PQ were high (TQ: 100%; PQ: 96%) with PQ efficacy (69.6%) and TQ efficacy (62.4%).

Directly observed therapy for 14 days has been shown to increase compliance [Takeuchi, 2010], but it requires increased use of resource not always available in already-stretched national public health programs in malaria-endemic countries.

7.3. TQ is an Efficacious and Simpler Treatment for *P. vivax* Malaria

The pivotal Phase 3 trial (Study 582 part 2) showed that 300 mg single dose TQ had high recurrence-free efficacy. In this trial, at the 6-month primary endpoint, TQ reduced the risk of recurrence by 70% compared to placebo. In addition, TQ was highly efficacious in the two supporting trials, Study 582 Part 1 and Study 564.

TQ efficacy was consistent in all regions studied in Phase 2 and 3.

TQ offers important advantages over PQ. Of most significance, as a single dose treatment, TQ offers a greatly simplified regimen and highly efficacious treatment. In contract to PQ, the single dose regimen facilitates high compliance and would be predicted to ensure ease of use as well as consistent use even in real-world settings. TQ 300 mg single dose can be administered by a health care professional in conjunction with a point-of-care test for G6PD at time of diagnosis.

7.4. Safety Risks and Considerations

The safety profile of 300 mg single dose TQ is acceptable and broadly similar to that of PQ 15 mg for 14 days. TQ is a synthetic analog of PQ and so a similar safety profile may be expected. Neither TQ nor PQ produce clinically relevant Hb declines in G6PD-normal subjects, although both have the risk of drug-induced hemolysis for G6PD-deficient subjects. Both have the risk of methemoglobinemia and both are known to produce GI events such as nausea and vomiting. Both TQ and PQ can cause self-limited CNS events such as dizziness.

7.4.1. Patients at Risk of Clinically Significant Drug-induced Hemolysis can be Identified and Excluded

The primary safety concern for both TQ and PQ is drug-induced hemolysis in patients with G6PD deficiency. The data from Study 582 Part 2 and Study 564 show that excluding patients with a G6PD activity <70% of the site median in normal males is effective at protecting patients from clinically significant Hb declines. The number of subjects with Hb declines across all three studies (Studies 582 Parts 1 and 2, Study 564) was small and no subject required blood transfusion or any other medical intervention. The majority of Hb declines were within the normal range and none were of clinical concern.

Since it is not possible to determine the G6PD status of the unborn fetus, TQ must not be administered to women who are pregnant. TQ must not be used in lactating mothers where the G6PD status of the infant is unknown, because it is not known whether TQ is excreted in breast milk.

7.4.2. Other Safety Considerations

There were no deaths in the three primary studies, Studies 582 Parts 1 and Part 2, and Study 564, or across the radical cure program.

The majority of subjects had AEs that were mild or moderate in severity. Few AEs Grade ≥3 were reported. There were no clinically significant differences between the TQ+CQ group compared to the CQ alone group in the relative risk of hematological, psychiatric, hepatobiliary, ophthalmic, renal or urinary AEs.

TQ 300 mg single dose causes fully reversible asymptomatic elevations in methemoglobin. There is a theoretical increase in risk of symptomatic methemoglobinemia in patients with NADH-dependent methemoglobin reductase deficiency.

The 300 mg single dose TQ was associated with a number of transient and reversible CNS events (insomnia, anxiety, abnormal dreams, headache, dizziness, somnolence). These events are also reported for other antimalarials. None of the events resulted in withdrawal from the study or treatment discontinuation. The risk of CNS effects is judged to be low in subjects without a history of serious psychiatric disorders. Caution is

advised when administering TQ to patients with a history of, or current, serious psychiatric disorders.

In common with other cationic amphiphilic drugs, TQ has the potential to cause phospholipid accumulation in the cornea, which manifests as vortex keratopathy (also called, corneal verticillata). Vortex keratopathy was reported in the older TQ studies which used higher doses for much longer durations. There is no evidence of corneal changes associated with vision change for the proposed 300 mg single dose TQ. There is no evidence of retinal toxicity in the primary studies, in the interim analysis of the ophthalmic safety study 201807, or in the supportive safety study SB252263/057. AEs associated with ocular changes were infrequent and similar across the treatment groups; all events were mild or moderate in severity and there were no ophthalmic SAEs.

Transient, asymptomatic dose-related elevation in liver transaminases were observed in healthy volunteers who received TQ single doses of 300 mg, 600 mg and 1200 mg in placebo-controlled Phase 1 studies. None of the elevations were severe or considered to be clinically significant. In the primary studies of *P. vivax* infected patients, small ALT increases were observed at baseline and at early timepoints in all three treatment groups and were considered disease-related.

No renal toxicity signal was observed for TQ. There were no renal or urinary SAEs and no events leading to study withdrawal or discontinuation of study medication. The proposed 300 mg single dose TQ was associated with small reversible increases in creatinine consistent with its known renal transporter inhibition (OCT2 and MATEs). Renal transporter inhibition by TQ means that patients with creatinine above the normal range should not be co-dosed with metformin, because of the increased risk of lactic acidosis. Drugs with a small therapeutic index that are substrates of the renal transporters OCT2 and MATE must be excluded regardless of renal function (for example, phenformin, buformin, dofetilide, procainamide, and pilsicainide).

TQ 300 mg single dose does not increase QTcF. CQ is known to increase QT, but TQ does not have a clinically significant additional effect on QT when co-dosed with CQ.

7.5. Tafenoquine Risk:Benefit Profile

Tafenoquine 300 mg single dose has a favorable risk:benefit profile in adults and adolescents ≥16 years with G6PD levels ≥70% of normal for the radical cure (prevention of relapse) of *P. vivax* malaria. This is based on safety and efficacy data in 483 *P. vivax* infected subjects exposed to the recommended 300 mg single dose TQ in Phase 2b/3 studies and the broader TQ safety database of > 4000 subjects exposed to various doses and dose regimens.

GSK and MMV believe that TQ can be an important tool in the armamentarium available to clinicians for the treatment of US patients, as well as contribute to global efforts to eradicate *P. vivax* malaria.

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9. APPENDIX

9.1. Inclusion/Exclusion Criteria for Study 582 Part 2

9.1.1. Inclusion Criteria

Subjects eligible for enrollment in the study must have met all of the following criteria:

1. Positive Giemsa smear for *P. vivax*
2. Parasite density >100 and <100,000/μL
3. Age: ≥16 years (≥18 years in Ethiopia)
4. A female was eligible to enter and participate in this study if she was non-pregnant, non-lactating, and if she was of:
    a. non-child bearing potential defined as: post-menopausal (12 months of spontaneous amenorrhea or <6 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] >40 mIU/mL), pre-menopausal and had had a hysterectomy or a bilateral oophorectomy (removal of the ovaries) or a bilateral tubal ligation with medical report verification, negative pregnancy test or,
    b. child-bearing potential, had a negative pregnancy test at screening, and agreed to comply with one of the following during the treatment stage of the study and for a period of 90 days after stopping study medication:
        - Use of oral contraceptive, either combined or progestogen alone used in conjunction with double-barrier method
        - Use of an intrauterine device with a documented failure rate of <1% per year
        - Use of depo provera injection
        - Double-barrier method consisting of spermicide with either condom or diaphragm
        - Male partner who was sterile prior to the female subject's entry into the study and was the sole sexual partner for that female.
        - Complete abstinence from intercourse for 2 weeks prior to administration of study medication, throughout the study and for a period of 90 days after stopping study medication.
5. A signed and dated informed consent was obtained from the subject or the subject's legal representative prior to screening. Informed assent was obtained from subjects <18 years, where applicable and written or oral witnessed consent had been obtained from parent or guardian.
6. The subject was able to understand and comply with protocol requirements, instructions, and protocol-stated restrictions and was likely to complete the study as planned.

7. The subject was willing to be hospitalized for 3 days and return to clinic for all follow-up visits, including Day 180
8. QTc <450 msec at screening (based on an average of triplicate ECGs obtained over a brief recording period by machine or manual over-read, if first was >450 msec).

9.1.2. Exclusion Criteria

Subjects meeting any of the following criteria were not eligible for study enrollment:

1. Mixed malaria infections (e.g., identified by Giemsa-stained smear or rapid diagnostic test)
2. Severe *P. vivax* malaria as defined by World Health Organization (WHO) criteria (see study protocol Appendix 4).
3. Severe vomiting (no food or inability to take food during previous 8 hours)
4. Screening hemoglobin (Hb) concentration <7 g/dL.
5. G6PD deficiency, assessed by a quantitative spectrophotometric phenotype assay; any subject with an enzyme level <70% of the site median value for G6PD normals was excluded.
6. Liver function test ALT >2x the upper limit of normal (ULN).
7. Any clinically significant concurrent illness (e.g., pneumonia, septicemia), pre-existing conditions (e.g., renal disease, malignancy), conditions that may have affected absorption of study medication (e.g., vomiting or severe diarrhea), or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure or severe coronary artery disease). These abnormalities may have been identified on the screening history and physical or laboratory examination.
8. Subject who had taken antimalarials (e.g., ACTs, mefloquine, PQ, CQ) or drugs with antimalarial activity (see study protocol Appendix 5) within the past 30 days by history.
9. History of allergy to CQ, mefloquine, TQ, PQ or to any other 4- or 8-aminoquinolines.
10. Any contraindications to CQ or PQ administration including a history of porphyria, psoriasis, or epilepsy (please refer to CQ and PQ locally approved prescribing information).
11. Subject who had previously received study medication for this protocol (all parts) or had received treatment with any other investigational drug within 30 days or 5 half-lives (whichever was longer) preceding the first dose of study medication.
12. History of illicit drug abuse or heavy alcohol intake within 6 months of the study.
13. Subjects who had taken or were likely to require the use of medications from the prohibited medication list (see study protocol Appendix 5), which included the following medications and medication classes:
    - Histamine-2 blockers and antacids.

- Drugs with hemolytic potential.
- Drugs known to prolong the QTc interval.
- The biguanides phenformin and buformin (but excluding metformin).
- Drugs that were substrates of the renal transporters organic cation transporter-2 (OCT2), MATE1, and MATE2-K and have a narrow therapeutic index (e.g., the antiarrhythmic agents dofetilide, procainamide, and pilsicainide).

Ophthalmic sites only - Subjects who had a history of significant ocular disease (e.g., surgery to the globe, glaucoma, diabetic retinopathy) or had evidence of corneal or retinal abnormalities identified in the clinical screening ophthalmologic examination (see study protocol Section 6.1) were excluded from the ophthalmologic portion of the trial (these subjects were permitted to participate in the main portion of the study). For these subjects, definitive central results of the screening digital retinal photographs were *not* required prior to randomization in the study.

9.2. Inclusion/Exclusion Criteria for Study 582 Part 1

9.2.1. Inclusion Criteria

Subjects eligible for enrolment in the study must have met all of the following criteria:

1. Positive Giemsa smear for *P. vivax*
2. Parasite density >100/μL and <100,000/μL
3. Age: ≥16 years
4. A female was eligible to enter and participate in this study if she was non-pregnant, non-lactating and if she was of:

a. non-child bearing potential defined as: post-menopausal (12 months of spontaneous amenorrhoea or <6 months of spontaneous amenorrhoea with serum FSH >40 mIU/mL), pre-menopausal and had had a hysterectomy or a bilateral oophorectomy (removal of the ovaries) or a bilateral tubal ligation with medical report verification, negative pregnancy test or,

b. child-bearing potential, had a negative pregnancy test at screening, and agreed to comply with one of the following during the treatment stage of the study and for a period of 90 days after stopping study drug

c. Use of oral contraceptive, either combined or progestogen alone used in conjunction with double barrier method as defined below

d. Use of an intrauterine device with a documented failure rate of <1% per year

e. Double barrier method consisting of spermicide with either condom or diaphragm

f. Male partner who was sterile prior to the female subject's entry into the study and was the sole sexual partner for that female

g. Complete abstinence from intercourse for 2 weeks prior to administration of study drug, throughout the study and for a period of 90 days after stopping study drug

5. A signed and dated informed consent was obtained from the subject or the subject's legal representative prior to screening. NB Assent was obtained from subjects <18 years, where applicable and written or oral witnessed consent had been obtained from parent or guardian
6. The subject was able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and was likely to complete the study as planned
7. Willing to be hospitalised for 3 days and return to clinic for all follow-up visits including Day 180
8. QTc <450 msec at screening*

* based on a single QTcF value at screening or as an average of triplicate ECGs obtained over a brief recording period by machine or manual over-read if first was >450 msec.

9.2.2. Exclusion Criteria

Subjects meeting any of the following criteria must not have been enrolled in the study:

1. Mixed malaria infections (e.g., identified by Giemsa-stained smear or rapid diagnostic test)
2. Severe *vivax* malaria as defined by WHO criteria (see Protocol Appendix 4)
3. Severe vomiting (no food or inability to take food during previous 8 hours)
4. Screening Hb concentration <7 g/dL
5. G6PD deficiency, assessed by a quantitative spectrophotometric phenotype assay:

   Males: Any subject with an enzyme level <70% of the site median value for G6PD normals were excluded.

   Females: (i) Those females with a screening Hb ≥10 g/dL were only excluded if their enzyme level was <70% of the site median value for G6PD normals.

   (ii) Those females with Hb ≥7 but <10 g/dL were excluded if an enzyme level was not >90% of the site median value for G6PD normals.

6. Liver function test ALT >2x ULN
7. Any clinically significant concurrent illness (e.g., pneumonia, septicaemia), pre-existing conditions (e.g., renal disease, malignancy), conditions that may affect absorption of study medication (e.g. vomiting or severe diarrhoea) or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure or severe coronary artery disease). These abnormalities may have been identified on the screening history and physical or laboratory examination

8. Subject had taken antimalarials (e.g., ACTs, mefloquine, PQ, CQ) or drugs with anti-malarial activity (see Protocol Appendix 5) within the past 30 days by history
9. History of allergy to CQ, mefloquine, TQ, PQ or to any other 4- or 8-aminoquinolines
10. Any contraindications to CQ or PQ administration including a history of porphyria, psoriasis or epilepsy (please refer to CQ and PQ locally approved prescribing information)
11. Subject who had previously received study medication for this protocol (all parts) or had received treatment with any other investigational drug within 30 days or five half-lives (whichever is longer) preceding the first dose of study medication
12. History of illicit drug abuse or heavy alcohol intake within 6 months of the study

Subjects who had taken or were likely to require the use of medications from the prohibited medication list (see Protocol Appendix 5) which included the following classes:

- Histamine-2 blockers and antacids
- Drugs with haemolytic potential
- Drugs known to prolong the QTc interval

Ophthalmic sites only - Subjects who had a history of significant ocular disease (e.g., surgery to the globe, glaucoma, diabetic retinopathy) or had evidence of corneal or retinal abnormalities identified in the clinical screening ophthalmologic examination were excluded. Definitive central results of the screening digital retinal photographs were *not* required prior to randomisation in the study.

9.3. Data Tables for Supportive Study 582 Part 1

Table 43 Subject Disposition for Study 582 Part 1 (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Completion Status, n (%)							
Completed	54 (98)	54 (95)	56 (98)	54 (96)	47 (94)	54 (100)	319 (97)
Withdrawn (lost to follow up)	1 (2)	3 (5)	1 (2)	2 (4)	3 (6)	0	10 (3)

Table 44 Discontinuation from Study Treatment in Study 582 Part 1 (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Discontinuation from study treatment, n (%)						
No	54 (98)	57 (100)	57 (100)	56 (100)	49 (98)	53 (98)
Yes	1 (2)	0	0	0	1 (2)	1 (2)
Primary for discontinuation, n (%)						
Adverse event	0	0	0	0	0	0
Subject met QTc withdrawal criteria (protocol-defined stopping criterion)	1 (2)	0	0	0	1 (2)	1 (2)

Table 45 Demographic Characteristics for Study 582 Part 1(ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Age (yrs)							
Mean	36.3	34.6	36.2	35.7	36.0	33.6	35.4
SD	13.28	14.09	13.49	15.06	13.91	14.16	13.94
Median	36.0	34.0	36.0	35.0	34.0	28.0	34.0
Minimum	17	16	16	17	16	16	16
Maximum	68	74	64	68	72	68	74
Sex, n (%)							
Male	37 (67)	44 (77)	43 (75)	45 (80)	35 (70)	39 (72)	243 (74)
Female	18 (33)	13 (23)	14 (25)	11 (20)	15 (30)	15 (28)	86 (26)
Race[a], n (%)							
American Indian or Alaska Native	27 (49)	28 (49)	29 (51)	29 (52)	25 (50)	27 (50)	165 (50)
Asian – Central/South Asian Heritage	11 (20)	11 (19)	9 (16)	10 (18)	6 (12)	10 (19)	57 (17)
Asian – South East Asian Heritage	16 (29)	16 (28)	19 (33)	16 (29)	16 (32)	16 (30)	99 (30)
Mixed Race	1 (2)	2 (4)	0	1 (2)	3 (6)	1 (2)	8 (2)
Weight (kg)							
Mean	59.9	59.4	59.4	62.2	60.0	59.3	60.0
SD	11.17	10.55	9.78	13.58	12.61	13.79	11.93
Median	59.0	57.0	59.0	60.0	59.4	57.4	59.0
Minimum	37	44	43	42	40	34	34
Maximum	91	95	84	106	99	101	106
G6PD enzyme activity (IUg/Hb)							
Mean	9.9	9.4	9.2	9.4	9.5	9.2	9.4
SD	2.98	2.89	2.36	2.65	2.55	2.49	2.65
Median	9.1	8.9	8.6	8.8	9.0	8.7	8.8
Minimum	6	6	4	5	5	5	4
Maximum	18	19	15	18	16	17	19
G6PD enzyme activity (as % of site median)							
Mean	116.0	110.7	107.3	113.0	114.3	108.7	111.6
SD	34.53	23.66	20.28	24.62	27.71	19.25	25.45
Median	108.8	106.4	105.9	106.7	108.3	104.0	106.8
Minimum	71	74	74	79	71	72	71
Maximum	246	194	178	190	208	172	246

a. Subjects were categorized based on standard racial groupings, even though all subjects were ex-US.

Table 46 Malarial Signs and Symptoms in Study 582 Part 1(ITT Population)

Severity	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Chills and rigours, n (%)							
Absent	1 (2)	4 (7)	5 (9)	5 (9)	2 (4)	7 (13)	24 (7)
Mild	23 (42)	22 (39)	24 (42)	22 (39)	24 (48)	18 (33)	133 (40)
Moderate	17 (31)	12 (21)	15 (26)	13 (23)	14 (28)	15 (28)	86 (26)
Severe	14 (25)	19 (33)	13 (23)	16 (29)	10 (20)	14 (26)	86 (26)
Headache, n (%)							
Absent	6 (11)	4 (7)	8 (14)	4 (7)	7 (14)	6 (11)	35 (11)
Mild	22 (40)	26 (46)	22 (39)	24 (43)	16 (32)	23 (43)	133 (40)
Moderate	11 (20)	7 (12)	13 (23)	13 (23)	12 (24)	10 (19)	66 (20)
Severe	16 (29)	20 (35)	14 (25)	15 (27)	15 (30)	15 (28)	95 (29)
Dizziness, n (%)							
Absent	26 (47)	32 (56)	33 (58)	31 (55)	24 (48)	27 (50)	173 (53)
Mild	28 (51)	19 (33)	23 (40)	22 (39)	21 (42)	22 (41)	135 (41)
Moderate	1 (2)	6 (11)	0	1 (2)	5 (10)	3 (6)	16 (5)
Severe	0	0	1 (2)	2 (4)	0	2 (4)	5 (2)
Abdominal Pain, n (%)							
Absent	36 (65)	35 (61)	40 (70)	37 (66)	26 (52)	36 (67)	210 (64)
Mild	16 (29)	16 (28)	13 (23)	18 (32)	19 (38)	16 (30)	98 (30)
Moderate	1 (2)	5 (9)	3 (5)	0	4 (8)	1 (2)	14 (4)
Severe	2 (4)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	7 (2)
Anorexia, n (%)							
Absent	32 (58)	29 (51)	38 (67)	33 (59)	16 (32)	29 (54)	177 (54)
Mild	18 (33)	20 (35)	16 (28)	18 (32)	24 (48)	21 (39)	117 (36)
Moderate	5 (9)	7 (12)	2 (4)	5 (9)	9 (18)	4 (7)	32 (10)
Severe	0	1 (2)	1 (2)	0	1 (2)	0	3 (<1)
Nausea, n (%)							
Absent	29 (53)	23 (40)	33 (58)	29 (52)	28 (56)	31 (57)	173 (53)
Mild	24 (44)	28 (49)	21 (37)	23 (41)	20 (40)	18 (33)	134 (41)
Moderate	2 (4)	6 (11)	2 (4)	3 (5)	1 (2)	5 (9)	19 (6)
Severe	0	0	1 (2)	1 (2)	1 (2)	0	3 (<1)
Vomiting, n (%)							
Absent	47 (85)	44 (77)	47 (82)	46 (82)	39 (78)	47 (87)	270 (82)
Mild	6 (11)	8 (14)	9 (16)	8 (14)	8 (16)	4 (7)	43 (13)
Moderate	2 (4)	5 (9)	1 (2)	2 (4)	3 (6)	3 (6)	16 (5)

Severity	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Severe	0	0	0	0	0	0	0
Diarrhoea, n (%)							
Absent	53 (96)	53 (93)	52 (91)	50 (89)	45 (90)	49 (91)	302 (92)
Mild	1 (2)	3 (5)	5 (9)	5 (9)	4 (8)	3 (6)	21 (6)
Moderate	1 (2)	1 (2)	0	1 (2)	1 (2)	2 (4)	6 (2)
Severe	0	0	0	0	0	0	0

Table 47 Previous Episodes of Malaria in Study 582 Part 1 (ITT Population)

Previous malarial episode?	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Yes, n (%)	35 (64)	36 (63)	28 (49)	31 (55)	31 (62)	33 (61)	194 (59)
No, n (%)	20 (36)	20 (35)	27 (47)	25 (45)	18 (36)	21 (39)	131 (40)
Unknown, n (%)	0	1 (2)	2 (4)	0	1 (2)	0	4 (1)

Table 48 Study Medication Compliance and Exposure in TAF112582 Part 1 (Safety Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Number of compliant doses of CQ, n (%)							
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	1 (2)	0	0	0	1 (2)	0	2 (<1)
3	54 (98)	57 (100)	57 (100)	56 (100)	49 (98)	54 (100)	327 (>99)
Subject compliance with TQ treatment, n (%)							
Yes	55 (100)	57 (100)	55 (96)	56 (100)	50 (100)	54 (100)	327 (>99)
Number of outpatient doses of PQ/placebo dosing taken [a], n (%)							
10 or fewer	19 (35)	21 (37)	20 (35)	22 (39)	16 (32)	23 (43)	121 (37)
11 to 13	15 (27)	12 (21)	14 (25)	13 (23)	13 (26)	10 (19)	77 (23)
14 or more	21 (38)	24 (42)	23 (40)	21 (38)	21 (42)	21 (39)	131 (40)

Note: An in-clinic dose which was vomited but where the subject was re-dosed within 4 hours was considered to be compliant.

a. 12 tablets taken was considered perfect compliance. The count of tablets taken was entirely dependent on tablets returned and not directly observed therapy

Table 49 Recurrence-Free Efficacy at Six Months in TAF112582 Part 1 (Kaplan-Meier Analysis) (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Number of Subjects, n (%)						
Subjects observed to relapse prior to Study Day 180	22 (40)	25 (44)	6 (11)	4 (7)	12 (24)	31 (57)
Censored, prior to 6 month assessment [a]	4 (7)	3 (5)	3 (5)	9 (16)	4 (8)	2 (4)
Censored, relapse-free at 6 months	29 (53)	29 (51)	48 (84)	43 (77)	34 (68)	21 (39)
Relapse-free efficacy rate at 6 months, %						
Estimate	57.7	54.1	89.2	91.9	77.3	37.5
95% CI	(43,70)	(40,66)	(77,95)	(80,97)	(63,87)	(23,52)
Difference from CQ at 6 months, %						
Estimated Difference	20.3	16.6	51.7	54.5	39.9	NA
95% CI	(0,40)	(-3,36)	(35,69)	(38,71)	(21,59)	NA
Log Rank Test [b]						
p-value	ND	0.158	<0.0001	<0.0001	0.0004	NA

a. Subjects are censored if they did not have P. vivax at baseline, or failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 6 month assessment.
b. A two-sided log rank test was performed over 6 months using a 5% significance level.
c. ND Not done due to step-down testing procedure to adjust for multiple comparisons.

Table 50 Recurrence-Free Efficacy at 4 Months in TAF112582 Part 1 (Kaplan-Meier Methodology) (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Number of Subjects, n (%)						
Subjects observed to relapse prior to Study Day 120	19 (35)	22 (39)	5 (9)	2 (4)	10 (20)	28 (52)
Censored, prior to 4 month assessment [a]	3 (5)	3 (5)	1 (2)	8 (14)	6 (12)	2 (4)
Censored, relapse-free at 4 months	33 (60)	32 (56)	51 (89)	46 (82)	34 (68)	24 (44)
Relapse-free efficacy rate at 4 months, %						
Estimate	62.3	60.3	89.4	98.1	78.4	46.5
95% CI	(46,75)	(46,72)	(75,96)	(87,100)	(64,88)	(32,60)
Difference from CQ at 4 months, %						
Estimated Difference	15.8	13.8	42.9	51.6	32.0	
95% CI	(-5,36)	(-6,33)	(26,60)	(37,66)	(13,50)	
Log Rank Test [b]						
p-value		0.091	<0.0001	<0.0001	0.002	

a. Subjects are censored if they did not have *P. vivax* at baseline, or failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 4-month assessment.

b. A two-sided log rank test was performed over 4 months using a 5% significance level.

Table 51 Analysis of Recrudescence (Blood Stage Failure) Rates in TAF112582 Part 1 (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Number of Subjects, n (%)						
Recrudescence before Study Day 33	0	1 (2)	0	0	1 (2)	2 (4)
Censored, prior to Study Day 33[a]	2 (4)	1 (2)	1 (2)	0	1 (2)	2 (4)
Censored, no recrudescence by Study Day 33	53 (96)	55 (96)	56 (98)	56 (100)	48 (96)	50 (93)
Recrudescence rate						
Estimate	0.0	1.8	0.0	0.0	3.0	6.1
95% CI	(0,0)	(0,12)	(0,0)	(0,0)	(0,20)	(2,22)

a. Subjects are censored if they did not have *P. vivax* at baseline, or failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 28 days assessment.

Table 52 *P. falciparum* Asexual Parasite Emergence in TAF112582 Part 1 (ITT Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)	Total (N=329)
Number of subjects with emergent *P. falciparum* at any stage	0	1 (2)	0	0	1 (2)	2 (4)	4 (1)

Table 53 Summary of Time to Parasite, Fever, and Gametocyte Clearance (Intent-to-Treat Population)

	TQ+CQ 50mg (N=55)	TQ+CQ 100mg (N=57)	TQ+CQ 300mg (N=57)	TQ+CQ 600mg (N=56)	PQ+CQ (N=50)	CQ (N=54)
Parasite Clearance, n (%)						
Parasite clearance	46 (84)	51 (89)	50 (88)	45 (80)	44 (88)	51 (94)
Censored	9 (16)	6 (11)	7 (12)	11 (20)	6 (12)	3 (6)
Time to Parasite Clearance (Hours)						
Median	45.0	43.0	42.0	47.0	44.5	42.5
95% CI	(42,49)	(38,50)	(40,45)	(43,59)	(39,48)	(38,48)
Fever Clearance, n (%)						
Fever clearance	20 (36)	24 (42)	19 (33)	21 (38)	14 (28)	21 (39)
Censored	35 (64)	33 (58)	38 (67)	35 (63)	36 (72)	33 (61)
Time to Fever Clearance (Hours)						
Median	11.0	6.5	15.0	19.0	19.5	8.0
95% CI	(4,22)	(4,19)	(5,21)	(5,26)	(4,37)	(5,16)
Gametocyte Clearance, n (%)						
Gametocyte clearance	41 (75)	44 (77)	47 (82)	44 (79)	36 (72)	41 (76)
Censored	14 (25)	13 (23)	10 (18)	12 (21)	14 (28)	13 (24)
Time to Gametocyte Clearance (Days)						
Median	2.0	1.0	1.0	1.0	2.0	2.0
95% CI	(1,2)	(1,2)	(1,2)	(1,2)	(1,2)	(1,2)

9.4. Inclusion/Exclusion Criteria for Study 564

9.4.1. Inclusion Criteria

Subjects eligible for enrollment in the study must have met all of the following criteria:

Safety

9. A female is eligible to enter and participate in the study if she is non-pregnant, non-lactating and if she is of:

   a. Non-childbearing potential defined as: post-menopausal (12 months of spontaneous amenorrhea or <6 months of spontaneous amenorrhea with serum FSH >40 mIU/mL), or pre-menopausal and has had a hysterectomy or a bilateral oophorectomy (removal of the ovaries) or a bilateral tubal ligation, negative pregnancy test or,

   b. Child-bearing potential, has a negative pregnancy test at screening, and agrees to comply with one of the following during the treatment stage of the study and for a period of 90 days after stopping study medication:

   - Use of oral contraceptive, either combined or progestogen alone used in conjunction with double barrier method as defined below.

- Use of an intrauterine device with a documented failure rate of <1% per year
- Use of depo provera injection
- Double barrier method consisting of spermicide with either condom or diaphragm
- Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female.
- Complete abstinence from intercourse for 2 weeks prior to administration of study medication, throughout the study and for a period of 90 days after stopping study medication.

10. The subject has a glucose 6-phosphate dehydrogenase (G6PD) value (measured by a quantitative spectrophotometric phenotype assay) as follows:
    - **Female subjects** must have an enzyme level ≥40% of the site median value for G6PD normal males.
    - **Male subjects** must have an enzyme level ≥70% of the site median value for G6PD normal males.
11. The subject has a screening Hb value as follows:

    •Any subject with a G6PD value ≥70% of the site median value must have a screening Hb value ≥70 g/L.

    •Female subjects with a G6PD value is ≥40% - <70% of the site median value must have a screening Hb value ≥80 g/L.
12. The subject has a QTcF of <450 msec.

    N.B. Reading based on an average of triplicate ECGs obtained over a brief recording period by machine or manual over-read.

Efficacy

13. The subject has a positive malarial smear for *P. vivax*.
14. The subject has a parasite density of >100 and <100,000/μL.

Other

15. Male or female subject aged 16 years or older (18 years or older in Ethiopia) at the time of signing the informed consent.
16. The subject agrees to G6PD genotyping.
17. The subject is willing and able to comply with the study protocol.
18. The subject or parent/legal guardian, as applicable, has given written informed, dated consent; and the subject has given written assent, if applicable, to participate in the study.

9.4.2. Exclusion Criteria

Subjects meeting any of the following criteria were not to be enrolled in the study:

Safety

13. The subject has a mixed malaria infection (identified by a malarial smear or rapid diagnostic test).
19. The subject has severe *P. vivax* malaria as defined by WHO criteria.
20. The subject has a history of allergy to chloroquine, mefloquine, tafenoquine, primaquine, or to any other 4- or 8-aminoquinoline.

Hepatic Disease

21. The subject has a liver ALT >2x ULN.

Concurrent Disease

22. The subject has severe vomiting (no food or inability to take food during the previous 8 hours).
23. The subject has a clinically significant concurrent illness (e.g., pneumonia, septicemia), pre-existing condition (e.g., renal disease, malignancy), condition that may affect absorption of study medication (e.g., vomiting, severe diarrhea), or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure, severe coronary artery disease).
24. The subject has a history of porphyria, psoriasis, or epilepsy.
25. The subject has a history of significant ocular disease (e.g. surgery to the globe, glaucoma, diabetic retinopathy) or has evidence of corneal or retinal abnormalities identified in the clinical screening ophthalmologic examination.

Concurrent Medication

26. The subject has taken anti-malarials (e.g., ACTs, mefloquine, primaquine, or any other 4- or 8-aminoquinoline) within 30 days prior to study entry.
27. The subject has taken or will likely require during the study the use of medications from the following classes:

    - Histamine-2 blockers and antacids

    - Drugs with hemolytic potential

    - Drugs known to prolong the QTcF interval

    - The biguanides phenformin and buformin (but excluding metformin)

    - Drugs that are substrates of the renal transporters OCT2, MATE1 and MATE-2K and have a narrow therapeutic index (for example, the anti-arrhythmic agents dofetilide, procainamide and pilsicainide)

Other

28. The subject has received treatment with any investigational drug within 30 days of study entry, or within 5 half-lives, whichever is longer.
29. The subject has a recent history of illicit drug abuse or heavy alcohol intake, such that full participation in the study could be compromised.

9.5. Data Tables for Supportive Study 564

Table 54 Subject Disposition in Study 564 (Safety Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Completion status, n (%)			
Completed	160 (96)	83 (98)	243 (97)
Withdrawn	6 (4)	2 (2)	8 (3)
Primary reason, n (%)			
Lost to follow-up	4 (2)	2 (2)	6 (2)
Withdrawal by subject	2 (1)	0	2 (<1)

Table 55 Discontinuation from Study Medication in Study 564 (Safety Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Premature discontinuation from study treatment, n (%)			
No	160 (96)	82 (96)	242 (96)
Yes	6 (4)	3 (4)	9 (4)
Reason for discontinuation from study medication, n (%)			
Adverse event	1 (<1)	1 (1)	2 (<1)
Subject reached protocol-defined Hb stopping criteria	2 (1)[a]	1 (1)	3 (2)[a]
Lost to follow-up	1 (<1)	1 (1)	2 (<1)
Physician decision	1 (<1)	0	1 (<1)
Other	1 (<1)	0	1 (<1)

a. In addition to the 2 subjects in the TQ+CQ group reported in Source Table 1.4, another subject in the TQ+CQ group met the Hb stopping criteria and discontinued study medication, but this was not properly recorded in the eCRF.

Table 56 Demographic Characteristics in Study 564(Safety Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Age (years), n (%)			
n	166	85	251
Mean (SD)	37.5 (14.28)	37.7 (14.69)	37.6 (14.39)
Sex, n (%)			
n	166	85	251
Male	114 (69)	53 (62)	167 (67)
Female	52 (31)	32 (38)	84 (33)
Race[a], n (%)			
n	166	85	251
American Indian or Alaska native	87 (52)	43 (51)	130 (52)
Asian (Southeast Asian heritage)	41 (25)	23 (27)	64 (25)
Black or African American	2 (1)	0	2 (<1)
Multiple	36 (22)	19 (22)	55 (22)
Ethnicity, n (%)			
n	166	85	251
Hispanic or Latino, n (%)	122 (73)	61 (72)	183 (73)
Not Hispanic or Latino, n (%)	44 (27)	24 (28)	68 (27)
Body mass index (kg/m^2)			
n	166	85	251
Median (Min, Max)	24.79 (16.7, 48.9)	25.24 (17.4, 40.4)	24.91 (16.7, 48.9)
G6PD enzyme activity (IU/g Hb)			
n	166	85	251
Median (Min, Max)	8.17 (6.0, 13.5)	8.01 (5.1, 14.2)	8.14 (5.1, 14.2)
G6PD enzyme activity (as % of site median)			
n	166	85	251
Median (Min, Max)	97.73 (70.8, 170.5)	94.49 (62.0, 169.2)	96.88 (62.0, 170.5)

Note: All subjects were confirmed to be at least 16 years of age at study entry, consistent with inclusion/exclusion criteria. No subjects from Ethiopia, where subjects were required to be at least 18 years of age, were enrolled in the study (Source: Table 1.5).

a. Subjects were categorized based on standard racial groupings, even though all subjects were ex-US.

Table 57 Malarial Signs and Symptoms in Study 564 (Safety Population)

Symptom/Severity	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Chills and rigors, n (%)			
Absent	9 (5)	5 (6)	14 (6)
Mild	32 (19)	22 (26)	54 (22)
Moderate	62 (37)	23 (27)	85 (34)
Severe	63 (38)	35 (41)	98 (39)
Headache, n (%)			
Absent	7 (4)	5 (6)	12 (5)
Mild	23 (14)	13 (15)	36 (14)
Moderate	59 (36)	28 (33)	87 (35)
Severe	77 (46)	39 (46)	116 (46)
Dizziness, n (%)			
Absent	72 (43)	36 (42)	108 (43)
Mild	64 (39)	27 (32)	91 (36)
Moderate	28 (17)	21 (25)	49 (20)
Severe	2 (1)	1 (1)	3 (1)
Abdominal pain, n (%)			
Absent	117 (70)	68 (80)	185 (74)
Mild	40 (24)	12 (14)	52 (21)
Moderate	9 (5)	5 (6)	14 (6)
Anorexia, n (%)			
Absent	80 (48)	49 (58)	129 (51)
Mild	46 (28)	15 (18)	61 (24)
Moderate	36 (22)	19 (22)	55 (22)
Severe	4 (2)	2 (2)	6 (2)
Nausea, n (%)			
Absent	76 (46)	44 (52)	120 (48)
Mild	63 (38)	27 (32)	90 (36)
Moderate	26 (16)	13 (15)	39 (16)
Severe	1 (<1)	1 (1)	2 (<1)
Vomiting, n (%)			
Absent	117 (70)	71 (84)	188 (75)
Mild	38 (23)	11 (13)	49 (20)
Moderate	11 (7)	3 (4)	14 (6)
Diarrhea, n (%)			
Absent	140 (84)	73 (86)	213 (85)
Mild	24 (14)	11 (13)	35 (14)
Moderate	2 (1)	0	2 (<1)
Severe	0	1 (1)	1 (<1)
Pruritus/itching, n (%)			
Absent	151 (91)	76 (89)	227 (90)
Mild	7 (4)	6 (7)	13 (5)
Moderate	8 (5)	3 (4)	11 (4)

Symptom/Severity	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Coughing, n (%)			
Absent	141 (85)	65 (76)	206 (82)
Mild	20 (12)	19 (22)	39 (16)
Moderate	5 (3)	1 (1)	6 (2)

Table 58 Previous Malarial Episodes in Study 564 (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Previous malarial episode, n (%)			
Yes	132 (80)	63 (74)	195 (78)
No	32 (19)	22 (26)	54 (22)
Unknown	2 (1)	0	2 (<1)

Table 59 Study Medication Compliance and Exposure in Study 564 (Safety Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)	Total (N=251)
Number of compliant doses of CQ, n (%)			
n	166	85	251
2	1 (<1)	1 (1)	2 (<1)
3	165 (>99)	84 (99)	249 (>99)
Subject compliance with TQ treatment, n (%)			
Yes	165 (>99)	84 (99)	249 (>99)
Total number of PQ doses taken, n (%)			
n	166	85	251
<12	6 (4)	1 (1)	7 (3)
at least 12	160 (96)	83 (98)	243 (97)
Missing	0	1 (1)	1 (<1)
Subjects with detectable PK at Day 8 or Day 15 visits, n (%)			
n		84	
Yes		84 (100)	
Subjects with at least 12 doses of PQ and detectable PK at Day 8 or Day 15 visits, n (%)			
n		83	
Yes		82 (99)	

Table 60 Recurrence-Free Efficacy over 6 Months in TAF116564 (Kaplan-Meier Analysis) (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)
Number of Subjects, n (%)		
Subjects observed to recurrence prior to or at 6 months	42 (25)	20 (24)
Censored, prior to 6-month assessment	12 (7)	5 (6)
Censored, recurrence-free at 6 months	112 (67)	60 (71)
Recurrence-free efficacy rate at 6 months, %		
Estimate (95% CI)	72.7 (64.8,79.2)	75.1 (64.2,83.2)
Hazard ratio of risk of recurrence TQ+CQ vs PQ+CQ		
Estimate (95% CI)	0.984 (0.577,1.678)	

Figure 9 Survival Curves for Recurrence-Free Efficacy over 6 Months in TAF116564 (mITT Population)

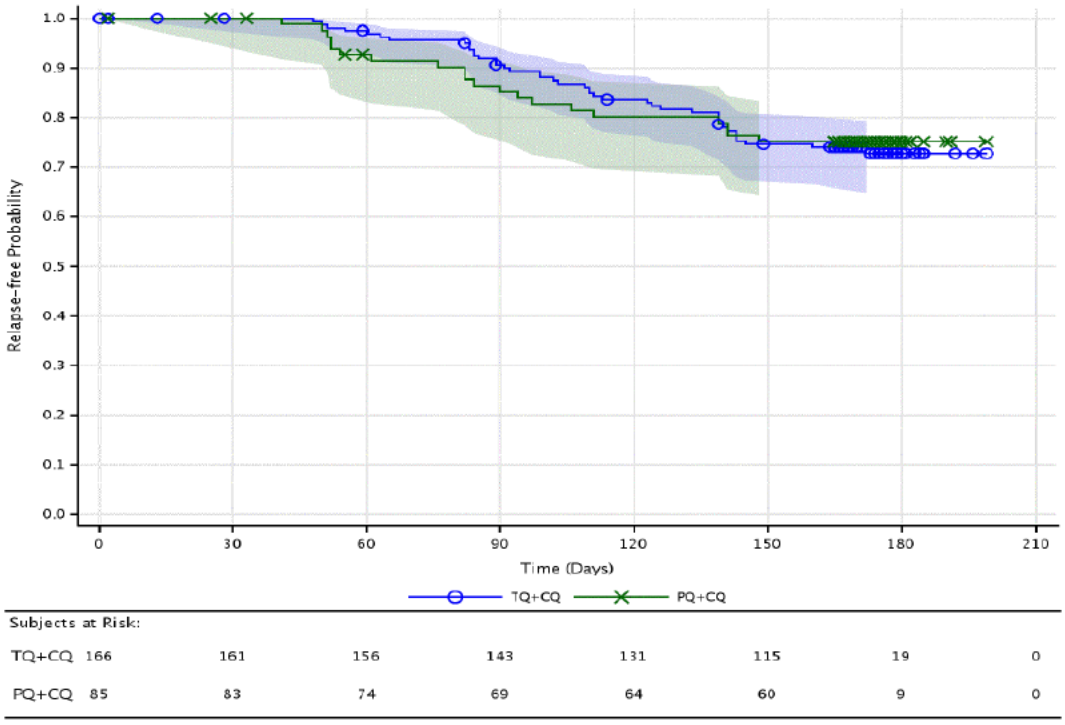

Table 61 Recurrence-Free Efficacy at 6 Months in TAF116564 with Missing=Failure (Logistic Regression) (mITT Population)

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

a. Odds ratios <1 suggest a smaller chance of recurrence as compared with PQ+CQ.

Table 62 Recurrence-Free Efficacy at 4 Months in TAF116564 (Kaplan-Meier Methodology) (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)
Number of Subjects, n (%)		
Subjects observed to recurrence prior to or at 4 months	29 (17)	16 (19)
Censored, prior to 4-month assessment	10 (6)	6 (7)
Censored, recurrence-free at 4 months	127 (77)	63 (74)
Recurrence-free efficacy rate at 4 months, %		
Estimate (95% CI)	82.3 (74.9,87.7)	79.7 (68.9,87.1)
Hazard ratio of risk of recurrence TQ+CQ vs PQ+CQ[a]		
Estimate (95% CI)	0.815 (0.442,1.503)	

a. A hazard ratio less than 1 indicates a lower chance of recurrence with TQ+CQ as compared with PQ+CQ.

Table 63 Recurrence-Free Efficacy at 4 Months in TAF116564 with Missing = Failure (Logistic Regression) (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)
Number of subjects, n	166	85
Subjects recurrence-free, n (%)	127 (77)	63 (74)
Subjects with a recurrence, n (%)	39 (23)	22 (26)
Odds ratio of recurrence (TQ+CQ comparison with PQ+CQ)		
Estimate (95% CI)[a]	0.858 (0.465, 1.583)	

Odds ratios less than 1 suggest a smaller chance of recurrence as compared with PQ+CQ.

Table 64 Analysis of Time to Parasite, Fever, and Gametocyte Clearance in TAF1164564 (mITT Population)

	TQ+CQ (N=166)	PQ+CQ (N=85)
Parasite Clearance, n (%)		
Parasite clearance achieved	166 (100)	85 (100)
Censored, parasite clearance not achieved	0 (0)	0 (0)
Time to Parasite Clearance (hours)		
Median (95% CI)	41 (38,45)	44 (41,49)
Fever Clearance, n (%)		
Fever clearance achieved	65 (39)	32 (38)
Censored, at Baseline	101 (61)	53 (62)
Censored, fever clearance not achieved	0	0
Time to Fever Clearance (hours)		
Median (95% CI)	10 (7, 19)	13 (8, 22)
Gametocyte Clearance, n (%)		
Gametocyte clearance achieved	102 (61)	54 (64)
Censored, at Baseline	64 (39)	31 (36)
Censored, gametocyte clearance not achieved	0	0
Time to Gametocyte Clearance (hours)		
Median (95% CI)	38 (37, 43)	41 (37, 48)

9.6. Pooled Data Tables

Table 65 Adverse Events in the Nervous System Disorders SOC Reported Across the TQ Development Program (All Studies Safety Population)

Preferred Term, Grouped by Medically and/or Symptomatically-Related	All Placebo[a] (N=794) n (%)	300 mg TQ Total ≤3 days (N=807) n (%)	>300 mg TQ Total ≤3 days (N=1482) n (%)	>300 mg TQ Total >3 days (N=1445) n (%)	All TQ[b] (N=4129) n (%)
Any event	**170 (21)**	**142 (18)**	**240 (16)**	**269 (19)**	**734 (18)**
Headache	149 (19)	98 (12)	164 (11)	211 (15)	544 (13)
Migraine	4 (<1)	3 (<1)	0	3 (<1)	8 (<1)
Sinus headache	1 (<1)	0	0	4 (<1)	4 (<1)
Tension headache	0	0	0	2 (<1)	2 (<1)
Head discomfort	0	0	1 (<1)	0	1 (<1)
Visual field defect	0	0	0	1 (<1)	1 (<1)
Lethargy	0	0	28 (2)	28 (2)	56 (1)
Somnolence	1 (<1)	3 (<1)	21 (1)	1 (<1)	25 (<1)
Amnesia	0	0	0	1 (<1)	1 (<1)
Depressed level of consciousness	0	1 (<1)	0	0	1 (<1)
Disturbance in attention	0	0	1 (<1)	0	1 (<1)
Dysgeusia	1 (<1)	0	17 (1)	1 (<1)	18 (<1)
Paraesthesia	0	0	3 (<1)	4 (<1)	8 (<1)
Hypoaesthesia	1 (<1)	0	3 (<1)	1 (<1)	4 (<1)
Hyperaesthesia	0	0	0	1 (<1)	2 (<1)
Burning sensation	0	0	0	0	1 (<1)
Coordination abnormal	0	0	0	2 (<1)	2 (<1)
Balance disorder	0	1 (<1)	0	0	1 (<1)
Dizziness	24 (3)	62 (8)	56 (4)	33 (2)	171 (4)
Syncope	0	2 (<1)	1 (<1)	2 (<1)	5 (<1)
Presyncope	0	0	0	1 (<1)	1 (<1)
Dizziness postural	1 (<1)	0	0	0	0
Loss of consciousness	1 (<1)	0	0	0	0
Tremor	0	1 (<1)	1 (<1)	2 (<1)	4 (<1)
Muscle contractions involuntary	0	0	1 (<1)	0	1 (<1)
Sciatica	0	0	0	2 (<1)	3 (<1)
Post herpetic neuralgia	0	0	1 (<1)	1 (<1)	2 (<1)
Trigeminal neuralgia	0	0	0	1 (<1)	1 (<1)

Note: Preferred terms are grouped by those considered medically and/or symptomatically related; only selected columns are displayed.

Note: Data from clinical pharmacology studies SB252263/003, SB252263/050, SB252263/051, SB252263/052, SB252263/053, and SB252263/054 were not included in the All Studies grouping because validated datasets containing subject-level data could not be located (SB252263/003) or were not available to GSK (i.e. remaining 5 US army-sponsored studies). A manual review of safety listings for these studies was conducted and important safety data are described.

a. The placebo group includes healthy volunteers treated with placebo and *P. vivax* subjects treated with CQ alone in Study TAF112582 and Study SB252263/047.

b. Includes 392 subjects who received < 300mg total dose and 3 subjects who received a total 300mg dose > 3 days

Table 66 Adverse Events in the Psychiatric Disorders SOC Reported Across the TQ Development Program (All Studies Safety Population)

Preferred Term, Grouped by Medically and/or Symptomatically-Related	All Placebo[a] (N=794) n (%)	300 mg TQ Total ≤3 days (N=807) n (%)	>300 mg TQ Total ≤3 days (N=1482) n (%)	>300 mg TQ Total >3 days (N=1445) n (%)	All TQ[b] (N=4129) n (%)
Any Event	**8 (1)**	**16 (2)**	**19 (1)**	**37 (3)**	**79 (2)**
Insomnia	8 (1)	15 (2)	12 (<1)	15 (1)	48 (1)
Abnormal dreams	0	1 (<1)	0	6 (<1)	7 (<1)
Sleep disorder	0	0	0	3 (<1)	3 (<1)
Nightmare	0	0	0	2 (<1)	2 (<1)
Agitation	0	0	0	2 (<1)	2 (<1)
Anxiety	0	2 (<1)	0	0	2 (<1)
Anxiety disorder	0	0	0	2 (<1)	2 (<1)
Irritability	0	0	1 (<1)	0	2 (<1)
Neurosis	0	0	0	1 (<1)	1 (<1)
Panic attack	0	0	0	1 (<1)	1 (<1)
Psychotic disorder	0	0	1 (<1)	0	1 (<1)
Stress	0	0	0	1 (<1)	1 (<1)
Euphoric mood	0	0	1 (<1)	2 (<1)	3 (<1)
Depressed mood	0	0	1 (<1)	1 (<1)	2 (<1)
Depression	0	0	0	2 (<1)	2 (<1)
Bipolar disorder	0	0	0	1 (<1)	1 (<1)
Disinhibition	0	0	1 (<1)	0	1 (<1)
Mood altered	0	0	1 (<1)	0	1 (<1)
Alcoholic hangover	0	0	0	1 (<1)	1 (<1)
Tic	0	0	1 (<1)	0	1 (<1)

Note: Preferred terms are grouped by those considered medically and/or symptomatically related; only selected columns are displayed.

Note: Data from clinical pharmacology studies SB252263/003, SB252263/050, SB252263/051, SB252263/052, SB252263/053, and SB252263/054 were not included in the All Studies grouping because validated datasets containing subject-level data could not be located (SB252263/003) or were not available to GSK (i.e. remaining 5 US army-sponsored studies). A manual review of safety listings for these studies was conducted and important safety data are described.

Note: A subject in Study SB252263/043, included in the All Studies grouping, was reported to make a suicide attempt associated with alcohol intoxication. The event was not assigned a body system and therefore does not appear in the psychiatric disorders output. The event is described in Table 36.

a. The placebo group includes healthy volunteers treated with placebo and *P. vivax* subjects treated with CQ alone in Study TAF112582 and Study SB252263/047.

b. Includes 392 subjects who received < 300mg total dose and 3 subjects who received a total 300mg dose > 3 days

9.7. Additional TQ Clinical Studies

Table 67 Tabular Listing of All Clinical Studies Submitted to NDA210975 – Tafenoquine for the Radical cure of *P. vivax* malaria

Study Identifier	Study Description
Studies of tafenoquine for the Radical Cure (prevention of relapse) Indication	
TAF112582 (Part 1)	Subjects >=16 years with confirmed P. Vivax infection and >70% normal G6PD levels, stratified by baseline parasite count (<=7500/uL, >7500/uL)
TAF112582 (Part 2)	Subjects >=16 years with confirmed P. Vivax infection and >70% normal G6PD levels
TAF116564	Normal and G6PD-deficient P. Vivax-infected subjects
SB252263/022	Phase I Food effect study in healthy volunteers
TAF114582	Phase I Thorough QT study in healthy volunteers
201807	Phase I Ophthalmic safety study in healthy volunteers
SB252263/015	Phase I Drug-drug interaction study with desipramine in healthy volunteers
SB252263/040	Phase I Drug-drug interaction study with midazolam, flubiprofen and caffeine in healthy volunteers
TAF106491	Phase I Drug-drug interaction study with chloroquine in healthy volunteers
200951	Phase I Drug-drug interaction study with artemether-lumefantrine, and dihydroartemisinin-piperaquine tetraphosphate in healthy volunteers
TAF110027	Phase I dose escalation study in healthy volunteers and G6PD deficient healthy volunteers
201780	Phase I study in healthy volunteers to determine the effects of tablet aging (dissolution profiles) on the PK of TQ
TAF115226	Non-interventional study in healthy volunteers to establish site level normal ranges for G6PD enzyme activity
Supportive studies of tafenoquine in other indications or with other dose regimens	
SB252263/050[a]	Phase1 PK study in healthy male subjects
SB252263/051[a]	Phase1 PK study in healthy male subjects
SB252263/052[a]	Phase1 PK study in healthy male subjects
SB252263/053[a]	Phase1 Malaria challenge study healthy subjects
SB252263/054[a]	Phase1 Malaria challenge study in healthy subjects
SB252263/001	Phase 1 study in normal and G6PD-deficient healthy female subjects
SB252263/003[a]	Phase 1 PK, Food effect in healthy subjects
SB252263/014	Phase 1 relative bioavailability study in healthy subjects
SB252263/057	Phase 1 Ophthalmic and Renal Safety Study in healthy subjects
SB252263/006	Phase II Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/030	Phase III Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/033	Phase III Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/043	Phase II Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/044	Phase II Malaria Prophylaxis Non-immune male subjects
SB252263/045	Phase II Malaria Prophylaxis Semi-Immune Healthy Subjects
SB252263/049	Phase II Malaria Prophylaxis Non-immune healthy Subjects
SB252263/036[a]	Pediatric subjects (6 mo to 14 yrs)
SB252263/046	Phase II treatment P. vivax-infected subjects with no documented G6PD deficiency
SB252263/047	Healthy subjects and P. Vivax-infected subjects with normal G6PD
SB252263/058	Treatment of 20-60 year-old subjects with confirmed P. Vivax infection and normal G6PD

a. Complete and validated datasets from studies SB252263/003, 036, 050,051, 052,053, and 054 were unavailable and have been excluded from pooled analyses